STUDY OF BONE DENSITY : AN AFTER EFFECT OF CHRONIC TREATMENT WITH ANTIEPILEPTIC DRUGS IN EPILEPTIC CHILDREN

Thesis Submitted for Fulfillment of
Ph.D in Childhood Studies

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قالوا سبحانك

لا علم لنا إلا ما علمتنا

إنك أنت العليم الحكيم

صدق الله العظيم

سورة البقرة . آية ٣٢

Dedication

Dedicated

To

My Family

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LIST OF ABBREVIATIONS

AA	Amino acid.
AED_S	Antiepileptic drugs.
ACTH	Adrenocorticotrophic hormone..
Alk.Phos.	Alkaline phosphatase.
AMP	Adenosine monophosphate.
ATP	Adenosine triphosphate.
BMC	Bone mineral content.
BMD	Bone mineral density.
BZP	Benzodiazepine.
Ca	Calcium.
CAE	Childhood absence epilepsy.
CBZ	Carbamazepine.
CCB_S	Calcium channel blockers.
CNS	Central nervous system.
CPS	Complex partial seizures.
CT	Computerized tomography.
DEXA	Dual energy x-ray absorptiometry
DNA	Deoxyribonucleic acid.
DPA	Dual photon absorptiometry.
DPH	Diphenyl hydantoin.
ESM	Ethosuximide.
EEG	Electroencephalogram.
Fig	Figure.
GABA	γ- amino butyric acid.
GAD	Glutamic acid decarboxylase.
GTCS	Generalized tonic-clonic seizures.
GTCS	Generalized tonic-clonic convulsions
HS	Highly significant.
Ht	Height.
IGE	Idiopathic generalized epilepsy.
ILAE	International League Against Epilepsy
JAE	Juvenile absence epilepsy.

JME	Juvenile myoclonic epilepsy.
K	Potassium.
KA	Kainic acid.
MCT	Medium chain triglycerides.
MEG	Magnetoencephalogram.
Mg	Magnesium.
MRI	Magnetic resonance imaging.
Na	Sodium.
NMDA	N-methyl-D-aspartate.
No	Number of subjects.
NS	Non significant.
OD	Optical density.
P	Phosphorus.
PB	Phenobarbitone.
PET	Positron emission tomography.
PHT	Phenyl hydantoin.
PICP	Procollagen type I-carboxyl terminal peptide.
PRM	Primidone.
PTH	Parathyroid hormone.
S	Significant.
SD	Standard deviation.
SE	Status epilepticus.
SPECT	Single photon emission computerized tomography.
SPS	Simple partial seizures
VNS	Vagus nerve stimulation.
VPA	Valproic acid.
V/V	Volume / volume.

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Abstract

Objective : this study aims to examine the effect of valproate and carbamazepine monotherapy or polytherapy on bone mineral density in epileptic children.

Methods : axial bone mineral density (L_2-L_4) was measured by dual-energy x-ray absorptiometry in 30 children with idiopathic epilepsy (patients group) and 12 healthy children (control group) of the same cohort as the patients group. The epileptic children treated with either valproate monotherapy (n=14) or carbamazepine monotherapy (n=8) or both drugs as polytherapy (n=8) for more than one year. Serum level of 25(OH)D_3, Ca, P and alkaline phospharase were also measured.

Results : the results of this study showed that the patients group had a highly statistically significant reduction in bone mineral density. This reduction increased with the increase duration of the therapy. Valproate monotherapy reduced BMD in 7 patient (4 osteopenic and 3 osteoprotic), while carbamazepine monotherapy reduced BMD in 1 patient (osteoprotic). Polytherapy reduced BMD in 5 patients (4 osteopenic and 1 osteoprotic). There were a highly statistically significant decrease in serum level of 25(OH)D_3; statistically significant decrease in serum level of P and a statistically significant increase in serum level of alkaline phosphatase in patients group.

Conclusion : it is concluded that valproate and carbamazepine either in monotherapy or polytherapy reduce axial bone mineral density in children with idiopathic epilepsy and may increase their risk of osteoporotic fractures.

Key words :

Primary epileptic children, antiepileptic drugs (valproate-carbamazepine), bone mineral densitometry (Z-score), osteomalacia, osteopenia, osteoprosis.

Introduction

Introduction

Epilepsy is a chronic condition requiring careful long-term management. The treatment is complex, involving classification and diagnosis, selection and monitoring of the appropriate antiepileptic agent, and evaluation of the chosen drug's side effects and drug interaction ***(French, 1994).***

Childhood and adolescence are critical periods of skeletal mineralization ***(Matkovic et al, 1994).*** Bone mineral density (BMD) peaks by age 20 years and after a long plateau, decreases after age 40 years ***(Melton et al, 1988***). Peak bone mineral density is influenced by genetic, hormonal and exogenous factors. The exogenous factors that adversely affect it include cigarette smoking, physical disabilities, poor calcium intake and certain medications ***(Riggs and Melton, 1986).***

Antiepileptic osteomalacia is a condition in epileptic patients chronically treated with antiepileptic drugs has been recognized since 1968 ***(kruse, 1968).*** Altered biochemical changes suggestive of osteomalacia include hypocalcemia, reduced serum 25-hydroxy vitamin D concentrations, elevated serum alkaline phosphatase activity ***(Dent et al, 1970***) and decreased bone mass ***(Sotaniemi et al, 1972).***

The mechanism of anticonvulsant osteomalacia is not fully understood. The presumed mechanism by which rickets develops in epileptics is the induction by anticonvulsant drugs of hepatic microsomal enzymes that convert vitamin D and its

major active metabolites to biologically inactive forms ***(Winnacker et al, 1977).***

The development of anticonvulsant osteomalacia and rickets is related to the dosage, number of anticonvulsant drugs employed and the duration of therapy ***(Kruse, 1968).*** However, the published reports disagree considerably as to the incidence of anticonvulsant rickets in epileptic children, this may be due to the inborn qualitative nature of the radiological examination ***(Christiansen et al., 1973)***

Phenytoin , primidone and phenobarbital are established contributors to osteomalacia and rickets ***(Winnacker et al, 1977).*** Alterations in bone metabolism have been reported with carbamazepine ***(Hoikka et al, 1984)*** and with valproate ***(Sheth et al., 1995).***

Interference with bone mineralization by antiepileptic medications could place a large number of children at increased risk for involutional osteoporosis ***(Sheth et al., 1995)***

Since BMD values might change during chronic antiepileptic therapy, BMD values must be evaluated during chronic antiepileptic therapy ***(Trias et al., 1998).***

Aim Of The Work

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The aim of the present study is to examine prospectively the effects of chronic antiepileptic drugs therapy on bone mineral density in epileptic children receiving valproate (VPA) and /or carbamazepine (CBZ) either as monotherapy or polytherapy and highlight the proper preventive measures to avoid loss of bone mass.

Review Of Literature

Epilepsy

Definitions

The terms seizure and convulsion may be incorrectly used interchangeably with epilepsy.

Seizures :

A seizure (convulsion) is defined as paroxysmal involuntary disturbance of brain function that may be manifested as an impairment or loss of consciousness, abnormal motor activity, behavioral abnormalities, sensory disturbance or autonomic dysfunction. Some seizures are characterized by abnormal movements without loss or impairment of consciousness ***(Behrman et al., 2000).***

Epilepsy :

The word "epilepsy" is derived from a Greek word meaning "to seize" and refers to the patient being seized by an epileptic attack ***(O'Donohoe, 1985).***

Epilepsy is defined as recurrent seizures unrelated to fever or to an acute cerebral insult. The seizure is the phenomenon by which epilepsy expresses itself while epilepsy is the disease of which the seizure is the symptom ***(Dreifuss, 1989).***

Epilepsy is the clinical sign and symptom of excessive or hypersynchronoous, usually self limited, abnormal activity of neurons in the cerebral cortex. It is not a specific disease, but rather symptom complex secondary to abnormal brain function ***(Rudolph and Kamel , 1994).*** Epilepsy is recurrent fits due to repeated primary cerebral dysrhythmias ***(Campbell and Neil McIntosh, 1998).***

Non Epileptic Events:

There are many conditions which are characterized by the sudden onset of abnormal consciousness, behavior, posture, tone, sensation or autonomic function. Syncope, breath-holding spells, migraine, hypoglycemia, narcolepsy, cataplexy, gasrtroesophageal reflux, parasomnias feature an abrupt or "paroxysmal" alteration of brain function and suggest the possibility of epilepsy. Pseudoseizures or hysterical seizures are abnormal attacks modeled after the patient's subconscious and occur without any abnormal electrical discharges of neurons in the central nervous system ***(ILAE Commission Report, 1997).***

Epidemiology

Incidence:

Regarding the incidence of epilepsy, which refers to the number of new cases occurring within a given period of time, ***Hauser and colleagues (1991),*** who studied the incidence of epilepsy in Rochester, Minnesota reported very high incidence rates in the first year of life reaching 80 per 100,000 infant.

The rates then decline through childhood and adolescence reaching a plateau of 40 per 100,000 person per year in middle age. Epilepsy is relatively rare in the early months of life, very common between 6 months and 4 years and declines in frequency until puberty ***(O'Donohoe, 1986).*** Epilepsy most commonly starts in the first two decades of life. ***(Besag, 1996).***

The incidence rates of epilepsy are slightly higher, about 15%, in men than in women at all ages and for most seizure types. In contrast to other major seizure types, absence of epilepsy has an incidence twice as high in girls than in boys ***(Annegers, 1997).*** A study conducted by ***El-Khayat et al., (1994),*** reported sex incidence in primary epileptic male: female of about 1.4 : 1.

Epilepsy manifested by generalized onset seizures accounts for most of the newly diagnostic cases of epilepsy in the first 5 years of life ***(Hauser, 1995).*** After that age, epilepsy manifested by partial seizures accounts for 50% or more of the newly identified convulsive disorders ***(Hauser et al., 1993).*** Myoclonic seizures are the most common type during the first year of life, diminish in incidence rapidly thereafter. The incidence of generalized tonic-clonic epilepsy is 15 per 100,000 in children younger than one year and gradually declines to 10 per 100,000 for children aged 10 to 15 years. The incidence of partial seizures with or without secondary generalization, remains remarkably consistent at 20 per 100,000 from infancy through age 65. The incidence of absence of epilepsy with or without generalized tonic-clonic convulsion is 11 per 100,000 from ages 1 through 10, whereas its onset is uncommon after age 14 as shown in (figure 1).

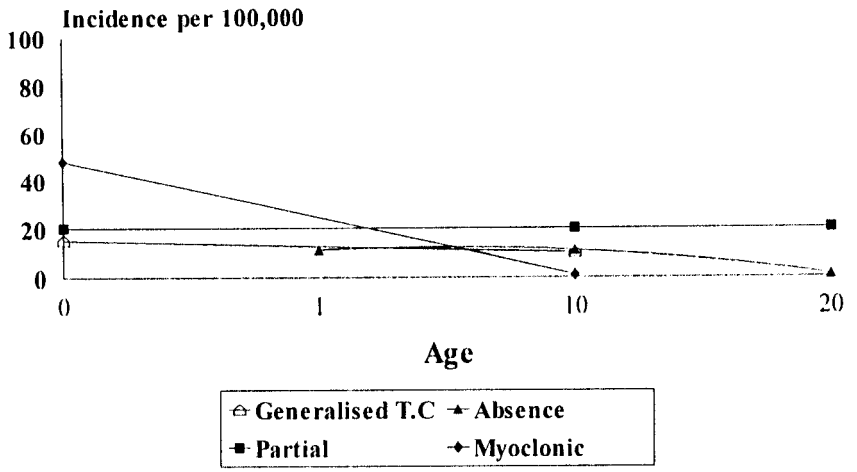


Fig. (1) : Incidence rates of epilepsy by seizure type from Rochester, MN, 1935-1979 ***(Annegers, 1997).***

In a study carried on 365 consecutive patients in the pediatric age group ***Kramer and Harel (1996)*** revealed that the frequencies of the different seizure types in a descending order were partial seizures secondarily generalized 23%, generalized tonic and tonic clonic seizures 14%, complex partial seizures 12%, simple partial seizures 10.4%, West syndrome 10%, benign rolandic epilepsy of Childhood 8.6%, absence seizures 7 %, myoclonic seizures 2.2 %, benign occipital epilepsy of childhood 2 %, Lennox-Gastaut syndrome 1.5 %, juvenile myoclonic epilepsy 0.9% , atypical absence 0.6 %.

Epilepsy is perhaps more common in developing countries as well as in tropics due to poverty and illiteracy promoting nutritional causes of brain damage, or birth trauma and perinatal hypoxia due to inadequate medical care

(De- Bittencourt et al., 1996). The high incidence rates in developing countries are mainly due to acute infections, parasitic infestations and poor postnatal care *(Shorvon, 1988).*

Prevalence

Epilepsy is a highly prevalent disease, affecting 0.5 % - 1.5 % of the world population *(Hauser, 1995)*. The overall prevalence of the epilepsies in childhood and adolescence is 4 – 6 per 1000 *(Cowan et al., 1989).* In Egypt, ***El -Khayat et al (1994)*** studying the prevalence of epilepsy in children, reported a prevalence rate of 3.5 per 1000, while ***Massoud (1997),*** in his study on school children in Cairo, reported even a lower overall prevalence of 1.9 per 1000.

Risk of seizure recurrence after a single attack :

It is likely that the etiology of the seizure is an important determinant of the risk of recurrence. Patients with an abnormal neurological examination are more likely to have a recurrence after a first seizure. The presence of a family history has been reported to increase the risk of recurrence *(Camfield et al., 1985).* Also, a number of studies have suggested that abnormal EEG is an important predictor of recurrence *(Shinnar et al., 1990).*

Etiology of Seizures

Although the majority of children with seizures have idiopathic epilepsy, a significant minority has an identifiable etiology ***(Behrman et al., 2000).***

Many systemic disorders and almost all local pathological processes that involve the brain can result in epilepsy. This is demonstrated in (figure 2) and in (figure 3) ***(Annegers, 1997).***

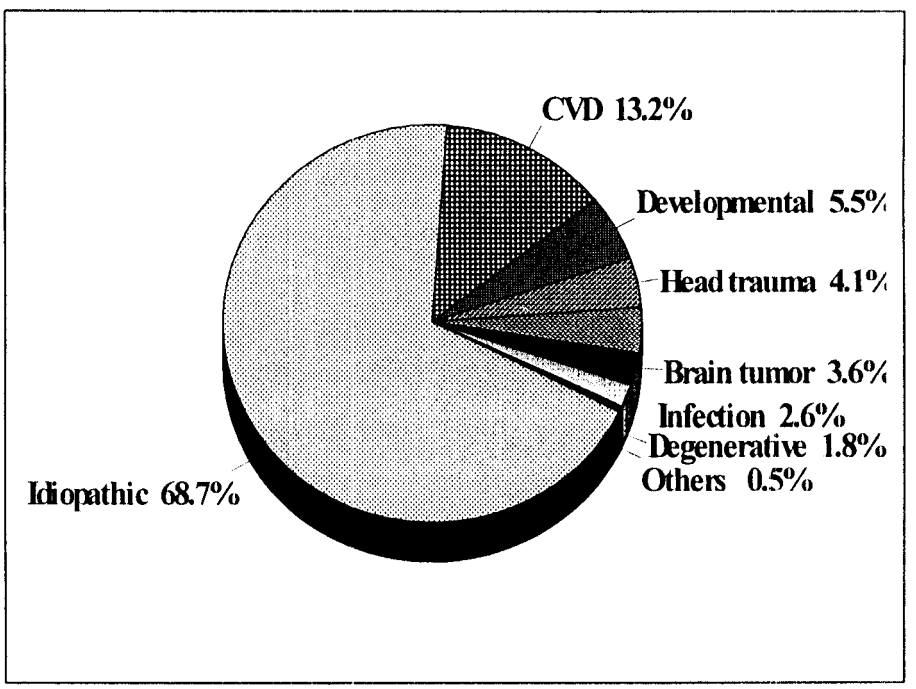


Fig. (2): Etiology of epilepsy; presumed predisposing cause of epilepsy. Incidence in Rochester, MN, 1935-1984 ***(Annegers, 1997)***

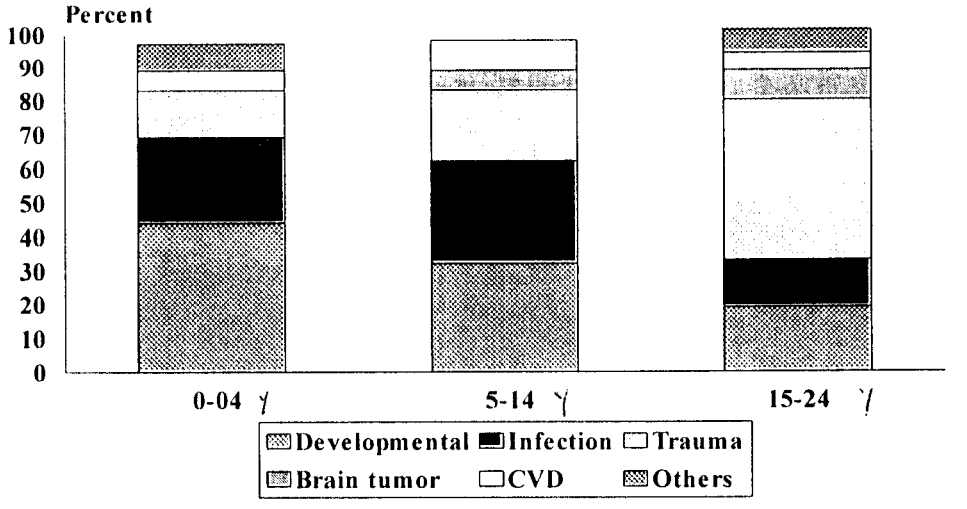


Fig. (3): Remote symptomatic epilepsy proportional incidence by age and etiology *(Annegers, 1997)*

Table (1): Shows the etiology of seizures in childhood *(Wright, 1984).*

Prenatal abnormality *Cerebral malformation. *Intrauterine infections	**Birth insult** *Anoxia. *Hemorrhage and/or ischemia
Infection *Meningitis *Encephalitis *Brain abscess	**Intoxication.** *Drug ingestion *Lead poisoning
Genetic *Familial. *Neurocutanous syndromes *CNS degenerative diseases. *Aminoacidurias. *Lipidosis. *Ceroid storage diseases.	**Metabolic disorders.** *Hypoglycemia. *Hypocalcemia. *Hypo and hypernatremia *Reye's syndrome *Uremia

Pathophysiology of Epilepsy

A-Mechanisms of Neuronal Excitation & Synchronization:

Although the precise mechanisms of seizures are unknown, several physiologic factors appear to be responsible for the development of a seizure ***(Behrman et al., 2000).***

Excitable membrane and microenvironment:

The resting membrane potential of the neuron is negative inside with a value of 60-80 mV, which is maintained by Na^+ and K^+ pump. Under resting condition, there is intracellular deficiency in the concentrations of Na^+, Ca^{2+} and Cl^-. Opening of any channel that permits their passage will result in their influx and membrane depolarization in case of Na^+ and Ca^{++} and hyperpolarization in case of Cl^-. On the other hand, there is excess of intracellular K^+, and opening of K^+ channels will result in membrane hyperpolarization ***(Ganong, 1995a).***

Maintenance of the potential across the membrane requires the energy ATP-dependent pump. Thus, a disturbance of energy production can result in failure of the Na-K pump, as in cases of hypoxia, ischemia and hypoglycemia ***(Volpe, 1986).***

Biochemical basis:

To initiate a seizure, there must be a group of neurons that are capable of generating a significant burst discharge and

a GABAergic inhibitory system. Seizure discharge transmission ultimately depends on excitatory glutamatergic synapses ***(Behrman et al., 2000).***

The facilitatory factors of seizure activity:

Glutamate and *aspartate* are the most important excitatory neurotransmitters in the central nervous system. They produce membrane depolarization with a rapid time course by inducing Ca^{++} currents ***(Bray et al., 1994).*** Their excessive release contributes to the death of postsynaptic neurons ***(Lee et al., 1996).***

The inhibitory factors of seizure activity:

GABA (γ–aminobutyric acid) is the major neuroinhibitory transmitter in the CNS, which can open either CL^- or K^+ channels. *Glycine*, which produces inhibitory effect on postsynaptic membrane by opening Cl^- channels is mainly limited to the spinal cord and brain stem. *Taurine* is reported to have an inhibitory effect. A relative excess of excitatory versus inhibitory neurotransmitters can result in excessive rate of depolarization ***(Olsen and Avoli, 1997).***

Neurotransmitter receptors:

These have been identified by agonist and antagonist drugs ***(Hauser and Hesdorffer, 1996).***

$GABA_A$ receptors are particularly important in epileptogenesis. It mediates rapid inhibition through generating large Cl- conductance while $GABA_B$ mediates slow inhibition through increasing K^+ conductance ***(Bormann, 1988).*** Overall, the major role of GABA in the epileptic brain is antiepileptic ***(Bradford, 1995).***

B-Seizure susciptibility and Epileptogenesis:

Kindling phenomenon

The phenomenon of kindling (i.e. normal neurons may become epileptogenic by repeated subconvulsive stimulation of the brain) has been described as the mechanism by which epilepsy develops after an injury to the brain. Also it proves the correlation between the site of epileptogenic focus and the resultant type of seizure disorder e.g., kindling of the temporal lobe produces generalized convulsions ***(Cavazos and Sulula, 1990).***

Cytological changes:

Cerebral gray matter, which is the focus of origin of epileptic discharge , shows a variety of cytologic changes irrespective of the primary cause of lesion ***(Meldrum and Bruton, 1992).*** It is known that seizures may arise from areas of neuronal death and that these regions of the brain may promote development of novel hyperexcitable synapses that can cause seizures ***(Behrman et al., 2000)***.

All pathogenic brain tissues (atrophic, malformed or neoplastic) are electrically inert and the functioning epileptogenic neurons are located around the periphery of various lesions ***(Menkes, 1985).*** The disturbance in cellular function can lead to changes in neurotransmitters level in the brain with a subsequent evolution of a seizure ***(Chevrie et al., 1987).***

C-Basic Mechanisms of Epilepsy:

Focal epilepsy:

The underlying dysfunction is excessive excitability of a population of cells in the neocortex "pacemaker cells". This will result in intermittent synchronized burst discharges within neuronal aggregates, reorganization of neocortical connections, extension of the area of epileptogenic zone and eventually appearance of the ictal behavior ***(Meldrum, 1989).***

Generalized epilepsy:

In generalized epilepsy, the sudden onset and the bilateral synchrony suggest very generalized disturbance of neural activity in both hemispheres ***(Sandstedt, 1990).*** It was proposed that the spike and wave discharges reflect an abnormal oscillatory activity between excitation (spike) and inhibition (wave) in the connected thalamo-cortical neurons ***(Smith and Huguenard, 1996).***

D-The developing brain and epilepsy:

Seizures are more common in infants , and certain seizures in the pediatric population are age specific (e.g., infantile spasms). This observation suggests that the underdeveloped brain is more susceptible to specific seizures than is the brain of an older child or adult (***Behrman et al., 2000).***

Several factors contribute to the propensity for the developing brain to have seizures. The immature cortex and hippocampus are shown to have an increased density of synapses and of excitatory amino acid receptors compared to adults. Also, enhanced regenerative response to injury, which is characteristic of the developng brain, may contribute to the formation of abnormal hippocampal connections ***(Johnston, 1996).***

E-Genetic factors and epilepsy:

Genetic factors account for at least 20% of all cases of epilepsy. Using linkage analyses, the chromosomal location of several familial epilepsies has been identified, including benign neonatal convulsions (20q and 8q), juvenile myoclonic epilepsy (6p), and progresive myoclonic epilepsy (21q22.3) (***Behrman et al., 2000).***

Classification of seizures

It is important to classify the type of seizure for several reasons, as the seizure type may provide a clue to the cause of the seizure disorder. In addition, precise delineation of the seizure may allow a firm basis for making a prognosis and choosing the most appropriate treatment. Clinical classification of seizures may be difficult because the manifestations of different seizure types may be similar. An electroencephalogram (EEG) is a useful adjunct to the classification of epilepsy because of the variability of seizure expressivity in children age group. A classification combining the clinical description of the seizure with the EEG findings has improved the delineation of childhood epilepsy (***Behrman et al., 2000***).

The International League Against Epilepsy (ILAE) Classification of Seizure Type:

ILAE classified epileptic seizures on the basis of clinical form and EEG ictal and interictal signs. This was first proposed in 1970 ***(Gastaut, 1970)*** revised in 1981and officially adopted in 1982 (***Commission on Classification and Terminology of the International League against Epilepsy, 1981***). Although criteria are ill –defined, this scheme is widely used, for virtue of simplicity and clinical utility ***(Sander et al., 1990).*** (Table 2).

Table 2: The International league Against Epilepsy (ILAE) Classification of Seizure Type ***(Commission on Classification and Terminology of the International League Against Epilepsy 1981).***

I – PARTIAL SEIZURES (seizures beginning locally)

A.Simple partial seizures:(consciousness not impaired)

1. With motor symptoms:focal motor with or without march, versive, postural, phonatory.
2. With somatosensory or special sensory symptoms: Somatosensory, visual, olfactory, gustatory, vertiginous, simple Hallucinations.
3. With autonomic symptoms or signs including epigastric aura
4. With psychic symptoms (disturbances of higher mental function): dysphasic, dysmnestic, cognitive, affective; illusion , structural hallucinations

B-Complex partial seizures (with impairment of consciousness)

1. Simple partial seizures followed by impairment of Consciousness.
   a) With simple partial features (A1 to A4) followed by Impaired consciousness
   b) With automatisms.
2. With impairment of consciousness at onset.
   a) With features as in A1 to A4
   b) With automatisms.

C. Partial seizures secondarily generalized

1. Simple partial seizures evolving to generalized seizures
2. Complex partial seizures evolving to generalized seizures
3. Simple partial seizures evolving to complex partial seizures, evolving to generalized seizures.

II. GENERALIZED SEIZURES (convulsive and non-convulsive)

A. Absence seizures

- Absence seizures with impairment of consciousness only, mild clonic components, tonic components, automatisms, autonomic components.
- Atypical absence seizures with changes in tone more pronounced than in A1 and with onset and / or cessation that is not abrupt.

B. Myoclonic seizures.
C. Clonic seizures.
D. Tonic seizures.
E. Tonic-clonic seizures.
F. Atonic seizures

(Combination may occur, such as B and For Band D)

III. UNCLASSIFIED EPILEPTIC SEIZURES

Partial seizures:

These are seizures in which the electrographic activity commences in a part (focus) of the cerebrum ***(Kotagal, 1990).*** They account for a large proportion of childhood seizures, up to 40% in some series. Partial seizures may be classified as simple or complex; consciousness is maintained with simple seizures and is impaired with complex seizures **(Behrman et al., 2000).**

Simple partial seizures (SPS):

There is no alteration of consciousness when the ictal discharge occurs in a limited area of the cortex. Almost any symptom can be the subjective "aura" or observable manifestation of simple partial seizures varying from elementary motor and sensory disturbance to emotional, psychoillusionary, hallucinatory or dysmensic phenomena ***(Pedley et al., 1995).***

Motor activity is the most symptom of SPS. Versive seizures consisting of head turning and conjugate eye movements are particularly common in SPS. Automatism do not occur with SPS, but some patients complain of aura (e.g., chest discomfort and headache), which may be the only manifestation of a seizure. Unfortunately, children have difficulty in describing aura and often refer to it as "feeling funny" or "something crawling inside me". The average seizure persists for 10-20 sec. The distinguishing characteristic of SPS is that the patients remain conscious and may verbalize during the seizure. Furthermore, no postictal phenomenon follows the event ***(Holmes, 1986).***

Complex partial seizures (CPS):

As emphasized by the international classification of seizures, must include some impairment of consciousness ***(Kotagal, 1990).*** They originate most commonly in the medial temporal lobes, but may arise from the frontal or parietal lobes as well ***(Fenichel, 1997).*** An aura consisting of vague, unpleasant feeling, epigastric discomfort, or fear is present in approximately one third of children with CPS. The presence of an aura always indicates a focal onset of the seizure ***(Holmes, 1986).***

Automatisms are a common feature of CPS in infants and children, occurring in approximately 50-75% of cases; the older the child, the greater is the frequency of automatisms. An automatism is defined as a "more or less coordinated involuntary motor activity occurring during the state of clouding of consciousness either in the course of, or after, an epileptic seizure and is usually followed by amnesia of the event" ***(Delgado- Escueta et al., 1982).*** Automatisms develop after the loss and may persist into the postictal phase, but they are not recalled by the child. Automatic behavior consists of semipurposeful, incoordinated and unplanned gestural automatisms, including picking and pulling at clothing or the bed sheets, rubbing or caressing objects, and walking or running in a nondirective, repetitive, and often fearful fashion. The average duration of a CPS is 1-2 minute, which is longer than an SPS or an absence seizure ***(Holmes, 1986).***

The age of onset of CPS ranges from 2 to 11 years, with 75% beginning between 3 and 10 years. The first symptom

may be aphasia or epilepsy. Hyperactivity and personality changes are noted in one half of affected children and may be caused by aphasia ***(Fenichel, 1997).***

Partial seizures may spread to become generalized. The partial seizures are often experienced as an aura in the seconds before the generalized seizures. The generalized seizure is usually tonic-clonic, tonic or atonic ***(Chadwick, 1993).***

Generalized seizures:

A generalized seizure is defined as an attack in which the epileptic disturbances involve wide areas of both cerebral hemispheres simultaneously from the onset of the attack, with no evidence of an anatomical or functional focus ***(Jallon et al., 1993).***

Absence seizures:

Simple (typical) absence seizures (petit mal):

They are characterized by a sudden cessation of motor activity or speech with a blank facial expression and flickering of the eyelids. These seizures are uncommon before age 5 years, are more prevalent in girls, never associated with an aura, rarely persist longer than 30 seconds, and not associated a postictal state. Automatic behavior frequently accompanies simple absence seizures. Hyperventilation for 3-4 minutes routinely produces an absence seizure. The EEG shows a

typical 3/sec spike and generalized wave discharge ***(Behrman et al., 2000).***

Complex (atypical) absence seizures:

They have associated motor components consisting of myoclonic movements of the face, fingers, or extremities and, on occasion, loss of body tone. These seizure produce atypical EEG spike and wave discharges at 2-2.5/sec ***(Behrman et al., 2000).***

Atypical absences occur in the symptomatic epilepsies and are associated with neurological abnormalities and multiple seizure types. They form part of the Lennox-Gastaut syndrome ***(Chevrie and Aicardi, 1972).***

Myoclonic seizures:

This is a brief contraction of a muscle or muscle groups or several muscle groups. It can be single or repetitive varying in severity from an almost imperceptible twitch to a severe jerking resulting, for instance, in a sudden fall. Recovery is immediate and the patient often maintains consciousness ***(Kotagal, 1990).***

Myoclonic epilepsies include a heterogeneous group of conditions with multiple causes and variable outcomes. However, at least five distinct subgroupings can be identified; benign myoclonus of infancy, typical myoclonic epilepsy of early childhood, complex myoclonic epilepsy, juvenile myoclonic epilepsy (Janz syndrome) and progressive myoclonic epilepsy ***(Behrman et al., 2000).***

Generalized Clonic seizures:

They can occur without a preceding tonic phase. The jerking is often asymmetric and irregular; the postictal state is often but not always short. Clonic seizures are most frequent in neonates, infants or young children and are always symptomatic ***(Commission on Classification and Terminology of the International League Against Epilepsy, 1996).***

Generalized Tonic seizures:

They take the form of a tonic muscle contraction with altered consciousness and without a clonic phase. Axial tonic seizure comprises a sequence of extension of the neck, contraction of the facial muscles with upturning of eye balls, contraction of muscles of respiration causing a cry and apnea. In axorhizomelic tonic seizures, this pattern is followed by tonic contraction of the proximal upper limb muscles causing abduction and elevation of the semi-flexed arms and shoulders. In global tonic seizures, the tonic contractions spread distally and the arms rise up and are held as if defending against a blow ***(Dreifuss and Henrikson, 1992).***

Generalized Tonic-Clonic seizures:

These seizures are extremely common and may follow a partial seizure with a focal onset (second generalization) or occur de novo. They may be associated with an aura, suggesting a focal origin of the epileptiform discharge. Patients suddenly lose consciousness and in some cases emit a

shrill, piercing cry. Their eyes roll back, their entire body musculature undergoes tonic contractions, and they rapidly become cyanotic in association with apnea. The clonic phase of the seizure is heralded by rhythmic clonic contractions alternating with relaxation of all muscle groups. The clonic phase slows toward the end of the seizure, which usually persists for a few minutes, and patients often sigh as the seizure comes to an abrupt stop (***Behrman et al., 2000***). During this phase, breathing starts though may be stertorous ***(Gram, 1990a).***

Autonomic features, such as flushing, changes in the blood pressure and in the pulse rate are common. The clonic phase lasts 30-60 sec. and is followed by a further period of brief tonic contraction of all muscles and sometimes incontinence. The final phase lasts between 2 and 30 minutes and is characterized by flaccidity of the muscles ***(Duncan et al., 1995a).***

Atonic seizures:

They may take several forms; the classic drop attack (astatic seizure) is a seizure in which postural tone is suddenly lost, and the patient collapses to the ground. The sudden loss of tone may be more restricted and less severe, resulting for instance in nodding of the head or sagging at the knee. Serial atonic attacks may occur and atonic seizures are often associated with myoclonic jerks ***(Pedley et al., 1995).***

The International League Against Epilepsy (ILAE) Classification of Epilepsy and Epilepsy Syndromes

Epilepsy in children has been also classified by syndrome, using the age at onset of seizures, cognitive development, and neurologic examination, description of seizure type and the 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 appropriate anticonvulsant medication, identifying potential candidates for epilepsy surgery, and providing patients and families with a reliable and accurate prognosis (***Behrman et al., 2000***).

In 1993, the commission on epidemiology and prognosis encouraged the use of the ILAE classification of epilepsy syndromes (1989). Appropriate categorization would thus require the use of state of art of technologies and procedures ***(Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993).***

Table 3: The ILAE classification of the epilepsies and epileptic syndromes.(***Commission on Classification and Terminology of the International League Against Epilepsy, 1989***).

1. Generalized Epilepsies and Syndromes

Idiopathic "with age related onset" listed in order of age

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with generalized tonic-clonic seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

Cryptogenic "in order of age"

- West syndrome "infantile spasms"
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures
- Epilepsy with myoclonic absence seizures

Symptomatic

- Non specific etiology
  - Early myoclonic encephalopathies
  - Early infantile epileptic encephalopathy
  - Other symptomatic epilepsies not defined above
- Specific syndrome
  - Epilepsies in other disease states

2. Localization related (focal, local, partial) epilepsies and syndromes

Idiopathic with age related onset

- Benign epilepsy with centrotemporal spikes
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

Cryptogenic

Symptomatic

- Epilepsia partialis continua
- Syndromes characterized by specific modes of precipitation
- Temporal lobe epilepsies
- Parietal lobe epilepsies
- Occipital lobe epilepsies

3.Epilepsies and syndromes undetermined as to whether focal or generalized

with both generalized and focal seizures

- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Electrical status epilepticus in slow wave sleep
- Acquired epileptic aphasia

Other undetermined epilepsies (not defined above)

With unequivocal generalized or focal features

4.Special syndromes

- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycemia

Another classification was proposed, concentrating on the age incidence of the syndromes and ignoring the dichotomies generalized versus localized and cryptogenic versus symptomatic. It is shown in table (4).

Table (4): Main epileptic syndromes in childhood and adolescence (*Aicardi, 1989*).

Early Childhood • West syndrome. • Lennox-Gastaut syndrome (may begin also in late • childhood and adolescence). • Myoclonic epilepsy. • Febrile convulsions. • Grand mal epilepsy of early childhood. • Partial epilepsy with brain damage (may begin also in late childhood and adolescence).
Later Childhood • Typical absence epilepsy. • Myoclonic epilepsies of late childhood. • Grand mal epilepsy of late childhood. • Partial epilepsy with rolandic spikes. • Partial epilepsy with occipital spikes. • Other partial benign epilepsies. • Landau-Kleffner syndrome.
Adolescence • Juvenile myoclonic epilepsy (Janz syndrome). • Grand mal on awakening. • Typical absence epilepsy of adolescence.

Generalized epilepsy syndromes

A- Idiopathic generalized epilepsies (IGE):

These are a spectrum of epileptic conditions with a genetic basis and characteristic clinical symptoms. It has been estimated that IGE syndromes comprise 8.1 % of all epilepsies ***(Manford et al., 1992).***

There is undoubtedly a strong heritable basis. It seems likely that some, if not all, of IGE syndromes have an autosomal dominant pattern of inheritance with a marked age-specific expression. The genetic expression of both clinical and electrographic findings is greatest between the ages of 5 and 15 years. No gross pathological lesions are found in the brain imaging of patients with IGE, although recent studies reported microscopic developmental abnormalities in some cases ***(Meencke, 1994; Fish, 1995).***

Benign myoclonic epilepsy of infancy

This rare syndrome develops between 4 and 24 months of life without other neurological features. The myoclonic seizures may be initially imperceptible; attacks are frequent, mostly lasting 1-3 seconds. There is often a family history of idiopathic generalized epilepsy ***(Fenichel, 1997).*** It has a good prognosis as it stops at 2 years old without treatment ***(Dravet et al., 1985).***

Childhood absence epilepsy (CAE) (pyknolepsy)

This occurs in children of school age with peak manifestation at age 6-7 years with strong genetic predisposition in otherwise normal children. It appears more frequently in girls than in boys ***(Commission on Classification and Terminology of the International League Against Epilepsy, 1989).***

Absences may be noted hundreds of times a day lasting few seconds, usually less than 15 seconds and comprises a blank stare and unresponsiveness. There may be also clonic movement of the eyelids or a transient loss of postural tone ***(Panayiotopoulos et al., 1989).***

40% of patients develop generalized tonic-clonic seizures 10-15 years after the onset of the absences, more likely if absences do not readily come under control ***(Loiseau, 1992).***

Juvenile absence epilepsy (JAE)

It is approximately one quarter as common as absence epilepsy. The age of onset is around 10 years. Absences tend to be less frequent than in childhood absence epilepsy but of longer duration and associated with a less profound impairment of consciousness ***(Panayiotopoulos et al., 1989).***

Juvenile myoclonic epilepsy (JME)(impulsive petit mal)

It comprises 5–10 % of cases of idiopathic generalized epilepsy. Males and females are equally affected. The usual age of onset is 7 to 13 years ***(Panayiotopoulos et al., 1994).*** A gene locus has been identified on chromosome 6p ***(Camfield et al., 1993).***

Three types of seizures occur; myoclonic jerks usually of the upper extremities with dropping of whatever being held, generalized tonic-clonic seizures and in one third of patients, typical absences ***(Janz and Waltz, 1995).***

Epilepsy with GTCS on awakening:

Several studies reported that 16-50% of generalized tonic clonic seizures occur on awakening. There is a slight male predominance and a positive family history in 12% of cases ***(Wolf, 1992).***

It is a syndrome with onset occurring mostly in the second decade of life. The GTCS occur exclusively or predominately shortly after awakening regardless of the time of day or in a second seizure peak in the evening period of relaxation. If other seizures occur, they are mostly absence or myoclonic, as in juvenile myoclonic epilepsy. Seizures may be precipitated by sleep deprivation and other external factors ***(Commission on Classification and Terminology of the International League Against Epilepsy, 1989).***

B-Cryptogenic generalized epilepsy syndrome:

Although epilepsy may result from a variety of different causes, in many cases no cause is found. Such cases are best designated as cryptogenic rather than idiopathic, which is a term reserved for the genetically determined idiopathic generalized epilepsies ***(Commission on Classification and Terminology of the International league Against Epilepsy, 1989).***

West syndrome (Infantile Spasms):

Usually, West syndrome consists of a characteristic triad: infantile spasms, arrest of psychomotor development, and hypsarrhythmia, although one element may be missing. Spasms may be flexor, extensor, but most commonly they are mixed. They generally occur in clusters, shortly after the infant awakens from sleep, and are not activated by stimulation ***(Fenichel, 1997).*** Onset peaks between the ages of 4 and 7 months and always occur before the age of 1 year. Boys are more commonly affected. ***(Commission on Classification and Terminology of the International League against Epilepsy, 1989).***

Infantile spasms are classified into cryptogenic (20% of cases with a lack of previous signs of brain damage and of known etiology and good prognosis) and symptomatic (80% of cases with previous existence of brain damage signs and mental retardation in 90% of cases) ***(Pellock and Low, 1986).*** The prognosis appears to be partly based on early therapy with adrenocoticotropic hormone (ACTH) or oral steroids

(Fenichel, 1997). These drugs suppress the metabolism and secretion of corticotropin-releasing hormone (CRH) which is a potent neurotransmitter *(Behrman et al., 2000).*

Lennox-Gastaut syndrome (LGS)

This syndrome is characterized by the triad of intractable seizures of various types, a slow spike wave EEG during the awake state, and mental retardation (*Behrman et al., 2000*).

It manifests itself in children aged 1-8 years, but appears mainly in preschool – age children. It accounts for 1-2% of all childhood epilepsies. It may develop in patients who have had infantile spasms, but more often occurs spontaneously. The most devastating seizures are atonic; the head may drop suddenly onto the breakfast table, or the patient may fall precipitously to the floor. The absence seizures are usually brief and atypical *(Holmes et al., 1987).*

Myoclonic- Astatic epilepsy

This is another childhood myoclonic syndrome characterized by myoclonic and astatic seizures. It accounts for 1-2 % of all childhood epilepsies. Onset is usually between 2 and 5 years. About 40% of patients exhibit at least one episode of absence status. There is no underlying neurological deficit and no associated neurometabolic or degenerative disorders *(Doose, 1992).*

Epilepsy with myoclonic absences

This rare syndrome develops in children (mean age of 7 years) with a male predominance. Absences are accompanied by severe bilateral rhythmical myoclonic seizures causing rhythmic jerking of the shoulders, head or limbs. About 50% of cases show existing mental retardation ***(Tassinari et al., 1992).***

C- Symptomatic generalized epilepsy syndromes

With nonspecific etiology (age-related)

Early myoclonic encephalopathy.

The principal features are onset occurring before age 3 months, initially fragmentary myoclonus and then erratic partial seizures, massive myoclonias, or tonic spasms. Death may occur in the first year ***(porter, 1989).***

Early infantile epileptic encephalopathy with suppression burst.

It is defined by very early onset, within the first few months of life, frequent tonic spasms, and suppression burst EEG pattern in both waking and sleeping states. Often there is evolution to the West syndrome at age 4-6 months ***(Commission on Classification and Terminology of the international league Against epilepsy, 1989).***

Specific syndromes:

Epilepsies in other disease states.

Localization – related epilepsies

A – Idiopathic (with age related onset)

These benign epilepsies usually occur in otherwise normal children with normal neurological and psychological functions. There is often a positive family history and the ultimate prognosis is usually good ***(Fenichel, 1997).***

Benign epilepsy of childhood with rolandic spikes

It is the most common primary partial epilepsy of childhood (15 % of all childhood epilepsies). Seizures are typically focal involving the face often with secondary generalization. Despite an electroclinical phenotype initially suggestive of the syndrome, the presence of atypical clinical features should raise the possibility of underlying structural lesion and a negative neuroimaging study may be essential for the definitive accurate diagnosis ***(Shevell et al., 1996).***

Childhood epilepsy with occipital paroxysms

This syndrome shows a male preponderance with a peak age of onset of 7 years. The partial seizures have occipital symptomatology: hemianopia and visual hallucinations and illusions. Head deviation and blinking are common motor phenomena ***(Panayitoopoulos, 1989).***

Primary reading epilepsy

The age of onset of this syndrome is usually the second decade. Myoclonic jerks involving the orofacial and jaw muscles develop while reading. Reading time before seizure onset is variable. Myoclonic jerks of the lids may follow. Generalized tonic-clonic seizures may also occur ***(Radhakrishnan et al., 1995).***

B-Symptomatic localization-related epilepsies and syndromes.

These syndromes include epilepsia partialis continua, the symptomatic reflex epilepsies and all other symptomatic partial epilepies that can be categorized according to the anatomic location of the lesion.

Epilepsia Partialis Continua:

This form of status epilepticus is defined as spontaneous regular or irregular clonic twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body and continuing for hours, days or weeks. Sensory symptoms occur in one fifth of cases ***(Duncan et al., 1995a).***

Epilepsies and syndromes undetermined as to whether they are focal or generalized.

Neonatal seizures

The neonate is at particular risk for development of seizures, as the immature brain is especially susceptible to seizures due to enhanced excitation and diminished inhibition. So, metabolic, toxic, structural and infectious diseases are more likely to become manifested during this time than at any other period of life ***(Calciolari et al., 1980).***

Neonatal seizures differ from those of older children and adults because the GTCC tend not to occur during the 1st month of life. At least five seizure types are recognized in newborn infants. *Focal seizures* consist of rythmic twitching of muscle groups, particularly those of the extremities and face. *Multifocal clonic* convulsions involve many muscle groups simultaneously. *Tonic* seizures are characterized by rigid posturing of the extremities and trunk and sometimes associated with fixed deviation of the eyes. *Myoclonic* seizures are brief focal or generalized jerks of the extremities of body that tend to involve distal muscle groups. *Subtle* seizures consist of chewing motions, excessive salivation, alterations in the respiratory rate including apnea, blinking, nystagmus, bicycling or pedaling movements and changes in color (***Mizzahi and Kellaway, 1987***) .

Acquired Epileptic aphasia (Landau-Kleffner Syndrome) (LKS)

It is a childhood disorder in which an acquired aphasia, associated with focal EEG abnormality. It was first detected by Landau and Kleffner in 1957 . The incidence is unknown but it is an uncommon condition with a male preponderance 2:1 ***(Landau, 1992).***

It is characterized by loss of language skills in a previously normal child. At least 70% have an associated seizure disorder. Language regression may be sudden or the speech loss protracted. The aphasia may be primarily receptive or expressive, and auditory agnosia may be so severe. Hearing is normal, but behavioral problems are common. The seizures are of several types including focal or GTC, atypical absence and occasionally myoclonic (***Behrman et al., 2000***).

Special syndromes:

Febrile convulsions:

Febrile convulsions are an age-related disorder almost always characterized by generalized seizures occurring during an acute febrile illness. They occur in 2 – 5 % of the population, the attacks are usually benign ***(Hauser, 1981).***

They occur between 3 months and 5 years of age. They are not associated with intracranial infection or any other defined cause specifically related to the central nervous system. They are the most common seizure disorders during

childhood with a uniformly excellent prognosis ***(Fenichel, 1997).***

Clinically, there are 2 identified types; the typical simple febrile convulsions which usually occurring at core temperature ≥ 39 C in the form of GTCC, lasting <15 minutes, do not recur within 24 hours and do not exhibit neurological abnormalities. Atypical (complex) febrile convulsions which is less common and occur at body temperature < 38 C, they are focal, longer than 15 minutes and can recur within 24 hours ***(Knudsen, 1990).***

Most febrile convulsions are brief and uncomplicated, but some may be more prolonged and followed by transient or permanent neuralgic sequelae. Febrile convulsions tend to recur in about one-third of affected patients . The risk factors for the development of epilepsy as a complication of febrile seizures include a positive family history of epilepsy, initial febrile seizures prior to 9 months of age, a prolonged or atypical febrile seizures, delayed developmental milestones and an abnormal neurologic examination ***(Offringa et al., 1994).***

The relationship between febrile seizures and later epilepsy is frequently genetic. Recent clinical and molecular genetic studies suggest that there are a number of syndrome-specific genes for febrile seizures ***(Berkovic and Scheffer, 1998).*** The incidence for development of subsequent epilepsy is approximately 9 % when several risk factors are present compared with 1 % incidence in children without risk factors ***(Knudsen, 1988).***

Status Epilepticus (SE)

It is a medical emergency, defined as a continuous convulsion lasting longer than 30 minutes or the occurrence of serial convulsions between which there is no return of consciousness. Neuropathologic consequences of SE are mostly due to continuos excitation of neurons ***(Martinez, 1997).***

There are 3 major subtypes of status epilepticus in children: *prolonged febrile seizures; idiopathic status epilepticus* in which a seizure develops in the absence of an underlying CNS lesion or insult and *symptomatic status epilepticus*, when the seizure occurs as a result of an underlying neurologic disorder or a metabolic abnormality. Status epilepticus is classified into generalized type (tonic-clonic, absence), which is the most common, and partial seizures (simple, complex or with secondary generalization) ***(Lowenstein and Alldredge, 1998).***

SE is most common in children; the frequency of total occurrence is 50 per 100000 residents ***(Delorenzo et al., 1995).*** There is a strong effect of age on the frequency and etiology of SE as well as on the type of child who has SE. In young children, SE occurs primarily in children who are neurologically normal and with no history of unprovoked seizures. In older children, SE occurs primarily in those who are known to have prior unprovoked seizures and who are often also neurologically abnormal ***(Shinnar et al., 1997).***

The increased duration of status epilepticus leads to exhaustive firing of neurons with subsequent transitional neuronal damage, if it is >30 minutes as well as increased metabolic demands, hypoxia and hyperglycemia that occur during seizure. ***(Gospe et al., 1994)***

The mortality rate is 5% and mostly occurring in symptomatic cases, who have a serious life threatening CNS disorder, known before the onset of status epilepticus ***(Maytal et al., 1989).*** Neurological sequale secondary to SE were identified in 15% of cases, and subsequent epilepsy in 23% of cases. It was found that the cut-off point of SE duration for significant risk for permanent neurological sequale was 2 hours ***(Eriksson and Koivikko, 1997).***

Diagnosis of epilepsy

History-Taking

It includes the age of patient, the presence or absence of neurologic findings and constitutional symptoms (***Behrman et al., 2000***). Should attempt to define factors that may promote the convulsions and to provide a detailed description of the seizure and the child's postictal state ***(Camfield et al., 1993).***

Clinical Examination

Clinical examination of the child with a seizure disorder should be geared towards the search for organic causes ***(Haslam, 1996).***

Investigations:

Electroencephalography (EEG)

Because epilepsy is fundamentally a physiological disturbance of brain function, the EEG is the most important laboratory test in evaluating patients with seizures. The EEG helps to characterize specific epileptic syndromes as well as helping in management and prognosis ***(Pedley et al., 1995).***

EEG is showing epileptiform activity, confirms the clinical diagnosis of epilepsy but can not make it because 15% of normal subjects have abnormal EEG ***(Paul and Alan. 1991).***

Ictal EEG.

The EEG is invariably abnormal if recorded during the ictus; however, rarely in certain complex partial seizures, the surface EEG is normal but an abnormal pattern is seen if sphenoidal or depth electrodes are used. A normal ictal EEG is a strong evidence that the "seizure" is nonepileptic ***(Weisberg et al., 1996).***

Ambulatory EEG

A portable cassette recorder used to monitor the EEG continuously over prolonged periods. This allows detection of infrequent interictal localized discharges ***(Glick, 1993).***

Video EEG telemetry (MEG)

This provides long-term monitoring of the EEG and time-locked video of the patient in a dedicated recording room. It is the most definitive method for the diagnosis of paroxysmal attacks ***(Taylor, 1993).*** Video EEG monitoring has a high diagnostic rate in differentiating seizure versus nonseizure events (70%), in classifying seizure types (88%), and in evaluating the candidacy for epilepsy surgery (64%) ***(Chen et al., 1995).*** It is reserved for complicated cases of protracted and unresponsive seizures (***Behrman et al., 2000***).

Intracranial EEG recordings

Chronic subdural EEG monitoring by strips or grids of electrodes allow precise localization of seizure foci prior to surgery as well as motor and speech mapping of the cortex ***(Adelson et al., 1995).***

Neuroimaging

A. Structural Imaging:

Computed Tomography (CT) Scans

This is by far the best method for detecting cerebral lesions responsible for epilepsy and for determining their nature and exact location ***(Taylor, 1993).***

The strength of CT is its low cost, ready availability and its ease to use; it provides a relatively reliable imaging modality for physiologically unstable patients. The biggest

disadvantage is the amount of radiation to which the brain is exposed, especially when performing repeated scans as in the measurement of ventricular size with shunted hydrocephalus ***(Campell and Neil Mc Intosh, 1998).***

Magnetic Resonance Imaging (MRI)

MRI is the imaging procedure of choice in the investigation of children with epilepsy ***(Jackson, 1994).*** This technique has been developed to measure cerebral blood flow ***(Shulman et al., 1993).***

MRI is more successful than CT in the resolution of small lesions. They also provide superb presentation of gray matter, white matter and ventricular outline. Furthermore, it identifies accurately small abnormalities in the middle or posterior cranial fossae ***(Kuzniecky, 1996).*** MRI can detect epileptogenic focus demonstrated by EEG, and evaluates patient who had surgery for intractable epilepsy ***(Wagner, 1990).***

Structural imaging of the brain is regarded as being indicated in :

- Partial seizures (history and / or EEG).
- Fixed / progressive neurological deficit.
- Difficult control of seizures with antiepileptic drugs.
- Significant cerebral trauma.
- Generalized seizures with onset before 1 year

(Theodore, 1992)

B-Functional Imaging:

Single Photon Emission Computed Tomography (SPECT)

SPECT may be used to image the distribution of cerebral blood flow and specific receptors in the brain. The brain SPECT is sensitive in detecting and localizing hypoperfused areas that could be associated with epileptic foci even when computerized tomographic brain scanning (CT) ***(Abu-Hadeed, 1995)*** or MRI imaging is normal ***(Otsubo et al., 1995; Vattimo et al., 1996).***

Positron Emission Tomography (PET)

It is much more expensive and less widely available than SPECT, but is of superior resolution. PET can be used to map cerebral blood flow, regional glucose metabolism, and demonstrate the binding of specific ligands ***(Henry et al., 1993).*** It has been claimed to be most effective in the selection of infants with infantile spasms due to hypermetabolic brain area, usually parietooccipital ***(Chugani et al., 1990).***

Serum antiepileptic drug level

The major indication for assaying serum antiepileptic drug concentration is to check the compliance of patients and to determine whether symptoms or signs are likely or not to be drug-related adverse effects. It can also be used to monitor pharmacokinetic interactions to which antiepileptic medications are subject to, on the addition or withdrawal of another drug ***(Brodie, 1992; Patsolos and Duncan, 1994).***

The therapeutic range simply gives an indication of the concentrations at which the majority of patients have optimal seizure control ***(Gram, 1990 b).*** Up to one third of newly diagnosed epileptic patients are controlled with blood levels below the optimum range. Conversely the level at which toxic signs appear varies among patients. It is the patient who is being treated, not the blood level ***(Commission on Antiepileptic drugs of International League Against Epilepsy, 1993).***

Other investigations

A serum biochemical profile including assessments of glucose, renal function, liver enzymes and liver function, and calcium metabolism is appropriate at the initial stage. Further investigations of systemic metabolic or biochemical disturbances may be indicated if there is evidence of abnormalities on screening tests or clinical evaluation ***(Meldrum, 1998; Aicardi, 1992).***

Neuropsychologic evaluation

A minority of patients with epilepsy, particularly those with poorly controlled seizures, are at risk of disorders of cognitive function. The possible effect of antiepileptic medications should be taken into consideration ***(Thompson, 1991).***

Differential Diagnosis Of Epilepsy

Nonepileptic Paroxysmal Disorders

Several conditions share common features with epilepsy. Because these disorders may be associated with altered levels of consciousness, tonic or clonic movements, or cyanosis, they are often confused with epilepsy. Conditions that mimic epilepsy are refractory to antiepileptic drugs. The treatment of these children differs significantly from those with epilepsy. Pseudoseizures occur typically between 10-18 years and are more frequent in females. The diagnosis of pseudoseizure should be made only after a thorough history and physical examination and exclusion of "true" seizures by prolonged EEG recording when indicated (***Behrman et al., 2000***). After a true epileptic seizure, there is a significant increase in serum prolactin, whereas there is no change from the base line at the termination of a pseudoseizure ***(Pritchard et al., 1985).***

Table (5): Shows symptoms of nonepileptic paroxysmal disorders

Unusual movements • Jitteriness • Masturbation • Shuddering • Benign sleep myoclonus • Startle responses • Paroxysmal torticolis • Self-stimulation • Tics (Tourette's syndrome) • Paroxysmal choreoathetosis or dystonia • Pseudoseizures • Eye movement • Head nodding	**Episodic features of specific Disorders** • Tetralogy spells • Hydrocephalic spells • Cardiac arrythmias • Hypoglycemia • Hypocalcemia • Periodic paralysis • Hperthyroidism • Gastroesophageal reflux • Rumination • Drug poisoning • Cerebrovascular events
Loss of tone or consciousness • Syncope • Drop attacks • Narcolepsy / cataplexy • Attention deficit • Acute hemiplegia	**Behavior disorders** • Head banging • Night terrors • Sleepwalking • Nightmares • Rage • Confusion • Fear
Respiratory derangements • Apnea • Breath holding • Hyperventilation	**Acute psychotic symptoms** • Fugue • Phobia • Panic attacks • Hallucinations • Autism
Perceptual disturbances • Dizziness • Vertigo • Headache • Abdominal pain	**Munchausen by proxy**

(Prensky, 1992)

Medical Treatment Of Epilepsy

The decision to treat seizures with antiepileptic drugs should not be taken lightly. Drugs are given to decrease the risk of seizure recurrence and are adjusted only when these risks outweigh the risks; medical and psychological, of medications *(Chadwick, 1993).*

Medical treatment strategies

The goal of anticonvulsant therapy is to achieve the maximum normal function by balancing seizure control against drug toxicity. Studies have indicated that monotherapy is associated with optimal seizure control in 80% of patients. Polytherapy poses several problems: (1) drugs compete with each other for protein binding sites, (2) one drug can increase the rate and pathway of catabolism of a second drug, (3) drugs have cumulative toxicity, and (4) compliance is more difficult *(Fenichel, 1997).*

Principles of antiepileptic drug therapy

1. The decision for prescribing anticonvulsant therapy could be determined according to the following criteria proposed by ***Elwan (1991):***

- Firm diagnosis of epilepsy.
- Definite identification of the type of epilepsy.
- Preparing the patient for regular compliance with therapy.
- No place for trial therapy in doubtful cases.

2. To start anticonvulsant therapy, **Elwan** ***(1991)*** recommended the following:

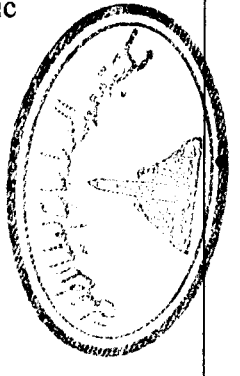
- To start with monotherapy as it has the advantage of being highly effective with minimal side effects, better compliance and less cost.
- To use one of the first line AEDs with simplified dosage regimen.
- To start drug treatment with a small dose and build up over a period of weeks.
- To increase dosage gradually to maximum maintenance dose, or achieving complete seizure control without toxic effects.

3. Substitution of anticonvulsant drugs: if there is poor control with maximum tolerated dose of the first-line anticonvulsant drug and/or poor tolerability. If control is not achieved with a 2nd first -line anticonvulsant drug, the use of two anticonvulsant drugs is recommended with close monitoring of the plasma levels of the both drugs ***(Elwan,1991).*** If a combination of two first-line agents is not helpful, replace the least beneficial drug by one of the second-line drugs. Similarly an unhelpful 2nd line agent, should not be continued ***(Appleton, 1995).***

4. Discontinuing therapy : weaning of AEDs in preschool children is after 2 years of being seizure free, where as in older children, after 3 years of being seizure free ***(Laurance and Bennett, 1992).*** The decision to stop therapy should be individualized to the child and cause of epilepsy ***(Shinnar et al., 1994).***

Table (6): Selection of an anticonvulsant drug. Antiepileptic drugs for different seizure types. ***(Duncan et al., 1995b)***

	First choice drugs	Second choice drugs
Partial seizures *(simple partial / complex partial / secondarily generalized)*	• Carbamazepine • Valproate	• Vigabatrin • Phenytoin • Lamotrigine • Clobazam • Gabapentin • Acetazolamide • Phenobarbitone • Felbamate
Generalized seizures		
Tonic-clonic / clonic	• Valproate • Carbamazepine	• Phenytoin • Lamotrigine • Clobazam • Vigabatrin • Acetazolamide
Absence	• Ethosuximide • Valproate	• Acetazolamide
Atypical absences / Atonic / tonic	• Valproate	• Lamotrigine • Acetazolamide • Clonazepam • Clobazepam
Myoclonic	Valproate	• Phenobarbitone • Acetazolamide • Clonazepam
Infantile Spasms	• ACTH	• Vigabatrin • Felbamate • Clonazepam



Carbamazepine (Tegretol) (CBZ)

Action:

Carbamazepine is structurally related to the tricyclic antidepressant "impiramine" ***(Dobson, 1989).*** It acts by stabilization of pre and post - synaptic neuronal membranes by blocking sodium-dependent channels and by decreasing depolarization-dependent calcium uptake ***(Duncan et al., 1995).***

Indication:

Carbamazepine is the drug of choice in tonic - clonic and partial seizures. Atypical absence and myoclonic seizures may be exacerbated to the point of status ***(Callahan and Noetzel, 1992).***

Administration:

Absorption from the gastrointestinal tract is slow and variable. The rectal route may be used for maintenance if the dose is increased by one third. Approximately 85% of the drug is protein bound. Carbamazepine induces its own metabolism, and the initial dose should be 25% of the maintenance dose to prevent toxicity. The usual maintenance dose is 15-20 mg/kg /day to provide a blood concentration of 4 to 12 ug/ml. However, 30 mg/kg is often required in infants. Half-life at

steady state is 5-27 hours and children usually require doses 3 times a day *(Fenichel, 1997).*

Adverse effects:

Acute; common predictable dose-related symptoms include blurring of vision, diplopia, sedation, nausea, ataxia and headache are seen in the first days and weeks after initiation of therapy and largely avoided by slow drug introduction *(Brodie, 1992).*

Idiosyncratic; about 5% of patients develop a skin rash which may be serious, resulting in exfoliative dermatitis or Stevens-Johnson syndrome. Aplastic anemia is an idiosync ratic reaction observed in some patients *(Brodie, 1992).*

Chronic; a depression of peripheral leucococytes is expected, but rarely sufficient to warrant discontinuation of therapy. It is reasonable to measure the white blood cell count 6 weeks after therapy is started *(Fenichel, 1997).* Osteomalacia caused by induction of microsomal enzymes including hepatic cytochrome p-450 system that convert vitamin D and its major active metabolites to biologically inactive forms *(Winnacker et al., 1977).*

Valproic Acid (Depakene) (VPA)

Action:

Valproic acid is a broad spectrum anticonvulsant. It acts by blocking voltage-dependent sodium channels and increases calcium-dependent potassium conductance (***Behrman et al., 2000***).

Indication:

It is the drug of choice for treatment of the typical absence, myoclonic seizures and generalized tonic-clonic seizures. Valproate is especially useful for mixed seizure disorders ***(Fenichel, 1997)***

VPA also used in all other seizure types, with effectiveness in reducing risk of recurrence of febrile convulsions, although the place of regular prophylactic therapy is very limited ***(Duncan et al., 1995b).***

Administration:

Oral absorption is rapid, and half-life is 6 -15 hours. Doses 3 times a day are needed to achieve constant blood concentration. An enteric coated capsule (Depakote) slows absorption and allows twice - a - day in many children ***(Fenichel, 1997).***

The initial dosage is 20 mg/ kg / day. Increments of 10 mg/ kg/ day are administered to provide a blood concentration of 50 to 100 ug/ml ***(Fenichel, 1997).***

The usual maintenance dose is 600 - 3000 mg/ day ***(Chokroverty1996).*** Valproate can be taken rectally with peak concentration after 3 hours and the serum concentration is approximately 75% of the oral dose ***(Fenichel, 1997***).

Adverse effects:

Valproate has dose-related and idiosyncratic hepatotoxicity. Dose related hepatotoxicity is harmless and characterized by increased serum concentrations of transaminases. Important dose-related effects are a reduction in the platlet count, pancreatitis and hyperammonemia. These adverse reactions are reversible when the daily dose is reduced ***(Fenichel, 1997).***

The mojor idiosyncratic reaction is fatal liver necrosis attributed to the production of an aberrant and toxic metabolite. The major risk (1:800) in children younger than 2 years of age receiving polytherapy. Many such cases may be caused by an underlying disorder that causes both hepatic and cerebral degeneration. Fatal hepatotoxicty has not been reported in children over 10 years of age treated with valproate alone ***(Fenichel, 1997).***

Valproic acid may cause a decrease in serum-free carnitine levels by inhibition of plasmalemmal carnitine uptake. Some studies suggest that carnitine deficiency is a major cause of valproate hepatotoxicity and that

supplementation with L-carnitine, 50-100 mg/kg/24 hours, may prevent this fatal complication (***Behrman et al., 2000***).

It was reported that VPA monotherapy in children reduces bone mineral density at the lumbar spine and femoral neck (***Sheth et al., 1995; Gillis, 1996***).

Phenytion (Dilantin) (PHT)

Action:

PHT is believed to have an inhibitory effect on calcium mediated neurotransmitter release ***(Fritz and Dreifuss, 1994).***

Indication:

Tonic - clonic seizures and partial seizures. It can be administered intravenously and is essential in the treatment of status epilepticus and neonatal seizures ***(Bourgeois, 1995).***

Administration:

Oral absorption is not reliable until 3 to 5 years of age. Once absorbed, phenytoin is 70% to 95% protein bound. A typical maintenance dosage is 5 mg/ kg/ day in children, the half-life is up to 5 -14 hours. Capsules are usually taken in two divided doses, but tablets are more rapidly absorbed and may require 3 divided doses a day ***(Fenichel, 1997).***

Rapid loading of phenytoin can be performed by giving three times the maintenance dosage by either the oral or intravenous route. Intramuscular injections are not absorbed and should not be used ***(Fenichel, 1997).***

Adverse effects:

The major adverse reactions are hypersensitivity, gum hypertrophy and hirsuitism. Hypersensitivity reactions usually occur within 6 weeks of the initiation of therapy and are characterized by rash, fever and lymphadenopathy. Gum hypertrophy is caused by a combination of phenytoin metabolites and plaque on the teeth. The importance of good oral hygeine should be discussed at the onset of the therapy. Hirsuitism is rarely a problem, when it occurs, the drug can be discontinued without permanent harm ***(Fenichel, 1997).***

Memory impairment, decreased attention span, and personality changes may occur at therapeutic concentrations ***(Fenichel, 1997).***

Phenobarbitone (PB)

Action:

Barbiturates depress Ca^{++} dependent action potentials and reduce the Ca^{++} - dependent release neurotransmitters *(Fritz and Dreifuss, 1994).*

Indication:

Phenobarbitone is the oldest and cheapest AEDs in regular clinical use. It is used in tonic - clonic and simple partial seizures *(Fenichel, 1997).*

Administration:

Oral absorption is slow and is better given with the evening meal. Initial and maintenance dosages are 3 to 5 mg / kg / day. The half - life is 37 - 73 hours in children because of the very long half - life, once - a - day doses are usually satisfactory, and steady - state blood concentrations should be measured after 2 weeks of therapy. Therapeutic blood concentrations are 10 to 40 ug / ml. *(Fenichel, 1997).*

Adverse effects:

Hyperactivity is the most common and limiting side effect in children. Adverse behavioral changes occur in half of

children between ages 2 and 10. Idiosyncratic reactions are unusual *(Fenichel, 1997).*

Ethosuximide (Zarontin) (ESM)

Action:

It inhibits the low threshold calcium currents in the thalamus, and reduces excitatory transmitter release *(Sherwin, 1995).*

Indication:

Treatment of absence; also useful for myoclonic absence and atonic seizures *(Duncan et al., 1995b).*

Administration:

The drug is absorbed rapidly and peak blood concentrations appear within 4 hours. It is not bound to plasma proteins. The half- life is 30 hours in children and a blood concentration above 40 ug/ml. The initial dosage is 20 mg/kg /day in three divided doses after meals to avoid gastric irritation. *(Fenichel, 1997).*

Adverse effects:

Common toxic reactions include nausea, abdominal pain, headache and sedation. Aplastic anemia is a rare complication. Idiosyncratic reactions include dystonia and a lupus-like syndrome *(Fenichel, 1997).*

Primidone (Mysoline)

Action:

Primidone is a barbiturate that is largely metabolized to phenobarbital, and its effects are very similar to those of phenobarbital *(Schmidt and Shorvon, 1996).*

Indication:

Generalized tonic- clonic and partial seizures *(Fenichel, 1997).*

Administration:

Primidone is metabolized in the liver to at least two active metabolites; phenobarbital and phenyl - ethyl – malonamide (PEMA). Primidone half life is 6-12 hours and PEMA half life is 20 hours. The usual maintenance dosage is 10 to 15 mg/kg / day, but initial dosage should be 25% of maintenance or intolerable sedation occurs. A therapeutic blood concentration of primidone is 8-12 ug / ml. *(Fenichel, 1997).*

Adverse effects:

The same adverse effects as for phenobarbital, except that the risk of intolerable sedation from the first tablet is great *(Fenichel, 1997).*

Acetazolamide

Action:

Acetazolamide inhibits carbonic anhydrase in glia and myelin resulting in accumulation of Co_2 in the brain ***(Resor et al., 1995).***

Indication:

It has a marked effect against partial, secondary generalized, tonic-clonic, absence and myoclonic seizures when used as adjuvant to a first-line drug ***(Resor and Resor, 1995).***

Administration:

It is rapidly absorbed from the gastrointestinal tract. Its half life is about 12 hours ***(Resor and Resor, 1990).*** Oral dose is 3.8-22 mg/kg/day ***(Eadie, 1992).***

Adverse effects:

While acetazolamide is generally well tolerated, tingling in exterimities, sedation, alteration of taste and nausea may occur. Allergic skin rash occur rarely ***(Resor et al., 1995).***

Clonazepam (Rivotril)

Action:

It is potent agonist at a-subunit of GABA receptor complex *(Duncan et al., 1995 b).*

Indication:

As a 2nd line anticonvulsant for myoclonic, absence and partial seizures. Tolerance often develops in children with severe myoclonic epilepsy; such as those with infantile spasms and the Lennox-Gastaut syndrome *(Fenichel, 1997).*

Administration:

The initial dosage is 0.025 mg/kg/day in two divided doses. Increments of 0.025 mg/kg are recommended every 3 to 5 days as needed and tolerated. The usual maintenance dosage is 0.1 mg/kg/day in three divided doses. The therapeutic blood concentrations are 20 to 25 ug/L and the half life is 20 to 40 hours *(Fenichel, 1997).*

Adverse effects:

Toxic effects with doses within the therapeutic range include sedation, cognitive impairment, hyperactivity and excessive salivation. Idiosyncratic reactions are unusual *(Fenichel, 1997).*

Table (7) : Antiepileptic drugs (in alphabetical order). [Collected from data in the mentioned references]

Mode of action	Indications	Oral dose	Therapeutic Serum level	Adverse effects
Acetazolamide Inhibits carbonic anhydrase enzyme in glia and myelin → Co2 accumulation in the brain *(Resor et al.,1995)*	*Partial, *Partial with secondary generalization, *Tonic-clonic, *Absence, *Myoclonic seizures (as adjuvant to first line drugs) *(Resor and Resoe, 1990)*	3.8~22.0 mg/kg/24 hr. *(Eadie, 1992)*	1~22 ug /ml *(Eadie, 1992)*	*Tingling in extremities *Sedation *Nausea *Allergic skin rashes *(Resor et al., 1995)*
Carbamazepine *Blockage of Na+ channels *Blockage of NMDA-receptor activated Na+ and Ca++ flux *(Duncan et al., 1995b)*	*Tonic-clonic, *Partial, *Secondarily generalized seizures *(Verity et al., 1995; Mattson et al., 1992)*	10 mg/kg/day to be increased to 30 mg/kg/day *(Bannister, 1992)*	4-7 ug/ml *(Eadie,1992)*	***Acute*** Blurring of vision, diplopia and sedation. ***Idiosynchratic*** Skin rash, hepatic failure, bone marrow depression *(Duncan et al., 1995b)* ***Chronic*** *Less severe cognitive adverse effects, compared to barbiturates and phenytoin *(Duncan et al., 1995b)*
Clonazepam (Rivotril) Potent agonist at a-subunit of GABA receptor complex *(Duncan et al., 1995b).*	As a 2nd line drug for : *Myoclonic *Atonic *Absence *Lennox –Gastaut *(Sato and Malow, 1995).*	0.1 mg/kg/day to be increased to 0.2 mg/kg/day *(Weisberg et al., 1996)*	25~75 ug/L *(Eadie, 1992).*	*Depression *Irritability *Behavioral abnormalities *Excessive salivation *(Duncan et al., 1995).*

Ethosuximide *(Zarontin)* Inhibits low threshold Ca++ current in the thalamus. Enhancement of non GABA mediated inhibition. *(Shorvon, 1995)*	Drug of choice in absence seizures *(Duncan et al., 1995b)*	10~25 mg/kg/day *(Bannister, 1992).*	40~100 ug/ml *(Eadie, 1992).*	*Acute* Nausea, abdominal discomfort, sedation, headache, ataxia *Chronic* Liver dysfunction *Idiosynchratic* Allergic skin rash *(Shorvon,1995).*
Phenobarbitone (Somnileta) Enhancement of GABA mediated inhibition *(Eadie, 1992)*	*Tonic-clonic *Partial *Status epilepticus seizures (In developed countries, it is a 2nd line because of its adverse effects) *(Painter and Gaus, 1995)*	3 mg/kg/day to be increased to 6mg/kg/day *(Pedley et al., 1995)*	15~40 ug/ml *(Panegyres, 1992)*	*Acute* *Sedation *Giddiness *Stevens - Johnson syndrome *Chronic* *Cognitive impairment *Poor memory *Depression *Conduct disorder *Idiosyncratic* *Allergic skin rash *Hepatotoxicity *(Haslam, 1996)*
Phenytoin (Epanutin) Stabilization of neuronal membrane by inhibition of Na+ channels *(Meldrum, 1996)*	2nd line for: *Partial *Tonic-clonic *Tonic *Atonic *Clonic *(Duncan et al., 1995b)*	5mg/kg/day *(Weisberg et al., 1996)*	10~20 ug/ml *(Weisberg et al., 1996)*	*Acute* *Ataxia *Abnormal movement disorder *Chronic* *Gingival hypertrophy *Hirsuitism *Folate deficiency

				*Cerebellar atrophy ***Idiosyncratic*** *Skin rash *Swelling of lymph nodes *Rarely hepatitis (***Eadie, 1992***)
Primidone (Mysoline) Acts via the primary metabolite phenobarbitone ***(Johannessen et al., 1990)***	As phenobarbitone ***(Duncan, 1990)***	6-12 mg/kg/day ***(Pedley et al, 1995)***	5-15 ugol/ml ***(Johannessen et al., 1990)***	As phenobarbitone ***(Duncan et al., 1995b)***
Sodium valproate (Depakine) Elevation of GABA concentration through inhibiting GABA transaminase and succinic semialdehyde dehydrogenase ***(Bannister, 1992)***	First line drug for: Tonic-clonic Myoclonic Absence Partial ***(Dam,1990; Eadie, 1992; Heller et al., 1995; Verity et al., 1995)***	10 mg/kg/day to be increased to 30-40 mg/kg/day ***(Haslam, 1996)***	50 - 100 ug/ml ***(Eadie, 1992)***	***Acute*** *Anorexia, nausea, vomiting *Dose related thrombocytopenia and tremors ***(Haslam, 1996)*** ***Idiosyncratic*** Severe hepatic reaction and fatal hepatic Failure ***(Dreifuss et al., 1989)*** *Encephalopathy which may be associated with low carnitine ***(Coulter,1991)*** ***Chronic*** Ataxia and weight gain ***(Haslam,1996)***

Novel Antiepileptic Drugs

This is a rapidly changing field with new agents emerging and being withdrawn ***(Patsalos and Duncan, 1994).***

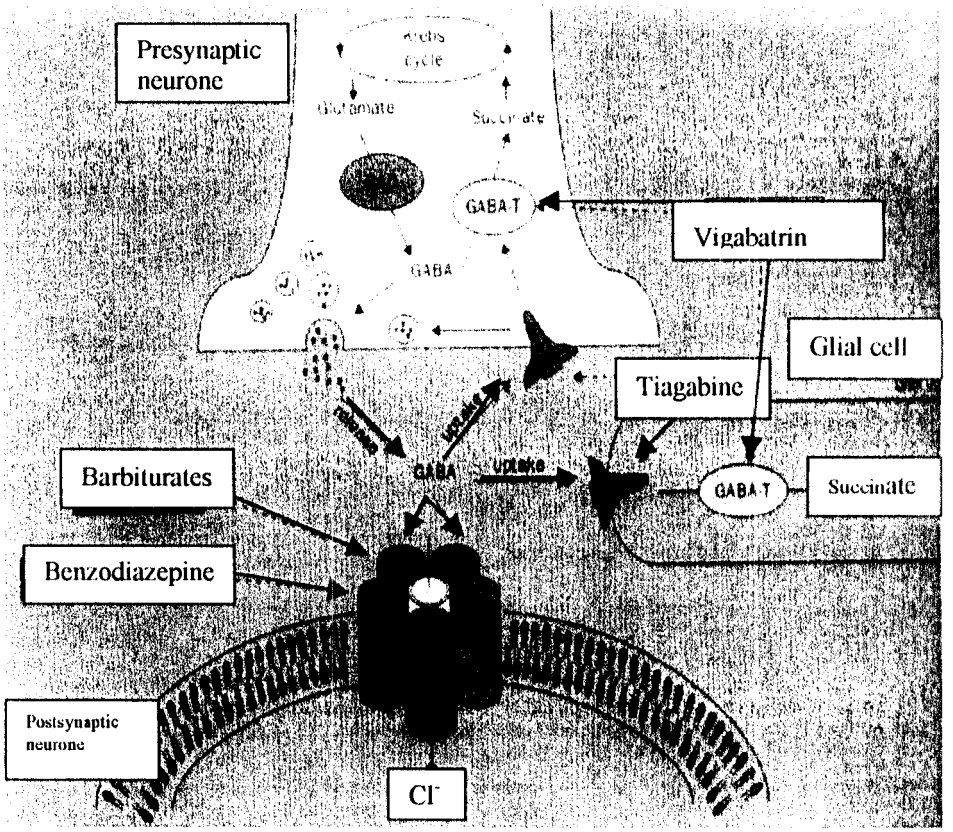


Fig (4) : Pharmacological effects of antiepileptic drugs at $GABA_A$ receptor ***(Leach and Brodie.,1998).***
GABA-T = GABA transaminase .
Vigabatrin irreversibly binds to GABA-T to inhibit degradation of inhibitory neurotransmitter GABA . Tiagabine blocks uptake of synaptically released GABA into both presynaptic neurons and glial cells, allowing GABA to remain at site of action for longer periods.

Table (8) : Recent anti-epileptic drugs
(Collected from data in the mentioned references)

Trade name	Mode of action	Indications (seizure type)	Oral dose	Sid effects	
				Dose related	Allergic
Vigabatrin (VGB) **(Sabril)**	Specific irreversible inhibitor of GABA transaminase ***(Ring and Reynolds, 1992).***	*Infantile spasms *Adjunctive therapy for refractory partial seizures ***(Curatolo, 1994).***	Starting dose 30 mg/kg /day increased to 100 mg/kg/day ***(Arteaga et al., 1992)***	Somnolence , fatigue , irritability, headache , weight gain , enceohalopathy , depression, psychotic episodes , manic affective disorder ***(Gillham et al .,1993).***	Rash ***(Gilham et al., 1993).***
Lamotrigine (LTG) **(Lamital)**	Decreases voltage dependent Na channels and depresses release of excitatory amino acid aspartate and glutamate ***(Loscher and Schmidt , 1994; and Buchanan , 1993).***	Adjunctive and single-drug therapy for refractory and newly diagnosed partial and generalized seizure ***(Richens, 1993)***	2 mg/kg/day increasing to maintenance dosage of 5-15 mg/kg/day . In children taking VPA , the starting dose should be 0.5 mg/kg/day ***(Kalviainen et al., 1993)***	Dizziness , headache, ataxia , nausea , diplopia , vomiting , asthenia , depression , somnolence , insomnia , hyperkinesia , leukopenia ***(Richens, 1993).***	Rash. Stevens – Johnson syndrome ***(Richens , 1993).***
Gabapentin (GBP) **(Neurontin)**	Alteration in the concentration of brain amino acid glutamate. It is also a weak inhibitor of GABA transaminase ***(MacDonald and Kelly , 1994).***	Adjunctive therapy for refractory partial seizures ***(Chadwick , 1994).***	Dosage for children less than 12 years beginning with 300 mg/24 hr. Then increased by 300 mg/every 3-5 days to total dose of 900-1200 mg/day ***(Ramsay , 1994).***	Somnlence , dizziness , ataxia , fatigue , nystagmus , headache , tremor , diplopia , nausea , vomiting , rhinitis , weight gain , tantrums , aggression , hyperactivity ***(Chadwick , 1994).***	Rash ***(Chadwick , 1994).***
Oxcarbazepine (OCBZ) **(Trileptol)**	Stabilization of pre-and post synaptic neuronal membrane by blockade of Na ***channels (Grant and Faulds , 1992 ; and Dam ., 1994).***	Adjunctive drug for refractory partial seizures , single drug therapy for newly diagnosed partial seizure ***(Dam, 1994).***	Starting dose 10 mg/kg/day , and maintenance dosage in children between 5-10 years is 450 mg/day and750 mg/day for children aged 11-15 years ***(Dam , 1994).***	Drowisiness , dizziness , headache, diplopia , ataxia , nystagmus , nausea , vomiting , diarrhea , poor appetite , Parkinson –like syndrome , hyponatremia ***(Frils et al ., 1993) .***	Rash ***(Frils et al , 1993).***

Table (8) : Recent anti-epileptic drugs (cont)

Trade name	Mode of action	Indications (seizure type)	Oral dose	Sid effects	
				Dose related	Allergic
Felbamate (FBM)	Increases seizure threshold and prevent seizure spread *(Rho et al., 1994)*	Adjunctive therapy for refractory partial seizure and refractory Lennox –Gastaut syndrome *(Ditcher , 1995).*	15-45 mg/kg in 2-3 divided doses *(Rho et al., 1994) .*	Nausea, dizziness , vomiting , insomnia , weight loss , diplopia , headache , somnolence *(Rho et al., 1994).*	*Hypersensitivity Syndromes *Stevens –Johnson Syndrome *Hepatic failure *Aplastic anemia *(Rho et al., 1994)*
Zonisamide (ZNS)	Suppresses the epileptic focus activity and blocks sustained firing of action potential *(Wyllie, 1997).*	*Adjunctive therapy for refractory partial and myoclonic seizures *(Richens and Percucca , 1993).* *It is effective as monotherapy *(Wyllie, 1997)*	2-3 mg/kg in two divided doses increased to 6-8 mg/kg *(Schmidt et al., 1993).*	Drowsiness , ataxia , loss of appetite , slowing of mental activity and speech , headache , weight loss , leukopenia , abnormal liver function test , renal calculi, parasthesia , psychotic episodes *(Ditcher , 1995) .*	Rash , Stevens – Johnson syndrome *(Ditcher , 1995).*
Tiagabine (TGB)	Potent and specific GABA inhibitors *(Suzdak and Jenesen , 1995).*	*Adjunctive therapy for complex partial seizures and secondary generalized seizures *(Patsalos and Duncan , 1994).*	3-6 mg/kg , in two divided doses (*Mengel, 1994)*	Headache , dizziness , somnolence, difficult concentration *(Mengel , 1994).*	Rash *(Mengel , 1994).*
Racemide	A blocker of NMDA receptors *(Wyllie, 1997)*	Rrefractory partial or 2ry generalized seizures *(Wyllie, 1997)*		Lightheadedness, GI upset, somnolence, diplopia *(Wyllie, 1997).*	
Stiripenol	Inhibits GABA uptake and GABA transaminase *(Wyllie, 1997)*	The main therapeutic niche in refractory absence epilepsy *(Wyllie, 1997)*		Only fatigue and GI distress *(Wyllie, 1997)*	
Toprimate (TOP)	Affects the voltage dependent Na channels in neuronal membrane . Also , affects glutaminergic and GABA-ergic transmission *(Reife , 1996).*	Adjunctive therapy for partially and secondarily generalized seizures *(Reife , 1996).*	Starting dose .1-2 mg/kg in 2 divided doses , increased to 8-10 mg/kg *(Reife , 1996)*	Dizziness , nystagmus , ataxia , headache , sedation , paresthesia , asthenia , confusion , agitation , loss of weight , nausea , diarrhea , abdominal pain *(Reife , 1996)*	Renal calculi *(Reife , 1996).*

(Table 9) : Possible roles for new AEDs ***(Walker and Duncan, 1994)***

Drug	Partial seizures	Generalized seizures			Infantile spasms
	Simple partial, complex partial, secondary generalized	Tonic-clonic, tonic, clonic	Absences	Atypical absences	
Vigabatrin	+	+			
Lamotrigine	+	+	+	+	+
Gabapentin	+				
Zonisamide	+	+	+	+	
Felbamate	+	+		+	+

Indications of Multiple Drug Therapy

It is indicated when the patient has multiple seizure types (e.g., seizures of different pathophysiologic types), for the treatment of status epilepticus and when adequate monotherapy fails ***(Chokroverty, 1996).***

Intractable epilepsy

Intractable epilepsy is defined as seizures that have not been completely controlled with AEDs one year from the onset despite accurate diagnosis and careful monitoring treatment ***(Leppik, 1992).***

Approximately 20-30% of all epileptic patients have been estimated to be refractory to routine therapeutic measures even when AEDs are used in adequate dosage and plasma levels are monitored ***(Hauser, 1992).***

It is associated with structural lesions of the brain e.g., hypoxic-ischemic cerebral insults, congenital brain abnormalities and arterio-venous malformations ***(Nakken and Lossius, 1993).*** The mechanism responsible for drug resistance is the amplification and over expression of the multi drug-resistance genes (MDR) ***(Ambudkar et al., 1992).*** It is thought to act as an ATP dependent effusion pump that decreases intracellular accumulation of drugs and increases resistance to their effects ***(Abraham et al., 1993).***

In Egypt, ***Skoukry et al (1998)*** provided useful observation on the role of microcephaly, severe epileptiform EEG abnormalities and severe epileptic syndromes e.g., severe myoclonic epilepsy in infancy, early Lennox-Gastaut syndrome and early infantile epileptic encephalopathy, as significant independent predictors of intractability.

Epilepsy Surgery

The aim of surgical therapy is to stop or reduce the occurrence of seizures without causing or increasing neurological deficits ***(Loyning, 1990).*** Approximately 10-15% of patients with chronic medically refractory epilepsy may be potential surgery candidates ***(Ward, 1983).***

The surgical operations can be divided into two groups, those operations that depend upon resection of a known local pathology (lesional surgery), and those procedures which aim to alter brain function (functional operations) ***(Binne and polkely, 1992).***

Available surgical procedures include temporal lobectomy for refractory partial complex seizures, hemispherectomy for refractory unilateral seizures with hemiparesis and corpus callosotomy for atonic and secondarily generalized seizures that are refractory to medical treatment ***(Chokroverty, 1996).***

Ketogenic Diet or Medium-Chain Triglycerides (MCT) Diet in Treatment of Epilepsy.

It was first advocated for the treatment of seizures by ***Wilder (1921).*** This treatment should be considered for the management of recalcitrant seizures, particularly for children with complex myoclonic epilepsy with associated tonic-clonic convulsions. The diet restricts the quantity of carbohydrate and protein, and most calories are provided as fat. Some children older than 2-3 years will not tolerate this fatty, unpalatable diet. Although the mechanism of action of the ketogenic diet is unknown, some evidence shows that it exerts an anticonvulsant effect secondary to elevated levels of B-hydroxybutyrate and acetoacetate resulting from the ketosis. The use of valproic acid is contraindicated in association with the ketogenic diet, because the risk of hepatotoxicity is enhanced ***(Behrman et al., 2000).***

Last ditch agents in treatment of epilepsy:

Vagus Nerve stimulation (VNS)

High frequency VNS reduces the mean seizure frequency by 31% ; and low frequency VNS by 13%. The side effects are minimal and may be relieved by altering the stimulation ***(Terry et al., 1990).*** The neurologic mechanism underlying the use of an implanted vagal stimulator still lags behind its clinical efficiency. The current hypotheses relate to brain desynchronization of neuronal discharges, increase in seizure threshold, stimulation of inhibitory pathways and release of inhibitory neurotransmitters ***(Uthman et al., 1990)***

Calcium channel blockers (CCBs)

The movement of calcium into neurons may be the common denominator for the triggering and propagation of seizure activity. Researches proved that CCBs with high central nervous system affinity have anticonvulsant activity and have been investigated as putative AEDs ***(Myer et al., 1990).***

Biofeedback

Some patients are able to modulate cortical electrical activity with an associated decrease in seizure frequency. Teaching these methods of self control may increase morale, not only by reducing seizures but also by providing patients

with a sense of control of their epilepsy ***(Rockstroh et al., 1993).***

Intravenous immunoglobulin therapy

A beneficial effect of high doses of intravenous gamma globulins has been demonstrated in some children with intractable epilepsy and may be considered as a safe add-on medication in various types of idiopathic and symptomatic intractable epilepsy ***(Van Engelen, 1994).***

Prognosis of Epilepsy

It is defined as " the prospect of attaining terminal remission once an individual has established a pattern of recurrent epileptic seizures". It is found that 70-80% of people developing epilepsy will achieve this remission in the first 5 years ***(Sander, 1993).***

Morbidity of epilepsy

Individual factors that indicate a high chance of remission are absence of neurological abnormalities or brain lesions, normal intelligence, onset of seizures after the age of 3-4 years, low seizure frequency, brief duration of epilepsy prior to control , generalized tonic-clonic seizures, typical absence seizures or simple partial seizures, no episodes of status, normal EEG background and normalization of EEG after onset of therapy ***(Aicardi, 1994).***

Mortality of epilepsy

There is an excess mortality for epileptic children. This has been estimated as 5 % during the first 10 years after onset of seizures with a further risk over the next 10 years. The sudden unexpected death syndrome is now well recognized in epileptics and is postulated to be due to a cardiac dysrhythmia complicating the fit ***(Campbell and McIntosh., 1998).***

"Seizure-related deaths" is a tem used when the patient dies during or shortly after a seizure, with no evidence of status epilepticus and after autposy, no explanation is found. The hypothesis is that it is due to central apnea possibly consequent to endogenous opioid release ***(Nashef et al., 1995).*** This phenomenon was responsible for 12% of total deaths among children with epilepsy ***(Harvey et al., 1993).***

BONE METABOLISM

Bone Structure

Bone is a dynamic, highly vascular, living tissue, with continuous modelling and remodelling by bone cells which allows the skeleton to grow and adapt itself to prevailing mechanical needs ***(Cunningham et al., 1990).*** Since bone growth and turnover rates are high during childhood, many clinical features of metabolic bone diseases are more prominent in children than in adults ***(Chesney, 1990).*** Microscopically bone is composed of cellular component and non cellular component.

A: Cellular elements

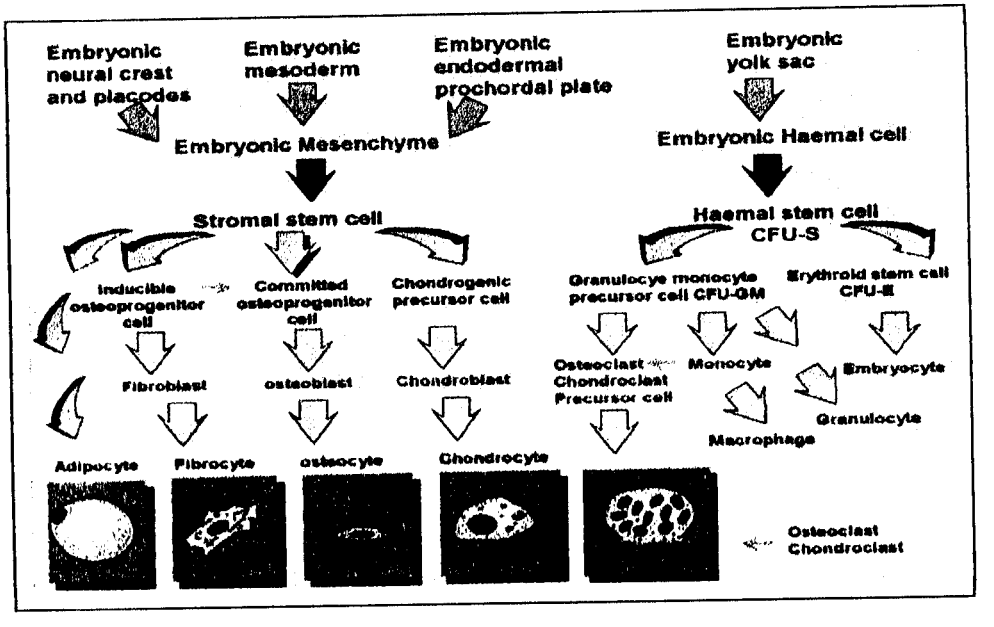


Fig (5) : Origins and fates of the cells of mature bone. ***(Gray, 1989).***

Types of Bone Cells

(1) Osteoprogenitor cells

Origin: Undifferentiated stromal cells of mesenchymal origin ***(Cunningham et al, 1990).***

Types & sites: There are 2 types of osteoprogenitor cells
1.**Committed osteoprogenitors**: which are found associated with bone and totally committed to bone formation.
2.**Inducible osteoprogenitors**: which are widely present in connective tissue and probably able to differentiate into various connective tissue cells depending on the nature of the inducer ***(Friedenstein, 1976).***

Function: They have the capacity to proliferate and differentiate into osteoblasts ***(Owen, 1970).***

(2)Osteoblasts

Origin : They arise from osteoprogenitor cells ***(Gray, 1989).***

Site : They are found lining the periosteal , endosteal or trabecular surface at which bone formation takes place ***(Stephen, 1992).***

Function : These bone-forming cells are responsible for the synthesis, deposition and mineralization of the bone matrix ***(Cunningham et al., 1990).*** They are concerned with synthesis of protein-polysaccharide, growth factor, osteocalcin and osteonectin. Also they may play an important role in hormonal regulation of bone resorption, since they bear receptors for

parathyroid hormone (PTH) and other stimulants of bone erosion ***(Martin et al., 1988).***

(3) Osteocytes

Origin : They are derived from osteoblasts when become surrounded by new bone ***(Aurbach et al., 1992).***

Site : They constitute the major cell type of mature bone. They are scattered within bone matrix but interconnected with each other, with bone lining cell and with cells at the surface of bone by numerous cellular process to form a complex cellular network ***(Stephen, 1992).***

Function : They play an essential role in bone maintenance and share in bone matrix synthesis ***(Warshwsky,1982).***

(4) Osteoclasts

Origin : They are believed to be derived from hematopoietic stem cells via monocytes ***(Ganong, 1995).***

Site : They are found where there is active erosion of bone. They lie in close contact with bone surface in pits termed *"resorption bays"* ***(Gray, 1989).***

Function : They appear to phagocytose bone, digesting it in their cytoplasm; this is why bone around an active osteoclast has a characteristic ruffled or chewed out edge ***(Ganong, 1995).*** They also cause bone demineralization and organic matrix destruction ***(Jee,1983).***

(5)Bone lining cells

Origin : They are derived from marrow stroma ***(Stephen, 1992).***

Site : These cells are found in the resting surface of bone, i.e.those not undergo deposition or erosion ***(Menton et al., 1982).***

Function : They may be inactive osteoblasts which can revert to the active state when suitably stimulated.They may play a role in maintenance of mineral homeostasis ***(Marie, 1982).***

B: Non cellular elements

They include collagenous protein matrix that has been impregnated with mineral salts, especially phosphates of calcium. Average compact bone contains by weight approximately 30% matrix and 70% salts. However, newly formed bone may have a considerably higher percentage of matrix in relation to salts ***(Guyton, 1996).*** Adequate amounts of both protein and minerals must be available for the maintenance of normal bone structure ***(Ganong, 1995).***

The organic matrix of bone is 90 to 95% collagen fibers, and the remainder is a homogenous medium called ground substance. The collagen fibers extend primarily along the lines of tensional force to give bone its powerful tensile strength. The ground substance is composed of extracellular fluid plus proteoglycans, especially chondroitin sulphate and hyaluronic acid ***(Guyton,*1996).**

Mineral in bone is mostly in the form of hydroxyapatites which are distributed regularly along the length of collagen fibers surrounded by the ground substance ***(Warshwsky, 1982).***

Types of Bone

Histologically, there are 3 types of bone. ***Compact bone*** is found in the shafts of long bones and the surfaces of flat bones. It is organized into cylinders of consolidated bone around a central blood vessel called osteons or Haversian systems. ***Cancellous bone*** makes up the trabeculae lining the marrow cavities. ***Woven bone*** is an immature form of bone that is also found at fracture sites. Bone is cellular and well vascularized; the total bone blood flow in humans has been estimated to be 200-400 mL/min. Throughout life, the mineral in the skeleton is being actively turned over, and bone is constantly resorbed and reformed. The calcium in bone turns over at a rate of 100% per year in infants and 18% per year in adults ***(Ganong,1995).***

Bone Turnover (Formation and Resorption)

Bone is continually being deposited by osteoblasts, and is continually being absorbed where osteoclasts are active ***(Guyton,1996).*** The rate of both processes can be assessed by measuring bone matrix components or enzymes released into the circulation during breakdown and renewal ***(Hassager et al., 1994).***

Bone Formation

A small amount of osteoblastic activity occurs continually in all living bones (on about 4% of all surfaces at any given time), so that at least some new bone is being formed constantly ***(Guyton, 1996).*** The initial stage in bone production is the secretion of collagen and ground substance by the osteoblasts. The collagen polymerizes rapidly to form collagen fibers, and the resultant tissue becomes osteoid. As the latter is formed, some of the osteoblasts become entrapped within and then are called osteocytes. Ca^{2+} salts begin to precipitate on the surfaces of the collagen fibers forming minute nidi that rapidly multiply and grow over a period of days or weeks into the finished product, hydroxyapatite crystals. The formation of initial crystals within the collagen fibers is called crystal seeding or nucleation ***(Guyton, 1996).***

Factors affecting bone formation

- ***Vitamin D and its metabolites***

  Will be discussed later in details.

- ***Calcitonin***

  Calcitonin is a polypeptide of 32 amino acids that is synthetized and secreted by the parafollicular or C cells of the thyroid gland. Calcitonin at high concentration can directly inhibit osteoclast activity ***(Stephen, 1992).***

- *Sex hormones*

Sex steroids, particularly estrogens have an anabolic effect on bone through receptors located on the osteoblasts ***(Stephen,1992).***

- *Growth hormone*

It stimulates bone and cartilage growth via promoting local production of type I insulin-like growth factor by osteoblasts and chondrocytes respectively ***(Stephen, 1992).***

Biochemical markers of bone formation:

1.Alkaline phosphatase:

It is a glycoprotein which is the most commonly used marker of bone formation ***(Millan, 1986).*** Its Increase coincides with increased osteoblastic activity ***(Mayne et al., 1987).*** A moderate rise is observed in osteomalacia, while in rickets, levels are 2 to 4 times the normal, and the highest levels are seen in Paget's disease ***(Minisola et al., 1989).***

2.Osteocalcin:

It originates from bone cell synthesis rather than from bone matrix degradation and therefore reflects bone formation. It is a vitamin K dependent calcium binding protein of 44 A.A. Osteocalcin activity is directly related and specific to osteoblastic activity ***(Deftos et al., 1982).*** It is a very useful marker in evaluating endocrinal bone disease and effects of drugs on bone formation, so it is increased with excess thyroid or growth hormones and decreased with administration of calcitonin, glucocorticoids and estrogen ***(Garrel et al., 1986).*** Also it was found that osteocalcin level is elevated in

osteoporotic patients and can be used as a diagnostic and follow up test for osteoporosis, having the privilege over bone mineral density measurement of being easy, less expensive and no hazards of radiation exposure ***(EL-Kadery et al., 1993).***

3.Procollagen type I carboxy terminal peptide (PICP):

PICP circulation in the blood represents bone formation as they are released only during collagen synthesis. Thus for each molecule of collagen deposited in bone tissue, one molecule of PICP is released ***(Risteli et al., 1995).*** It is used as a non invasive index to assess bone metabolism ***(Santi et al., 1995).*** PICP also identifies obvious high turn over states such as hyperthyroidism , Paget's disease of bone and low turn over states such as myxedema ***(Charles et al., 1992).***

Bone Resorption

Bone is being continually resorbed in the presence of osteoclasts, which are normally active at any time on less than 1% of the outer surfaces and cavity surfaces. The osteoclast is the main cell involved in the degradation of the organic bone matrix and the release of bone minerals ***(Posner, 1985).*** It is believed that the osteoclasts send out villous like projections towards the bone, these villi secrete two types of substances, the proteolytic enzymes such as collagenase enzyme and several acids including citric and lactic acids. The enzymes presumbly digest or dissolute the organic matrix of the bone, while the acids cause solution of the bone salts. Finally, the fragments of bone salts and collagen are literally phagocytosed

by the villi and then digested within the osteoclasts ***(Guyton, 1996).***

Osteocytes have a role in absorbing perilacunar bone. There is an evidence that mononuclear phagocytes including monocytes and tissue macrophages are involved in bone resorption ***(Posner, 1985).***

Factors regulating bone resorption :

- *Parathyroid hormone (PTH)*

It is a small protein composed of 84 A.A. It is a rapidly regulating hormone that sustains calcium and $1,25(OH)_2D_3$ and depresses phosphates in blood ***(Guyton, 1996).***

Action in bone:

PTH increases the skeletal mobilization of bone calcium through osteoclastic and osteolytic resorption. It also increases the rate of conversion of mononuclear phagocytes to osteoclasts ***(Mazzaferro et al., 1990).***

Action in kidney:

PTH acts on the distal portion of the nephron to increase tubular reabsorption of calcium. It stimulates the synthesis of $1,25(OH)_2D_3$ by increasing the activity of $25(OH)D_3$ 1-α hydroxylase in the proximal tubules. In addition, PTH inhibits phosphate reabsorption in the distal and perhaps also in the proximal tubules ***(Spigel, 1992)***.

Action in intestine:

PTH has no direct action on the intestine, however its direct renal action to increase serum $1,25(OH)_2D_3$ causes 2ry effects in the intestine ***(Guyton, 1996).***

- ***Thyroid hormone***

It has a direct effect on bone cells. Excess of thyroid hormone increases calcium release from bones ***(Stephen, 1992).***

- ***Glucocorticoids***

Physiological amounts of glucocorticoids are important regulators of bone growth, probably by actions on bone forming and bone resorbing cells, while high glucocorticoids concentration result in bone thinning as a consequence of osteoblasts inhibition ***(Cunningham et al., 1990).***

- ***Lymphokines***

Interleukin–I is a potent bone resorbing agent derived from activated macrophages. They believed to be one of the local regulators of bone resorption ***(Cunningham et al., 1990).***

Biochemical markers of bone resorption:

1. *Fasting urinary calcium*

It is the cheapest assay of bone resorption but it detects only the marked increase of bone resorption and also reflects renal handling of Ca^{2+} which is influenced by Ca^{2+} regulating hormones ***(Delmas, 1995).***

2. Hydroxyproline

It is not specific for bone resorption as it is a major component of all types of collagen and is present in all molecules containing collagen like structures ***(Robins, 1982).*** Also it can be influenced by the nature of diet that contains significant amount of collagen ***(Wilson et al., 1990).***

3. Hydroxylysine glycosides

It is an another constituent of collagen molecule, that is not a specific marker of bone resorption as it reflects collagen degradation anywhere in the body ***(Deftos, 1991).***

4. Pyridinium cross links

Pyridinoline and deoxy-pyridinoline are 2 components of the mature cross-links formed once collagen is incorporated into bone matrix. They are excreted through collagen degradation at the time of bone resorption ***(Kushido et al., 1995).***

They are relatively specific to bone resorption, and not be metabolized in vivo prior their urinary excretion ***(Delmos,1995).*** A study of these both components in 15 epileptic patients undergoing long –term anticonvulsant therapy found that both components had significantly higher levels than those in age-matched control groups ***(Oshidi et al., 1994).***

5. Type I collagen carboxyl terminal telopeptide (ICTP)

This new marker is an antigen composed of 3 cross-linked peptides. It shows diurenal variations where values being higher at night ***(Risteli and Ristli, 1993).***

Metabolic Bone Diseases

There are a variety of diseases in which bone changes are secondary to generalized disturbances in metabolism.

Osteomalacia :

This term is used to refer to disorders such as rickets in which the amount of mineral formation in bone per unit of bone matrix is deficient ***(Ganong, 1995).*** On biochemical assay, the serum calcium tends to be low normal, serum phosphate very low and serum alkaline phosphatase very high (released from stimulated osteoblasts). Serum 25(OH)D levels are usually markedly depressed while 1,25 (OH)2D3 levels may be initially normal, then too eventually fall ***(Bullough, 1997).***

Osteopenia :

It corresponds to an abnormally low bone density. It is accompanied by increased risk of fractures. Although it remains asymptomatic, therapeutic intervention may neverthless be justified ***(Durieux, 1992).*** It is a non specific condition that may result from any of a number of causes; including mineral and collagen disturbances, hematologic, endocrine abnormalities, neoblastic disorders or immobilization. The amount of bone tissue in the skeleton also decreases with age ***(Bullough,1997).***

Osteoporosis :

It is a decrease of bone mass with preservation of the normal ratio of mineral to matrix, that results from either defective bone formation (osteogenesis imperfecta or scurvy) or imbalance between bone formation and bone resorption ***(Bullough, 1997).***

It is a disease characterized by the development of fractures due to bone fragility. It is accompanied by a reduction in bone density and other abnormalities of bone architectures and metabolism, without any disturbance of mineralization. It is responsible for pain, a functional handicap which alters the patient's quality ***(Durieux, 1992).***

Bone Mass Measurements

Several methods are available for the noninvasive measurement of bone mass. They are all based on the use of X-or gamma rays and range from the subjective interpretation of radiographs to sophosticated quantitative techniques ***(Wahner and Fogrlman, 1995).***

Table (10): Methods for in vivo assessment of bone mineral.

(I) Total body bone mineral

Neutron activation analysis
Dual energy photon absorptiometry (DPA)
Dual energy X-ray absorptiometry (DXA)

(II) Bone mineral at specific sites

(1) Methods based on subjective evaluation of radiographs:

Biconcavity index
Singh index
Smith index
Fine-detail radiographs
Shapes of spinal vertebrae
Trabecular pattern of hip
Radiographic density of vertebrae
Periosteal bone resorption pattern

(2) Methods based on quantitative evaluations of radiographs :

Cortical thicknessof appendicular bones
Lumbar spine score (Nordin)
Exton-Smith index (children)
Bamett-Nordin index (osteoporosis)
Radiographic photodensitometry
Videodensitometry
Vertebral morphometry

(3) Methods based on photon absorptiometry:

Single photon absorptiometry (SPA)
Dual photon absorptiometry
    Isotope source (DPA)
    X-ray source (DXA)
Vertebral morphometry

(4) Methods based on the Compton scattering technique

(5) Methods based on computed tomography:

Single energy CT
DUAL energy CT
    Trabecular bone of spine or forearm
    Trabecular bone of spine

(6) Measurements based on neutron activation analysis:

Spine, trunk
Hand, forearm, leg

(Wahner and Dunn, 1987).

The information from these measurements ranges from cortical thickness (mm) or volume (cm^3) to bone mass (gm) and bone mineral content (g/cm) and to some approach to bone density (area density in g/cm^2 or density in mg/cm^3). The purpose of all these methods is to measure the quantity of a bone mineral of constant chemical composition ***(Wahner and Fogelman, 1995).***

Comparing BMD values with a normal population

The BMD measured for a patient is compared with age and sex matched controls as well as with young normals (that is, maximal bone mass). These values are then expressed as standard deviation scores, called Z or T scores ***(Wahner and Fogelman, 1995).***

Z score : Standard deviation from the age matched level.

T score : Standard deviation from the peak bone mass.

(Standard deviation = 10-13% at each site)

The Z score is a measure of the difference between the patient's BMD and the mean BMD of age and sex matched peers. The Z score, in SD values is calculated as:

$$\text{Z-score (SD)} = \frac{P\text{-}M_c}{SD_c}$$

Where P is the measured patient value, M_c is the mean value for sex-and age-matched controls, and SD_c is the

standard deviation of the mean value for sex-and age-matched controls.

e.g.: BMD of a patient = - 1.5 of the Z score which means – 1.5 standard deviation from the age matched level i.e., about 18% less than normal [1 SD = 12% (about)].

The T score is a measure of the difference between the patient's BMD and the mean BMD of young controls. The T score, in SD values is calculated as:

$$\text{T-score (SD)} = \frac{P\text{-}M_{cm}}{SD_{cm}}$$

Where P is the measured patient's value, M_{cm} is the mean value for young, sex-matched normals and SD_{cm} is the population standard deviation for young normals ***(Wahner and Fogelman, 1995).***

Description of Bone densitometry Methods

Dual Energy X-ray Absorptiometry (DEXA)

The first commercially available DEXA scanner was introduced by Hologic in 1987, it was based on an energy switching X-ray source. Later implementations introduced by Lunar and Norland in 1988 and by Sopha in 1989, use a constant –potential X-ray source combined with rare earth filters ***(Wahner and Fogelman, 1995).***

DEXA overcame many of drawbacks of Dual Photon Absorptiometry by replacing the radioisotope source with an X-ray tube. The higher photon flux of X-ray tubes allowed scan times to be reduced to 6 minutes. At the same time, measurement resolution and precision were substantially improved, while DEXA remained fully compatible with clinical DPA data ***(Wahner et al., 1988)***. In addition to measuring BMC and BMD, the DEXA technique also had been successfully applied to the measurement of body composition (fat mass versus lean mass) for the whole body. DEXA allows a fast, noninvasive, relatively inexpensive yet highly precise measurement of bone mass or density at any part of the skeleton ***(Wahner and Fogelman, 1995).***

A typical DEXA examination consists of a two-site BMD measurement including the antero-posterior lumbar spine (L1 – L4) and the proximal femur. To study bone densitometry of the lumbar spine and femur in children by DEXA, 84 healthy Finnish children and adolescents aged 6-19 years were examined. It was found that both BMC (g) and BMD (g/cm2) were closely related to age, height and weight. When the BMD values were adjusted for age, height and weight, the mean lumbar BMD was higher in girls than in boys, whereas in he femoral neck the situation was opposite ***(Kroger et al., 1992).***

Antiepileptics and Bone Mineral Density

Long term administration of anticonvulsants may cause osteopenic bone diseases with decreased bone density. This probably results from chronic mild osteomalacia and may appear as osteoporosis on bone radiographs ***(Christiansen et al., 1973).*** Also it is associated with significant cortical bone loss ***(Plukiewicz and Nowakowska, 1997).***

Quantitative studies of the influence of anticonvulsant drugs on bone mineral density reported that phenytoin, primidone and phenobarbital are established contributers to osteomalacia and rickets ***(Winnacker et al., 1977).*** Alterations in bone metabolism have been reported with carbamazepine ***(Hoikk et al., 1984).*** Interference with bone mineralization by antiepileptic medications could place a large number of children at increased risk for involutional osteoporosis ***(Sheth et al., 1995).***

Phenytoin monotherapy in epileptics reduces bone mineral density 1.2% per year of treatment. The addition of phenobarbital or carbamazepine increased the rate of mineral loss to 2% per year in these children ***(Wolschendorf et al., 1983).*** In children, neither phenytoin nor phenobarbital, administered for up to 9 years, is associated with reductions in bone mineral density although values suggestive of osteomalacia have been described during treatment with carbamazepine, phenobarbital and phenytoin ***(Gough et al., 1986).***

In order to clarify whether CBZ causes disturbances in calcium and bone metabolism, a study done on 30 epileptic outpatients that had been treated for at least 1 year with CBZ. The bone mineral was not significantly different from controls and the biochemical indices of bone metabolism were virtually unchanged during the treatment period. It is concluded that epileptic patients on CBZ monotherapy have normal bone metabolism ***(Tjellesen et al., 1983).***

Chung and Ahn ***(1994)*** showed that treatment with phenobarbital or phenytoin for more than 24 months in children is associated with significant reduction in BMD and it is recommended that vitamin D must be administered to children with epilepsy receiving AEDs over 24 months.

To examine the effect of carbamazepine (CBZ) and valproate (VPA) monotherapy on BMD in children, a study had measured axial (2,3,4 L.V) and appendicular (distal third of radius) BMD by dual –energy X-ray absorptiometry (DEXA) in 27 healthy children and 26 children with uncomplicated idiopathic epilepsy treated with either CBZ or VPA for more than 18 months. It had found that children treated with VPA had a 14% and 10% reduction in BMD at axial and appendicular sites respectively. The reduction in BMD increased with the duration of VPA therapy. On the other hand CBZ did not significantly reduce BMD ***(Sheth et al 1995)***.

The effect of VPA on BMD on a 14-years old white boy examined and the measurements were done by DEXA at the lumbar spine and femoral neck, and were 0.585 and 0.703

gm/cm3 respectively *(Gillis et al., 1996).* Normal range for 14-years old boy is 0.879 to 1.084 and 0.893 to 1.136 gm/cm3 respectively *(Kroger et al., 1992).* This observation supports the findings of **Sheth et al (1995)** that long term VPA therapy can lead to significant osteoporosis in children. Moreover, it demonstrates that the increased risk of fractures is not limited to adult or elderly life, but can already occur during adolescence. The impact of protective measures must be evaluated.

The effects of valproic acid and carbamazepine monotherapies on BMD were evaluated in 53 children with primary epilepsy taking drugs for longer than one year and in 26 healthy control children as a control. BMD values of both valproic acid and carbamazepine groups were not statistically different from that of the control group *(Akin et al., 1998).*

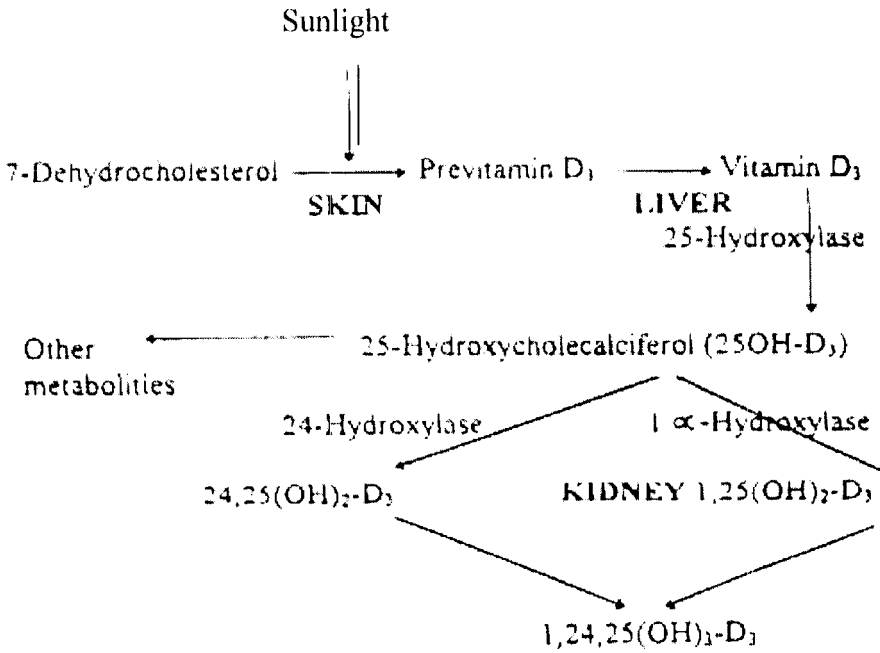
To study the effects of anticonvulsant drugs therapy on BMD in a pediatric population , BMD in 44 children receiving chronic antiepileptic therapy and 49 healthy controls were measured. The mean BMD values were 0.537± 206 gm/cm3 and 0.500± 0.157 gm/cm3 in study and control groups respectively. Also there was a significant decrease in BMD of patients using phenobarbitone (PB) in comparison to patients using CBZ *(Trias et al., 1998).*

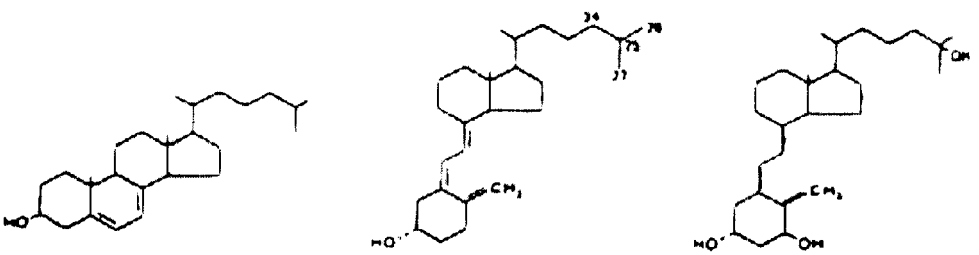
In order to assess the bone atrophy lesions of epileptic patients, BMD of their lumbar spines and femoral necks were measured. The study group were on long term medication for epilepsy taking phenytoin, barbiturates, and/or acetazolamide for at least 5 years. BMD at both sites were significantly lower

in the patient group than in the control group. These results confirm the presence of bone atrophy lesions in epileptic patients on long-term AEDs ***(Kubota et al., 1999).***

Vitamin D & The Hydroxycholecalciferols

The term vitamin D is used to refer to a group of closely related sterols produced by the action of ultraviolet light on certain provitamins (Fig.6) ***(Murray et al., 1996).***





7 Dehydrocholesterol Vit. D_3 1.25 Dihydroxycholecalciferol

Fig (6) : Formation and hydroxylatin of Vitamin D_3
(Murray et al., 1996)

Vitamin D is a steroid hormone with 2 molecular forms; vitamin D_3 (cholecalciferol) which is produced in the skin of mammals by the action of sunlight and vitamin D_2 (ergocalciferol) which is derived from the plant sterol ergosterol. They have equivalent potency and mechanism of action in human despite subtle difference in physiology and biochemistry ***(Daniel, 1992).***

Metabolism of vitamin D:

The steps of vitamin D metabolism are briefly outlined in figure(6).

It has been firmly established that vitamin D requires metabolic alterations before it can exert its physiological role as a positive regulator of calcium and phosphate metabolism ***(Deluca and Schnoes, 1976).***

(1)Absorption of vitamin D:

It is absorbed in the small intestine, mainly in the duedenum by an active transport system that delivers vitamin D to the enterocytes, where it is incorporated into chylomicrons for delivery to the liver ***(Deluca, 1988).*** Most of the vitamin D absorbed passes through the lymphatic system before entering the blood stream. This process is facilitated by bile salts, fatty acids and monoglycerides ***(Daniel, 1992).***

After absorption, vitamin D is distributed in the fat and muscles where it undergoes a series of further metabolic conversions ***(Ganong, 1995).***

(2)Activation of vitamin D :

Vitamin D must undergo 2 activation reactions in order to achieve its physiological role ***(Sedrani, 1986).***

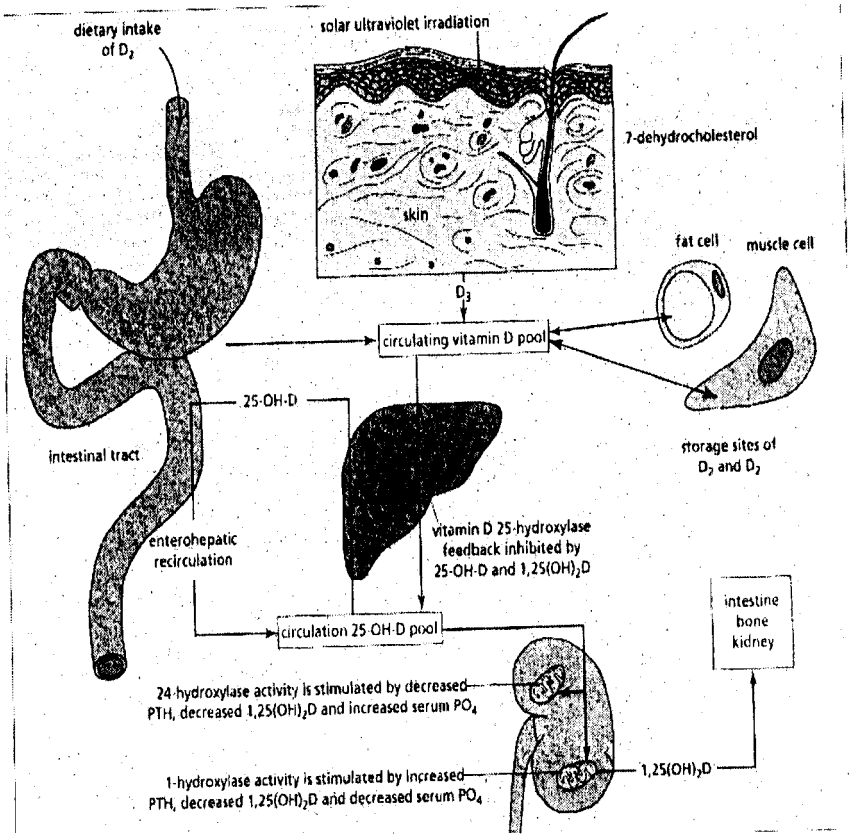


Fig (7) : Regulation of vitamin D metabolism ***(Bullough, 1997).***

Hepatic activation:

The circulating vitamin D in blood is taken by the liver within 60 minutes and rapidly metabolized into 25(OH) cholecalciferol by the action of 25- hydroxylase (cytochrome

P-450 mixed function oxidase) in hepatocytes. It is 2-3 times more active than vitamin D_3 ***(Pamela and Richard, 1994).***

This activation process is a limited one because the 25-hydroxy. cholecalciferol has a feedback inhibitory effect on the conversion reactions. This feedback effect is extremely important as it regulates very precisely the concentration of 25(OH) D3 in the plasma and conserves the vitamin D for future use ***(Guyton, 1996).*** 25(OH)D_3 did not accumulate in the liver, and is transported in the plasma bound to a specific globulin vitamin D-binding protein (DBP) to the kidney for more hydroxylation ***(Daniel, 1992).***

Renal activation:

25 (OH) D_3 in the kidney is furtherly hydroxylated enzymatically at 2 positions. It is either hydroxylated at the 1 position, a process catalyzed by 1-α hydroxylase enzyme to produce 1,25$(OH)_2$ D_3; the most active form of vitamin D or hydroxylated at the 24 position, a process catalyzed by 24 hydroxylase to produce 24,25 $(OH)_2D_3$ ***(Pamela and Richard, 1994).***

Both the 1-hydroxylase and 24-hydroxylase in the kidney are cytochrome P-450 mixed function, located exclusively in the mitochondria of proximal renal tubules ***(Daniel. 1992).***

The principle modulator of 1-α hydroxylase activity appears to be PTH and serum calcium concentration. When Ca supply is adequate, 1,25 $(OH)_2D_3$ formation decreases and the formation of other metabolite 24,25 $(OH)_2$ D_3 increases. On

the other hand, the activity of 24-hydroxylase is induced by the presence of 1,25 $(OH)_2$ D_3. The latter process appears to be essential for the inactivation of vitamin D molecule ***(Jarnagin et al., 1983).***

Factors affecting 1, 25 $(OH)_2$ D_3 production:

The regulation of 1,25 $(OH)_2$ D_3 production occurs at the position of 25-hydroxylation in the liver and at the position of 1-α hydroxylation in the kidney ***(Papapoulos et al., 1979).***

The production of 25 $(OH)D_3$ is a limited reaction because it has a feedback inhibitory effect on the conversion reaction ***(Martin et al., 1983).*** Also 1,25 $(OH)_2$ D_3 inhibits 25 $(OH)D_3$ by negative feedback mechanism ***(Bell,1985).***

Endocrinal control of vitamin D production occurs through regulation of renal 1-α hydroxylase and 24 hydroxylase activities as shown in figure (8) ***(Berne & Levy, 1988).***

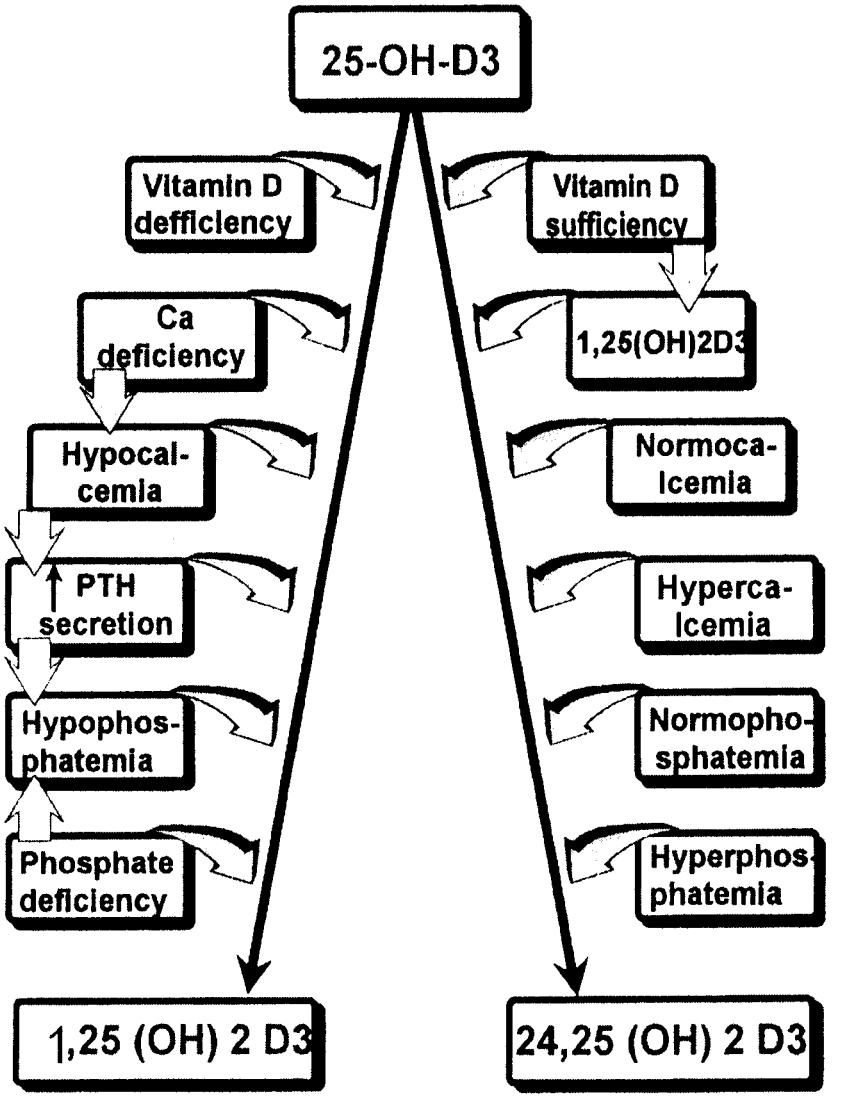


Fig (8) Factors that regulate conversion of 25-OH-D_3 to either 1,25-$(OH)_2$ D_3 or 24,25 $(OH)_2$ D_3 ***(Berne&Levy, 1988).***

Actions of vitamin D:

Because 1,25 $(OH)_2$ D_3 (calcitriol) is produced in the body and transported in the blood stream to act at a distance from its site of production, it is probably called a hormone ***(Ganong, 1995).*** It complexes with a polypeptide receptor with high affinity and low capacity (vitamin D receptor = VDR). This occupied receptor is phosphorylated and bound in a sequence-specific manner with unique regulatory elements of DNA in the nucleus of target cells and modulates gene expression which controls protein synthesis of cells and hence , the action of vitamin D takes place ***(Anderson, 1990).***

The action of 24,25 $(OH)_2$ D_3 on bone metabolism is largely unknown. Although it only weakly accelerates the absorption of calcium by the gut, some important role in bone cell differentiation is suspected. By contrast 1,25 $(OH)_2$ D_3 is the most biologically potent form of vitamin D known and has multiple and profound actions on osseous metabolism. It accelerates the gut absorption of calcium and phosphorus, promotes bone cell differentiation and mineralization of osteoid tissue and enhances the sensitivity of bone to PTH-induced resorption to maintain serum calcium ***(Bullough, 1997).***

In addition to its effects on bone metabolism, 1,25 $(OH)_2$ D_3 also has other biologic actions including inhibition of the production of Interleukin 2 and immunoglobulins, and the stimulation of insulin and thyroid stimulating hormone secretion. With respect to its effect on cell proliferation and differentiation, it is of interest that 1,25

$(OH)_2$ D_3 induces monocytes to become multinucleated giant cells which act in vivo as osteoclast-like cells ***(Bullough,1997).***

Calcium and Phosphorus Homeostasis

Calcium and phosphorus are present in three principal pools; the bone tissue, the intracellular fluid (ICF) and the extracellular fluid (ECF). They are added to the system from the gut, and lost from the system through the gut, the kidneys and by sweating. It should be noted that most of the blood calcium and phosphorus lost by glomerular filteration is reabsorbed through the renal tubular epithelium. Also, most of the bone mineral incorporated into the bone matrix is not available for rapid exchange with the ECF ***(Bullough, 1997).***

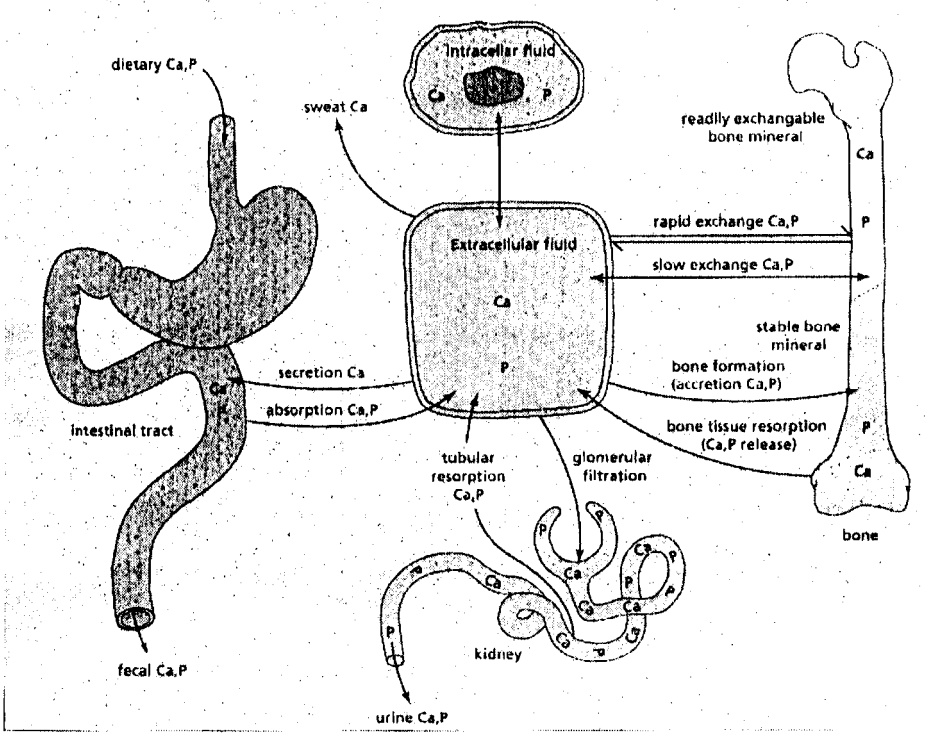


Fig (9) : Schematic model of calcium and phosphorus metabolism ***(Bullough, 1997).***

The required daily calcium intake is 800 mg of elemental calcium, while that for phosphorus is about 800-1000 mg. Most of calcium and phosphorus are obtained from dairy products. The interactive and interdependent endocrine control of calcium and phosphorus homeostasis is shown in figure (9) ***(Bullough, 1997).***

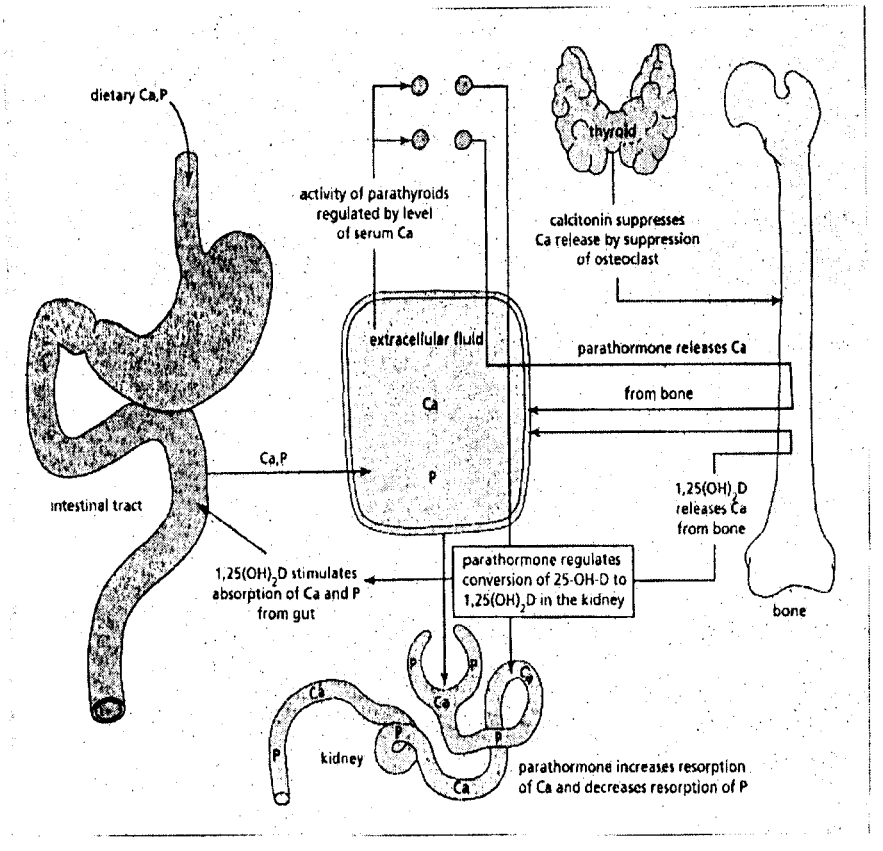


Fig (10) : Endocrine regulation of calcium and phosphorus homeostasis ***(Bullough, 1997).***

Parathyroid gland activity is largely regulated by the level of Ca^{2+} in the ECF; an increase in serum Ca^{2+} supresses PTH release, and vice versa. PTH acts on the renal tubules to increase the tubular reabsorption of calcium while decreasing phosphorus reabsorption. It also directly stimulates the osteoblasts to synthesize new bone and through activation of a second messenger, stimulates osteoclastic resorption of bone, and hence the release of Ca^{2+} into the circulation ***(Bullough,1997).***

Antiepileptics (AED) and Osteomalacia

Alterations in biochemical parameters suggestive of osteomalacia have been recognized in epileptic patients since 1968 ***(Kruse, 1968).*** The biochemical changes include reduced calcium and 25(OH)D levels and raised alkaline phosphatase levels ***(Richens and Rowe, 1970; Dent et al., 1970).*** Alterations depend on the number of drugs used, the doses, level and type of drug treatment ***(Hahn et al., 1975).*** Phenytoin and phenobarbitone have been implicated ***(Davie et al., 1983),*** but the effects of carbamazepine are controversial ***(O'Hare et al., 1980; Tjellesen et al., 1983).***

Long term administration of AED may cause osteopenic bone disease with florid osteomalacia or rickets. When overt osteomalacia does develop, blood chemistry values resemble those of vitamin D deficiency with a decreased serum calcium concentration, a low or low-to normal phosphate concentration and increased parathyroid concentration ***(Mallette, 1977).***

To study the effects of carbamazepine on bone metabolism, **O'Hare et al (1980)** studied 31 patients on carbamazepine as a single drug for epilepsy for a duration 20.5±10 months. Three patients (10%) had hypocalcemia and serum calcium was significantly lower ($P < 0.01$), and serum alkaline phosphatase was significantly higher ($P<0.05$) than matched control subjects. Serum phosphorus was significantly inversly correlated and serum alkaline phosphatase was positively correlated with drug dose and duration but not with blood levels of carbamazepine. These findings are consistent with mild biochemical changes of osteomalacia .

On the other hand, calcium metabolism was examined in 30 epileptic outpatients on carbamazepine monotherapy. The patients had a normal bone mass and normal serum concentrations of 25 (OH) D. The serum calcium was decreased ($P<0.001$) and the serum alkaline phosphatase increased ($P< 0.001$). The clinical significance of this study is that carbamazepine monotherapy does not have the side effects on the bone metabolism known as "anticonvulsant osteomalacia" ***(Tjellesen et al., 1983).***

The biochemical parameters associated with vitamin D metabolism, calcium, 25 (OH) D and alkaline phosphatase levels were assessed in 226 outpatients with epilepsy. Patients were grouped depending on the drug treatment; carbamazepine, phenytoin, phenobarbitone and sodium valproate used alone as monotherapy and in combination as polytherapy. The most severe alterations occurred in polytherapy group. Hypocalcemia was more severe in the phenobarbitone monotherapy group than the carbamazepine or

phenytoin groups. No patients on sodium valproate monotherapy had subnormal levels of calcium. 25 (OH) D levels were similarly reduced in the carbamazepine, phenytoin and the phenobarbitone groups with no reduction in the sodium valproate group. Significant elevations in alkaline phosphatase levels were evident in all patient groups except the sodium valproate group ***(Gough et al., 1986).***

A survey of calcium metabolism in epileptic patients in a residential center showed subnormal serum calcium level in 22.5% of patients and a raised alkaline phosphatase in 29%. Hypocalcemia was related to the dose, multiple drug therapy and the individual anticonvulsant drugs with decreasing order of importance : primidone, phenytoin and phenobarbitone ***(Richens and Rowe, 1970).***

A small group of children receiving anticonvulsant therapy will present with calcium-deficient rickets, despite apparently adequate vitamin D intake. This condition is more common after the combination of phenobarbital and phenytoin, but it has been associated with almost all anticonvulsant drugs ***(Chesney, 1990).***

Mechanism of Anticonvulsant Osteomalacia

The mechanism of anticonvulsant osteomalacia is not fully understood. Children and adults who are taking anticonvulsants have reduced concentrations of 25 (OH)D in their plasma for any given vitamin D exposure and their serum calcium concentrations correlate well with the 25 (OH)D concentrations. Healing of the osteomalacia will occur on

treatment with small amounts of 25 (OH) D_3, thus, a deficiency of 25 (OH) D appears to be the direct cause of the osteomalacia. Anticonvulasant drugs induce hepatic cytochrome P-450 enzymatic activity, which hydroxylates vitamin D and other steroids at sites other than the 25 carbon, and form products that are biologically inactive. Several findings have supported this hypothesis. Urinary excretion of glucaric acid, which is an index of liver-enzyme induction, correlates inversly with the serum calcium levels in epileptics ***(Christiansen et al., 1973).***

Phenytoin may also inhibit gut calcium absorption directly and may have direct effects on bone metabolism ***(Mallett, 1977).***

Dietrich and Duffield (1980) stated that the AEDs inhibit PTH-induced bone resorption and bone collagen synthesis in tissue culture. This means that AEDs exert a direct effect on bone metabolism.

Carbamazepine is a potent inducer of hepatic microsomal enzyme (P-450) with subsequent excessive enzymatic degradation of vitamin D resulting in bone demineralization ***(O'Hare et al., 1980).*** Incidence of reversible Fanconi syndrome in individuals receiving valproate was reported, with subsequent increased urinary loss of Ca and P **(Lande et al .,1993).**

Alterations in vitamin D metabolism are generally thought to account for the hypocalcemia and osteopenia caused by long term treatment with AEDs. Serum ionized

calcium levels in 109 ambulatory adult epileptic outpatients receiving chronic AEDs in Georgia were decreased, PTH concentrations were increased, while BMC was reduced averaging only 88.8% of the predicted normal values. Hypocalcemia and osteopenia occurred in spite of normal mean levels of serum 25 (OH) D and 1,25 $(OH)_2$ D_3. The indirect relationship between serum concentrations of AEDs and the serum ionized calcium level, and the lack of correlation with vitamin D metabolites levels suggested that hypocalcemia was independent of the effect of drugs on vitamin D metabolism. Bone biopsies revealed increased osteoid but normal calcification front formation, accelerated mineralization rate, and decreased mineralization lag time indicative of increased skeletal turnover, rather than osteomalacia ***(Weinstein et al., 1984).***

Management of Anticonvulsant Biochemical Osteomalacia

Hahn et al (1975) suggested that most children treated chemically with anticonvulsant drugs should be maintained on vitamin D supplementation in a dose of 10,000 IU/week.

It was found that during treatment of osteomalacic epileptic patients with 2,000 IU of vitamin D for 3 months an average BMC increases of 4% whereas the BMC values remained unchanged in the placebo group ***(Christiansen et al., 1973).***

Much of the reported data on vitamin D supplementation in patients suffering from AEDs induced osteomalacia is an individual patient's response. In some

cases, ultraviolet irradiation, calcium or phosphate supplements and increased weight-bearing exercises have been included with vitamin D treatment ***(Hahn and Halstead, 1979; Sheth et al., 1995).*** This form of antiepileptic rickets usually can be prevented by providing an extra 500-1000 IU of vitamin D_2 each day and by ensuring that the dietary intake of calcium is adequate ***(Chesney, 1990).***

Collins et al (1991) suggested that vitamin D should be prescribed for epileptic patients who are at greatest risk of developing osteomalacia, these include long term institionalized patients, those with reduced ultraviolet exposure or poor dietary intake, patients with multiple anticonvulsant drugs. Dose adjustment and monitoring of serum 25 (OH) D is necessary.

Patients & Methods

Patients and Methods

The patients group:

This study was conducted on 30 primary epileptic patients recruited from the Outpatient Neurology Clinic, Children's Hospital, Ain Shams University. The study carried on from March 1998 to August 1999. The studied group included 20 males and 10 females with a male to female ratio 2:1, their ages ranged from 6 to 16 years with a mean of 9.50±3

Exclusion criteria:

- Secondary epilepsy
- Patients receiving AEDs for less than 12 months.
- Patients with motor handicap or mental retardation.
- Patients with congenital anomaly or with past-history of fracture to lumbar spine.

Patients were divided into three groups:

Group I: This group included 14 patients receiving VPA only as monotherapy. Their ages ranged between 6 – 16 years with a mean of 10.28± 3.34 years. They were 8 males and 6 females. The range of duration of treatment was 1 to 7 years with a mean of 3.75 ± 1.95 years.

Group II : This group included 8 patients receiving CBZ only as monotherapy. Their ages ranged between 6 – 12 years with a mean of 8.75 ± 2.05 years. They were 6 males and 2 females. The rang of duration of treatment was 2 to 6 years with a mean of 4.43 ± 1.45 years.

Group III : This group included 8 patients receiving both CBZ and VPA as polytherapy. Their ages ranged between 6 - 14 years with a mean of 8.87 ± 3.13 years. They were 6 males and 2 females. The range of duration of treatment was 1 to 6.5 years with a mean of 4.62 ± 1.86 years.

The control group:

A group of 12 healthy children of the same cohort served as a control group. They were 6 males and 6 females. Their ages ranged between 6.5 - 10 years with a mean of 8.06 ± 1.18 years.

All subjects were subjected to:

1. Careful history taking. For patients group, a review of each subject's seizure history, cerebral imaging, electroencephalogram and medications records was undertaken to confirm eligibility.
2. Thorough general and neurological examination and anthropometric measures (height in cm and weight in kg and expressed in percentiles).
3. Investigations :
   - Estimation of serum Ca, P and alkaline phosphatase by colorometric methods (Elitech Diagnostic kits for Ca and P; and Randox diagnostic kits for alkaline phosphatase).
   - Estimation of serum 25 (OH) D_3 by radioimmune assay (Medgenix Diagnostoc kits).

Where 5 c.c. fasting blood samples were withdrawn from all children (patients and controls) under aseptic technique, left to clot and centrifuged and the sera were frozen till the time of assay.

4. Imaging
   - Lumbar spine osteodensitometry

Statistical Analysis

Data were analyzed with Statistica Software Package V.5 (Statsoft, Tulsa, OK, USA). All numeric data were expressed as mean ± standard deviation (SD). Data were analyzed using student 't' test to compare values of different variables. Person 'r' correlation coefficient was used to determine the relationship between different quantitative variables. Chi-square (X^2) test was used to compare the frequency of qualitative variables among the different groups. For all tests a probability of <0.05 was considered as significant.

Determination of Serum Vitamin D

Principle

After extraction of fat soluble vitamin D with acetonitrile, standard and test samples were incubated with fixed amount I^{125} labeled 25(OH) vitamin D_3 competes with 25 (OH) vitamin D_3 from either extracted samples or standards for a fixed amount specific antibody sites immobilized to the lower and inner surface of plastic tubes.

After 2 hours incubation at room temperature, an aspiration step stops the competition reaction, the tubes were then washed with 3 ml washing solution and counted in a gamma counter.

Reagent Preparation

At the time of assay, all standards (0, 1.5, 5, 15, 50 and 150 mg/ml) were reconstituted with 1 ml distilled water, controls reconstituted with 0.5 ml distilled water.

I^{125} "25(OH) D_3" was reconstituted with 6 ml of a mix of distilled water / ethanol 50/50 (v/v). The content of washing solution buffer was diluted in 700 ml distilled water, using a magnetic stirrer to homogenize.

Spicemen Preparation

Sera were thawed and mixed by vortex then centrifuged to get rid of any insoluble particles.

Procedure

I. Extraction Step:

Fourty two glass tubes (12x75mm) were labeled, 0.5 ml acetonitrile was added to all tubes. In corresponding tubes 200_µl of each standard, control or samples were dispensed, mixed for 7 seconds with a vortex and lastly centrifuged (800g) for 5 minutes at room temperature.

II. Incubation Step

Coated tubes were labeled in duplicate for each standard, control and sample for determination of total counts. Two normal tubes were labeled and 100 µl of the supernatant obtained after the extraction step were added in the corresponding tubes. Pipette tips have to be saturated with corresponding supernatant before addition in the tube, then 400 µl of incubation buffer were dispensed in each tube except those for total counts.

In each tube including those for total counts 50 µl tracer was added, shaked gently and incubated for two hours at room temperature. The content of each tube (except total counts) was aspirated. Tubes were washed twice with 2 ml wash solution, aspirated and left standing upright for two minutes and then the remaining drop of liquid was aspirated. The tubes were counted in a gamma counter for 60 seconds.

Calculation of Results

The means were calculated rejecting obvious outlyers. The bound radioactivity (B) was calculated as a percentage.

The binding determined at the zero standard point (0) according to the following formula:

$$B/B_0 = \frac{\text{Counts (Std or sample)} \times 100}{\text{Counts (Zero standard)}}$$

Using a 3 cycle semi-logarithmic or logit-log graph paper, (B/B_0 x 100) values for each standard point was plotted as a function of the 25 (OH) D_3 concentration of each standard point. By interpolation of the sample (B/B_0 x 100) value 25 (OH) D_3 concentration of the samples was determined from the reference curve.

For each assay, the percentage of total tracer bound in the absence of unlabeled 25(OH)D_3, (B_0 / T) was checked.

Direct Colorimetric Measurement of serum Calcium

Principle

Colorimetric measurement with ortho-resolphtalein. The 8-hydroxy quinoline prevents Mg^{2+} from interference up to 4 m mol/L (100 mg/L).

Reagents

Reagent 1:

Diethylamine	360 m mol/L

Reagent 2:

0-Cresolphtalein	0.15 m mol /L
1- Hydroxyquinoline	17.2 m mol /L

Samples

Serum: all reagents were ready for use, and stable at 2-25°C until expiry date.

Preparation of Working reagent

One volume of the reagent 1 was mixed with one volume 2. This reagent was stable for 4 hours at 20-25°C according to manufacturer instructions.

Procedure

	Blank	Standard	Sample
Reagent	1 ml	1 ml	1ml
Distilled water	10 µl	-	-
Standard	-	10µl	-
Sample	-	-	10 µl

The contents of each tube were mixed and incubated for 5 minutes at room temperature. Optical density (OD) was read at 570 nm in 1 cm light path cuvette.The final color was stable for at least 1 hour.

Calculation

$$\frac{\text{OD Sample} \times n}{\text{OD Standard}}$$

n = concentration standard = 10 mg / dl = 2.5 m mol /L

Direct Coloremetric determination of Serum Phosphorus

Determination of inorganic phosphorus according to the following reaction:

Ammonium molybdate + sulfuric acid $\xrightarrow{\text{phosphorus}}$ Phosphomolybdic complex

Reagent

Sulfuric acid	210 m mol / L
Ammonium molybdate	650 μ mol /L

Samples: Serum

The working reagent was ready for use and stable at 2-25°C until expiry date.

Procedure

	Blank	Standard	Sample
Working reagent	1 ml	1 ml	1 ml
Distilled water	10 μl	-	-
Standard	-	10 μl	-
Sample	-	-	10 μl

The content of each tube was mixed and incubated for 5 minutes at room temperature. Optical density (OD) was read at 340 nm wave length in 1 cm light path cuvette, the final color is stable for at least one hour.

Calculation

$$\frac{\text{OD Sample x n}}{\text{OD Standard}}$$

Where n=standard concentration = 5 mg / dl=1.62 m mol /L.

Direct Colorimetric Determination of Alkaline Phosphatase

Principle

$$\text{P-nitrophenol phosphate} + H_2O \xrightarrow{AP} \text{phosphate} + \text{P-nitrophenol}$$

Sample

Serum

Reagents

Contents	*Concentrations in test*
1.Buffer	
Diethanolamine buffer	1 m mol /L, PH 9.8
Mg Cl_2	0.5 m mol /L
2.Substrate	
P-nitrphenyl phosphate	10 m mol/L

Preparation of Solutions

1. Buffer

Contents ready for use, stable up to the expiry date when stored at 2-8°C.

2.Substrate

One vial of substrate was reconstituted in 6.5 ml for the (20 x 6.5 ml) kit (AP 500).it is stable for 30 days at 2-8°C or for 3 days at 15-25°C.

procedure

At room temperature, 0.02 ml of each sample was pipetted, 1 ml of the reagent was added, mixed and initial absorbance was read at 405 nm in 1 cm light path cuvette against air. Readings were taken also after 1, 2 and 3 minutes.

Calculation

It is calculated from the following formula:

$$U / L = 2760 \times A_{405\ nm} / \text{min}$$

Bone Mineral Densitometry:

Bone mineral density (BMD) was measured with a Lunar DX-L dual energy X-ray absorptiometry and expressed as the amount of mineral (BMC) (in grams) divided by the area scanned (in cm^2).

BMD = BMC(g)/Area ($cm^{2)}$

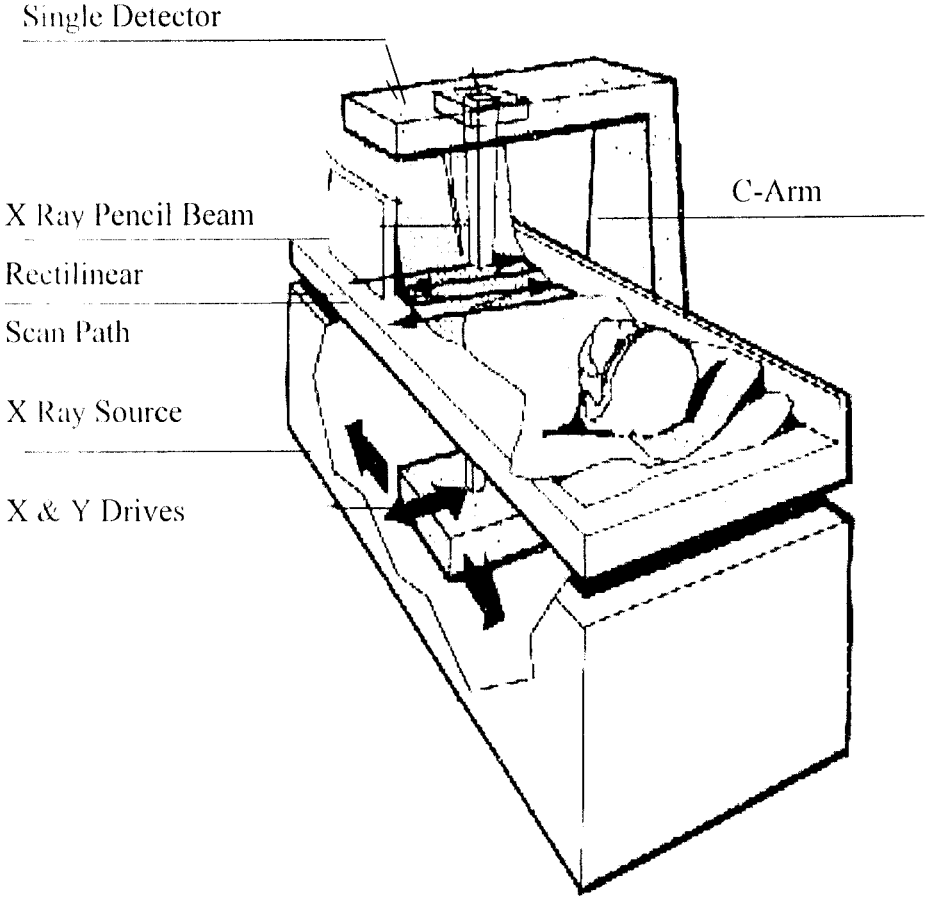


Fig. (11): Schematic illustration of DXA system using pencil beam single detector ***(Wahner & Fogelman, 1995).***

Fig (12) : Dual energy X –ray absorptiometry

Patient positioning

Children were examined while they were in the supine decubitus position with partial elevation of the lower limbs to obtain optimal separation of the lumbar vertebrae, thus decreasing physiologic spinal lordosis. The patient should be aligned in the middle of the table parallel to the longitudinal table axis. All metal items should be removed from clothing. Metal in belts, coins in pockets, and wires in corsets, brassieres or trusses can interfere. The abdominal thickness should be measured routinely if subjects appear unusually obese or thin. Weight and height should be determined for calculating the body index. Body index is determined by weight (kg)/height $(m)^2$. Though the need for data correction in case of obesity is well documented. Data from patients over 90 Kg of weight require normalization of data for body index or weight.

Scanning

In the lumbar spine, selected regions of interest include the second, third and fourth lumbar vertebrae. The area to be scanned ranges from 2.5 to 5 cm below the anterior margins of the iliac crest to just above the tip of the xiphoid. Some laboratories routinely include L1 for a longer region of interest (L1-L4). BMD tends to be slightly lower when L1-L4 is used, because BMC and BMD of lumbar vertebrae is lowest in L1.

During the entire period work, quality assurance calibration was performed on the apparatus three or more times per week. There was no long term drift in the X-ray voltage (76 kVp) or X-ray current (150 μA), and collimation was a constant 1.68 mm for the Lunar DX-L absorptiometer.

There were no changes in the X-ray source nor in the technique utilized.

Comparison of measurements with a reference population

The patient's measured BMD is compared with both age- and sex-matched normal people and with young normals (that is, maximal bone mass). The comparisons are indicated in both SD (standard deviation) and percent values, and can be converted to percentiles. The Z-score is calculated as:

$$\text{Z score} = \frac{P - M_c}{SD_c}$$

Where P is the measured patient value, M_c is the mean value for sex and age-matched controls and SD_c is the standard deviation of the mean value for sex- and age-matched controls. The Z score is a measure of the difference between the patient's BMD and the mean value of the age - matched peers [Normal range +1 to –1 (figure 13)]; osteopenia [= if Z score < -1 (figure 14)] and osteoporosis[= if Z score < -2 (figure 15)].

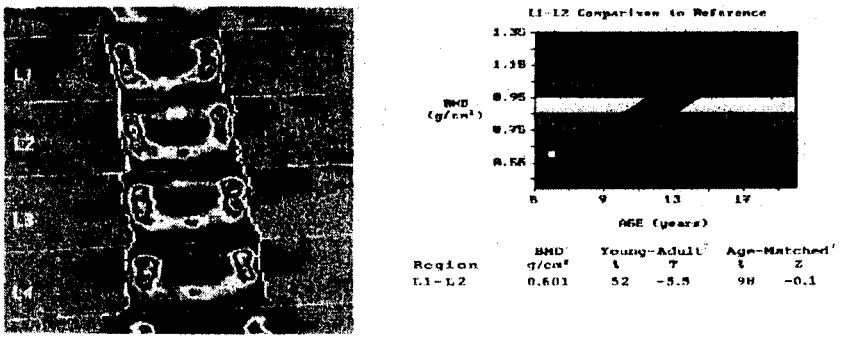


Figure (13): Osteodensitometry of lumbar spines showing normal bone density (Z score –0.1).

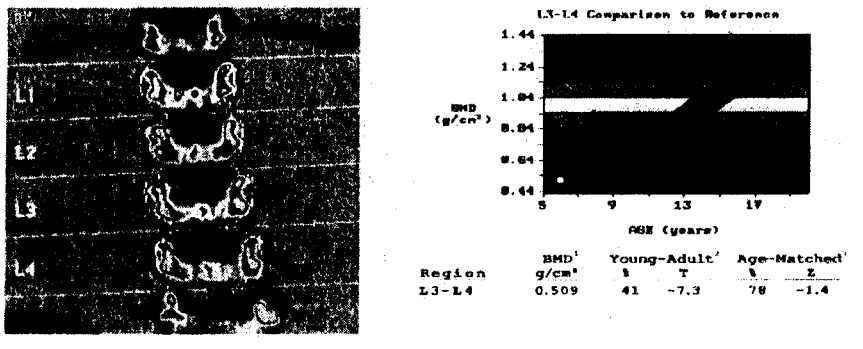


Figure (14): Osteodensitometry of lumbar spines showing osteopenia (Z score –1.4).

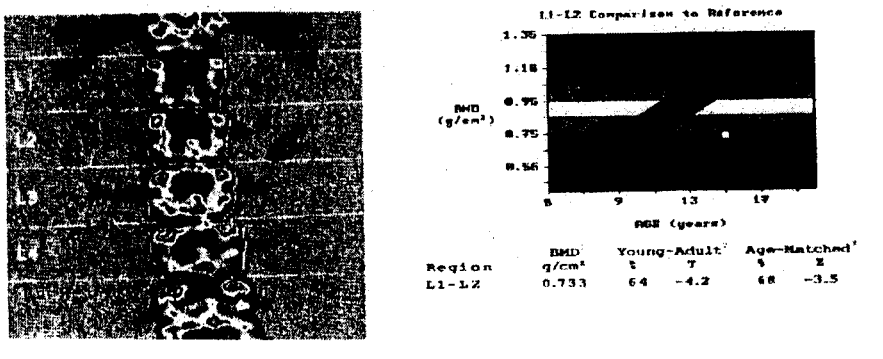


Figure (15): Osteodensitometry of lumbar spines showing osteoporosis (Z score –3.5).

- For every standard deviation of reduction in bone mass, the fracture risk doubles
- The principle of DXA is that we use a pencil –beam of x-rays emitted from an x-ray tube to provide the dual energies.
- The energies are produced either by rapid switching between 70 and 140 kvp to produce effective energies of 45 and 100 kev or by filtering the output of a constant – potential X-ray tube with rare earth filters.
- Recently fan- beam DXA systems were intrcdnced in this system we use fan beam of X- rays in conjunction with a multi detector array counters. In this technique the examination time is shorter and the quality of images is more better.
- Data expressed on curve in which the range of energy is blotted and translated into BMD. The low energy area corresponds to the low BMD and the high energy area corresponds to the high BMD.

Results

RESULTS

This study was done on two groups; patients group and control group. **The patients group** included 30 well known cases of primary epilepsy (20 males and 10 females). They were treated by valproic acid (VPA) or carbamazepine (CBZ) or both drugs. Their ages ranged from 6-16 years (mean age 9.50 ± 2.99). We have 22 epileptic patients were under treatment with monotherapy of AEDs (either VPA or CBZ) and 8 patients were on polytherapy (both VPA and CBZ). The selected group of patients were under treatment for more than one year where 80% were diagnosed as GTC seizures, 13.3% as absence seizures and 6.6% as focal seizures. **The control group** included 12 healthy children (6 males and 6 females) of the same age and social class (mean age 8.05± 1.18).

Antiepileptic drug therapy in our study showed that 36% of our patients had decreased mean serum level of vitamin D, 50% had hypocalcemia, 40% had hypophosphatemia and 56% had increased mean serum level of alkaline phosphatase .

Our results are illustrated in the following tables and figures.

Table (11) : Collective data of patients group

Ser. No.	Age Yr.	Sex	Wt Cent	Ht. Cent.	Seizure Type	Freq./ Mon.	Therapy	Duration Yr..	Neuro-exam.	Vit. D ug/ml	Ca++ mg/dl	P++ mg/dl	Alk.ph U/L	Bio. Ost.	Z-Score
1	12	M	50	75	GTC	1	VPA &CBZ	5	Free	8.6	6.4	4.3	260	+	-1. 2
2	6.5	M	25	25	GTC	0	VPA	3.5	Free	36.8	9.5	6.5	220		-0. 7
3	12	F	50	75	Abs.	0	VPA	1.5	Free	20.4	10.8	4.9	150		+0.4
4	11.5	M	25	25	Abs.	1.25	VPA	4.5	Free	18.5	9.3	5.3	180		-1.2
5	14	F	10	25	GTC	1	VPA &CBZ	6	Free	10.1	8.4	3.1	390	+	-1.3
6	6	M	75	50	Abs.	0	VPA &CBZ	3	Free	19.1	9.4	4.8	350		-0.3
7	7.5	M	25	15	GTC	1.25	CBZ	6	Free	12.1	8	4.2	385	+	-0.9
8	11	F	90	75	Foc.	1	VPA &CBZ	5.5	Free	10.2	8.7	4.3	500	+	-0.4
9	15	F	50	25	GTC	2	VPA	2.5	Free	14.7	8.7	5.1	206		-3.5
10	10.5	M	75	75	GTC	0.25	CBZ	4	Free	24.9	9.3	4.9	292		+0.3
11	8	M	90	59	GTC	0.5	VPA	1.5	Free	34.1	10.2	5.2	177		+0.7
12	6	m	75	50	GTC	0.6	VPA &CBZ	1	Free	15.7	9	6.5	123		-0.2
13	8.5	M	25	25	GTC	3	CBZ	3	Free	10.9	8	3.2	309	+	-3.0
14	7	F	75	75	GTC	0.5	CBZ	5.5	Free	15.1	8.2	4.4	530		-0.1
15	6	F	75	90	GTC	0	VPA	1	Free	30.7	10.2	4.7	182		-0.1
16	12	M	10	25	Foc.	1	CBZ	4	Free	24.9	8.6	4.1	298		-o.7
17	10.5	M	75	75	GTC	0.16	CBZ	2	Free	22.5	8.8	5	206		+0.3
18	6	M	10	10	GTC	2.5	VPA &CBZ	6	Free	9.3	7.1	3.2	299	+	-2.3

Cont.Table (11)

Ser. No.	Age Yr.	Sex	Wt Cent.	Ht. Cent.	Seizure Type	Freq./ Mon.	Therapy	Dur. Yr..	Neuro-exam.	Vit. D ug/ml	Ca++ mg/dl	P++ mg/dl	Alk.ph U/L	Bio. Ost.	Z-Score
19	13	M	20	20	GTC	2	VPA	7	Free	18.9	8.0	5.1	300		-3. 4
20	11.5	F	10	35	GTC	5	VPA	4.5	Free	19.6	9.1	5.7	210		-0. 8
21	8	M	75	75	GTC	1.25	CBZ	5	Free	8.6	8.4	4	395	+	-0.9
22	7	M	50	50	GTC	2.25	VPA	3	Free	21.6	10.1	4.5	180		-1.8
23	6	M	95	95	GTC	0.5	VPA	4	Free	34.8	9.7	5	202		-0.9
24	12.5	M	10	25	Abs	6.25	VPA	5	Free	25.6	9	5.2	286		-1.8
25	11	M	50	50	GTC	0.5	VPA	2.5	Free	21.6	10.1	4.5	216		-0.4
26	16	F	5	25	GTC	3.5	VPA	7	Free	20.3	8.2	4.6	253		-2. 3
27	7	M	30	30	GTC	3	VPA &CBZ	4	Free	12.4	7.8	3.4	373	+	-1.9
28	6	F	25	35	GTC	10	CBZ	6	Free	8.1	7.9	3.9	255	+	+ 0.2
29	9	M	10	10	GTC	9.5	VPA &CBZ	6.5	Free	10.2	6	3.4	510	+	-1.1
30	8	F	25	35	GTC	3	VPA	5	Free	21.6	10.1	4.6	200		-1. 5

*VPA = Valproic acid
*GTC = Generalized tonic clonic
*M = Male * F = Female
*Vit. D : 15-80 ug/ml
* P : 4.5-6.5 mg/ml
* CBZ = Carbamazepine
*Abs. = Absence * Foc = Focal
*Bio. Ost. = biochemical osteomalacia
* Ca : 8.8-10.8 mg/dl
*Alk phos : up to 220 IU.

Table (12) : Collective data of control group

Ser. No.	Age Yr.	Sex	Wt. Cent.	Ht. Cent.	Gen. Exam	Neuro-Exam.	Vit. D ug/ml	Ca++ mg/dl	P++ mg/dl	Alk.ph U/L	Z Score
1	9.5	M	50	95	Free	Free	31. 4	8. 9	4. 3	190	+0. 5
2	7	M	75	95	Free	Free	50. 8	10. 3	5. 2	240	+1
3	7. 5	F	50	75	Free	Free	14. 3	8. 8	5. 3	210	-0. 3
4	8. 9	F	75	75	Free	Free	35. 2	8. 7	5. 6	270	+0. 8
5	7	F	90	50	Free	Free	21.6	9.7	6. 1	200	+0. 5
6	8. 8	M	75	75	Free	Free	55.0	9. 3	6. 5	122	+1. 0
7	7	M	75	90	Free	Free	11. 3	8. 7	6. 1	209	-0. 4
8	8. 5	F	75	75	Free	Free	55.7	9. 5	5. 4	275	+0. 2
9	9	F	75	95	Free	Free	58.3	8.7	6. 0	193	+0. 4
10	7	M	90	95	Free	Free	42. 6	9. 4	5. 6	200	+1. 0
11	10	F	50	90	Free	Free	50. 3	10. 3	5. 7	234	-0. 7
12	6.5	M	90	75	Free	Free	31.7	10. 2	3. 9	180	+0. 6

Table (13): Comparison of different parameters in patients as regards the age.

variable	Mean B *Age > 8 Yr* n=16	Mean A *Age:6-8Yr.* n=14	P- value
Age years	11.1±2.1	6.8±.7	0.000
Weight cent.	43.8±28.1	61.0±27.9	0.055
Height cent.	52.7±29.4	58.2±27.8	0.536
VitD ug/dl	25.5±15.7	21.1±12.2	0.324
Ca mg/dl	8.7±1.0	9.1±0.9	0.251
P mg/dl	4.8±0.9	4.7 ±1.0	0.863
Alk.phos. IU/L	265 ±97	255 ±101	0.736
Z score	-0.8 ±1.3	-0.4 ±0.9	0.247

Table (13) shows no significant difference regarding the mean anthropometric measures, biochemical results and Z score between the two studied groups.

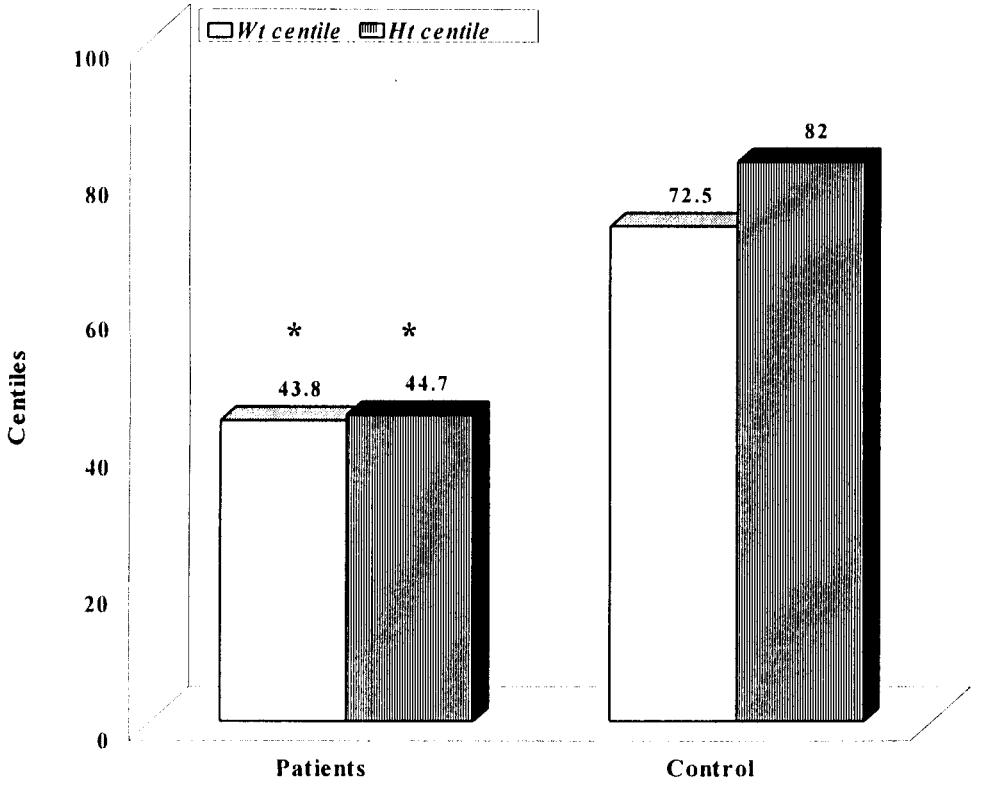
Table (14) : Comparison between patients and control groups.

	Patients n = 30	Control n = 12	P-value
Weight centile	43.8±29.4	72.5±.15.0	0.02 (S)
Height centile	44.6±25.6	82.0±13.7	0.03 (S)
Vit D ug/ml	17.5±7.4	38.2± 16.4	0.000 (HS)
Ca mg/dl	8.6±1.1	9.3± 0.6	0.08 (NS)
P mg/dl	4.5± 0.8	5.3± 1.0	0.02 (S)
Alk.phos IU/L	281±107	210±41	0.03 (S)
Z-score	-1.0 ± 1.10	0.38±0.5	0.000 (HS)

NS = Non significant HS = Highly significant S = Significant

This table shows a significant decrease in the mean weight and height percentiles ($P<0.05$) in patients group compared to control group, a highly significant decrease in mean serum $25(OH)D_3$ ($P<0.001$), a significant decrease in serum P ($P<0.05$) and a significant increase in serum alkaline phosphatase ($P<0.05$) of patients group compared to control group.and a highly significant decrease in Z score ($P<0.001$) of patients group compared to control group.

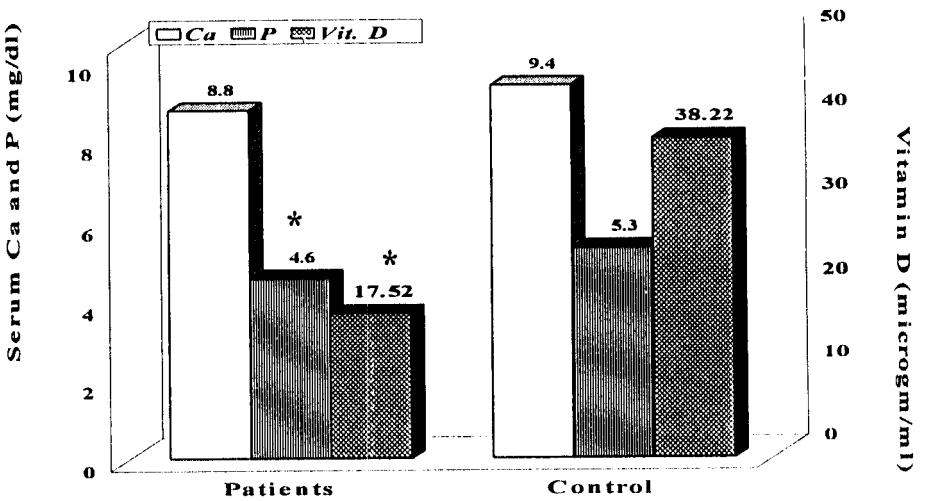
Fig (16) : Comparison between patients and control groups as regards anthropometric measures.



***= p<0.05**

Fig (16) shows a significant decrease in the weight and height percentiles (P<0.05) in patients group compared to control group.

***Fig (17) : Comparison between patients* and control groups as regards biochemical results.**



***= p<0.05**

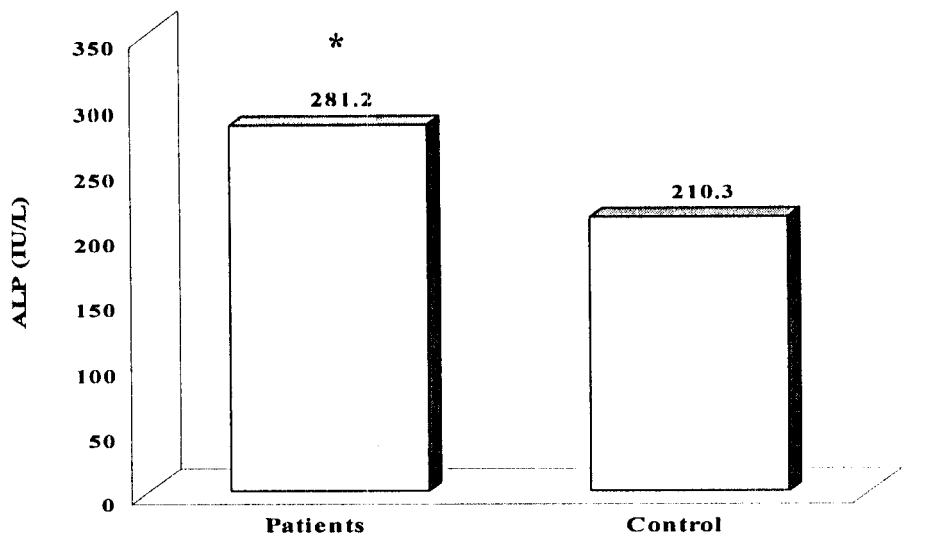
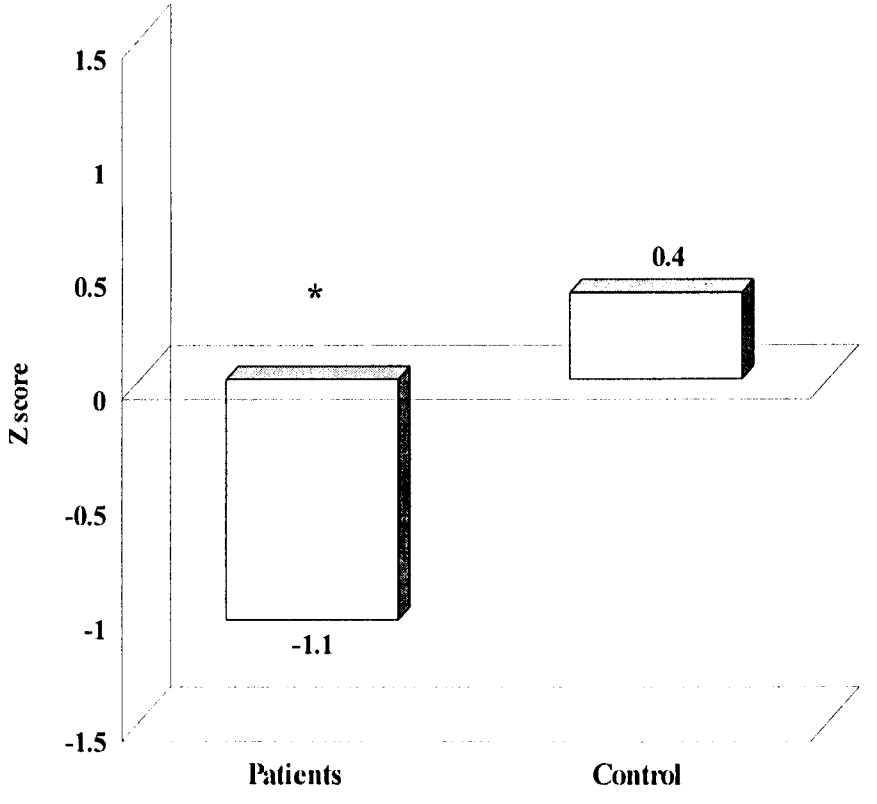


Fig (17) shows a highly significant decrease in mean serum $25(OH)D_3$, a significant decrease in mean serum P and a significant increase in mean serum alkaline phosphatase in patients group compared to control group

***Fig (18) : Comparison between patients* and control groups as regards Z-score.**



***= p<0.05**

Fig (18) shows a highly significant decrease in mean Z score ($P<0.001$) of patients group compared to control group.

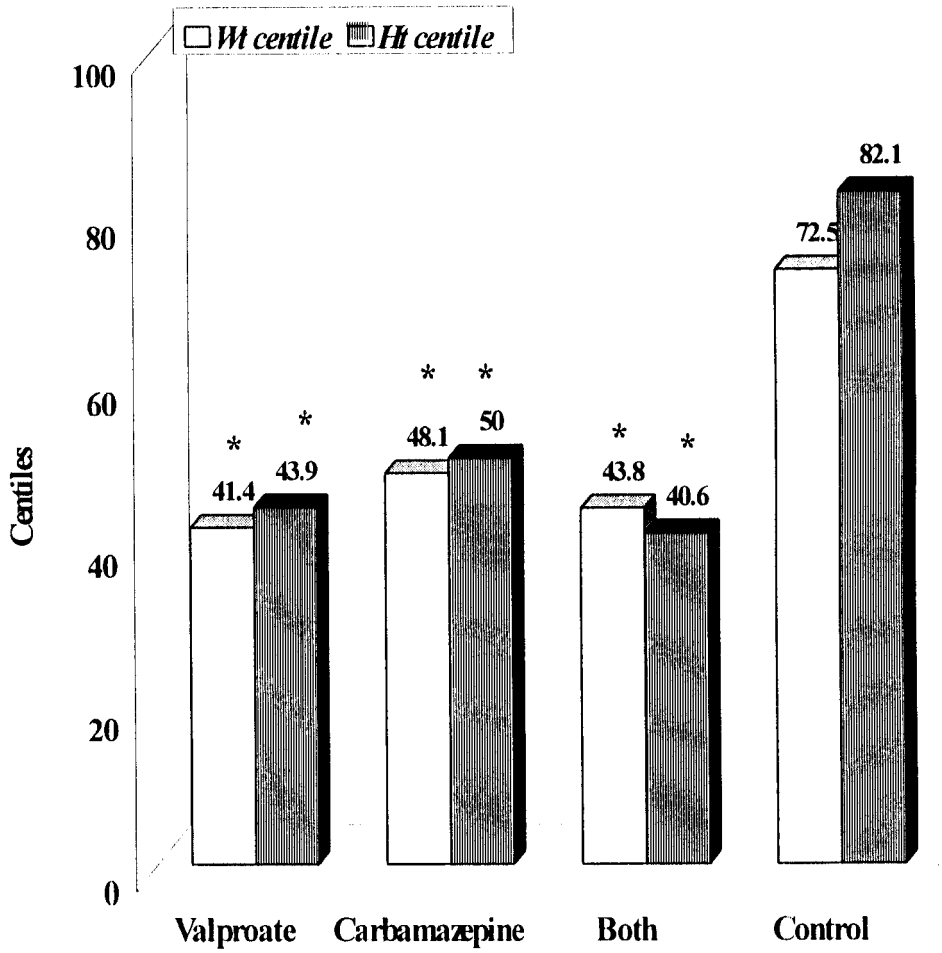
Table (15) : Comparison between mean levels of anthropometric measures, biochemical results and Z score of the 4 studied groups.

Variable	Gr. I VPA n=14	Gr. II CBZ n=8	Gr. III Polyth. n=8	Gr. IV Control n=12	P-value					
					IvsIV	IIvsIV	IIIvsIV	IvsII	IvsIII	IIvsIII
Duration	3.7 ± 1.8	4.4 ± 1.4	4.6 ± 1.8	--	--	--	--	0.387 (NS)	0.308 (NS)	0.825 (NS)
Weight Centile	41.1 ±29.3	48.1 ±29.1	43.7 ± 35.2	72.5 ± 15.0	0.002 (S)	0.02 (S)	0.01 (S)	0.61 (NS)	0.86 (NS)	0.79 (NS)
Height Centile	43.9 ±26.0	50.0 ±27.2	31.8 ±27.3	82.0 ± 13.7	0.000 (HS)	0.002 (S)	0.000 (HS)	0.61 (NS)	0.77 (NS)	0.91 (NS)
Vit. D ug/dl	22.4 ± 6.6	14.6 ± 6.1	11.7 ± 3.8	38.2 ± 16.6	0.003 (S)	0.001 (S)	0.0001 (HS)	0.01 (S)	0.0004 (HS)	0.2 (NS)
Ca mg/dl	9.5 ± 0.8	8.4 ± 0.4	7.8 ± 1.2	9.3 ± 0.6	0.67 (NS)	0.001 (S)	0.001 (S)	0.002 (S)	0.001 (S)	0.26 (NS)
P mg/dl	5.0 ± 0.5	4.2 ± 0.5	4.0 ± 1.1	5.3 ± 1.0	0.46 (NS)	0.01 (S)	0.02 (S)	0.002 (S)	0.01 (S)	0.72 (NS)
Alk.phos IU/L	211 ± 42	333 ± 100	350 ± 126	210 ± 41	0.93 (NS)	0.001 (S)	0.002 (S)	0.001 (S)	0.001 (S)	0.77 (NS)
Z-score	-1.2 ± 1.2	-0.6 ± 1.0	-1.0 ± 0.7	0.3 ± 0.5	0.000 (HS)	0.01 (S)	0.001 (S)	0.22 (NS)	0.70 (NS)	0.32 (NS)

NS = Non significant HS = Highly significant S = significant

Table (15) shows a significant decrease ($P<0.05$) of weight percentiles of the three groups of patients when compared to control group, a significant decrease of height percentiles of CBZ group when compared to control group, and a highly significant decrease ($P<0.001$) of height percentiles of VPA group and polytherapy group when compared to control group. As regards biochemical measures there is a significant decrease ($P<0.05$) of mean serum level of Ca, P and a significant increase ($P<0.05$) of alkaline phosphatase of both CBZ and polytherapy groups when compared to control group. Serum vitamin D shows a significant decrease in both VPA and CBZ groups and a highly significant decrease in polytherapy group . As regards Z-score there is a highly significant decrease in VPA group while CBZ and polytherapy groups show a significant decrease when compared to control group.

Fig (19) : Comparison between the 4 studied groups as regards anthropometric measures



*= p<0.05

Fig (19) shows a significant decrease of weight and height percentiles of the 3 groups of the patients compared to control groups

Fig (20) : Comparison between the 4 studied groups as regards biochemical results

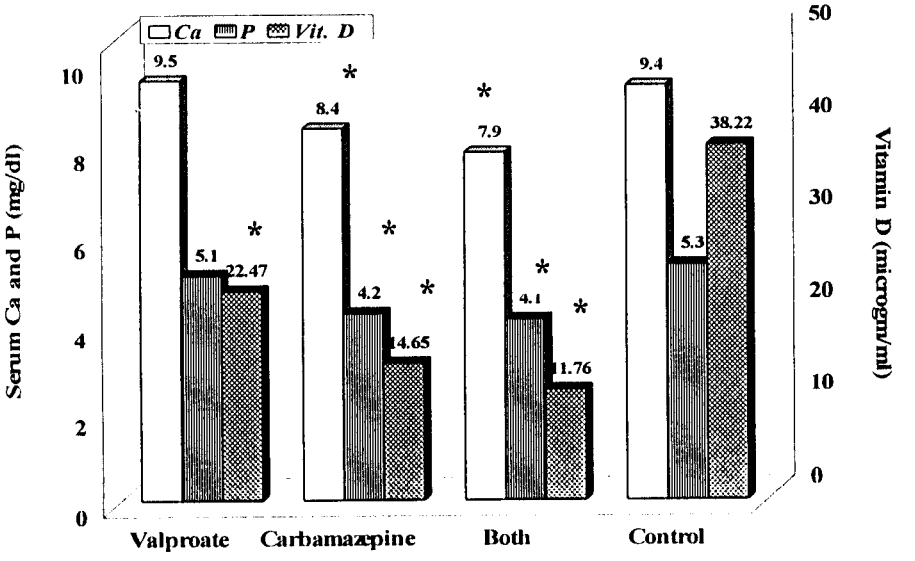


Fig (20) shows a significant decrease of mean serum level of Vit.D_3 of the 3 groups of patients. Mean serum level of Ca, P of CBZ and polytherapy groups show a significant decrease. Mean serum level of alkaline phosphatase of CBZ and polytherapy groups show a significant increase when compared to control group.

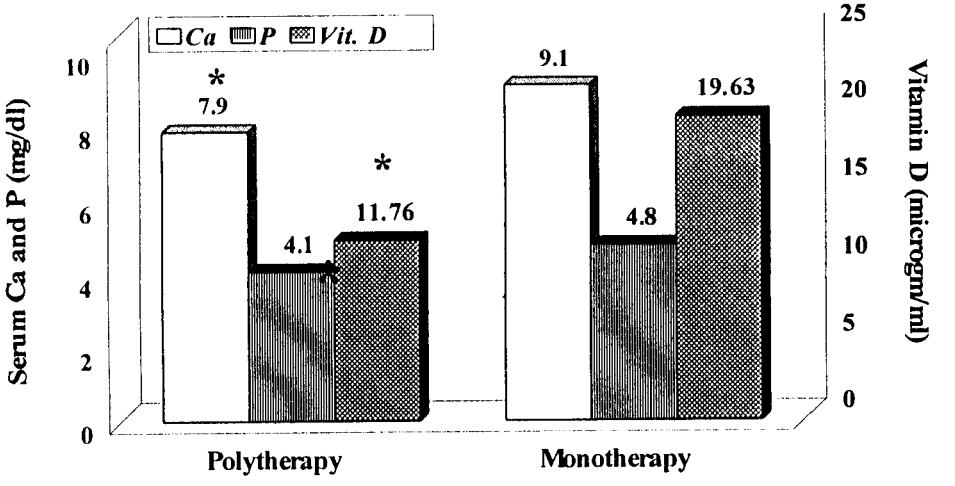
Table (16) Comparison between polytherapy Vs monotherapy groups.

	Polytherapy P n = 8	Monotherapy M n = 22	P value P vs M
Weight Centile	43.7 ± 33.2	43.8 ± 28.7	0.99 (NS)
Height centile	40.6 ± 26.1	46.1 ± 26.0	0.61 (NS)
Vit.D ug/dl	11.7 ± 3.8	19.6 ± 7.3	0.008 (S)
Ca mg/dl	7.8 ± 1.2	9.1 ± 0.8	0.004 (S)
P mg/dl	4.0 ± 1.1	4.7 ± 0.6	0.58 (NS)
Alk.ph IU/L	350 ± 126	256 ± 90	0.03 (S)
Z-score	-1.0 ± 0.7	-1.0 ± 1.2	0.90 (NS)

NS = Non significant HS = Highly significant S = Significant

Table (16) shows a significant decrease ($P<0.05$) of mean serum level of vitamin D, Ca and a significant increase of mean serum level of alkaline phosphatase of polytherapy group when compared to monotherapy group.

Fig (21) : Comparison between polytherapy versus monotherapy groups as regards biochemical results



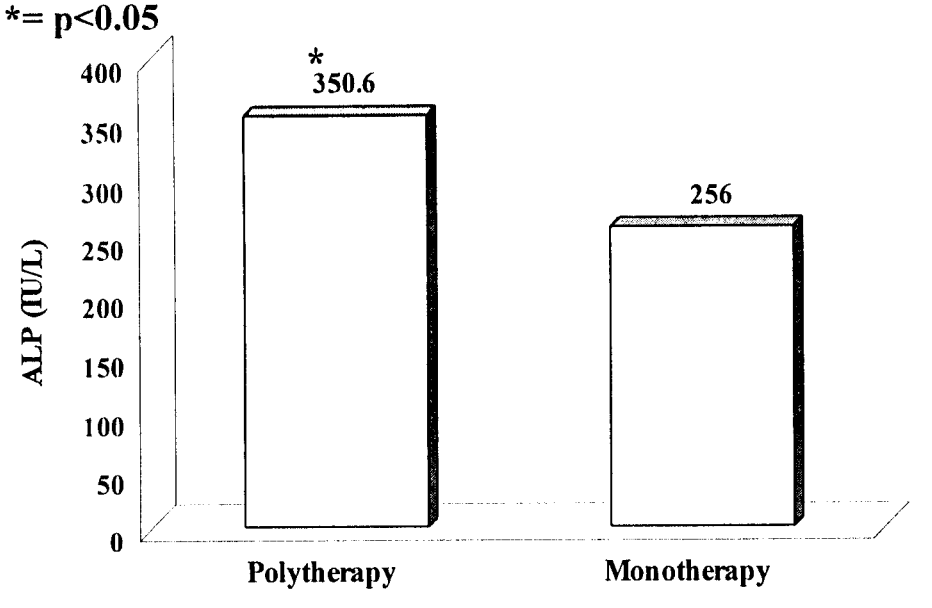


Fig (21) shows a significant decrease of mean serum Ca and vitamin D_3, and a significant increase of mean serum alkaline phosphatse of polytherapy group compared to monotherapy group.

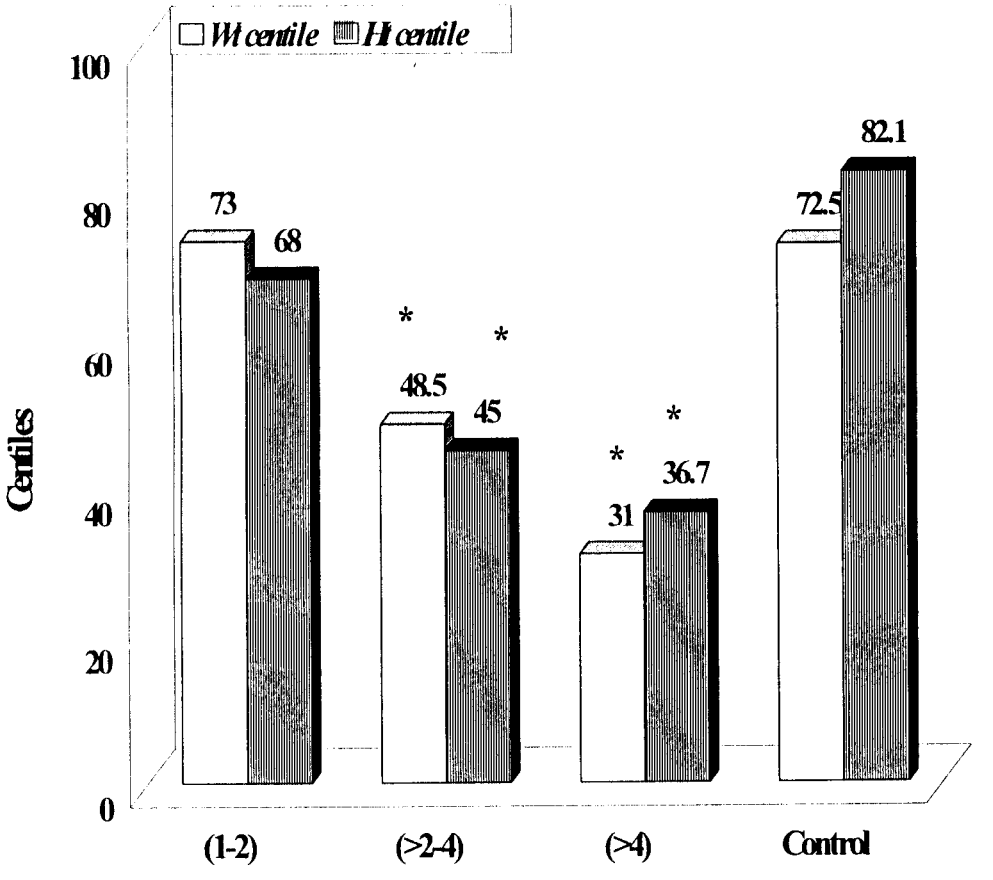
Table (17) : Effect of duration of drug therapy on patients groups

Variable	Gr. I D=1-2 Yr. n=5	Gr. II D=>2-4 Yr. n=10	Gr. III D=>4 Yr. n=15	Gr. IV Control n=12	P-value					
					IvsIV	IIvsIV	IIIvsIV	IvsII	IvsIII	IIvsIII
Duration	1.4 ± 0.4	3.3± 0.6	5.6± 0.8	--	--	--	--	0.000 (HS)	0.000 (HS)	0.000 (HS)
Weight Cent.	73.0± 14.4	48.5± 26.8	31.0± 27.8	72.5± 15.0	0.95 (NS)	0.01 (S)	0.000 (HS)	0.08 (NS)	0.005 (S)	0.13 (NS)
Height Cent.	68.0± 17.5	45.0± 24.2	36.6± 25.2	82.0± 13.7	0.09 (NS)	0.000 (HS)	0.000 (HS)	0.08 (NS)	0.01 (S)	0.42 (NS)
Vit D ug/dl	24.7± 7.5	18.6± 7.2	14.3± 5.3	38.2± 16.4	0.10 (NS)	0.002 (S)	0.000 (HS)	0.15 (NS)	0.005 (S)	0.11 (NS)
Ca mg/dl	9.8 ± 0.8	9.1± 0.8	8.1± 1.0	9.3± 0.6	0.27 (NS)	0.41 (NS)	0.002 (S)	0.15 (NS)	0.007 (S)	0.02 (S)
P mg/dl	6.2± 0.7	4.6± 0.9	4.3± 0.8	5.3± 1.0	0.93 (NS)	0.10 (NS)	0.01 (S)	0.19 (NS)	0.03 (S)	0.45 (NS)
Alk.phos U/L	167± 31	261± 68	330± 115	210± 41	0.058 (NS)	0.03 (S)	0.002 (S)	0.01 (S)	0.006 (S)	0.12 (NS)
Z score	-0.2± 0.3	-1.2± 1.2	-1.4± 0.9	0.3± 0.5	0.57 (NS)	0.000 (HS)	0.000 (HS)	0.02 (S)	0.002 (S)	0.96 (NS)

D = duration of therapy

This table shows a significant decrease in anthropometric measures, mean serum vitamin D, Ca, Pand Z score and a significant increase in mean serum level of alkaline phosphatase of group1 compared to groupIII. There is also a significant decrease in serum Ca of group II compared to group III. There is a significant decrease in Z-score, a significant increase in mean serum level of alkaline phosphatase of group I compared to group II.

Fig (22) : Effect of duration of drug therapy on patients group as regards anthropometric measures



***= p<0.05**

Fig (22) shows a significant decrease of weight and height percentiles of group II and group III when compared to control group. Group III shows a significant decrease of weight and height percentiles when compared to group I.

Fig (23) Effect of duration of therapy on patients groups as regards biochemical results

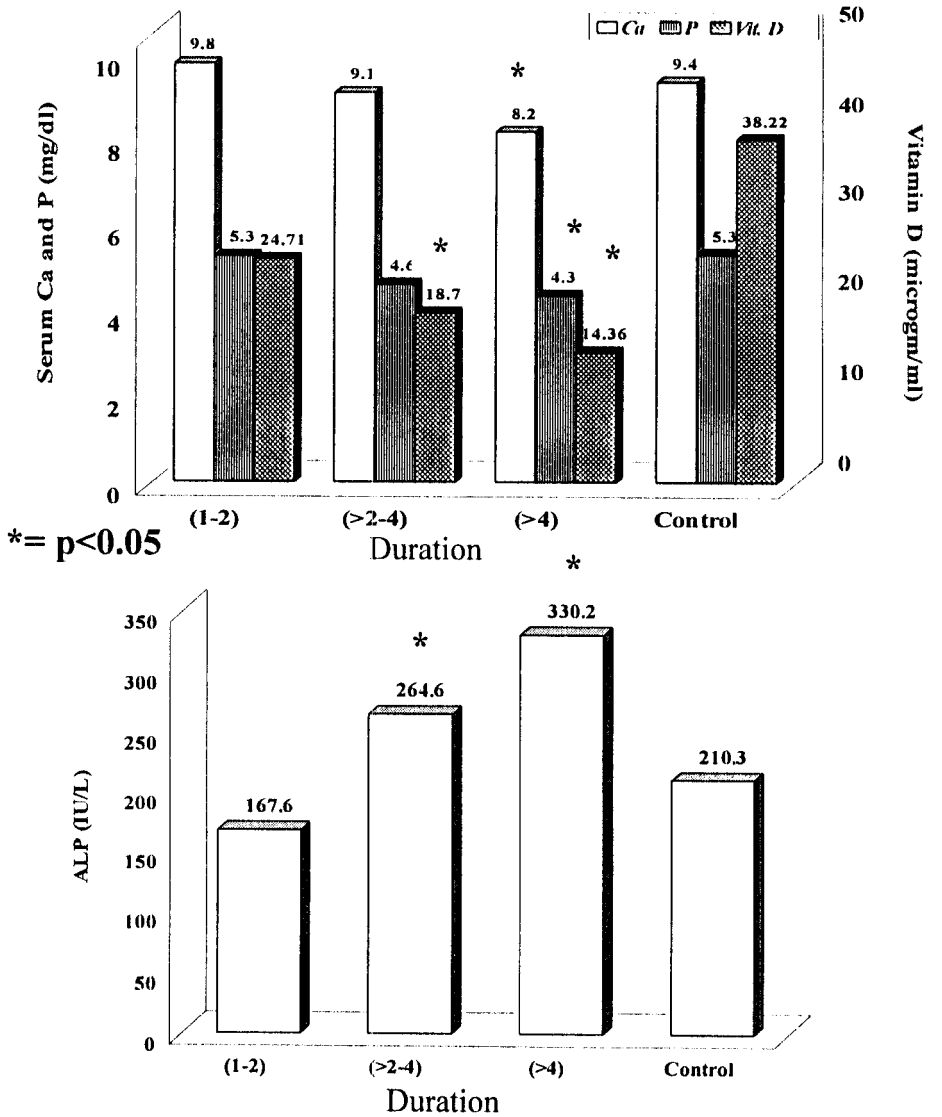


Fig (23) shows a significant decrease in mean serum level of vitamin D_3, Ca and P of group III when compared to group I. There is a significant increase in mean serum level of alkaline phosphatase of group II and group III compared to group I.

Fig (24) : Effect of duration of drug therapy on patients groups as regards Z score

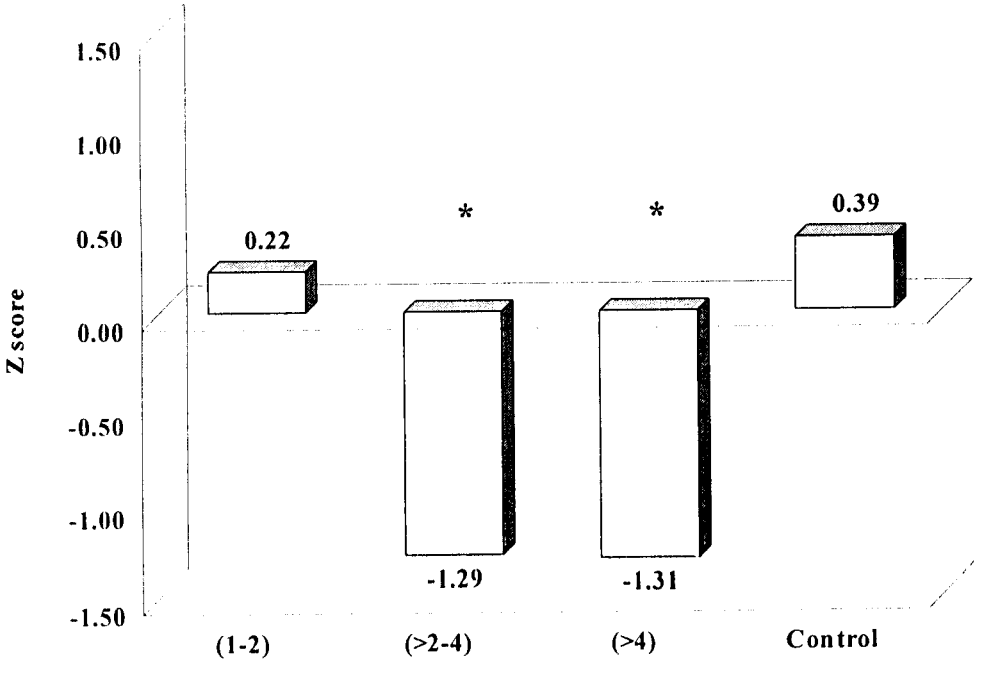


Fig (24) shows a highly significant decrease of Z score in group II and III compared to control group. There is a significant decrease of Z score in group II and group III compared to group I .

Table (18) : Chi – square test (BMD vs therapy) Observed values (Cell format : count/percent :total/percent :row/percent :column)

	Normal BMD (+1 to-1)	Osteopenia <-1	Osteoporosis <-2	Total
VPA group	7 23.33% 50.00% 41.18%	4 13.33% 28.57% 50.00%	3 10.00% 21.43% 60.00%	14 46.67 %
CBZ group	7 23.33% 87.50% 41.18%	0 .00% .00% .00%	1 3.33% 12.50% 20.00%	8 26.67%
VPA & CBZ group	3 10.00% 37.50% 17.65%	4 13.33% 50.00% 50.00%	1 3.33% 12.50% 20.00%	8 26.67%
Total	17 56.67%	8 26.67%	5 16.67%	30 100.00%

Table (18) shows that osteopenia (Z-score <-1) was reported in 8 patients about (26%) of all patients; of which 4 patients (13%) in VPA group and 4 patients (13%) in polytherapy group. Osteoporosis (Z-score <-2) was reported in 5 patients, about (16%); of which 3 patients in VPA group, 1 patient (3%) in CBZ group and 1patient (3%) in polytherapy group. Normal BMD was reported in 17 patients, about (56%); of which 7 patients (23%) in VPA group, 7 patients (23%) in CBZ group and 3 patients in polytherapy group. This table shows that VPA had the worst effect on BMD.

Table (19) : Comparison between patients and control groups on the view of BMD results

Variable	Gr.I N n=17	Gr. II P N=8	Gr. III O n=5	Gr. IV Control N=12	P-value					
					NvsC	PvsC	OvsC	NvsP	NvsO	PvsO
Duration	3.5 ± 1.7	4.8 ± 1.0	5.1 ± 2.1	–	–	–	–	0.6 (NS)	0.04 (S)	0.80 (NS)
Age Yr.	8.5± 2.4	10.1±2.7	11.7± 4.2	8.0± 1.1	0.51 (NS)	0.03 (S)	0.01 (S)	0.15 (NS)	0.04 (S)	0.43 (NS)
Weight Cent	58.5± 2.4	26.2± 16.6	22.0± 17.5	72..5± 15.0	0.13 (NS)	0.000 (HS)	0.000 (HS)	0.007 (S)	0.01 (S)	0.06 (NS)
Height Cent.	57.0±24.3	38.1± 20.8	21.0± 6.5	82.0± 13.7	0.003 (S)	0.000 (HS)	0.000 (HS)	0.07 (NS)	0.004 (S)	0.23 (NS)
Vit. D ug/dl	19.3±8.1	14.6± 6.4	15.8± 5.2	38.2± 18.4	0.000 (HS)	0.001 (S)	0.01 (S)	0.16 (NS)	0.37 (NS)	0.72 (NS)
Ca mg/dl	9.1±0.8	8.3± 1.5	8.0±0.5	9.3± 0.6	0.4 (NS)	0.6 (NS)	0.01 (S)	0.11 (NS)	0.009 (S)	0.69 (NS)
P mg/dl	4.8±0.7	4.1±0.9	4.2±0.9	5.3±1.0	0.19 (NS)	0.02 (S)	0.06 (NS)	0.06 (NS)	0.58 (NS)	0.9 (NS)
Alk.phos. U/L	275± 119	297± 118	273± 43	210± 41	0.07 (NS)	0.02 (S)	0.01 (S)	0.67 (NS)	0.96 (NS)	0.67 (NS)
Z-score	-0.2± 0.5	-1.5± 0.3	-2.9± 0.5	0.3± 0.5	0.003 (S)	0.000 (HS)	0.000 (HS)	0.000 (HS)	0.000 (HS)	0.000 (HS)

N = Normal BMD P = Osteopenia O = Osteoporosis

This table shows a significant increase in duration, age; a significant decrease in weight and height percentiles, mean serum Ca when osteoporotic group compared to normal BMD group . There is a highly significant decrease in Z score in osteoporotic group compared to normal BMD group or osteopenic group. There is a highly significant decrease in Z score of osteopenic group compared to normal BMD group.

Table (20) shows percentage frequency of positive bone resorption by BMD versus biochemical results. Observed values (Cell format : count/percent : total/percent :row/ percent : column)

	Abnormal BMD	Normal BMD	Total
Abnormal BIO.	6 20% 60% 46%	4 13% 40% 23.5%	10 33.3%
Normal BIO .	7 23.3% 35% 53.8%	13 43.3% 65% 65.4%	20 66.6%
Total	13 43.3%	17 56.6%	30 100%

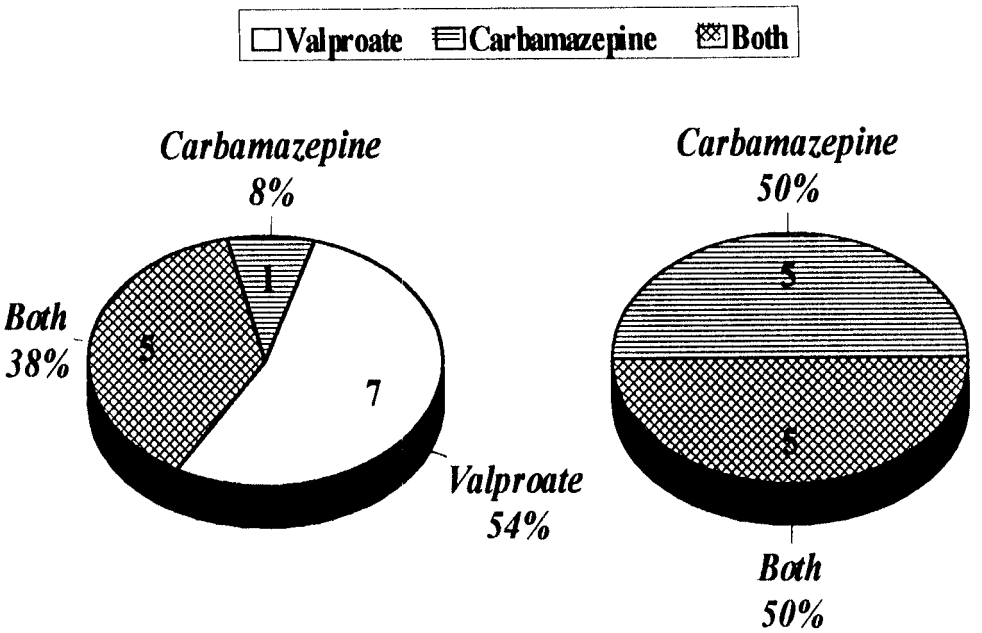
Table (20) shows that abnormal biochemical results suggestive of antiepileptic osteomalacia were seen in 10 patients (33.3%) of cases, of which 6 patients (20%) had abnormal BMD and 4 patients (13.3%) had normal BMD. On the same time abnormal BMD was seen in 13 patients (43.3%) of which 6 patients (20%) had abnormal biochemical results and 7 patients (23.3%) had normal biochemical results.

Table (21) shows percentage positivity of BMD compared to antiepileptic biochemical osteomalacia in patients group.

	Abnormal BMD	Biochemical osteomalacia
VPA group	23%	00%
CBZ group	3%	17%
VPA & CBZ group	17%	17%

Table (21) shows that abnormal BMD appear in about 43% of patients while biochemical osteomalacia appear in about 34% of patients. VPA therapy had the worst effect on BMD as it results in abnormal BMD in about 23% of all patients. CBZ therapy had the worst effect on biochemical results as it results in biochemical osteomalacia in about 17% of all patients.

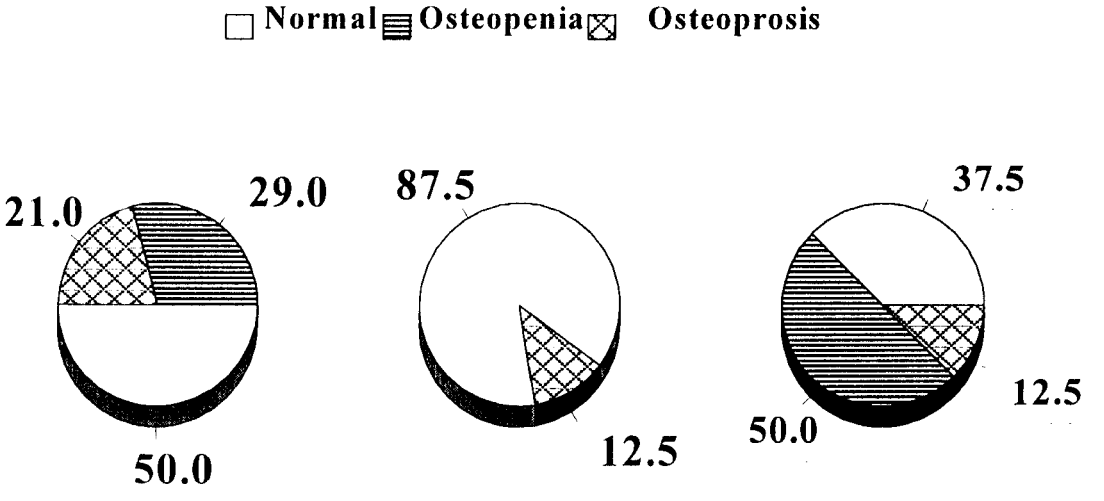
Fig (25) : Distribution of abnormal BMD and antiepileptic osteomalacia in patients groups



Abnormal BMD

Antiepileptic Biochemical Osteomalacia

Fig (26) Distribution of abnormal BMD among patients groups



Discussion

Discussion

Long term therapy with AEDs is associated with many toxic and hypersensitive reactions; of these are disturbances in vitamin D and Ca which was first noticed by ***Kruse (1968).*** Anticonvulsants are known to increase the metabolism of vitamin D in the liver with the resultant formation of inactive vitamin D metabolite, with consequent decrease in serum level of vitamin D, Ca, P and increase in serum alkaline phosphatase This state of biochemical osteomalacia is called antiepileptic osteomalacia ***(Winnacker et al., 1977).***

The present study showed a statistically significant decrease in mean weight and height percentiles ($P<0.05$) in children treated with AEDs compared to control group. This agrees with the work of ***AL Abd (1996)*** and ***Invitti et al (1988)*** who stated that chronic administration of VPA increases the activity of aminobutyric acid system resulting in blunting of the stimulated adrenocorticotrophic and growth hormones resulting in reversible arrest of skeletal growth. Moreover ***Robinson et al (1983)*** stated that antivonvulsants produce a state of hypoparathyroidism in epileptic children, manifested by reduced skeletal growth, premature epiphyseal fusion and smaller teeth. This is on the contrary to ***Macardle et al (1987)*** who reported that children with epilepsy treated with AEDs grow and mature normally with no evidence of deviant growth patterns. Also, ***Penry and Dean (1989)*** stated that some AEDs especially sodium valproate may lead to weight gain in medicated patients.

Treated group in our study showed decreased mean serum vitamin D in 36% of patients, hypocalcemia in 50% hypophosphatemia in 40% and lastly increased mean serum alkaline phosphatase in 56% of patients. The full picture of biochemical osteomalacia appeared in 10 patients (33%). This agrees with ***Kruse (1968)*** who reported that 15% of epileptic patients under treatment showed serum chemical and radiologic features of osteomalacia. ***Richen and Rowe (1970)*** showed a subnormal serum calcium level in 22.5% of patients and a raised alkaline phosphatase in 29%.

Our results agree with the study done by ***EL-Sayed et al (1999)*** who reported that VPA and CBZ either in monotherapy or polytherapy can result in anticonvulsant osteomalacia. ***Gough et al (1986)*** confirmed biochemical evidence for anticonvulsant osteomalacia with CBZ only and not with VPA and stated that the severity of anticonvulsant osteomalacia depends upon the dose, duration and number of AEDs.

On the contrary, ***Tjellesen et al (1983)*** stated that CBZ monotherapy does not has the side effects on bone metabolism known as anticonvulsant osteomalacia as their patients on CBZ had normal serum level of $25(OH)D_3$, but they had significant reduction in their serum Ca and significant increase in serum alkaline phosphatase. Also, ***Trias et al (1998)*** stated that there was no significant difference in the mean calcium and phosphorus levels but there was a statistically significant increase ($P<0.05$) in the mean alkaline phosphatase levels in

the study group on CBZ therapy compared to the control group.

Until now there has been no exact pathophysiologic theory for the explanation of the anticonvulsant-induced osteomalacia, but several mechanisms have been suggested. They generally assume that the drug mediated liver enzyme production causes an accelerated metabolic turnover of the active $1,25(OH)_2D_3$ to biologically inactive vitamin D metabolite. The resultant decrease of the $1,25(OH)_2D_3$ level then entails a deficiency of serum Ca and an increase in parathyroid hormone (PTH) which finally leads to an increased mobilization of Ca from the bone. Moreover, AEDs reduce gastrointestinal absorption of Ca thus producing an additional Ca deficiency and some authors assume this to be the primary effect ***(Wolschendorf, 1983).***

Chesney ***(1990)*** found that patients under antiepileptic treatment have reduced serum level of $25(OH)D_3$ and Ca because these drugs induce hepatic cytochrome P-450 hydroxylation enzyme activities. ***Michael and Nancy (1995)*** and ***Chesney (1990)*** found that patients under treatment with P-450 stimulating drugs as AEDs may decrease hydroxylated vitamin D with subsequent decrease in serum Ca which is presented clinically as osteomalacia in adults and rickets in children.

Although most of these biochemical investigations presented quantitative results, they do not admit immediate conclusions about the BMD since it has been found that the observed alterations of serum levels did not generally

correspond to the degree of demineralization. Non destructive methods only will be considered. Since both Ca and P the major components of bone mineral exhibit a relatively high mass absorption coefficient for ionizing radiation, radiologic investigation appears to be the most suitable technique for a non destructive determination of the actual BMD ***(Wolschendorf et al., 1983).*** It was proved that dual-energy X-ray absorptiometry provides a direct and precise measure of bone mineral density ***(Johnston et al., 1991).***

Spinal BMD in the present study showed a highly statistically significant reduction in epileptic children treated with VPA, and a statistically significant reduction in patients treated with either CBZ alone or CBZ and VPA together (polytherapy) as the mean Z score of the first group was statistically highly significantly lower than the control group and the mean Z score of the other 2 groups were statistically significantly lower than the control group. Dual energy x-ray absorptiometry showed that 8 patients (26% of all patients) had osteopenia (Z score <-1) distributed as 4 in VPA group and the other 4 in polytherapy group and 5 patients (16% of all patients) had osteoporosis (Z score <-2) distributed as 3 in VPA group, 1 in CBZ group and the other 1 in polytherapy group.

There is no statistically significant difference between the mean Z score of our patients on polytherapy compared to monotherapy as each type of therapy had a highly significant decrease in mean Z-score when compared to control group. Also, the duration of AEDs therapy for more than 2 years had a highly significant decrease in mean Z-score when compared

to control group and also there is a significant decrease in the mean Z score of patients as the duration increases.

Our results agree with ***Gillis et al (1996)*** who reported that VPA monotherapy reduces BMD at the lumbar spine and femoral neck. ***Sheth et al (1995)*** reported that VPA and not CBZ monotherapy showed significant reduction in BMD of children with idiopathic epilepsy and may increase the risk of osteoporotic fractures. Children treated with valproate had a 14% (P=0.003) and 10% (P=0.005) reduction in bone mineral density at the axial and appendicular sites respectively. The reduction in BMD increased with the duration of valproate therapy. These findings agree with our study. In carbamazepine-treated children a reduction of less than 5% (not statistically significant) was found in BMD at both sites i.e; carbamazepine did not significantly reduce bone mineral density.

Our results are in agreement with ***EL Sayed et al (1999)*** who showed a statistically significant reduction in spinal BMD in epileptic children taking either VPA or CBZ monotherapy or polytherapy (VPA and CBZ). ***Chung and Ahn (1994)*** reported that AEDs significantly reduce BMD only if taken for more than 24 months, whereas BMD was normal if treatment was for less than 24 months.

Our study disagrees with ***Wolschendorf et al (1983)*** who reported that phenytoin monotherapy in adults reduces bone mineral density 1.2% per year of treatment and the addition of phenobarbital or carbamazepine increased the rate of mineral loss to 2% per year in these patients. This may be

due to different types of drug therapy. Also we disagree with ***Guichot-Garcia et al (1992)*** who demonstrated statistically significant reduction in spinal BMD in epileptic patients on multitherapy compared to the controls, but those on monotherapy (VPA or CBZ) did not show this significant reduction. On the other hand ***Collins et al (1991)*** stated that in children, carbamazepine administered for up to 9 years is associated with reduction in BMD, although alterations in serum Ca, P, alkaline phosphatase and $25(OH)D_3$ values suggestive of osteomalacia have been described earlier.

The results of our study disagree with that done by ***Akin et al (1999)*** who stated that BMD values of both VPA and CBZ groups were not statistically different from that of the control group ($P>0.05$). This difference may be due to the shorter mean duration of treatment of each drug that was 2.4 +- 0.2 years for VPA and 2.6 ± 0.5 years for CBZ compared to our mean duration of treatment that was 4.8 ± 1.8 years for VPA and 4.4 ± 1.4 years for CBZ. Also, ***Trias et al (1998)*** stated that CBZ has no significant effect on BMD as the mean BMD values in study and control groups were 0.53±0.20 g/cm^2 and 0.50±0.20 g/cm^2 respectively ($P>0.05$). This difference with our results may be due to different duration of therapy which was not mentioned in Trias study .

Kubota et al (1999) reported that BMD at lumbar spines and femoral necks were significantly lower in the patients group taking phenytoin, barbiturates and/or acetazolamide for at least 5 years, than in the control group. BMD of the 15 patients were measured again 7 years later, and were found to be significantly lower at both sites than in the

previous examination. These results confirm the presence of bone atrophy lesions in epileptic patients on long-term antiepileptic medication. This finding agrees with our results.

The clinical implications of the observed reduction in BMD in children treated with either VPA or CBZ are yet to be determined. Since, a normal reduction of 7% of BMD occurring in healthy adults is associated with a 50% increase in osteoporotic fractures ***(Matkovic et al., 1979),*** consequently the reduction in BMD with the use of VPA or CBZ might be expected to increase the risk of future fracture.

Our results can be explained by the fact that CBZ is a potent inducer of hepatic microsomal enzyme (P 450), with subsequent excessive enzymatic degradation of vitamin D resulting in bone demineralization. Though, VPA is not a significant inducer of hepatic enzyme and would not be expected to reduce BMD by this mechanism ***(Collins et al., 1991).*** The pathogenesis of valproate-associated reduction in BMD remain undefined. It is suggested that BMD reduction with VPA could be due to either increase in the renal tubular excretion of Ca and P; and/or due to direct action on bone modeling as speculated by ***Sheth et al (1995).*** In fact the first hypothesis goes well with ***Lande et al (1993)*** who reported incidence of reversible Fanconi syndrome in individuals receiving VPA with subsequent renal tubular dysfunction with increased urinary loss of Ca and P. This explanation is in agreement with ***Weinstein et al (1984)*** who found that serum ionized calcium levels in epileptic outpatients receiving chronic AEDs were decreased, PTH concentrations were increased while BMC was reduced averaging only 88.8% of

the predicted normal values. Hpocalcemia and osteopenia occurred in spite of normal mean levels of serum 25(OH)D and 1,25(OH)2D3. This indirect relationship between serum concentrations of AED and the serum ionized calcium level and the lack of correlation with vitamin D metabolism levels suggested that hypocalcemia was independent of the effect of drugs on vitamin D metabolism. Bone biopsies in epileptic patients under AEDs therapy had revealed increased osteoid tissue but normal calcification front formation, accelerated mineralization rate and decreased mineralization lag time indicative of increased skeletal turnover rather than osteomalacia similar to that in hyperparathyroidism. A similar explanation has been proposed for the inhibitory effect of AEDs on PTH-stimulated and $1,25(OH)_2D_3$-stimulated bone resorption ***(Hahn et al., 1978).*** The direct inhibitory effects of anticonvulsant drugs may be of greater clinical importance than the indirect effects on vitamin D metabolism.

Our results showed that abnormal BMD appears in about 43% of all patients while biochemical osteomalacia appears in about 34% of all patients. VPA monotherapy has the worst effect on BMD results as 50% of patients had abnormal BMD, while CBZ monotherapy and polytherapy have the worst effect on biochemical results as 62.5% of each had biochemical osteomalacia.

Our explanation for the discrepancy between radiological and biochemical detective value of resorption is the role of calcitriol in resorption. ***Beresford et al (1987)*** and ***Daniel (1992)*** reported that calcitriol is a potent stimulator of bone resorption and inhibitor of collagen production through

affecting the cross linking of bone collagen. It also increases the activity and number of osteoclasts and increases the synthesis of non-collagenous calcium binding protein ***(Delmas, 1995).***

From the previous discussion we record the importance of BMD, and this agrees with ***Cosman et al (1996)*** who demonstrated that biochemical markers can not replace serial bone densitometry for accurate determination of changes in bone mass at the most clinically relevant studies.

Neurologically impaired children with seizures frequently require multiple antiepileptic medications in high doses, may have a questionable nutritional status, and are often unable to perform optimal levels of physical activity. These factors may make this group especially vulnerable to delirious effects of VPA and CBZ on bone mineralization. It may be possible to diminish the impact of VPA or CBZ therapy on bone mineralization by modification of external factors e.g., dietary supplementation of 1 to 1.5 gm Ca per day, encouraging weight bearing exercises. The degree to which bone mineralization can be improved by modification of these external factors, however, remains to be determined ***(Sheth et al., 1995).***

Summary & Conclusion

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Childhood and adolescence are critical periods of skeletal mineralization. A lower peak bone mass in adolescence is associated with greater involutional osteoporosis and risk of fracture in elderly persons. Quantitative studies of the influence of antiepileptic drugs on bone mineral density, the results showed a lot of discrepancy.

This study is aiming to spotlight the effects of antiepileptic drugs on bonedensitometry of epileptic children, 30 patients (patients group) were chosen from the Outpatient Neurology Clinic, Children's Hospital, Ain Shams University Hospitals, their ages ranged between 6-16 years, all were suffering from primary epilepsy and were under treatment with AEDs (valproic acid and/or carbamazepine) for not less than one year. We chose 12 apparently healthy children (control group) of the same age, social class and geographical area comparable to the patients group.

Both groups were subjected to full history, general as well as neurological examination; and anthropometric measures (weight and height) were measured. Estimation of serum 25(OH)D_3 by radioimmune assay, and serum calcium, phosphorus and alkaline phosphatase by colorometric method. Assessment of lumbar spine osteodensitometry by Lunar DX-L dual energy X-ray absorptiometry and expressed as Z-score.

The results of this study showed that the patients group had a highly statistically significant decrease in Z-score, serum 25(OH)D_3, a statistically significant decrease in serum phosphorus and a statistically significant increase in serum alkaline phosphatase when compared to control group. It was

found that there is a statistically significant decrease in the weight and height percentiles in patients group.

Patients on valproate monotherapy had a highly significant decrease in Z-score, as well as a significant decrease in serum 25(OH)D_3 when compared to controls. Patients on carbamazepine monotherapy had a significant decrease in Z-score, serum 25(OH)D_3, calcium, phosphorus and a significant increase in serum alkaline phosphatase when compared to controls. Patients on both drugs had a highly significant decrease in Z-score and serum 25(OH)D_3, a significant decrease in serum calcium and phosphorus while there is a highly significant increase in serum alkaline phosphatase when compared to controls.

Patients treated with polytherapy (valproate and carbamazepine) showed a significant decrease in serum 25(OH)D_3, calcium and a significant increase in serum alkaline phosphatase when compared to patients treated with monotherapy (valproate or carbamazepine).

Patients treated with AEDs for more than 2 years showed a highly significant decrease in Z-score, a significant decrease in serum 25(OH)D_3, a significant increase in serum alkaline phosphatase and a significant decrease in weight and height percentiles. Increased duration for more than 4 years showed worse effects.

AEDs alter bone mineralization directly by either direct action on bone modeling or increase renal tubular excretion of calcium and phosphorus, and indirectly by acceleration of vitamin D degradation by liver enzyme induction.

Prolonged treatment with AEDs is accompanied by decreased weight and shorter stature. This is due to the fact that AEDs cause a state of pseudohpoparathyroidism in epileptic children with premature epiphyseal fusion and delayed growth with blunting of the stimulated growth hormone and adrenocorticotrophic hormone.

Lastly we concluded :

- Spinal osteodensitometry is an important parameter in detection of early bone changes in epileptic children.

- AEDs therapy result in reduced bone mineralization in the form of osteopenia and osteoporosis with increased risk of future fracture when therapy continues for more than 2 years. Increased duration of therapy is associated with extensive bone demineralization.

- AEDs cause a state of biochemical osteomalacia represented clinically in the form of short stature and decreased weight, and the growth pattern of children treated with AEDs is affected by the duration of treatment.

Recommendations

Recommendations

We recommend:

- Early diagnosis of reduced BMD and biochemical osteomalacia is necessary to prevent further deterioration in bone metabolism. Since it is observed that the alterations in serum levels of vitamin D and calcium are not (or only to a relative degree) correlated to the densitometrically determined deviations of mineral content, both biochemical and densitomety surveys of epileptic children are required during anticonvulsant drug therapy.

- Children on long-term antiepileptic treatment must receive calcium and vitamin D daily to increase peak mineral density and reduce the risk of future fracture. Encouraging weight bearing exercises as they have been shown to increase bone mineral density in normal children.

- Evaluation of the effect of the new antiepileptic drugs on bone metabolism and growth in epileptic children should be assessed.

- Careful supervision of neurologically impaired children with seizures as they frequently require multiple antiepileptic medications in high doses and may have poor nutritional status and are unable to perform physical activity and so they are highly vulnerable to osteoporotic fractures.

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Arabic Summary

الملخص العربى

تهدف هذه الدراسة إلى توضيح العلاقة بين الأدوية المضادة للصرع و مقياس كثافة العظام و التغيرات البيوكيميائية فى الأطفال. و قد أجريت هذه الدراسة على ثلاثين طفل من مرضى الصرع الأولى الذين تناولوا العقاقير المعالجة للصرع (حمض الفلبرويك أو كربامازبين أو كلاهما) لمدة سنة على الأقل و كانت أعمارهم تتراوح بين ٦ –١٦ سنة و الذين يترددون على عيادة الأعصاب الخارجية بمستشفى الأطفال– بمستشفيات جامعة عين شمس– و تم تقسيمهم إلى ثلاث مجموعات:

١–المجموعة الأولى : تكونت من ١٤ طفلاً تناولوا عقار الفالبروات فقط

٢–المجموعة الثانية : تكونت من ٨ أطفال تناولوا عقار الكاربامازيين فقط

٣–المجموعة الثالثة : تكونت من ٨ أطفال تناولوا عقار الفالبروات و الكاربامازيين سوياً

كذلك اشتملت الدراسة على مجموعة مقارنة من الأطفال الأصحاء و عددهم ١٢ طفل و كونت المجموعة الرابعة كمجموعة ضابطة.

و قد تم أخذ التاريخ المرضى و إجراء فحص إكلينيكى دقيق مع بعض القياسات الجسمية الأساسية، قياس كثافة العظام بالأشعة و اختبارات معملية مشتملة : نسبة الكالسيوم و الفسفور و إنزيم الفوسفاتيز القلوى الكلى و ٢٥ أحادى هيدروكسى فيتامين د ٣

و قد أظهرت الدراسة إنخفاضاً ذات دلالة إحصائية فى القياسات الجسمية، مستوى فيتامين د٣ و الفسفور بالدم فى المرضى بمقارنتهم بالمجموعة الضابطة بينما أظهرت الدراسة إرتفاعاً ذات دلالة إحصائية فى مستوى إنزيم الفوسفاتيز القلوى فى مرضى الصرع بمقارنتهم بأطفال المجموعة الضابطة – كذلك أظهرت الدراسة إنخفاضاً ذات دلالة إحصائية فى كثافة عظام الفقرات القطنية فى مرضى الصرع بالمقارنة بالأصحاء.

و قد وجد أن العلاج بعقار الفالبروات فقط يؤدى إلى انخفاض ذات دلالة إحصائية فى كثافة عظام الفقرات القطنية و مستوى فيتامين د فى الدم، بينما العلاج بعقار الكاربامازيبن فقط أو عقار الفالبروات و الكاربامازيبن معاً قد أدى إلى انخفاض ذات دلالة إحصائية فى كثافة عظام الفقرات القطنية و مستوى فيتامين د و الكالسيوم و الفسفور و كذلك ارتفاع ذات دلالة إحصائية فى مستوى إنزيم الفوسفاتيز القلوى. و قد وجد أن العلاج بأكثر من دواء واحد قد أدى إلى انخفاض ذات دلالة إحصائية فى مستوى فيتامين د و الكالسيوم و أرتفاع ذات دلالة إحصائية فى مستوى إنزيم الفوسفاتيز القلوى عند مقارنتة بالعلاج بدواء واحد.

أوضحت الدراسة أن الأطفال الذين يعالجون بمضادات الصرع لمدة أكثر من سنتين يعانون من انخفاض فى معامل قياس كثافة العظام و مستوى فيتامين د و فى القياسات الجسمية و أنه كلما طالت مدة العلاج ازداد تأثيرها السلبى على العظام.

و استخلصت الرسالة أن العلاج بالعقاقير المذكورة لفترات طويلة (أكثر من سنتين) يؤدى إلى هشاشة العظام.

و لتوضيح التأثير السلبى للأدوية المضادة للصرع على العظـــام, وجـد أنها تغير فى التركيب العنصرى للعظام إما بطريقة مباشرة على تركيبة العظـام أو زيادة إخراج الكلى للكالسيوم و الفسفور, أو بطريقة غير مباشـــرة بزيـــادة أيض فيتامين "د" عن طريق استثارة إنزيمات الكبد و منع امتصاص الكالســيوم مباشرة من الإثنى عشر و العظام. كما أن هذه الأدوية تؤثر على نمـــو الطفـل من حيث الوزن و الطول حيث أنها تؤدى إلى حالة قصور كاذب للغـدة الجـار درقية و غلق غير ناضج للعظام و تأخير فى النمو عن طريق إيقـــاف نشـاط هرمون النمو و الهرمون المنبه للغدة الفوق كلوية .

و يستنتج من هذه الدراسة أهمية دراسة كثافة عظام الفقـــرات القطنيـــة بالأشعة التشخيصية فى الأطفال المصابين بالصرع و يتناولون الأدوية المضادة للصرع لمدة أطول من سنتين و نصحت الداســـة بضـــرورة إعطـاء هـــؤلاء المرضى فيتامين "د" و كالسيوم لزيادة كثافة العظام و كذلـــك نصحـت أيضـا بتشجيع ممارسة التمرينات الرياضية المقوية للعضلات حيث وجد إنها تزيد من كثافة العظام فى الأطفال الطبيعيين .

مستخلص الرسالة

اسم الباحث : خالد أحمد يحيى الخولى

عنوان الرسالة : دراسة كثافة العظام : تأثير العلاج المزمن للصرع في الأطفال

جهة البحث : معهد الدراسات العليا للطفولة- قسم الدراسات الطبية - جامعة عين شمس

الهدف : تهدف هذه الدراسة إلى اختبار تأثير عقاري الفالبروات و الكاربامازبين على كثافة العظام في الأطفال المصابين بالصرع الأولى.

الوسائل : تم قياس كثافة العظام المحورية في الفقرات القطنية في ٣٠ طفل من مرضى الصرع الأولى (مجموعة الدراسة) و كذلك في ١٢ طفل من الأصحاء (المجموعة الضابطة) المماثلين لهم في السن و البيئة و المستوى الاجتماعي. تم تقسيم مجموعة الدراسة إلى ثلاث مجموعات, المجموعة الأولى تعالج بعقار الفالبروات فقط (العدد = ١٤) و المجموعة الثانية تعالج بعقار الكاربامازبين فقط (العدد = ٨) و المجموعة الثالثة تعالج بكلا العقارين (العدد = ٨)

النتائج :و قد وجد انخفاض ذات دلالة إحصائية عالية في مقياس كثافة العظام في الأطفال المصابين بالصرع و يزداد هذا الانخفاض بطول مدة العلاج . كما وجد أيضا أن العلاج بعقار الفالبروات له تأثير سلبى واضح على مستوى كثافة العظام أكثر من عقار الكاربامازبين . كما وجد انخفاض ذات دلالة احصائية عالية فى مستوى فيتامين "د" و كذلك انخفاض ذات دلالة احصائية فى مستوى الفسفور و

ارتفاع ذات دلالة احصائية فى مستوى انزيم الفوسفاتيز القلوى فـــى دم الأطفـــال المصابين بالصرع.

الخلاصة : استخلصت الدراسة أن كل من الفالبروات و الكاربامازبين يـــؤدى إلـــى نقص في كثافة العظام في الأطفال المصابين بالصرع الأولى مما يؤدى إلى زيـــادة خطورة حدوث كسور مستقبلية نتيجة هشاشة العظام.

الكلمات المفتاحية :الأطفال المصابون بالصرع الأولى, الأدوية المضادة للصـــرع (الفالبروات- كاربامازبين)- مقياس كثافة العظام, لين العظام, نقص كثافة العظـــام و هشاشة العظام .

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شكـــــــــــر

أشكـــر الســـادة الأســـاتذة الـــذين قـــاموا بالإشـــراف و هـــم :

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٣) أ.م.د. نيفين مصطفى إبراهيم

ثـــم الأشخـــاص الذيـــن تعـــاونـــوا معـــى فـــى البحـــث وهـــم :

١) أ. د. عمر حسين عمر

وكـــذلك الهيئـــات الآتيـــة :

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صفحـــة العنـــــوان

أســـــم الطالـــــب : خالد أحمد يحيى الخولى
الدرجـــة العلمـــية : دكتوراه الفلسفة فى دراسات الطفولة
القسم التابع لـــــه : قسم الدراسات الطبية
أســـــم الكليـــــة : معهد الدراسات العليا للطفولة
الجامعـــــــــة : جامعة عين شمس
سنة التخـــــرج : ٢٠٠٠
سنة المنـــــــح : ٢٠٠٠

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قسم الدراسات الطبية

رسالة دكتـــــــوراه

أســم الطـــــالب : خالد أحمد يحيى الخولى

عنوان الرســالـــة : دراسة كثافة العظام : تأثير العلاج المزمن للصرع فى الأطفال

أســـم الدرجـــة : دكتوراه الفلسفة فى دراسات الطفولة

لجنـــــة الإشـــــراف

١- الاسم / أ.د سناء يوسف شعبان — **الوظيفة : استاذ طب الأطفال**
كلية الطب جامعة عين شمس

٢- الأسم / د. خالد حسين طمان — **الوظيفة : أستاذ مساعد بقسم الدراسات الطبية**
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الدراســـــات العليـــــا

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دراسة كثافة العظام : تأثير العلاج المزمن للصرع فى الأطفال

دراسة مقدمة توطئة للحصول على درجة دكتوراة الفلسفة فى دراسات الطفولة

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تحت إشراف

الأستاذة الدكتورة / سناء يوسف شعبان

أستاذ طب الأطفال

كلية الطب - جامعة عين شمس

الدكتور / خالد حسين طمان

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