Effect of Antiepileptic Drugs on Thyroid Function in Epileptic Sudanese Children

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قال تعالى:

(وَلَوْ أَنَّمَا فِي الأَرْضِ مِن شَجَرَةٍ أَقْلَامٌ وَالبَحْرُ يَمُدُّهُ مِن بَعْدِهِ سَبْعَةً أَبْحُرُ مَا نَفْدَتْ كُلِّمَاتُ اللَّهِ إِنَّ اللَّهَ عَزِيزٌ حَكِيمٌ)

صدق الله العظيم

(سورة لقمان، الآية 27)
Dedication

To My Lovely Husband
To My Dear Kind Parents
To My Lovely Children
To All Nice Mothers of Handicapped Children
Acknowledgement

I would like to thank my supervisor Dr. El-Yahir M. El-Shibly for his valuable guidance, support and encouragement.

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Abstract

This is a cross-sectional hospital based study, aimed to study the effect of antiepileptic drugs on the thyroid function. It was conducted in Gafaar Ibn Ouf and Omdurman Children’s Emergency Hospital referral clinics, in the period from April – July 2006.

The total of 67 children with epilepsy, aged < 16 yrs and 30 healthy children were taken as control, males were predominant (68.7%). 56 patients were on Carbamazepine and 11 patients were on Sodium Valporate.

All children in the study group were surveyed and investigated for thyroid function by measuring serum T4, T3 and TSH levels.

- Carbamazepine group had significantly low serum T4 level (P = 0.00) and significantly higher T3 level (0.04) than control group.
- TSH level had insignificant difference from control group.
- Sodium Valporate group had insignificant difference in thyroid function from control.
- Serum T4 level in Carbamazepine group affected by age but not affected by sex, origin and duration of treatment.
- Serum T3 level in Carbamazepine affected by duration of treatment but not affected by sex, age or origin.
- Almost all patients were clinically euthyroid.
ملخص الارتباطة

شملت الدراسة 67 طفلاً من مصابي الصرع وعمرهم أقل من 16 عاماً – نسبة الأولاد المرضي (68.7%). بالإضافة إلى 30 طفلاً أصحاء اعمارهم أقل من 16 عاماً كمقياس. سلسة وخمسون طفلاً من المصابين بتعاطو الكاربامازبين و 11 منهم يتعاطون فلبروات الصوديوم. أجريت هذه الدراسة لمعرفة اثر الادوية المضادة للصرع على وظائف الغدة الدرقية.

تمت الدراسة في الفترة من اول ابريل حتى نهاية يوليو 2006م بالعيادات المحولة في كل من مستشفى جعفر بن عوف وحوادث ام درمان للاطفال. تم رصد كل الأطفال محور الدراسة واجري لهم فحص ووظائف الغدة الدرقية بقياس مستوي الهرمون الحاث للغدة الدرقية (TSH) والهرمون الدرقي (T3) والهرمون الدرقي (T4).

وجد أن هناك انخفاضاً ذا دلالة احصائية في معدل هرمون الغدة (T4) عند المرضى متعاطي الكاربامازبين مقارنة بمعدله عند الأصحاء. كما ان لديهم ارتفاع ذا دلالة احصائية (P = 0.4) في هرمون الغدة (T3) مقارنة بالإصحاء – معدل الهرمون الحاث للغدة الدرقية لم يتغير.

وظائف الغدة الدرقية عند المرضى متعاطي فلبروات الصوديوم لم تتأثر. كلینيكياً لا توجد أي اعراض لنقص هرمون الغدة الدرقية عند كل المرضى.

معدل هرمون الغدة الدرقية (T4) تتأثر فقط بعمر المريضي ولم يتأثر بجنس أو أصل المرضى أو مدة المعالجة بالدواء. معدل هرمون الغدة (T3) تتأثر باختلاف مدة استعمال الدواء ولم يتأثر بعامل العمر – الجنس أو أصل المرض.
List of abbreviations

AEDs: Antiepileptic drugs
CBZ: Carbamazepine
$\text{FT}_3$: Free Triiodothyromine
$\text{FT}_4$: Free Thyroxine
Mcg/d: Microgram/deciliter
PB: Phenobarbitone
pg/dl: Picogram/deciliter
$rT_3$: Reverse Triiodothyromine
SD: Standard deviation
T.S.H.: Thyroid Stimulating hormone
$T_3$: Triiodothyromine
$T_4$: Thyroxine
VAP: Sodium Valproate
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Chapter One

1- Introduction and Literature Review

1.1 General consideration:

The epilepsies are common and frequently devastating disorders, affecting approximately 2.5 million people in the United States alone\(^{(1)}\). At any one time 7 in 1000 people in the general population have epilepsy. Epilepsy usually begins in childhood, potentially impeding education, employment, social relationships and development of a sense of self-worth\(^{(2)}\).

History and examination, together with electroencephalography, will usually determine the epilepsy syndrome (category), forming the basis for any further investigation and possible antiepileptic therapy. Imaging may be required in some circumstances\(^{(2)}\).

Compliance with medications is a major problem because of the need for long term therapy together with unwanted effects of many drugs\(^{(1)}\). One of these is its effects on thyroid function.
1.2 Definition:

An epileptic fit may be defined as a brief disorder of cerebral function, usually associated with disturbance of consciousness and accompanied by a sudden electrical discharge of cerebral neurons\(^{(3)}\).

1.3 Epidemiology:

Seizures are common neurological disorders in the pediatrics age group and occurs 3-5% of children. Epilepsy occurs in 0.5-1% of the population and begins in childhood in 60% of cases. 30,000 children and adolescent are diagnosed each year with epilepsy in the U.S.A\(^{(4)}\).

1.3.1 Incidence:

The incidence of epilepsy ranges from 40 to 70 per 100,000 in most developed countries and from 100 to 190 per 100,000 in developing countries\(^{(5,6)}\).

1.3.2 Prevalence and incidence in Sudan:

No data available from Sudan.

Khalid\(^{(8)}\) in this study found that males more affected than females 1.2 :1. Generalized seizures are the commonest type of
seizures, occurring in 73.4% of epileptic children. The average age of onset of seizures was 46.3 months.

1.4 Etiological & predisposing factors\(^{(9)}\): 

- In many, perhaps the majority (60%) of cases, are cryptogenic or idiopathic\(^{(9, 10)}\).
- Other factors: Family history, trauma and surgery to the head, intracranial mass lesions, cerebral infarction, drugs (alcohol) and withdrawal, photosensitivity and auditory stimuli.

1.5 Mechanisms of the disease:

Epileptogenesis is a gradual process that can be specifically targeted\(^{(11)}\).

Current evidence suggests that generalized epilepsies originate from alterations in either network, as in absence seizures, or intrinsic neuronal function, as in channelopathies. Partial epilepsy syndromes, presumably, stem from a focal lesion.

Newer avenues of study (such as cortical malformations) and newer conceptual mechanism (such as
the role of glial cells and neuronal micro-environment. Many such malformations are associated with refractory epilepsy and are increasingly recognized as a common cause of epilepsy that was previously believed to be cryptogenic\textsuperscript{(12)}.

The mechanism that generate absence epilepsy is now believed to involve an alteration in the circuitry between the thalamus and cerebral cortex\textsuperscript{(13,14)}.

In addition to these morphologic features, changes at the molecular level may also be important. The most prominent of these are alterations in the composition and expression of GABA\textsubscript{A} receptors on the surface of hippocampal dentate granule cells\textsuperscript{(15)}.

Mutant genes have been identified for the following: Generalized epilepsy with febrile seizures (GEFS+ve) \{point mutation in SCNIB\textsuperscript{(16)}, two forms of benign familial neonatal convulsions: KCNQ2 and KCNQ3\textsuperscript{(17-19)}; and frontal lobe epilepsy\textsuperscript{CHRNA4}\textsuperscript{(20)} \}.

**1.6 Classification\textsuperscript{(21-25)}:**

There are many classifications:

a) International classification of epileptic seizures.
1) Partial seizures:
   a) Simple partial (consciousness retained):
      - Motor    - Sensory    - Autonomic    - Psychic
   b) Complex partial (Consciousness impaired):
      - Simple partial followed by impaired consciousness.
      - Consciousness impaired at onset.
   c) Partial seizures with secondary generalization.

2) Generalized seizures:
   A- Absence seizures    b- Atypical absence seizures
   B- Generalized tonic clonic.
   C- Tonic    D- Clonic    E- Myoclonic
   F- Atonic    G- Infantile spasm.

3) Unclassified seizures.
   Epilepsy in children has also been classified by syndromes. Using the age at onset of seizures, cognitive development and neurologic examination, description of seizure type, and EEG findings including the background rhythm. It has been possible to classify approximately 50%
of childhood seizures into specific syndromes.

The syndromic classification of seizures provides a distinct advantage over previous classification by improving management with the appropriate anti-convulsant medication, identifying potential candidates for epilepsy surgery and providing patients and families with a reliable and accurate prognosis.

Example of epilepsy syndromes include: Infantile spasm (West Syndrome), Benign myoclonic epilepsy of infancy, the Lennox-Gastaut syndrome, febrile convulsions, Landau-Kleffner syndrome, Benign childhood epilepsy with centrotemporal spikes (Rolandic epilepsy), Rasmussen encephalitis, Juvenile myoclonic epilepsy (Janz syndrome), and Lafora disease (Progressive myoclonic epilepsy).

b) The abbreviated International League against Epilepsy classifications of epilepsies & epileptic syndromes:

1) Generalized epilepsies and syndromes:
   - Idiopathic with age related onset:
     - Benign neonatal convulsions
- Childhood absence epilepsy
- Benign myoclonic epilepsy in infancy
- Juvenile myoclonic epilepsy
- Epilepsy with generalized tonic-clonic seizures in awakening

- Symptomatic or cryptogenic:
  - West syndrome
  - Lennox – Gastaut syndrome

- Symptomatic:
  - Early myoclonic encephalopathy.

(ii) Localization – related epilepsies and syndromes:

- Idiopathic with age related onset:
  - Rolandic epilepsy
  - Childhood epilepsy with occipital paroxysms

- Symptomatic:
  - Epilepsy with simple partial, complex partial or secondarily generalized seizures.

(iii) Epilepsies and syndromes undetermined focal or generalized.
• Severe myoclonic epilepsy in infancy.

(iv) Special syndromes:

1.7 Differential Diagnosis\textsuperscript{(23, 25-28)}:

a) Nonepileptic events mimicking epileptic seizures:
Syncope, Cardiacarrythmia, Breathholdingspells,
Psychogeni non-epilepticseizures. Familial paroxysmal
choreoathetosis, Shuddering attacks, and Narcolepsy
and cataplexy

b) True epileptic seizures caused by a non-neurological
conditions:

i- Febrile seizures,

ii- Metabolic disorders,

iii- CNS infection,

iv- Sleep deprivation,

v- Alcohol or drug withdrawal.

vi- Drug abuse.

vii- Acute traumatic seizures.

viii- Benign paroxysmal vertigo.
1.8 Clinical Features$^{(3,22,25)}$:

(1) **Grand-mal Epilepsy**:

- Tonic phase: sudden loss of consciousness, limbs extend, back arches, teeth clench, breathing stops. Tongue may be bitten. Lasts about 20 – 30 sec.
- Clonic phase: intermittent jerking movements, irregular breathing, mutation and salivation.
- Post-ictal phase: child sleeps and disoriented.

(2) **Simple absence seizures (petit-mal)**:

Fleeting impairment of consciousness (day dreaming), no falling or abnormal movements.

(3) **Myoclonic seizures**:

Stroke-like jerks, often causing sudden falls usually occurs in children with a structural neurological or cerebral degenerative condition.

(4) **Simple partial seizures**:

Twitching or jerking of face, arms or leg – consciousness usually retained. Jacksonian pattern (starts focally and spreads)
Temporary weakness of involved part of the body after attack.

May progress to full-blown tonic-clonic attacks.

(5) **Complex partial seizures (temporal lobe)**

Altered or impaired consciousness associated with strange sensations, hallucinations or semi-purposeful movements.

Post- octal phase with amnesia.

(6) **Infantile spasm:**

Onset at 3-8 months of age.

Flexion spasms (Jacknife or Salaam seizures)

Lasts for few seconds, occur in clusters.

Regression of developmental skills

History of perinatal asphyxia or meningitis.
1.9 Diagnosis and Management:

The first step in epilepsy management is identification of the syndrome. Syndrome determination hinges on seizure description and frequency, age at onset, neurological history and functional enquiry, neurological exam and one or more EEGs. Neuro-imaging may aid in evaluation, but most syndromes are defined by the mentioned means\(^{(2,3,22)}\).

Drug therapy is indicated to treat epilepsy when there is increased likelihood of seizure recurrence and usually after the second unprovoked seizure (Excluding febrile seizure). For most patients, the use of a single anti-epileptic drugs (Monotherapy) results in higher compliance rate, wider therapeutic window, and is more efficient than polytherapy in addition to producing fewer adverse effect \(^{(24)}\). The rational therapeutic approach consists of selecting the medication according to patient characteristics, taking into account the type of seizure, epilepsy syndrome, individual peculiarities, availability or cost of medication \(^{(29)}\).
1.10 Anti-epileptic drugs:

The chemical structures of most of the drugs introduced before 1965 were closely related to phenobarbital; these include the hydantoins, oxazolindinediones, and the succinides.

The agents introduced after 1965 exhibit a diversity of chemical structures. These include benzodiazepines (clonazepam & clonazepate), an imino stilbene carbamazepine (CBZ), branched chain carboxylic acid (valproic acid), a phenytriazine (lamotrigine), acyclic analogous of GABA (Gabapentin), asulfamate, substituted monosachride (Topiramate), anipecotic acid dereivative (Tiagabine) and apyrolidine denervative (Levertractor) \(^{(1)}\).

Drugs effective against the most common forms of epileptic seizures, partial and secondarily generalized tonic-clonic seizures, appear to work by one of two mechanisms. One is to limit the sustained, repetitive firing of a neuron, an effect mediated by promoting the in activated stage of voltage activated Na+ channels.
A second mechanism appears to involve enhanced GABA-mediated synaptic inhibition, an effect mediated by an action presynaptically for some drugs and post-synaptically for others drugs. Effective against a less common form of epilepsy (Absence seizures) limit activities of a particular voltage activated Ca⁺ channel known as the T current\(^{(1,30)}\).

### 1.10.1 Carbamazepine: (Tegretol):

Was initially approved in the U.S for use as an anti-seizure agent in 1974. It is now considered to be a primary drug for the treatment of partial and tonic-clonic seizures, chemically it is related to the tricyclic anti-depressants\(^{(1)}\).

#### 1.10.1.1 Pharmacological effects:

- CBZ have been found to produce therapeutic responses in manic depressive patients.
- Anti-seizure effect without causing general depression of CNS. Further, CBZ has anti diuretic effects that is sometimes associated with increase concentration of
antidiuretic hormone level in the plasma.

- CBZ limits the repetitive firing of action potentials evoked by a sustained depolarization of a mouse spinal cord or cortical neurons maintained in vitro.

- Trigeminal neuralgia\textsuperscript{(1,31,32)}.

\subsection*{1.10.1.2 Pharmacokinetic properties:}

CBZ is absorbed slowly and erratically after oral administration. Peak concentration in plasma is usually observed 4 - 8 hrs after oral ingestion, but may be delayed as much as 24 hr, specially following the administration of a large dose. It is distributed rapidly to all tissues. Binding to plasma protein occurs to the extent of about 75%. The predominant pathway of metabolism in human being involves conversion to the 10, 11-epoxide\textsuperscript{(1,31,32)}.

CBZ is inactivated by conjunction and hydroxylation. The hepatic cytochrome P450 isoform primarily responsible for biotransformation of CBZ is CYP3A4. CBZ induces CYP2C and CYP3A and also UDP-glucouronosyltransferse. Thus enhancing the metabolism of drug degraded by these
enzymes\(^{(1)}\).

Plasma drug concentration: There is no simple relationship between the dose and concentration of the drug in plasma.

Therapeutic concentrations are reported to be 6-12 microgram/mL, although considerable variations occur. Side effects referable to CNS are frequent at 9 microgram/mL\(^{(1)}\).

1.10.1.3 Toxicity:

- **Dose related:** Gastric irritability. Diplopia or blurred vision; Dizziness, Drowsiness, ataxia, headache, tremors dystonia, chorea, depression, convulsions, irritability, psychosis, water retention, congestive heart failure, cardiac arrythmias.

  Idiosyncratic: anaemia, agranulocytosis, leucopenia, thrombocytopenia, hypersensitivity syndrome (Dermatitis, eosinophilia, lymphadenopathy and splenomegally and jaundice.

- Interactions: Affects and affected by other antiepileptic drugs and other drugs e.g:Cimetidine Erythromycin
which may cause toxic elevations of serum carbamazepine \(^{(1,30,31)}\).

### 1.10.2 Valproic Acid: (Depakene)

Was approved for use in the U.S in 1978. It is a simple branched chain carboxylic acid (N-dipropyl acetic acid)\(^{(1)}\).

**Mechanism of action:** Valproic acid produce effects on isolated neurons at therapeutically relevant concentrations, valproate inhibits sustained repetitive firing induced by depolarization of a mouse cortical or spinal cord neurons\(^{(33)}\). The action appears to be mediated by a prolonged recovering of voltage activated and sodium channels from inactivation. In neurons isolated from distinct region, nodose ganglion, valproate reduces the low threshold (T) calcium current\(^{(33,34)}\).

It also increases the amount of GABA that can be recovered from the brain after the drug is administered to animals. In vitro, valproate can stimulate the activity of the GABA synthetic enzyme, glutamic acid decarboxylase \(^{(35)}\) and inhibit GABA degredative enzymes, GABA transaminase and succinyl semi aldehyde dehydrogenase \(^{(36)}\).
1.10.2.1 Pharmacokinetic properties:

- Absorbed rapidly and completely after oral administration.

- Peak concentration in plasma is observed within 1-4 hr, this can be delayed for several hrs if the drug is administered in enteric coated tablets or is ingested with meals. 90% bound to protein.

The vast majority of valproate (95%) undergoes hepatic metabolism, with less than 5% excreted unchanged. Its hepatic metabolism occurs mainly by UGT enzymes and B oxidation. Valproate is a substrate for CYP2C9 and CYP2C19 but its metabolism by this enzymes accounts for a relatively minor portion of its elimination.

The half-life of valproate is approximately 15hrs but is reduced in patient taking other antiepileptic drugs\(^1\).

1.10.2.2 Toxicity:

The most common side effects are transient GIT symptoms in about 60% of patients. Effects on CNS include sedation, ataxia and tremor. It also causes rash, alopecia, stimulation of appetite. It has also several effects on hepatic
functions, increases liver enzymes in 40% of patients, rare complication is fulminant hepatitis \(^{(37)}\), acute pancreatitis and hyperammonemia.

The concentration of valproate in plasma that is associated with therapeutic effects is approximately 30-100 microgram/mL\(^{(1)}\)

1.10.2.3 **Drug interaction of valproate:** With Phenytoin, Lamotrigine, Lorazepam, and Clonazepam\(^{(1)}\).

1.10.2.4 **Therapeutic uses:** Valproate is effective in the treatment of absence, myoclonic, partial and tonic-clonic seizures\(^{(31)}\).

1.11 **Surgical Treatment:**

Surgical treatment can be an option for epilepsy when an underlying brain abnormality, such as a benign tumor or an area of scar tissue (e.g. hippocampal sclerosis) can be identified. Also it is offered to patients when their epilepsy has not been controlled by adequate attempts with multiple medications\(^{(38)}\).
1.12 **Other treatment:**

Ketogenic diets may occasionally be effective in controlling some types of epilepsy; although the mechanism behind the effect is not fully understood, shifting of pH towards a metabolic acidosis and alteration of brain metabolism may be involved. Ketogenic diets are high in fat and extremely low in carbohydrates, with intake of fluids often limited[^39].

1.13 **Prognosis of epilepsy:**

Thirty percent of patients have mild epilepsy that does not require treatment and remits within a short period; 30% are easily controlled on AEDs; 20% have chronic epilepsy that responds only partially to AEDs and 20% have chronic unremitting epilepsy with little response to treatment.

**Syndromes:**

Good prognosis: Absence seizures, rolandic, benign idiopathic neonatal convulsions, benign epilepsies of childhood.
**Poor prognosis:** Infantile spasms, Lennox-Gastaut, Landau-Kleffner, severe myoclonic epilepsy of infancy

### 1.14 Thyroid Hormones:

Thyroid hormones (T3 & T4) are synthesized in the thyroid gland by the iodination of the amino acid tyrosine\(^{(1)}\).

The production of thyroid hormones is regulated by the hypothalamus and the pituitary gland.

T3 & T4 are carried largely bound to plasma protein principally thyroid hormone binding globulin, only about 0.3% of T3 and 0.03% of T4 is transported free. T4 is bound more tightly than T3 and its half life about 6 days whereas that of T3 is only one day. In the tissues, 85% of T3 (considered as the active hormone) is derived from T4 by the enzyme 5monodeiodoinase\(^{(40-43)}\).
1.14.1 Diagnosis of thyroid abnormalities\(^{(41,42)}\):

1) Serum thyroid hormones: methods are available to measure all the thyroid hormones in serum T4, T3, FT4, free T3, and TSH.

2) Serum thyroxine binding globulins (TBG).

3) TRH stimulation test of TSH release.

4) T3 suppression test.

5) Thyroid ultrasonographic studies.

1.14.2 Disorders of thyroid function\(^{(4,40,42)}\):

Defects of thyroid function could be either hypo or hyperthyroidism.

1.14.2.1 Hypothyroidism:

It is either primary or secondary

- Primary hypothyroidism: Results from deficient production of thyroid hormone or defect in thyroid hormonal receptor activity.

- Congenital hypothyroidism: sporadic and familial,
goitrous and non goitrus. In many cases the deficiency occurs and manifestations may develop in the early weeks of life or may be delayed for months.

- **Clinical features:** Large anterior fontanels, coarse faces, umbilical hernia, lethargy and irritability, large tongue, coarse voice, retarded development and growth.

*Neonatal Period Early Symptoms:*

1) Prolonged gestation with large bulk weight
2) Persistent jaundice
3) Temperature instability.
4) Delayed initial bowel opening for >24hrs.
5) Oedema
6) Hypo activity and poor feeding

Treatment should begin immediately after the diagnosis is established. Recommended dosage of synthetic thyroxine is 10 – 15 microg/kg for the newborn and less thereafter.

- **Acquired hypothyroidism:**

  Occurs in 1 : 500 school age children, it carries no risk
of permanent mental retardation but temporary behavior changes are frequent, as well as growth.

Aetiology:

1. Hashimotos thyroiditis
2. Subacute thyroiditis
3. Environmental causes: goitrogens ingestion, thyroidectomy, and radioactive iodine ablative therapy.
4. Infiltrative disease: eg. langherhans histocytosis

Clinical features are: cold intolerance, constipation, weight gain, dry skin and sparse brittle hair. Long standing hypothyroidism leads to enlargement of pituitary primary gland, poor growth (short stature), puberty is delayed or absent in teenage patients, precocious puberty occurs in some with delayed skeletal and dental age, goiter muscular pseudohypertrophy (rare), absent menses, bradycardia and galactorrhea (rare).

• Secondary hypothyroidism: Causes that lead to central hypothyroidism.
- Pituitary hypothalamic dysfunction
- Hypopituitarism could be idiopathic or due to, head trauma, tumor, infiltrative disease, surgery or, radiation therapy.

TSH deficiency is associated with generalized pituitary or hypothalamic dysfunction. Isolated TSH deficiency is rare and may be caused by lack of TRH stimulus (receptor defect, tumor invasion of the critical hypothalamic nuclei or idiopathic).

1.14.2.2 Hyperthyroidism \(^{[4,40,42]}\):

Occurs when excessive amount of thyroid hormone is present. Hyperthyroidism in childhood is rare and accounts for fewer than 5% of all cases of hyperthyroidism.

Goiter, anxiousness, tachycardia, widened pulse pressure, increased appetite, weight gain or loss, tremor, proptosis, heat intolerance, increased growth velocity, diarrhea’, fatigue, sleep disturbance.

- **Congenital Hyperthyroidism (Neonatal Thyrotoxicosis):**

Occurs almost exclusively in infants of mothers with
Graves disease. Occurs in as many as 1 of 70 infants of mothers with Graves disease with equal gender distribution.

The cause is the passage of TSI (maternal immunoglobulin) to the fetus. The prolonged form may be caused by endogenously produced persistent (TSI) from infant’s own lymphocytes or from transplacentally acquired maternal lymphocytes.

- **Acquired Hyperthyroidism:**

  Most often is caused by Graves disease, female : male is 3:1. It has familial tendency and an association with HLA type B8 and DR3. Thyroid hormone profile characteristically shows elevated total T4, free T4 and T3 level accompanied by very low or undetectable levels of TSH\(^{(42)}\).

- **Treatment\(^{(44)}\):**

  1) *Medical treatment:* Propythiouracil (PTU) or methimazole

     - Propanolol: for control of symptoms while
another mode of therapy exerts its effect.

2)  **Surgery:** Subtotal thyroidectomy.

### 1.15 Effects of anti-epileptic drugs on thyroid function:

Since 70\textsuperscript{th}, the side effects of antiepileptic drugs on the endocrine system are being reported\(^{45,46}\).

Metabolism plays a key role in regulating the biological activity of many hormones. In the case of thyroid hormones, a number of important metabolic pathways interact to balance synthesis, bioactivation, and deactivation\(^{47}\).

Because drugs, industrial chemicals and chemicals of environmental importance can increase thyroid hormone metabolism, it is important to consider the impact these compounds have on thyroid hormone and thyroid gland homeostasis\(^{48}\).

Thyroid hormones levels are regulated at the levels of synthesis and secretion by the thyroid gland and also metabolism in the periphery\(^{48}\).
As mentioned before thyroid hormones are synthesized and secreted under the influence of the hypothalamus – pituitary – thyroid axis\(^{(40)}\).

The principal pathways of peripheral thyroid hormone metabolism are deiodination and conjugation to glucuronic acid or sulfate\(^{(48)}\).

Conjugation of thyroid hormone involves glucuronidation or sulfation of the phenotic hydroxyl group, which increases water solubility\(^{(49-51)}\). Sulfation also inactivate thyroid hormones\(^{(52)}\).

The phase II drug metabolizing enzymes uridine 5’ diphosphate – glucuronomosyl transferase (UGT) and sulfotransferase (SULT) mediate glucuronidation and sulfation of thyroid hormone. Induction of these enzymes by the widely used antiepileptic drug phenobarbitol (PB) and other xerobiotics increases thyroid hormone metabolism and decreases TH levels in both animals and humans\(^{(51-54)}\).

The nuclear hormone receptor constitutive andrestane receptor (CAR) mediates the induction of
hepatic drug metabolism in response to PB and other xerobiotics\textsuperscript{(55,56)}. Thus the loss of CAR in mice results in the complete absence of CCY2B10 induction in response to PB and PB like inducer in the liver and decreased drug-metabolizing capability.

Recently the list of CAR target genes has been expanded to encompass genes involved in all phases of xerobiotic metabolism, including the CYP\textsubscript{3A} enzymes, UGTIA as well as SULT\textsubscript{2A} & SULTIA and the multidrug resistance associated protein family of transporters \textsuperscript{(57)}. Many of these genes are also involved in TH metabolism \textsuperscript{(58-61)}.

Antiepileptic drugs change circulating hormones concentration \textsuperscript{(62-64)} and also pituitary responsiveness to various stimuli\textsuperscript{(65-66)}.

The level at which the antiepileptic drugs affect the endocrine system is not certain \textsuperscript{(67)}. The influence of phenytoin and carbamazepine on the thyroid hormone has both interested and confused clinicians and investigators for more than three decades.
The first study about the effects of antiepileptic drugs on thyroid gland was made in 1961 by Oppenheimer et al. They found that phenytoin treatment reduces thyroid hormone concentration in patients with epilepsy\(^{(68,69)}\). Moreover, since 1970 it has been obvious that carbamazepine therapy also changes the thyroid hormones balance in epileptic patients\(^{(70-72)}\).

Since then several studies have been reported about the toxic effects of antiepileptic drugs on thyroid glands\(^{(67,73,75,77-84)}\). It was found that some antiepileptic drugs decrease thyroid function certainly for example; phenytoin and carbamazepine clearly decrease thyroid function but does not change the euthyroid state. It has been reported that these drugs decrease the free serum thyroxine concentration (FT4) but not change the serum FT3 and TSH level\(^{(76,77)}\).

Concerning mechanisms by which anti-epileptic drugs affect the thyroid hormones concentrations.

Oppenhimier\(^{(68)}\) et al reported that serum protein bound iodine concentration was significantly decreased in
patients treated with phenytoin.

In vitro studies showed that phenytoin competed reversibly with thyroxine (T₄) for binding sites on serum T₄ binding globulin. These findings would predict that serum free T₄ concentration should be normal in phenytoin treated patients. However, Chin & Schussler (85) and then Larsen et al (86) using ultra-filtration assay, reported that serum FT4 was actually decreased in phenytoin treated patients. Their findings were supported by many other investigations that used a variety of methods to determine serum T₄ concentration and were extended to patients treated with carbamazepine as well.

On the other hand Martin(87), et al re-evaluated the effect of phenytoin and carbamazepine on serum FT4 hormone concentration using an ultra-filtration assay for FT4 and FT3 fraction. This hypothesis is that therapeutic concentrations of these drugs displace thyroid hormone from their serum binding proteins resulting in normal FT4 hormone concentration. Moreover, he anticipated that the effect of these drugs on the interaction between the
iodothyronines and their serum binding protein would be lost upon dilution of serum \(^{87-89}\).

Generally, Phenobarbital, phenytoin and carbamazepine are called as “enzyme-inducing antiepileptic drugs” because of their activating effect on hepatic microsomal enzyme system \(^{67}\).

Despite the decreased serum T\(_4\) and F T\(_4\) levels during the carbamazepine treatment, the patients didn’t show any obvious signs of clinical hypothyroidism and no significant increase of the mean serum TSH concentration. Also serum T\(_3\) concentration was unaffected by carbamazepine therapy although possibly the conversion of T\(_4\) and T\(_3\) is also increased by enzyme-induction during carbamazepine therapy \(^{65}\). Moreover, one article suggests that carbamazapine may also have direct inhibitory effects on iodide uptake and hormone synthesis in the thyroid glands\(^{90}\).
Justifications

- Number of children taking anticonvulsant drugs is increasing.
- No previous study was done to investigate the effect of antiepileptic drugs on thyroid function in Sudanese children.
Objectives

- To study the effect of antiepileptic drugs (Sodium valproate and carbamazepine) on thyroid function in Sudanese epileptic children.
- To determine the variation in thyroid function in patients treated with these drugs as far as age, sex, origin and duration of treatment are concerned.
Chapter Two

2. Material and Methods

2.1 Nature of the Study:

A cross sectional hospital based study.

2.2 Study Area:

The study was conducted in Gaafar Ibn Auf Children’s Hospital and Omdurman Children’s Emergency Hospital at the referred clinics.

2.3 Duration of the Study:

The study was conducted in the period from April – July 2006.

2.4 Study Population:

The study populations were known epileptic children attending the referral clinics of Gaafar Ibn Auf Children’s Hospital and Omdurman Teaching Hospital. All children were below 16 years, they were on CBZ or Sodium valproute for ≥ 6 months.
2.5 Sample Size and Sampling Technique:

2.5.1 Inclusion criteria: All children < 16 years of age with diagnosis of epilepsy clinically and by EEG and who were maintained on regular carbamazepine or sodium valproate for > 6 month. Inclusion agreed after taking verbal consent from parents or caregiver.

2.5.2 Exclusion criteria:

- Patients with cerebral palsy
- Epileptic patients taking other antiepileptic drugs
- Patients with progressive cerebral disorders
- Patients with other chronic diseases eg: DM, chronic RF, etc.
- Patients on other long term medication that could affect thyroid function.
- Patients who (or their care taker) refused to participate in the study.
- Non-complaint patients.
- Patients on polytherapy.
2.5.3 **Sample size:**

All patients were presented to the study area with the diagnosis of epilepsy during the period from 1\textsuperscript{st} April to 30\textsuperscript{th} July and fulfilling the entry criteria were included in the study, they were 67 patients.

The control group included healthy children and children with simple upper respiratory tract infection who presented to the out patient department. They had no chronic disease and did not receive any drugs during the last two weeks prior to blood sampling. This group consisted of 30 cases 18 males and 12 females.

**2.6 Study Technique and Tools:**

**2.6.1 Research team:**

- The author
- A lab technician

**2.6.2 Research tools:**

**2.6.2.1 Questionnaire containing the following data:**

- Personal data
- History of the disease and treatment
- Symptoms of hypothyroidism
2.6.2.2 Clinical examination

a) General examination

b) Signs of hypothyroidism

2.6.2.3 Laboratory methods:

Total T₃, total T₄ and TSH were measured using RIA.

- Methods of reading total T₄:

  T₄ RIA method depends on the competition between Iodine125 labeled T₄ and T₄ contained in standard or in specimens to be assayed, for a fixed and limited number of T₄ antibody binding sites. After the incubation, the amount of Iodine 125 labeled T₄ bound to the antibody is inversely related to the amount of T₄ present in the sample.

  In the antibody suspension of kits used, the antibody is covalently bound to magnetisable particles. Separation of antibody bound fraction is achieved by magnetic separator and discounting the supernatant, by measuring the proportion of Iodine 125 labeled T₄ bound in the presence of reference standards containing various known amounts of T₄. The concentration of T₄ in known samples can be interpolated.
The sensitivity was calculated as the concentration which is two standard deviations above the zero standards. The sensitivity is above 4 mcg/ml.

- **Methods of TSH readings:**

  CI AE TSH IRMA kit utilizes two site sandwich immunoradiometric assays for the measurement of TSH in human serum. This involves the reaction of TSH present in serum with monoclonal and polyclonal antibody. The monoclonal antibody is labeled with Iodine 125 as tracer \( \text{I}^{125} \text{ - Mc Ab} \) and the polyclonal antibody is completed to magnetic iron oxide particles \( \text{PcAb} < \text{ M} > \). The formed \( 125 \text{I-McAb-TSH-PcAb} < \text{M} > \) complex (sandwich) is separated from unbound tracer by placing the assay tube in the magnetic separator and decanting supernatant. The radioactivity of tracer in the tubes is directly proportional to the cone of TSH in the specimen.

  The sensitivity of the assay is 0.04 ml U/L. It was calculated as the concentration. Which was two standard deviations above the zero standard.
Method of total T3 reading:

The RIA method depends on the competition between Iodine125 labeled T3 and T3 contained in standards or in specimens to be assayed, for a fixed and limited number of T3 antibody binding sites. After the incubation, the amount of 125 I-labeled T3 bound to the antibody is inversely related to the amount of T3 present in the sample. By measuring the proportion of 125 I-labeled T3 bound in the presence of reference standards containing various known amounts of T3, the case of present in unknown samples can be interpolated.

2.7 Data Analysis:

Data was analyzed using computer program. The Statistical Package of Social Sciences System (SPSS) and chi square and student T-test.

Results were expressed as mean. The level of significance of difference between mean values among cases and control group were determined by the Student independent test, with P<0.05 considered significant.

Thyroid hormones levels were categorized in ranges
(Normal, low, and high) according to standard level according to age:

T3 level (nmol/l):

1-5Yrs : 1.45-4.0
5-10yrs : 1.93-3.7
10-15yrs: 1.2 - 3.2
>15yrs :1.7 - 2.9

T4 level (nmol/l):

1-3yrs : 88 -174
4-10yrs: 71- 165
>10yrs : 54-176

TSH level (mlU/l):

5mon-20yrs: 0.7-6.5

Taking in consideration values lower than the lower limit as (low), values within the normal range as (normal), and values higher than the upper limit as (high).

With a value corresponding to P<0.05 for significance, testing of difference between proportions was conducted using the Chi-square test.
2.8 Ethics:

- Verbal consent was obtained from all parents or accompanying care takers of children in the study (i.e. both cases and control groups).

- Doctors in charge were informed about the results.
Chapter Three

3. Results

A total of 67 children with epilepsy and 30 normal children, age <16 years were enrolled in the study. Data was collected and a master sheet was performed. The data was analyzed using statistical package of social sciences, a soft program.

3.1 Socio-demographic Characteristic:

3.1.1 Age and sex characteristic of the study:

The mean (± SD) age of cases group in this study was 9.96 ± 3.349. While the mean age group of control group was 9.63(3.4) P=0.57. The majority of cases in both groups were between 5-15 years as shown in (Figure 1).

Regarding sex characteristic, males were predominant in cases groups as shown in (Figure 2).

3.1.2 Origin and residence:

Majority of the patients were from central tribes as shown in (Figure 3). And most of them reside in the capital (Figure 4).
3.2 Description of Seizures in the Study Group:

3.2.1 Type of epilepsy in children in the study group:

The majority of children in the study were classified as having generalized convulsions 50 (74.7%). 42 (84%) of them were grandmal epilepsy, 4 (8.0%) ronaldic and 4 (8.0%) were absence. Focal epilepsy were 9 (13.4%) and 8 (11.9%) children were having combination of more than one type. (Figure 5)

3.2.2 duration of the disease: mean(SD) duration of illness was 4.3(.04) years for CBZ group and 3.7(0.7) years for VAP group. The duration of illness in the majority of children, was 1-5. (Table 1).

3.2.3 Modality of treatment: 56 (83.6%) are on carbamazepine while only 11 (16.4%) are on sodium valproate. (Figure 6)

3.2.4 Duration of treatment: duration of treatment in most patients in CBZ group was <18 months and it was 18-36 months for VAP group (Table 2).
Table (1): Distribution of cases group according to duration of illness

<table>
<thead>
<tr>
<th>Duration of illness</th>
<th>VAP group</th>
<th>CBZ group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Illness (Years)</th>
<th>NO</th>
<th>%</th>
<th>NO</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
<td>7.1</td>
</tr>
<tr>
<td>1-5</td>
<td>6</td>
<td>54.5</td>
<td>30</td>
<td>53.6</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>5</td>
<td>45.5</td>
<td>22</td>
<td>39.3</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>100.0</td>
<td>56</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table (2): Distribution of patients according to duration of treatment

<table>
<thead>
<tr>
<th>Duration of treatment (Months)</th>
<th>VAP group</th>
<th>CBZ group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>%</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>3</td>
<td>27.3</td>
</tr>
<tr>
<td>18 – 36</td>
<td>7</td>
<td>63.6</td>
</tr>
</tbody>
</table>
Table 3: Shows that CBZ group had significant higher T3 and significant lower T4 than the control group. However the level of TSH was not significantly in CBZ and control groups.

Table 4: Shows no significant difference between VAP and control groups.

Table 5: Shows most of the patients of CBZ group have normal T4 level and a significant number have lower
level.

Table 6: Shows that the percentage of T4 level was not different between VAP and control groups.

Table 7: Shows almost half of the CBZ groups have lower T3 level.

Table 8: Shows that although there is high percentage of patients with low T3 level, there is no significant difference between VAP and control groups.

Table 9: Shows no different percentage in serum TSH level between CBZ and control groups.

Table 10: Shows no different percentage in serum TSH level between VAP and control group
Table (3): Thyroid function in CBZ and control groups

<table>
<thead>
<tr>
<th>Thyroid function test</th>
<th>CBZ group Mean(SD)</th>
<th>Control group Mean(SD)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum T3 (nmol/l)</td>
<td>1.56(0.89)</td>
<td>1.22(0.38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum T4 (nmol/l)</td>
<td>76.0(22.87)</td>
<td>101.4(22.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum TSH (mU/l)</td>
<td>2.84(1.45)</td>
<td>2.54(1.70)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Table (4): Thyroid function in VAP and control groups

<table>
<thead>
<tr>
<th>Thyroid function</th>
<th>Control group</th>
<th>VAP group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td></td>
</tr>
<tr>
<td>Serum T3 (nmol/l)</td>
<td>1.22(.38)</td>
<td>1.24(0.49)</td>
<td>0.87</td>
</tr>
<tr>
<td>Serum T4 (nmol/l)</td>
<td>101.4(22.45)</td>
<td>89.78(27.58)</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum TSH (mIU/l)</td>
<td>2.54(1.70)</td>
<td>3.04(1.44)</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Table (5): Serum total T₄ level in patients on CBZ and control groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>CBZ group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>%</td>
</tr>
<tr>
<td>Low</td>
<td>18</td>
<td>32.1</td>
</tr>
<tr>
<td>Normal</td>
<td>37</td>
<td>66.1</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>100.0</td>
</tr>
</tbody>
</table>

P=0.005

Table (6): Serum total T4 in patients taking Sodium
valproate and control groups

<table>
<thead>
<tr>
<th>T4 level</th>
<th>VAP group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>%</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>9.1</td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>90.9</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>100.0</td>
</tr>
</tbody>
</table>

P=0.95
Table (7): Serum T₃ level in patients on CBZ and control groups

<table>
<thead>
<tr>
<th>T3 level</th>
<th>CBZ group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>%</td>
</tr>
<tr>
<td>Low</td>
<td>25</td>
<td>44.6</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>100</td>
</tr>
</tbody>
</table>

P = 0.09
Table (8): Serum T₃ level in patients taking VAP and control groups

<table>
<thead>
<tr>
<th>T3 level</th>
<th>VAP group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>%</td>
</tr>
<tr>
<td>Low</td>
<td>8</td>
<td>72.7</td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>27.3</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>100.0</td>
</tr>
</tbody>
</table>

P=0.99

Table (9): TSH in patients taking CBZ and control
The table below shows the serum TSH levels in patients taking VAP and control groups.

<table>
<thead>
<tr>
<th>Serum TSH level</th>
<th>Study group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBZ group</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>%</td>
<td>NO</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>Normal</td>
<td>54</td>
<td>96.4</td>
<td>27</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>100.0</td>
<td>30</td>
</tr>
</tbody>
</table>

P=0.

Table (10): Serum TSH in patients taking VAP and control
<table>
<thead>
<tr>
<th>TSH level</th>
<th>VAP group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>%</td>
<td>NO</td>
</tr>
<tr>
<td>Low</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Normal</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>30</td>
</tr>
</tbody>
</table>

P=0.55

3.4: EFFECT OF AGE AND GENDER ON THYROID FUNCTION;

Concerning the age and sex effect on thyroid
function, there was no effect except in the age group < 10 years in CBZ group which have lower T4 level than the control group = 0.002 (Table 11).

3.5. **Effect of origin and residence of the study group on thyroid function:**

Regarding origin and residence of the study groups there was no significant difference between all groups in thyroid function.

3.6. **Effect of duration of treatment on thyroid function:**

Concerning the duration of treatment, the only difference was that in patients who are on CBZ, the percentage of patients who have low serum T3 level increase with the increase in duration of treatment. (Table 12).

**Table (11): Effect of age on T4 in patients taking CBZ**

<table>
<thead>
<tr>
<th>Serum T4 level</th>
<th>CBZ group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 yrs</td>
<td>&gt;10 yrs</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>NO</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----</td>
</tr>
<tr>
<td>Low</td>
<td>13</td>
</tr>
<tr>
<td>Normal</td>
<td>13</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
</tr>
</tbody>
</table>

P=0.002

Table (12): The effect of duration of treatment on T3 in patients taking CBZ
<table>
<thead>
<tr>
<th>(months)</th>
<th>No</th>
<th>%</th>
<th>no</th>
<th>%</th>
<th>No</th>
<th>%</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>10</td>
<td>37.0</td>
<td>15</td>
<td>55.6</td>
<td>2</td>
<td>7.4</td>
<td>27</td>
<td>100.0</td>
</tr>
<tr>
<td>18-36</td>
<td>6</td>
<td>42.9</td>
<td>7</td>
<td>50</td>
<td>1</td>
<td>7.1</td>
<td>14</td>
<td>100.0</td>
</tr>
<tr>
<td>&gt;36</td>
<td>9</td>
<td>60.0</td>
<td>6</td>
<td>40</td>
<td>0</td>
<td>0.0</td>
<td>15</td>
<td>100.0</td>
</tr>
</tbody>
</table>

P=0.042

Chapter 4

Discussion
The effect of antiepileptic drugs on thyroid function is known for a long time. There seems to be considerable individual variability of response to antiepileptic therapy, probably depending on peripheral changes in the hormone metabolism (90).

As in children, thyroid hormones are important for normal mental and physical growth, the study of the effect of antiepileptic drugs on thyroid function is important.

Our study was carried out in 67 Sudanese epileptic children with age less than 16 years, with predominance of male sex as in the studies done by Amani (91) and Khalid (8). The controls were 30 healthy children who came to the causality with upper respiratory infection or as co-patients. It was difficult to find the ideal control group which should either be epileptic patients with no treatment, or the same patients before and after treatment.
Mean (SD) of age was not significantly different between cases and controls showing good matching between the two groups (P=0.57).

The predominant age group was 10.0-15 years as was found by Amani (91).

Like in Amani’s (91) study the majority of cases in our study group 44.3% were from central tribes. And the majority of them reside in the capital.

Generalized seizures were the commonest type of epilepsy in our study group. Also this result was obtained by Amani (91) and Khalid (8).

. The majority of patients in our study were on CBZ while small number of patients (16.4%) were on VAP, and the mean (SD) duration of treatment for VAP in our study was almost half of that of CBZ, and these were the only patients who attended the referred clinics and fulfilled the criteria of our study group. While in Kirimi’s (80) study group it was almost the same in VAP and CBZ.
Serum total T4 level had significant lower level in CBZ than control group P=0.005. While there was no significant difference between VAP and control group P=0.20. This could be due to enzyme induction, which lead to increase in thyroid hormone metabolism and decrease in thyroxine level.

This result was consistent with the previous studies of: Caksen (89) who found that, there is low T4 and FT4 in patients treated with CBZ for a long time. Similar results were obtained by Yuksel et al (81).

Verma and Haidukewych (82), assessed the differential effects of AEDs on hepatic enzymes and thyroid hormones levels in 317 patients, they found significant different between control and these drugs and this is consistent with our study. Connacher, et al (83) in their study in 71 epileptic patients, T4 was normal in 40% of patients on CBZ and 85% in that who were on VAP.
Yong-Won et al also studied 45 patients who were on long term AED therapy and 45 control, they concluded that FT4 level was lower only in patients taking enzyme inducing AEDs compared to control group. Larkin (77) et al also studied thyroid function in 54 epileptic patients, also they found that serum total T4 concentration were reduced in patients taking enzyme-inducing drugs (CBZ or/and Phenytoin) compared with both control and patients taking VAP. Rozza et al (94) also concluded the same results.

De Luca et al (95), who studied T4, and FT4 in five hypothyroid children with partial epilepsy receiving L.Thyroxin. They found that serum total T4 and FT4 significantly decreased following 2 months of CBZ administration.

Among the studies searching the effect of antiepileptic drugs on thyroid hormones, the best and most consistent results are obtained with Valproate which doesn't change the thyroid hormone levels because it is
is not an inducing drug(67). Isojarvi et al reported that there was no significant difference between Valproate and control groups, and this is consistent with our study. Haidukewitych and Rodin(76) and Kirimi(80) et al reported the similar result to our study.

In contrast to our study, Ericsson et al (79) reported high total T3 and total T4 but normal TSH levels.

Because the number of patients taking VAP in our study was small we can not definitely compare to other results and may be we need other studies with large number of patients.

Although there was significant difference between CBZ and control groups, in T4 level, such a difference was not obtained between CBZ and VAP groups. This may mean that VAP does not lower T4 level to a statistically significant level. But there was no other study in literature review comparing CBZ and VAP.
Serum T3 level was significantly higher in CBZ group than control group. But it was not different between VAP and control groups in our study.

All previously mentioned authors found that administration of CBZ and VAP did not alter serum T3 level, except for Kimura (96) who found that serum T3 levels were reduced after CBZ discontinuation. They suggested that during treatment serum T3 level was increased and this could be due to an increased conversion of T4 to T3. There was no difference between VAP and control groups; and this is consistent with our study. Ericsson et al (79) also found high T3 level. Eiris – Punal (78), Liewendehl (69), and Gometric (97) found low T3 and /or rT3.

In our study, although the mean (SD) of T3 level in CBZ group was higher than the control; the percentage of patients who had low T3 levels increase with the increase of duration of treatment, this can be explained by
increase in T4 metabolism and increase in peripheral conversion of T3 to T4.

There was no significant difference between serum levels of T.S.H. in CBZ or VAP group than the control group in our study. And this is consistent with the results of other investigators, except Eiris-Punal (78) and Vainionpaa et al (92) who found increased serum T.S.H. levels (P<0.01).

Those patients <10 years had significant lower T4 than those >10 years group. In literature review we didn't find any author who studied this effect. I think this is because children less than ten years are more vulnerable to other factors which can affect thyroid function in addition to this drug (e.g. nutrition).

Sex and origin of the patients had no effect on thyroid function.

In our study and as was found by Isojarvi (63) our patients with low T4 had normal thyroid gland this suggest a hypothalamic interference caused by CBZ therapy.
It remains to be established whether epileptic patients receiving CBZ therapy are really suffering from a subclinical hypothyroid state caused by the increased metabolism of thyroid hormones.
CONCLUSION

- The study population were epileptic children with age group below 16 years; the predominant sex was males; and they were on CBZ or VAP for ≥ 6 months.
- Serum total T4 levels were found to be significantly low compared to control group in patients taking CBZ. While it has no difference from control group in patients taking VAP.
- T3 has significant higher levels in CBZ group; while it has no difference between VAP and control groups.
- T.S.H. levels have no significant difference between both groups and control group.
- Serum T4 was found to be affected by age, but not affected by sex, origin of the patients or duration of treatment.
- Serum T3 was found to be affected by duration of treatment in CBZ group, but was not affected by sex, age or origin.
- Almost all patients were found to be clinically euthyroid.
**Recommendations**

- Initiation of specialized clinics for epileptic patients
- Basal thyroid function test should be performed for every candidate for AEDs, e.g. CBZ.
- To make thyroid function test less expensive and attainable for all epileptic patients.
- In known cases of hypothyroidism, and those with altered basal thyroid function test, CBZ should be prescribed cautiously.
- We suggest further studies involving larger number of patients to elucidate more the effect of AEDs on thyroid function.
- To elucidate the effect of AEDs on thyroid function, thyroid function should be done before and during the treatment.
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University of Khartoum
Faculty of Medicine
Postgraduate Medical Studies Board
Questionnaire

Serial No:
Unit:
hospital : 

1) Name: ------------------------------------------ 
2) Age: ---------------------- 
3) Sex: ---------------------- 
4) Origin: ---------------------- 
5) Residence: ---------------------- 
6) Duration of illness: ---------------------- 
   1) 1-5yrs 
   2) 5-10yrs 
   3) >10yrs 
7) Type of epilepsy: 
   1) Generalized 
   2) Focal 
   3) Combination 
8) Modality of treatment: 
   1) Carbamazepine 
   2) Sodium Valproate 
9) Duration of treatment: ----------------------
10) Symptoms of hypothyroidism

1) Cold intolerance
2) Lethargy
3) Tiredness
4) Change of voice
5) Bowel habits:
   5.1) Normal
   5.2) Constipation
   5.3) Diarrhoea
6) Growth:
   6.1) Normal
   6.2) Little to no growth
   6.3) Weight gain
11) Family history of thyroid abnormality
12) Drug history:
13) Menstrual history (in females):
   13.1) Normal cycles
   13.2) Metrorrhagia
14) Examination:
   14.1) General:
   14.1.1) Pallor:
      1) yes      2) No
   14.1.2) Lethargy:
1) Yes                               2) No

14.1.3: Pulse:
1) Normal               2) Bradycardia

14.1.4: Skin:
1) Normal               2) Dry

14.1.5: Goitre:
1) yes                  2) No

15) Anthropometric measurements:
   15.1: Weight (kg)
   15.2: Height (cm)

16) Other systems
   1) normal             2) Abnormal (specify)

17) Investigations:
   17.1: Serum T4 level
   17.2: Serum T3 level
   17.3: Serum T.S.H. level