SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

PREVALENCE OF METABOLIC SYNDROME AND CORONARY ARTERY DISEASE IN EPIELPSY

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By

Dr Sruthi S. Nair

DM Neurology Resident

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Department of Neurology

Sree ChitraTirunal Institute for Medical Sciences and Technology

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DECLARATION

I, **Dr. Sruthi S. Nair**, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram **Dr. Sruthi S. Nair**

Date:

Forwarded

The candidate, Dr Sruthi S. Nair, has completed the project under my guidance.

Thiruvananthapuram
Date:

Dr Sanjeev V. Thomas,
Professor,
Department of Neurology,
SCTIMST.

Forwarded

The candidate, Dr. Sruthi S. Nair, has carried out the minimum required project.

Thiruvananthapuram
Date:

Dr.Muralidharan Nair,
Professor and Head,
Department of Neurology
SCTIMST.

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Dr Sruthi S. Nair

Senior Resident

Department of Neurology

SCTIMST, Trivandrum, Kerala

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INTRODUCTION

Epilepsy is the commonest neurological condition affecting people of all ages, race and social class. Patients with epilepsy have two to three times higher risk of mortality compared to general population [(1)]. In addition to the deaths related directly to epilepsy like sudden death, trauma, status epilepticus and aspiration pneumonia and deaths due to the underlying causative factors of the seizures, increased mortality has been reported from apparently unrelated causes like heart disease and non-cerebral neoplasias[(2)].

The Stockholm Heart Epidemiology Programme studied a large cohort of patients with history of acute myocardial infarction and the subset of population with epilepsy was found to have a higher incidence of acute myocardial infarction than general population with an Odd's ratio of 4.92[(3)]. The researchers also stated that patients with history of hospitalization for epilepsy had a worse prognosis with myocardial infarction. They have postulated multiple possible reasons for their observations including presence of common underlying pathology for both like a silent cerebrovascular disease and presence of common risk factors like smoking and alcohol abuse. The adverse metabolic profile induced by some of the popularly used antiepileptic drugs as well as direct seizure associated myocardial ischemia were also considered as probable explanations for the observation. Conflicting reports are also available claiming a lower cardiovascular risk in epilepsy patients as some antiepileptic drugs like carbamazepine increase the level of HDL cholesterol in blood.

In another study by Anneger's et al.[(4)], the mortality and morbidity due to sudden cardiac death, myocardial infarction and angina pectoris were found to be significantly higher in epilepsy patients, especially in symptomatic epilepsy and in patients younger than 65 years.

Although some studies have looked in to the mortality in epilepsy due to coronary artery disease, those which have studied the role of epilepsy as a potential risk factor for metabolic syndrome and coronary artery disease are scarce. No Indian studies on the relationship between epilepsy and vascular risk factors could be idenitfied. This is in spite of the fact that multiple previous studies have documented the higher susceptibility of the Indian population to metabolic syndrome and coronary artery disease.

This study was conceptualized to explore the prevalence of metabolic syndrome and coronary artery disease in the epilepsy patients in our population who is on regular treatment with special reference to the role of epilepsy medications in the relationship. The study would help in the planning of further prospective studies in this area as well as help in the clinical setting for monitoring and management of the patients.

REVIEW OF LITERATURE

Introduction

Epilepsy is a neurological disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure [(5)]. It is the commonest neurological condition affecting people of all ages, race and social class. Hence, the social and economic implications of the diagnosis of epilepsy are huge, especially in a developing country like India.

Incidence and prevalence of epilepsy

There are an estimated 50 million people with epilepsy in the world [(6)]. The lifetime prevalence of seizures (the risk of having a non-febrile epileptic seizure at some point in an average lifetime) is between 2 and 5%. Evidence from community-based studies have shown that 70−80% of people with epilepsy will achieve remission, usually in the early course of the condition. The longer epilepsy remains active, the poorer the prognosis [(7)].

Most incidence studies show that epilepsy is more common in males than females, both in developed and resource-poor countries but this difference is rarely significant. In the systematic review of incidence studies, the median annual incidence of epilepsy was 50.7 per 100,000 for males and 46.2 per 100,000 for females [(8)].

The prevalence of epilepsy reported from different parts of the world indicate geographic variations exist in the prevalence of epilepsy. The prevalence of epilepsy from Asia (mainly China and India) have demonstrated rates similar to those in the Western world, however those reported from Africa are lower. Moreover there can be marked variation in incidence and prevalence rates between different regions within the same country. Most, but

not all studies have shown that rates are higher in rural than in urban areas [9]. A lower income was related to a higher incidence of epilepsy in most of the studies.

In population-based studies, the most frequent causes of epilepsy are cryptogenic (presumed symptomatic) or idiopathic (presumed genetic), ranging from 44.5% to 67% [10, 11], with the proportion of identified causes (symptomatic or localization-related epilepsy – remote or progressive) increasing with age.

Partial seizures predominate in most studies from developing countries: National General Practice Study of Epilepsy (59% vs 39%) [12], the Rochester study (57% vs 40%) [13], and the Umeå study (Sweden) (68% vs 16%) [14]. A systematic review found that partial seizures occurred in 55% of patients compared to 45% with generalized seizures [8].

Prevalence of epilepsy in India

A meta-analysis of twenty studies on the population prevalence of epilepsy from India was done by Sridharan and Murthy [15]. The total sample population was 598,910, among whom 3,207 had epilepsy. This gave a crude prevalence of epilepsy as 5.35 per 1,000 population. The prevalence rates in the urban and rural areas were 5.27 and 5.38 respectively, however the difference was not statistically significant. The prevalence rates for men and women, determined from the studies which reported data separately by sex, were 5.25 and 4.56, respectively. The age-specific prevalence rates were highest in men in their second decade of life and women in their third and fourth decades.

Comorbidities in epilepsy

Many somatic and psychiatric illnesses may precede, co-occur with or follow the diagnosis of epilepsy. Disorders co-occurring with epilepsy increase the demand on the

health services by the people [16] as well as increase the financial burden on the patient's family.

Psychiatric diseases are well established co-morbidities with epilepsy. Mental health disorders were twice as common in persons with epilepsy compared to general population [17]. The most common psychiatric condition in adults with epilepsy are depression, anxiety and psychoses. Suicide is associated with up to 5% of all epilepsy deaths [18], and most of these deaths are thought to be related to psychiatric co-morbidities. A study from Sweden showed increased prevalence of psychiatric disorders in epilepsy patients, and specifically for alcohol and drug use disorders, and depression [19]. This increase may be related to the similar mechanisms of disease in epilepsy and psychiatric disorders. Psychiatric disorders may also result from the seizure activity due to the effects of seizures in amygdala, hippocampal and septal areas [20].

The association between epilepsy and somatic disorders are less well characterized. In a large population based prospective study from the United Kingdom with 1,041,643 subjects among whom 5,834 had epilepsy [17], it was seen that with the exception of musculoskeletal and connective tissue diseases, most of the other somatic disorders were more common in epileptic patients compared to general population. Fractures and asthma were identified as the most common somatic disorders. Cerebrovascular accidents, transient ischemic attacks, ischemic heart disease, heart failure and diabetes mellitus were identified as common co-morbidities especially in the older adults. Migraine was seen in 8% of the younger patients, more in women. The prevalence was 60% higher in adults with epilepsy, but only 40% more in young females.

A smaller study with 220 epilepsy patients from a population based cohort study failed to demonstrate any relationship of epilepsy with somatic diseases and was able to

identify significant association only with psychiatric comorbidities. However the younger age of the cohort and the small sample size were limitations of the study [21].

The etiological factors which may result in epileptic seizures are more common in epileptics like brain tumours and cerebrovascular disease with very high odds of 55 and 12 times respectively ([17].

There are many reasons postulated for the increased risk of apparently unrelated somatic diseases in epilepsy. A comorbid condition may be the cause of epilepsy like a stroke or cerebral neoplasm or may be associated with epilepsy via a shared genetic or environmental risk factor [22]. Treatment of epilepsy with antiepileptic medications may also contribute to co-morbidities like cardiovascular diseases and gastrointestinal diseases. Higher intake of alcohol and higher rates of smoking reported in the epileptic patients may also be responsible for diseases like gastrointestinal diseases, emphysema and asthma [23]. The lower socioeconomic status of the patients also contribute to increased comorbidities [24].

Mortality in epilepsy

Patients with epilepsy have consistently been found to have a higher death rate than the general population [1, 25]. Premature mortality is substantial in them and almost half of epilepsy-related deaths occur in those younger than 55 years, corresponding to standardised mortality ratios above 10 for hospitalised patients [2].

In a population based cohort of epilepsy patients [2] the standardized mortality rate (SMR) in epilepsy was 3.6. The SMR was significantly increased in all ages but was more pronounced in younger patients. The various causes of death fall into three different categories: (a) an underlying disease of which epilepsy is a symptom, such as brain tumor or cerebrovascular disease; (b) an underlying disease that has no obvious causal relation to epilepsy, such as pneumonia; and (c) epilepsy that contributes directly to the death, such as

status epilepticus, accidents due to epileptic seizures, and sudden unexpected death. Part of the increased death rate is explained by the presence of stroke or neoplasms which contribute to death and epilepsy. However even after correcting for these, there is a doubling of risk of death in epilepsy.

A recent large study from Sweden noted that persons with epilepsy had a substantially elevated odds of premature mortality compared to [19] general population controls and unaffected siblings with adjusted odds ratio of 11·1 and 11·4 respectively. 6155 of 69,995 (8.8%) people with epilepsy in that cohort died during follow-up, at a median age of 34·5 years compared with 4892 (0.7%) controls. Of those deaths, 15·8% were from external causes, with high odds for non-vehicle accidents and suicide. Of those who died from external causes, 75·2% had comorbid psychiatric disorders, with strong associations in individuals with co-occurring depression (Odds ratio 13·0, 10·3–16·6) and substance misuse (Odds ratio 22·4, 18·3–27·3), compared with patients with no epilepsy and no psychiatric comorbidity. The number of deaths from mental disorders was not higher than expected, except for suicide, dementia, and disorders related to alcohol or drug abuse. The SMR for injury and poisoning is five times increased in epilepsy [2].

The mortality due to apparently unrelated causes was also noted to be elevated in the study by Nilsson et al [2]. Specifically, a higher SMR was noted from heart disease non-central nervous system neoplasia, and pulmonary disease. If tumors of the brain, which had a 30-fold increased SMR, were excluded from all malignancies, the SMR was still doubled. Previous studies have suggested that intake of antiepileptic drug might increase the risk of some malignancies, particularly lung cancer, breast cancer, hepatobiliary and pancreatic tumors [26], and cancer of lymphoid and hematopoietic tissue [27]. However, the results have been non-uniform in different studies and currently no definite data exists to indicate such a causal relationship.

The SMR for heart disease, including ischemic heart disease, arrhythmias, and other diseases in the heart and lung circulation was 2.6 and this was highly dominated by ischemic heart disease [2].

The SMR for pneumonia was four times elevated and especially elderly individuals with epilepsy are thought to be at a higher risk for pulmonary infections [2].

Cardiac morbidity and mortality in epilepsy

An interesting detail that has emerged from the various studies on comorbidities in epilepsy is the increased prevalence of cardiovascular mortality and morbidity in these patients. The data on this is not uniform and the association between epilepsy and coronary artery disease (CAD) remains a complex and controversial subject.

A study by Hauser et al. [1] did not reveal any significant increase in mortality due to heart disease in patients with epilepsy. Another study showed that deaths due ischemic heart disease may in fact be lower in epileptic patients. Mortality due to CAD was found to be 29% lower than controls and this effect was attributed to the changes in lipid profile induced by antiepileptic medications [28].

In contrast, Nilsson et al. [2] followed all patients above 15 years of age admitted with a diagnosis of epilepsy for in-patient care in Stockholm between 1980 and 1989 and found that epilepsy was associated with a standardized mortality ratio of 2.5 for mortality from CAD. Ding et al. [29] observed a standardized mortality ratio for AMI over 10 for epilepsy patients when compared to the general population in China.

Annegers et al. [4] reported increased SMR for heart disease, but only in persons aged less than 65 years. Similarly in the study by Nilsson et al [2], the SMR for heart disease was increased two to three times including all age groups, but maximally in the group aged 45-64

years. Hence the SMR due to cardiovascular diseases in epilepsy populations is higher among younger people in whom the expected number of deaths is low.

A retrospective study of the records of persons with epilepsy registered in a hospital registry was done in Rochester, Minnesota and the etiology of deaths in these patients over a prolonged period was analyzed [(4)]. The investigators specifically looked into the subset of patients who died from cardiovascular causes. The incidence of ischemic heart disease and of sudden cardiac death as the initial manifestation of ischemic heart disease was significantly increased in persons with epilepsy, but the increase was primarily limited to those with symptomatic epilepsy attributed to cerebrovascular disease. The standardized morbidity ratio due to ischemic heart disease was 1.63. The increase was greatest among those with remote symptomatic epilepsy, with a ratio of 1.9. The occurrence of ischemic heart disease and sudden cardiac death was not related to anticonvulsant medication status.

A large population based case control study from Sweden evaluated the relationship of epilepsy with acute myocardial infarction (AMI) [(3)]. The study included 1799 cases with first AMI and 2339 controls. Among them 36 cases and 9 controls had a diagnosis of epilepsy. The odd's ratio for AMI associated with a diagnosis of epilepsy was 5.36 (95% CI 2.57–11.18) in the study.

The study also suggested that a history of epilepsy was associated with AMI prognosis. The risk for AMI was increased with higher frequency of hospitalizations for epilepsy. Odd's ratios were 4.45 for one or two hospitalizations and 6.54 for three or more hospitalizations. Moreover, epilepsy was strongly associated with poor prognosis even when patients who, before their inclusion, had any manifestation of cardiovascular disease, were excluded.

Sudden unexpected death in epilepsy

Approximately 1 in 1000 patients with epilepsy dies suddenly and unexpectedly with no obvious medical cause [30]. Because arrhythmias follow neural activation in both humans and experimental models, one explanation is that the patient with epilepsy dies of a cardiogenic cause [31].

The risk of sudden death is assessed at 23.7 fold higher compared to general population and up to 40 times that for healthy people [32]. In the majority of the thoroughly studied cases, the deaths were noted to occur during or shortly after seizure attacks. The mechanism of death proved to be predominantly associated with cardiovascular system pathology [33]. The leading causes involved complex ventricular arrhythmia (dependent on autonomical neuroregulatory dysfunction), the proarrhythmic effect of AEDs and myocardial damage. Some have suggested the role of electrolyte disturbances, i.e. hyponatremia and hyperkalemia as cardiotoxic factor [33].

There is ample evidence to suggest that pathological neuronal activity in specific areas of the brain triggers tachy- or bradyarrhytmias. The susceptible anatomical structures involve the insular cortex and certain regions of the frontal cortex [34]. However, far less evidence exists regarding role of the AEDs.

The relationship between the primary cardiovascular disease and resulting epilepsy is also known, although less data is available. Arterial hypertension is associated with an increased risk for epileptic seizures. This does not seem to be a direct finding, however. The reason for this observation is most probably a link between epileptogenesis and episodes of

brain stroke and intracranial hemorrhage, representing complications of arterial hypertension [35].

In an autopsy study of patient with epilepsy with sudden death [36], pathologic conditions were found in 5 of the 7 hearts in the group with epilepsy and in none of the hearts in the comparison group. Four of the 7 hearts in the group with epilepsy had evidence of irreversible pathology in the form of perivascular and interstitial fibrosis as well as myocyte vacuolization. Lesions occurred predominantly in the subendocardium. All of the patients have evidence of cardiac ischemia in the form of colliquative myocytolysis.

From these findings it can be hypothesized that brain activation could produce coronary vasomotion in the absence of coronary pathologic conditions with resulting ischemic disease in the heart. In a study of insula cortex stimulation in rats in which cardiac arrhythmias leading to asystole were produced, myocyte vacuolization was found in 58% of the animals [36].

Association between epilepsy and heart disease

One possible explanation for the association is that epilepsy and cardiovascular disorders might have a common underlying cause. For example, seizures can be the first sign of otherwise clinically undetectable cerebrovascular disease. Cerebrovascular disease was associated with a five-fold increased risk of death, especially so in persons aged above 75 years in the study by Nilsson et al [2]. Because stroke is overrepresented as a possible etiology of epilepsy, it is reasonable to anticipate that other manifestations of vascular diseases, such as coronary artery disease will also be high.

In another study, late life onset seizures were associated with a markedly increased risk for subsequent stroke [37]. In line with these findings, hypertension and left ventricular

hypertrophy are strongly associated with risk for unprovoked seizures, especially with the late onset form [35, 38, 39].

A second possibility is that the treatment of epilepsy may play a role. The enzyme-inducing antiepileptic drugs (AEDs), phenytoin, carbamazepine and phenobarbital account for the majority of the drugs prescribed for epilepsy. These drugs alter the levels of high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol and affect the risk of vascular events. AEDs also often results in weight gain [40] which also influences the outcome.

Hyperhomocysteinaemia is another potential candidate mechanism as several AEDs are known to increase the level of homocysteine [41]. In the study from Sweden [3], participants with a history of epilepsy generally had a more favourable lipid profile but higher prevalence of current smoking, low education and diabetes mellitus and higher levels of von Willebrand factor, tissue plasminogen activator (tPA)/ plasminogen activator inhibitor 1 (PAI-1) complex and homocysteine. Increase in the level of haemostatic factors might be related to increased homocysteine levels [42].

In a recent study [43], people with epilepsy reported double the prevalence of cigarette smoking than the population without epilepsy. Alcohol abuse is also plausibly a common cause for both epilepsy [44] and AMI [45].

Finally, epileptic seizures themselves may induce cardiac ischaemia and thus increase the risk of subsequent AMI [46]. Tigaran et al. [47] found that 44% of patients with drug refractory epilepsy, without a history of heart disease or hypertension had an ST-segment depression at the cessation of their seizures.

Metabolic syndrome and cardiovascular risk factors

Metabolic syndrome (MetS) is a complex disorder with high socioeconomic cost that is considered a worldwide epidemic. MetS is defined by a cluster of interconnected factors that directly increase the risk of coronary heart disease, other forms of cardiovascular atherosclerotic diseases, and diabetes mellitus type 2 [48]. Its main components are dyslipidemia (elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins, and low HDL), elevation of arterial blood pressure and dysregulated glucose homeostasis, while abdominal obesity and/or insulin resistance have gained increasing attention as the core manifestations of the syndrome. Recently, other abnormalities such as chronic proinflammatory and prothrombotic states, non-alcoholic fatty liver disease and sleep apnea have been added to the entity of to the syndrome, making its definition even more complex.

Besides the many components and clinical implications of MetS, there is still no universally accepted pathogenic mechanism or clearly defined diagnostic criteria. Furthermore, there is still debate as to whether this entity represents a specific syndrome or is a surrogate of combined risk factors that put the individual at particular risk. A main evolving aspect of MetS is its increasing prevalence in both childhood and young adulthood and the future implications to the global health burden this may confer.

Criteria defining metabolic syndrome

Reaven was the first to put forward the concept of 'syndrome X', (which was later renamed MetS), hypothesizing that it was a central feature in the development of coronary heart disease and diabetes mellitus, mainly through target tissue resistance to insulin action [49]. Since then, many international organizations and expert groups, such as the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII), the American Association of Clinical Endocrinology (AACE), the International Diabetes

Federation (IDF), and the American Heart Association/ National Heart, Lung, and Blood Institute (AHA/NHLBI), have attempted to incorporate all the different parameters used to define MetS.

The first attempt to establish criteria to define MetS was made in 1998 by the WHO, which proposed that MetS may be defined by the presence of insulin resistance or its surrogates, impaired glucose tolerance or type 2 diabetes mellitus, as essential components of the syndrome, along with at least two of the following parameters: raised blood pressure, hypertriglyceridemia and/or low HDL-cholesterol, obesity (as measured by waist/hip ratio or body mass index (BMI)), and microalbuminuria [(50)].

In 2001, the NCEP: ATPIII published a new set of criteria that included waist circumference, blood lipids, blood pressure, and fasting glucose [(51)]. The NCEP: ATPIII definition differed from the WHO definition in that insulin resistance was not considered as a necessary diagnostic component. In 2005, the International Diabetes Federation (IDF) published newer criteria in an attempt to define the syndrome more precisely so that it could be used by different clinical and research groups [(52)]. The aim of this new definition was to enable comparisons between study results, in the hope that it would be a better predictor of risk particularly for coronary heart disease, stroke and type 2 diabetes mellitus. The IDF introduced abdominal obesity as a prerequisite of the diagnosis of MetS, with particular emphasis on waist measurement as a simple screening tool [(53)].

Currently, the two most widely used definitions are those of the NCEP:ATP III and IDF focusing specifically on waist circumference, which is a surrogate measure of central obesity. In contrast, the AACE, WHO and the EGIR definitions are all largely focused on insulin resistance.

A major drawback of these definitions is their lack of applicability to different ethnic groups, especially when trying to define obesity cut-offs. This is particularly evident for the risk of diabetes mellitus, which is apparent at much lower levels of obesity in Asians compared to Europeans. The IDF and NCEP: ATPIII criteria now incorporate ethnic and racial specific cut-offs to define obesity.

Cardiovascular risk factors in epilepsy

An increased prevalence of cardiovascular risk factors and metabolic syndrome has been reported in persons with epilepsy. This is significantly influenced by the AEDs which alter the levels of lipids and other factors influencing vascular risk like homocysteine in serum.

Elliot et al. [41] investigated the prevalence of cardiovascular risk factors (high cholesterol, hypertension, diabetes, obesity and smoking) and homocysteine in a young multiethnic epilepsy population. Fifty two percent of participants was noted to have two or more cardiovascular risk factors when compared with rates for the general population of 28%. Using the Framingham risk score (FRS) to assess the risk levels, it was seen that twenty-nine percent of men and 1% of women had a FRS indicating >5% level of risk, only 7% had a FRS > 10%.

A surrogate marker for atherosclerosis, the carotid artery intima-media thickness, is increased in adult patients with treated and untreated epilepsy. Markers of oxidative stress like total homocysteine, von Willbrand factor (vWF), fibrinogen, oxidized LDL, malondialdehyde, thiobarbituric acid reactive substances (TBARs) and uric acid are noted to be increased in epilepsy patients whereas total antioxidant capacity and HDL cholesterol are decreased [54].

Effect of antiepileptic medications on metabolic profile

Many of the patients require anticonvulsant medications for long term use and this exposure often starts in young ages. The older antiepileptic drugs (AEDs) with cytochrome P450 system inducing and inhibiting properties are known to profoundly influence the metabolic milieu. Phenytoin, carbamazepine and valproic acid are the most commonly implicated medications in these alterations.

Lipid profile and AEDs

AEDs alter the metabolism of lipids and drugs due to their enzyme inducing action in the liver function and increase in the activity of hepatic microsomal enzyme system [55, 56].

The effect of carbamazepine in the lipid profile has been studied extensively. In a longitudinal study of normolipidemic patients initiated on carbamazepine [57], it was noted that significant increases in total cholesterol, ApoB-containing lipoproteins (very-low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low-density lipoprotein (LDL)), and triglycerides, but not in high-density lipoprotein (HDL), occurred after starting the medication. Lipoprotein particle composition was found be unaltered. Carbamazepine does not influence endogenous cholesterol synthesis or intestinal absorption directly. The increase is neither related to increase in ApoB production nor to decrease in catabolism but is rather due to changes in the conversion cascade of IDL particles. There was a significant correlation between the decrease in free thyroxine and the increase in IDL cholesterol suggesting that this effect may be indirectly mediated through thyroid hormones.

Carbamazepine also effects an increase in the levels of total cholesterol, LDL cholesterol, and triglycerides [58, 59]. Patients using phenytoin or carbamazepine have

increased serum concentrations of HDL cholesterol which also suggests a protective role for these drugs [28].

Significant correlation between duration of anticonvulsant therapy and lipid profile was established. The longer the duration the greater was the increase in serum triglyceride, total cholesterol, HDL and VLDL cholesterol [60]. Increased levels of serum triglyceride, total cholesterol, HDL and VLDL cholesterol was observed in epileptic patients on monotherapy or combination therapy with phenytoin.

Lipoprotein(a) is a very potent atherogenic factor and is an independent risk factor for vascular disease. Carbamazepine treatment is shown to significantly increased the serum concentrations of lipoprotein(a) and contribute to the risk of atherosclerosis [58]. Phenyotin is not shown to have effect on the lipoprotein(a) level [61].

Different studies have reported contradictory effects on lipids with valproate use. Tomoum et al. [62] studied 22 children with epilepsy and found that total cholesterol, various lipid fractions, and apolipoprotein AI were elevated in carbamazepine treated patients and reduced in valproate treated patients relative to controls, reinforcing the notion that CYP450 activity is causative of these changes. In another study however, valproate use was noted to produce increased total serum cholesterol and triglyceride concentrations and low HDL [63]. This latter effect was pronounced in obese patients and is presumably related to the changes in insulin resistance and insulin mediated lipoprotein transport.

The newer AEDs, leviteracetam and lamotrigine were not show to have any effect on the lipid levels [59].

Influence of body weight

Changes in bodyweight are a typical chronic cumulative side effect of certain antiepileptic medications which can pose serious health hazards, impair self-esteem, and lead to non-adherence or discontinuation of treatment [64]. Weight gain is most commonly associated with valproate, gabapentin, pregabalin, vigabatrin, retigabine, and to a lesser extent, carbamazepine [64]. A recent study also showed that obesity is a common comorbidity in children with newly diagnosed untreated epilepsy and correlates with increasing age, idiopathic etiology, and absence of concomitant medication [65].

Among the AEDs valproate has been definitively shown to cause considerable increase in body weight, and valproate-induced obesity seems to be associated with many metabolic and endocrine disturbances [66, 67, 68, 69]. About 40% of patients on valproate develop obesity [66, 67]. Obesity has a role in promoting the development of metabolic diseases including glucose intolerance, dyslipidemia, hypertension, and atherosclerosis [70]. Women on carbamazepine and lamotrigine had higher body mass index compared to controls [59].

Poor fitness are reported at higher rates in epilepsy patients and is another factor contributing to obesity and higher metabolic risk in them [59, 71].

Blood sugar and AEDs

Phenytoin is the drug which has been consistently shown to have association with higher blood sugar. Phenytoin impairs the secretion of insulin and decreases the response of plasma glucose to insulin [28].

Abnormal glucose homeostasis in the form of hyperinsulinism and insulin resistance occur in 45% of patients on valproate [63].

Hypertension and epilepsy

Seizures may be associated with hypertension in two ways. Chronic hypertension is a risk factor for vascular disease and thus predisposes to subclinical and overt cerebrovascular disease. Such disease is a risk factor for both for late-onset seizures and epilepsy in elderly. A case control study suggested that history of hypertension is an independent risk factor for new-onset unprovoked seizures, especially, but not only, in conjunction with a history of stroke [(35)]. Secondly acute symptomatic seizures can occur in the setting of hypertensive emergency.

Seizures are shown to trigger a paroxysmal neurogenic hypertension and tachycardia. This generalized increase in sympathetic activity is permitted by a transient interruption of baroreflex feedback inhibition during the seizure [(72)].

Hypertension has not been shown to be a direct side effect of AEDs apart from the risk associated with weight gain and other metabolic factors.

Miscellaneous metabolic factors influencing vascular diseases

In addition to the traditional factors like diabetes mellitus, hypertension and lipid status, some other metabolic factors have been identified which are shown to be associated with increased vascular risk. These include c-reactive protein (cRP), homocysteine, von Willibrand factor (vWF) and fibrinogen.

C-reactive protein (cRP) is a highly important marker for vascular risk that is independent of serum lipids. It is synthesized primarily from liver and may be affected by enzyme inducing drugs. The prothrombotic amino acid homocysteine has been implicated as a risk factor for vascular events although its clinical relevance is still questioned. Studies have linked to with a higher risk for stroke [(73)] and dementia [(74)]. Fibrinogen and vWF are prothrombotic factors.

Both carbamazepine and phenytoin produce elevation of cRP. Patients on carbamazepine have been shown to have significantly elevated levels of homocysteine, and vWF [54]. Carbamazepine also raises serum homocysteine, presumably by inducing the metabolism of B vitamins, which are essential cofactors for its metabolism. Patients taken off phenytoin experience a decline in homocysteine levels [61]. Patients on valproate showed significant alteration in uric acid and thiobarbituric acid reactive substances (TBARs) resulting in an increased atherogenic state [54]. Valproate is also associated with reduction in cRP level [75].

Switching epilepsy patients from the enzyme-inducers carbamazepine or phenytoin to the noninducing drugs levetiracetam or lamotrigine produces rapid and clinically significant amelioration in several serological markers of vascular risk [61].

AEDs which induce the cytochrome P450 system adversely affect bone and gonadal steroid metabolism. Specifically, phenytoin causes loss of bone mass in women, and both phenytoin and carbamazepine produce decreases in bioactive testosterone in men. Patients treated with inducing AEDs are at increased risk of fracture [75].

Polycystic ovaries and menstrual disturbances seem to be common among women taking valproate for epilepsy. The frequency of polycystic ovaries or hyperandrogenism, or both, among valproate-treated women with epilepsy was 70% compared with 19% among control subjects. Both obese and non-obese patients on valproate tended to show these changes. The obese valproate-treated women with polycystic ovaries or hyperandrogenism, or both, had hyperinsulinemia and associated unfavorable changes in serum lipid levels consistent with insulin resistance [76].

Metabolic syndrome and AEDs

Metabolic syndrome associated with epilepsy is most extensively demonstrated in patients on valproate therapy. Valproate therapy, especially if started at a young age, is associated with increased circulating insulin concentrations relative to body mass index. This hyperinsulinemia and insulin resistance results in MetS [69]. In addition, obesity related to valproate use is an important contributor. It has also been demonstrated that obese patients with epilepsy treated with VPA are at higher risk of MetS than individuals who are "simply obese" but otherwise well [77].

Some studies suggest that valproate use per se does not cause MetS [63], because it is not present in all valproate-treated patients. It is probable that the metabolic changes reported in epileptic patients treated with valproate are secondary to excess fat mass, because these changes are not usually present in those epileptic patients treated with valproate who do not gain weight. In a study involving children with epilepsy on valproate, it was shown that 40.4% of the children had considerable weight gain at the end of 2 years follow up. 43.5 % of the children who were obese had metabolic syndrome [63]. There was a tendency for postpubertal children to have greater number of features of MetS than pubertal and pre-pubertal children. Body mass index at initiation of valproate therapy was not a predictor of the development of obesity and/or MetS. Many studies have demonstrated that obese patients on valproate therapy have high insulin level with insulin resistance [78, 79].

Genetic factors that influence the several molecular pathways in energy homeostasis (e.g., insulin receptor signaling pathway, lipid metabolism) might represent a possible explanation for certain people gaining weight with valproate therapy; in fact, it has been suggested [80, 81] that some mutations of genes responsible for insulin receptors, plasma cell membrane glycoprotein-1, glucose transporter 4, and peroxisomal proliferator-activated receptor-c can explain the development of MetS in a percentage of the obese subjects.

In the literature there are diverse statements on the impact of gender and puberty [82, 83], with a higher prevalence of MetS and its components in male compared to female subjects. The dyslipidemia of the MetS may increase cardiovascular disease risk through different mechanisms from those associated with high total or LDL cholesterol.

The relationship between insulin resistance and fasting lipids can be explained through the effect of insulin on lipoprotein metabolism. Insulin plays a central role in determining triglyceride clearance from the blood via activation of lipoprotein lipase and triglyceride output through effects on the synthesis and secretion of VLDL by the liver [84]. Furthermore, insulin controls the output of free fatty acids from adipose tissue [85]. It is possible that in the insulin-resistant state, triglyceride-rich lipoproteins accumulate in the circulation due to decreased activity of lipoprotein lipase [86], increased lipolysis in adipose tissue [85], and increased output of VLDL particles from the liver [84]. The delay in plasma lipoprotein triglyceride clearance allows for cholesterol esters to be passed on from HDL to triglyceride-rich particles, which results in potentially atherogenic lipoprotein particles [87].

HYPOTHESIS AND OBJECTIVES OF THE STUDY

HYPOTHESIS

The prevalence of metabolic syndrome and coronary artery disease is higher among epileptic patients on antiepileptic drugs as compared to general population

OBJECTIVES

1. To study the prevalence of metabolic syndrome and coronary artery disease among patients with epilepsy.
2. To study the relationship of the metabolic profile to antiepileptic drug use.

SUBJECTS AND METHODS

Study design and setting:

The study was a hospital based cross-sectional descriptive study. The subjects were selected from among the patients attending the epilepsy outpatient clinic of a single tertiary centre (Sree Chitra Institute of Medical Sciences and Technology, Thiruvananthapuram).

Study period:

The study was conducted over a period of 18 months from January 2012 to June 2013.

Methodology:

Consecutive patients attending the Epilepsy Clinic in the Sree Chitra Tirunal Institute of Medical Sciences and Technology every week were screened for eligibility for the study. Those fulfilling the inclusion and exclusion criteria were explained the procedure and those willing to give informed consent were recruited into the study. The subjects were interviewed using a detailed questionnaire to note the demographic data, characteristics of the epilepsy, presence of metabolic risk factors and cardiovascular disease. Fasting blood samples were drawn from them to estimate fasting blood glucose and fasting lipid profile. Cardiology evaluation was done with questionnaire, review of previous treatment documents and electrocardiogram in all patients and echocardiogram in patients with high suspicion of cardiac disease.

Ethical considerations:

The study was approved by the Institute Ethical Committee. Written informed consent was obtained from all the subjects participating in the study. The informed consent procedure

was done according to the guidelines provided in the Declaration of Helsinki and the ICH E6 Guideline for Good Clinical Practice.

Inclusion criteria:

1. Patients with epilepsy aged between 20 and 49 years consenting for the study
2. Patients on antiepileptic drugs for a minimum period of 3 years

Exclusion criteria:

1. Patients diagnosed with diabetes mellitus, systemic hypertension, dyslipidemia or other co-morbidities which can significantly alter the metabolic profile, predating the onset of epilepsy
2. Pregnant ladies and 6 months postpartum
3. Patients on medications like steroids or oral contraceptives which can alter the metabolic profile

Definition of metabolic syndrome: The Adult Treatment Panel III (National Institutes of Health, 2004) [(88)] criteria for metabolic syndrome modified for Asian Indian population [(89)] was adopted for the study.

Metabolic syndrome was defined as presence of three of five of

1. Central obesity (defined as waist circumference ≥ 90 cm in males and ≥ 80 cm in females)
2. Raised triglycerides (> 150 mg/dL or specific treatment for this)
3. Reduced HDL cholesterol (< 40 mg/dL in males, < 50 mg/dL in females or specific treatment for this)

4. Raised blood pressure (systolic BP > 130 or diastolic BP >85 mm Hg or treatment of previously diagnosed hypertension)
5. Raised fasting plasma glucose (FPG ≥ 110 mg/dL or previously diagnosed type 2 diabetes)

Definition of coronary artery disease [(90)]:

The methods used for identification of subjects with coronary artery disease (CAD) included

1. Subjects having a past history of symptomatic coronary artery disease (stable angina, unstable angina, myocardial infarction) as reported by the subject
2. Subjects with coronary angiogram showing more than 50% occlusion of a major vessel
3. Subjects who previously underwent percutaneous coronary angioplasty or coronary artery bypass grafting
4. ECG and echocardiogram suggestive of cardiac ischemia

The subjects were categorized into three groups – definite CAD, likely CAD and no CAD. The patients were designated as having definite CAD if they had documented myocardial infarction, had a coronary angiogram with more than 50% occlusion of a major vessel or had undergone percutaneous coronary angioplasty or coronary artery bypass grafting. They were designated as likely CAD if history was very suggestive of cardiac pain or if ECG and echocardiogram showed changes suggestive of cardiac ischemia. Those failing to satisfy either of the above criteria were considered as the no CAD group.

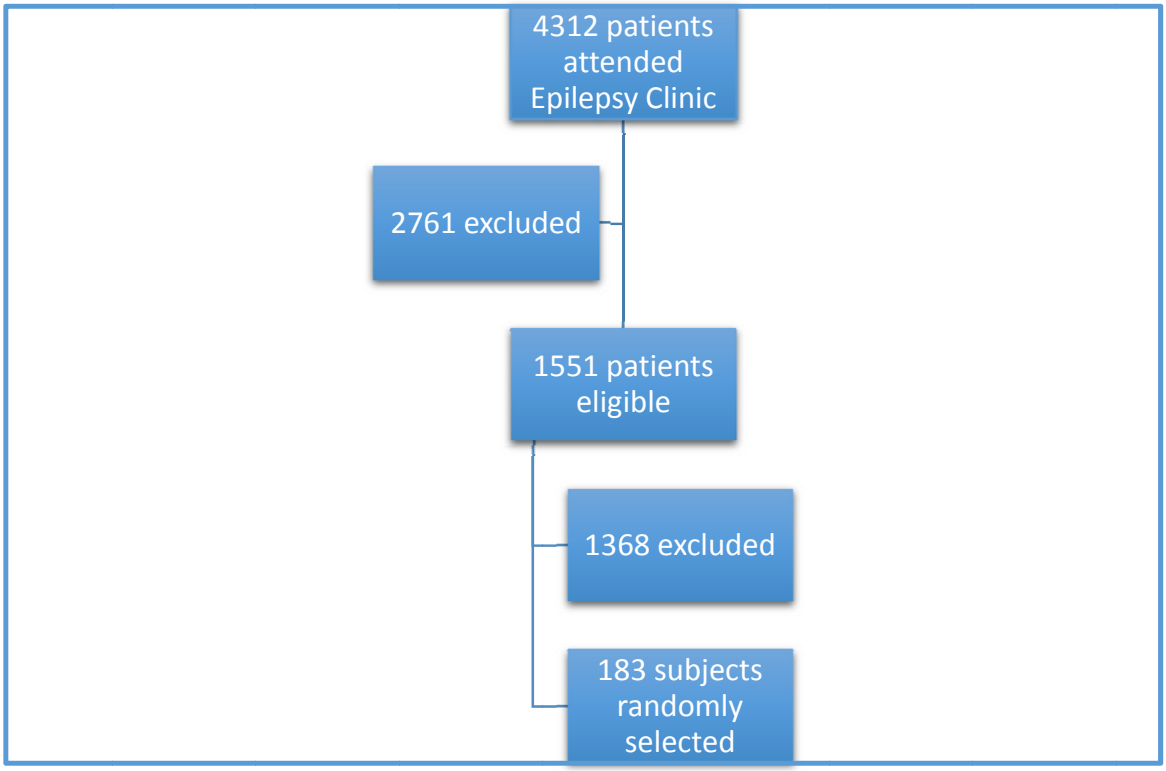
Statistical analysis:

Means of numeric variables were compared between groups by Students t-test. Proportions were compared by Chi-square test or Fisher's Exact test. P values of ≤ 0.05 were taken for statistical significance.

RESULTS

All patients attending the Epilepsy Clinic over the study period of January 2012 to June 2013 were screened for eligibility. Among them, one eighty three patients who satisfied the inclusion and exclusion criteria were randomly selected for the study.

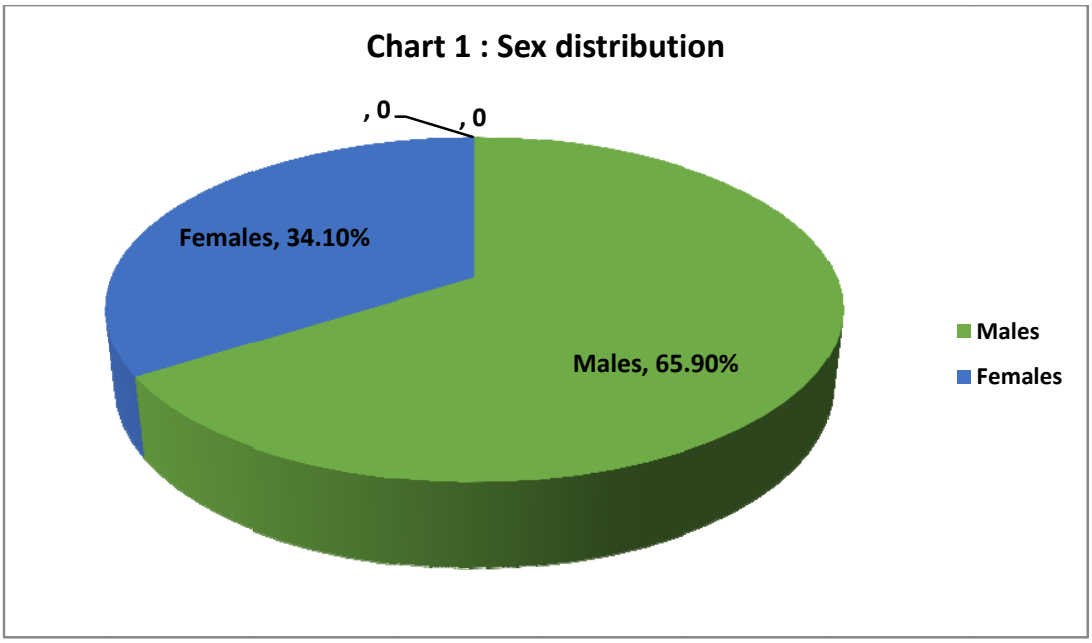
Fig 1: Selection procedure for the study



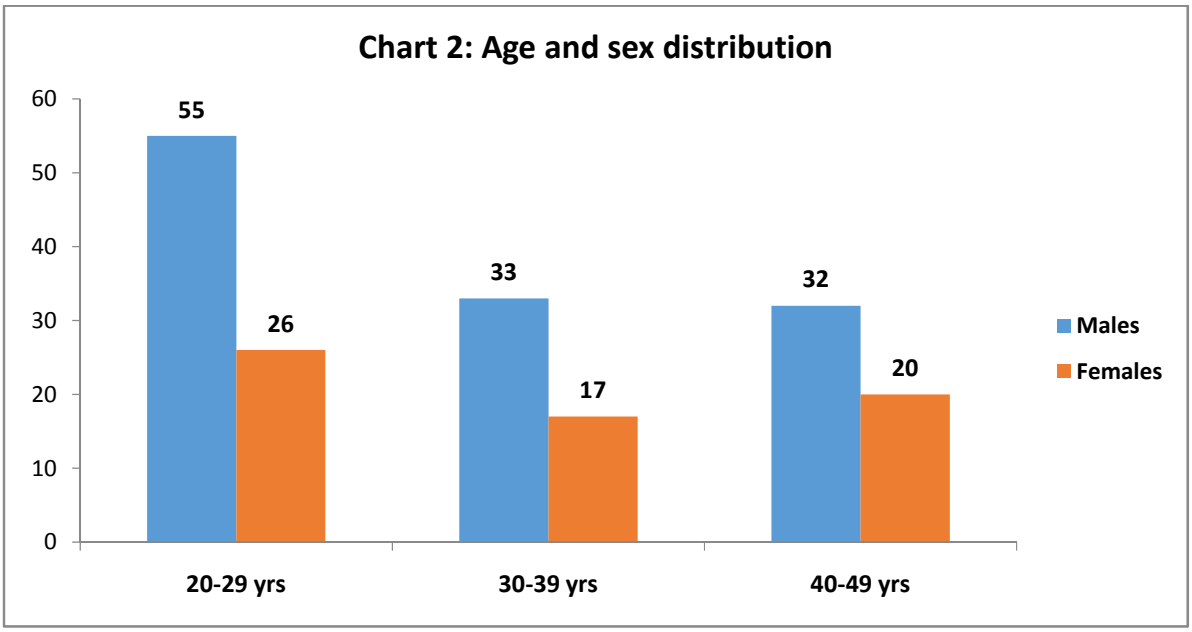
Demographic data

Age and gender:

Among the subjects 120 were males and 63 were females, i.e., 65.93% and 34.07% respectively, that is, males constituted two thirds of the subjects.



Subjects were chosen between 20 – 49 years of age to represent adults with lowest age related risk of coronary artery disease and metabolic syndrome. Of these, almost half (44.26 %) belonged to the age group 20 – 29 years. The 30 – 39 year age group comprised 27.32 % fo patients and 40 – 49 year age group, 28.42% of the patients. The average age of the subjects was 32.5 years.



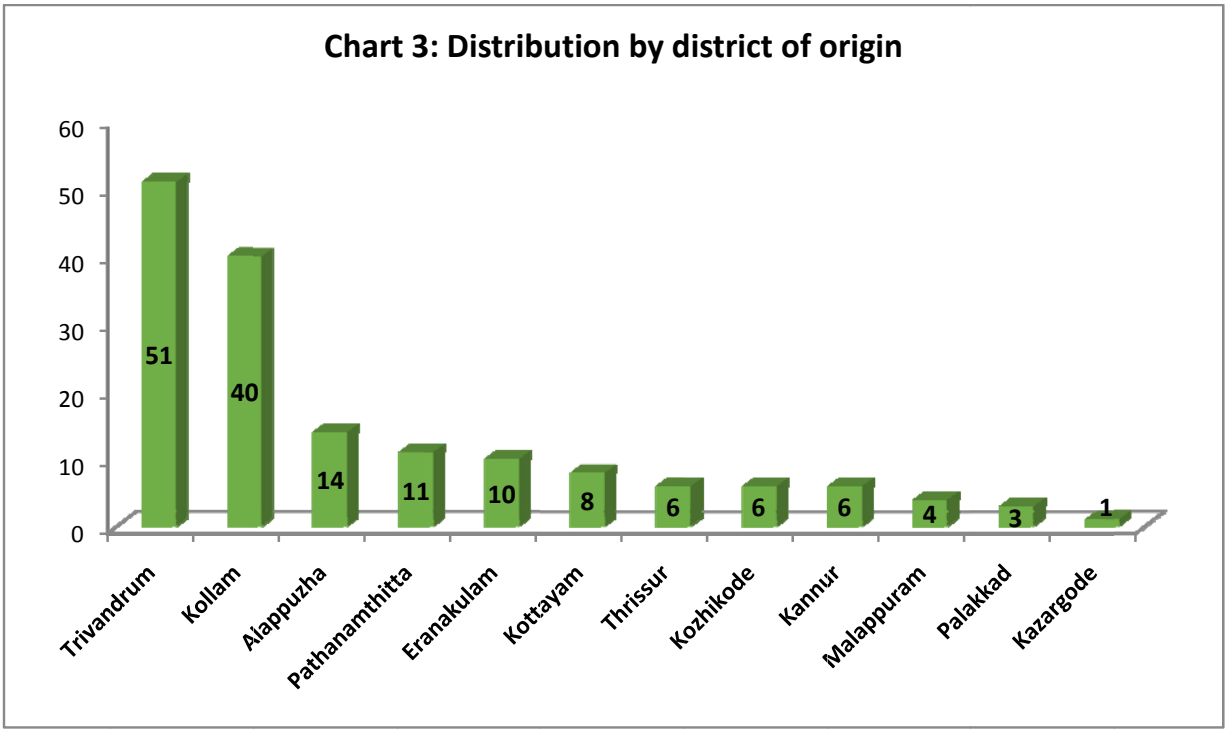
Age wise distribution showed almost similar distribution of males and females in all the age groups.

Table 1: Age and sex distribution

Age group	Males (%)	Females (%)	Total
20 – 29 yrs	55 (67.9%)	26 (32.1%)	81
30 – 39 yrs	33 (66%)	17 (34%)	50
40 – 49 yrs	32 (61.5%)	20 (38.5%)	52
Total	120	63	183

Place of origin:

Almost half of the subjects were from two districts in Kerala – Trivandrum (27.87%) and Kollam (21.85%).



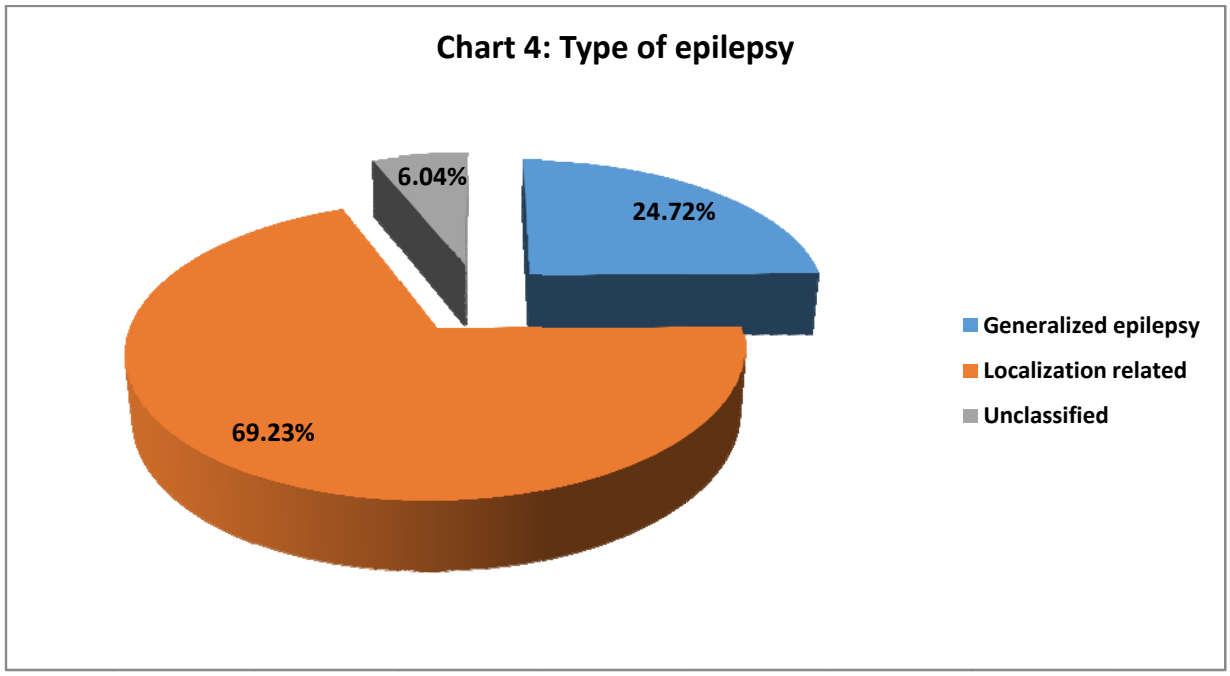
Characteristics of epilepsy

Age of onset and duration of epilepsy:

Age of onset of epilepsy ranged from birth to forty five years. The median age of onset was 15 years and the mean age of onset was 17.56 years. The mean duration of epilepsy was 15.4 years (range 3 – 48 years). Family history of epilepsy was present in first degree relatives for 20 (10. 93%) patients.

Type of epilepsy syndrome:

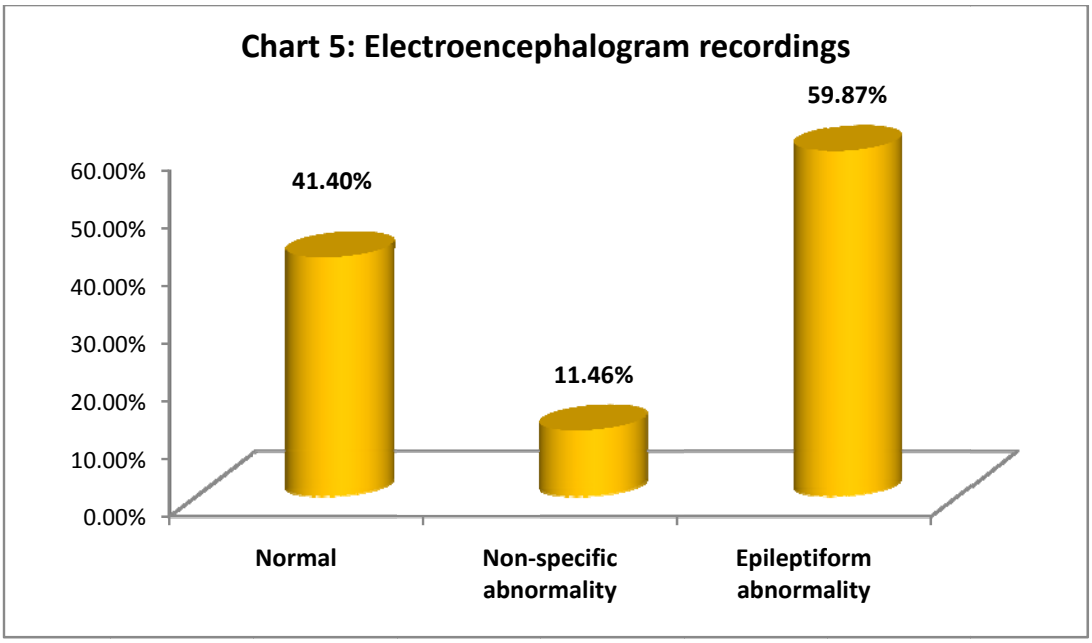
Majority of the subjects (127 subjects) had localization related epilepsy (69.23%). 45 (24.7%) patients had primary generalized epilepsy. The epilepsy syndrome could not be classified in 11 patients (6.04%).



Electroencephalogram:

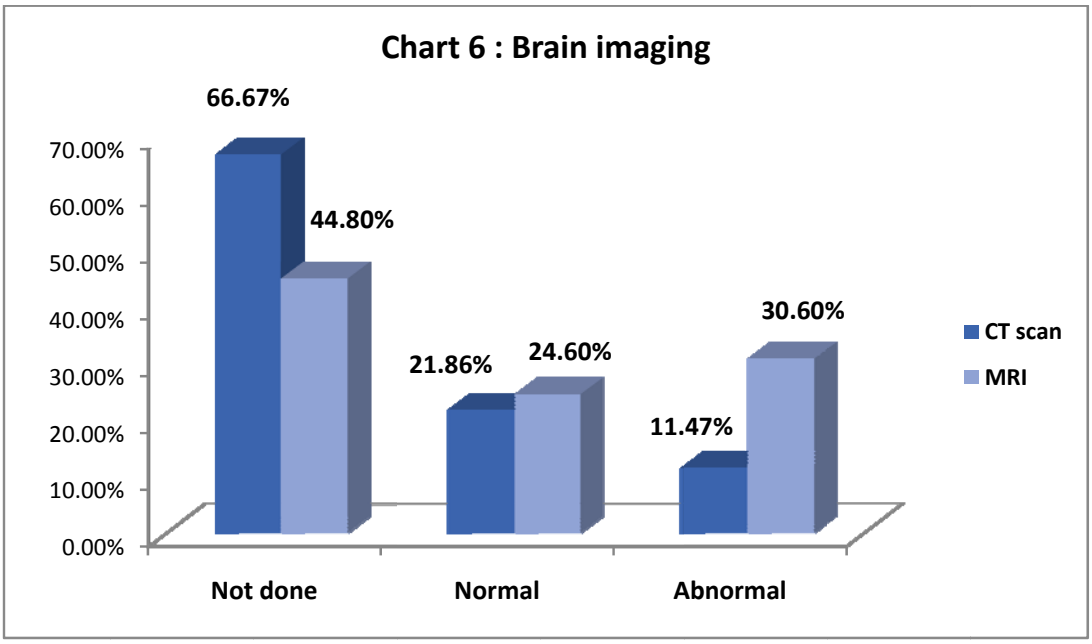
At least one electroencephalogram was available for one hundred seventy seven patients. Of the six patients who did not have an EEG, three had arteriovenous malformations, two had cavrenomas and one had a low grade glioma which were presumed to be the etiology of symptomatic epilepsy. At least one EEG showed abnormality in 112 of 177 patients, while all EEGs were normal in the remaining 65 patients.

Epileptiform abnormalities were noted in 94 patients (59.87 %) while the remaining 18 patients showed only non-specific slowing in the EEG.



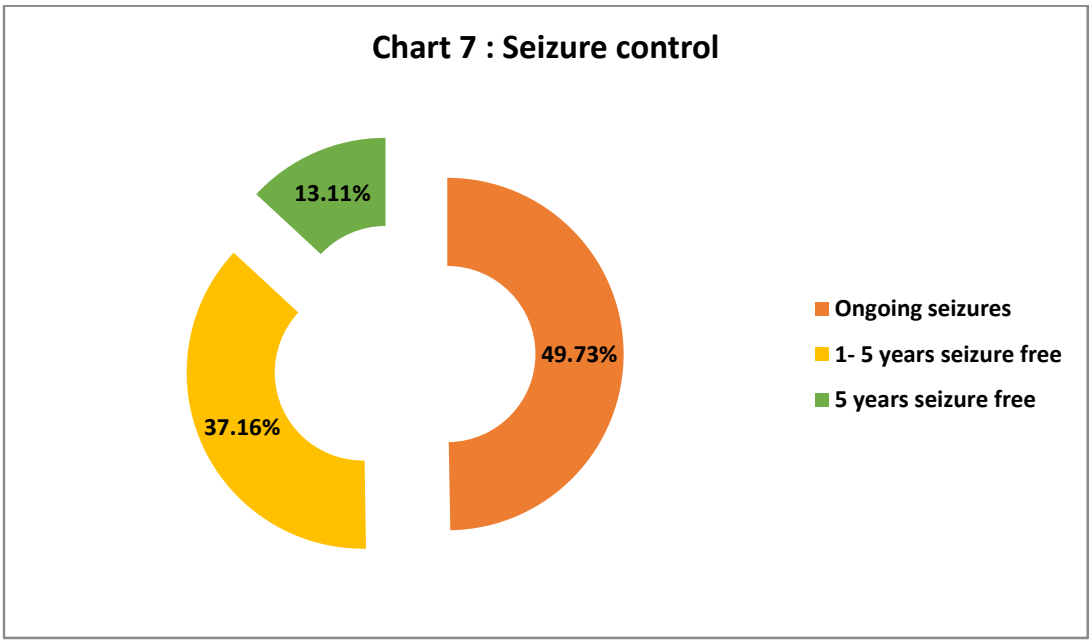
Brain imaging:

CT scan was available for 61 patients and MR imaging of the brain was available for 101 subjects. 45 of the 183 subjects did not have any imaging. CT scan showed definite abnormalities in 21(11.47%) patients and MRI brain was abnormal in 56 (30.6%) patients.



Control of epilepsy:

Seizures were ongoing in 91 (49. 73%) patients of whom only 24 had significant number of seizures (exceeding 15 per year). 13.11% patients had attained remission on medication (five or more years of seizure freedom) whereas 37.16% patients had attained seizure freedom for more than one year.



Severity of seizures:

History of clustering of seizures was noted in 39 (21.3 %) patients and status epilepticus in 10 (5.46%) patients. 29 patients (15.85%) had history of hospitalization for uncontrolled seizures.

Drug therapy for epilepsy

Duration of therapy:

The mean duration of treatment was 13.6 years (range 3 – 48 years). 129 patients (70.5%) started treatment within one year of onset. Regular antiepileptic treatment was started for 5.5 % patients only ten years after seizure onset.

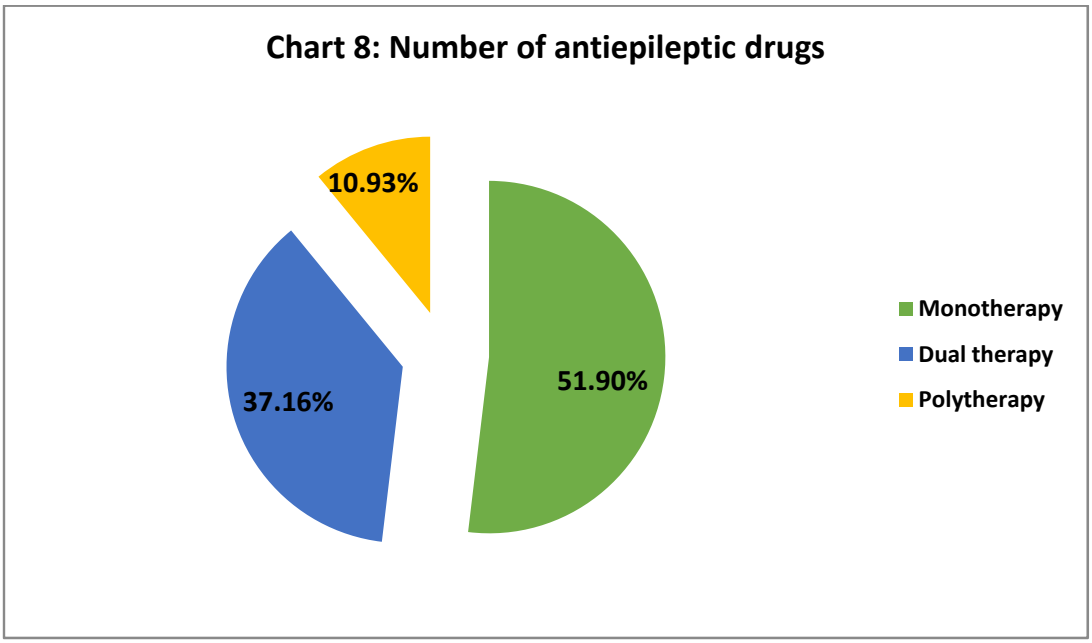
Monotherapy versus polytherapy:

95 patients (51.9%) were on monotherapy. Valproate was the commonest medication used for monotherapy contributing to 40% cases. Carbamazepine (26.32%) and phenytoin (17.9%) were also used in a significant number of patients as single drug for control of epilepsy.

Table 2: Distribution of patients based on monotherapy drug

Drug	Number of patients	% of monotherapy	% of total
Carbamazepine	25	26.3%	13.7%
Phenytoin	17	17.9%	9.3%
Valproate	38	40.0%	20.8%
Others	15	15.8%	8.2%

Dual therapy was given for 68 patients (37.16%). The combination of carbamazepine and clobazam was the commonest combination and was used in 36 (19.6%) patients. 20 patients (10.9 %) were on polytherapy with three or more medications.



Antiepileptic drug:

In the analysis of the currently used drugs and those to which the patient was exposed in the last five years, carbamazepine was noted to be the most common medication. 34.4% patients were on carbamazepine currently compared to 21.3% patients on phenytoin, 26.2% patients on valproate and 29.5% on clobazam. The newer antiepileptic medications, viz., levetiracetam, oxcarbazepine, lacosamide, topiramate, lamotrigine, and zonisamide, were used only in 15 patients (14.25 %) and of them only levetiracetam and oxcarbazepine were used as monotherapy.

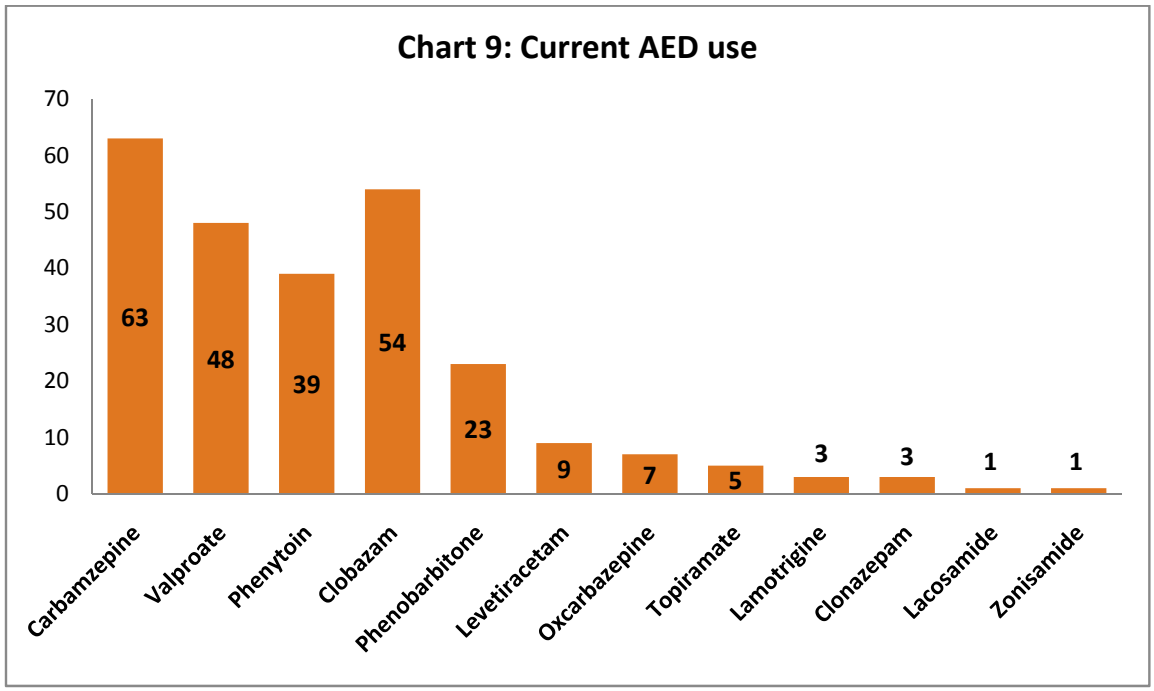


Chart 9: Current AED use
70
60
50
40
30
20
10
0
63
48
39
54
23
9
7
5
3
3
1
1
Carbamzepine
Valproate
Phenytoin
Clobazam
Phenobarbitone
Levetiracetam
Oxcarbazepine
Topiramate
Lamotrigine
Clonazepam
Lacosamide
Zonisamide

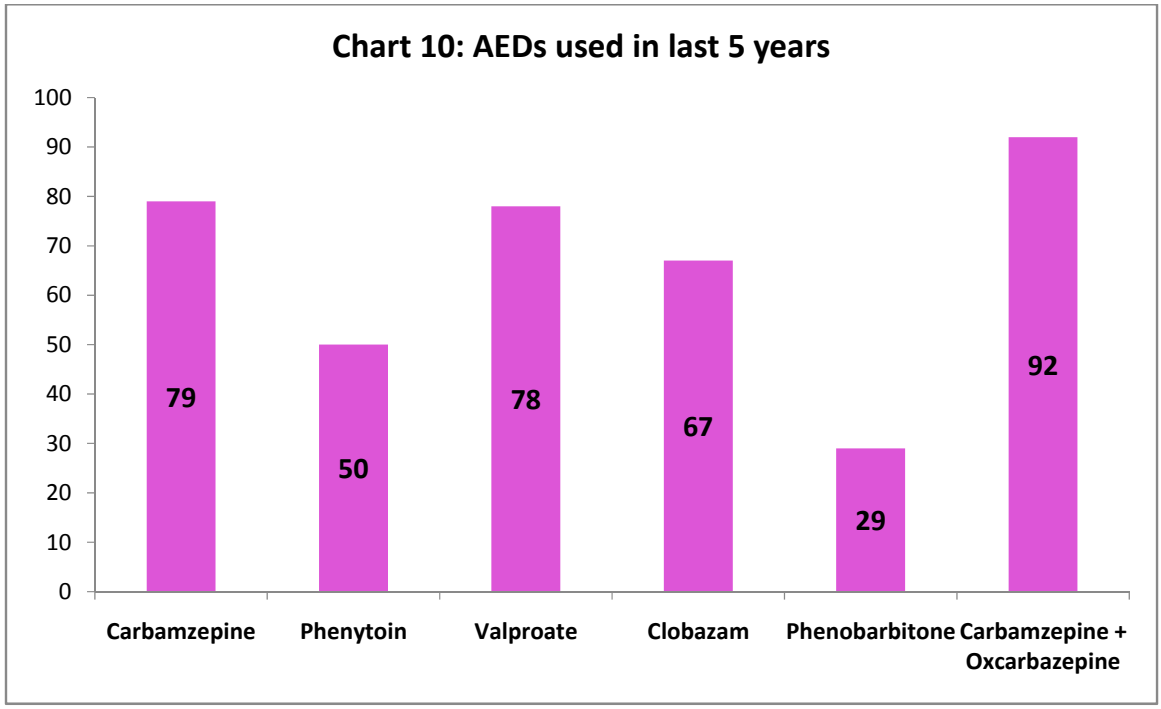


Chart 10: AEDs used in last 5 years
100
90
80
70
60
50
40
30
20
10
0
79
50
78
67
29
92
Carbamzepine
Phenytoin
Valproate
Clobazam
Phenobarbitone
Carbamzepine + Oxcarbazepine

Type of epilepsy and specific drug:

In patients with primary generalized epilepsy, the commonest drug used was valproate. Valproate was used in 33 of the 45 (73.33 %) patients. In those with localization related epilepsy, the commonest drug was carbamazepine used in 57.48% (73 of the 127 patients) patients. Phenytoin was used in 34 patients (26.77 %) with partial seizures and was the second most common drug used for this condition.

Risk factors for cardiovascular disease

Metabolic risk factors:

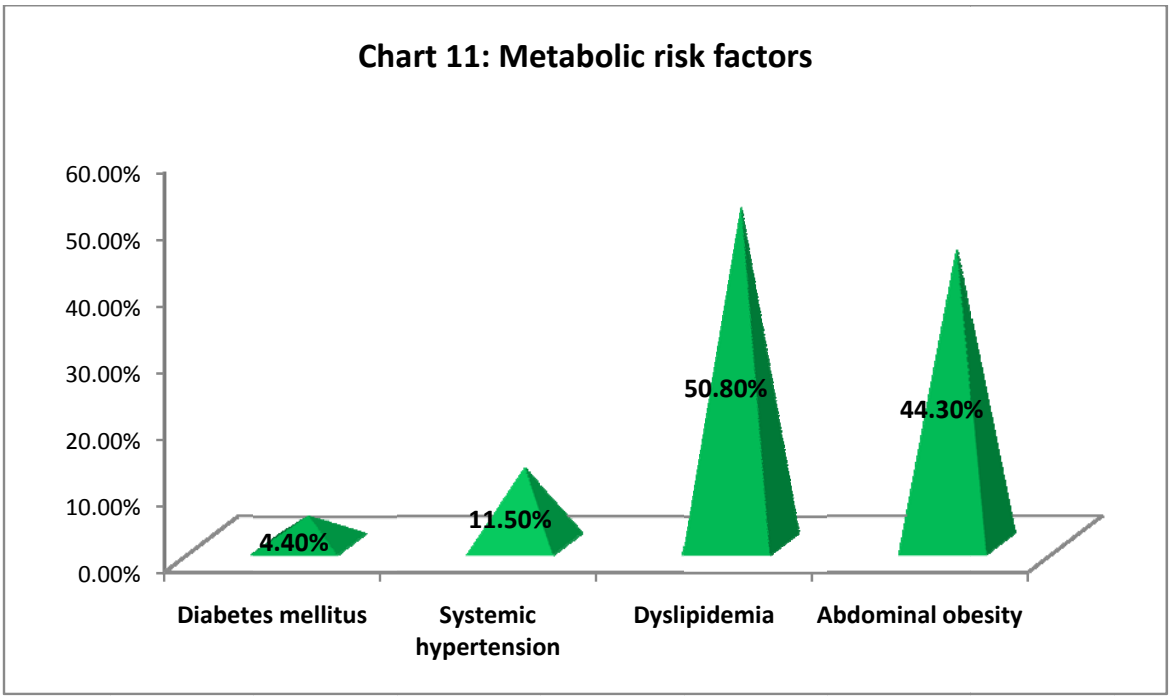
Five of the patients were on treatment for diabetes mellitus at the time of enrollment. Blood sugar analysis revealed abnormal fasting glucose diagnostic of diabetes mellitus in 3 patients. Overall, eight of the enrolled patients had diabetes mellitus and 35 had impaired fasting glucose. The fasting blood sugar values ranged from 60 to 202 mg/dL with an average fasting blood sugar value of 92. 78 (± 16.4) mg/dL.

Systemic hypertension was detected in 21 patients (11.5%). Eleven patients gave the history of dyslipidemia. 50.8 % (93) patients had abnormal fasting lipid levels or were on treatment for the same. The average total cholesterol level was 213.57 ± 49.9 mg/dL (range 121 – 405 mg/dL). The average values for serum LDL, HDL and triglycerides were 143. 78, 45.66 and 119.3 mg/dL respectively.

Abdominal obesity as defined by increased abdominal circumference was detected in 81 patients (44.3%); 46 males (38.33 %) and 35 females (55.55 %). The average abdominal circumference was 86.54 cm in males and 83.13 cm in females.

Table 3: Metabolic profile of the study cohort

Blood values	Mean (mg/dL)	Standard deviation	Median (mg/dL)	Range (mg/dL)
Fasting blood sugar	92.78	16.4	90	60 – 202
S. total cholesterol	213.57	49.9	205	121 – 405
S. LDL	143.78	42.68	140	42 – 314
S. HDL	45.66	12.81	44	18 – 95
S. Triglycerides	119.29	74.43	98	32 – 527



Other cardiovascular risk factors:

Only five of the subjects were smokers and another five were reformed smokers. Six patients had significant alcohol intake. Family history of premature coronary artery disease was present in three patients and premature stroke in one patient.

Metabolic syndrome

Metabolic syndrome as defined by presence of at least three out of five criteria was present in 54 patients, amounting to 29.5% of the population.

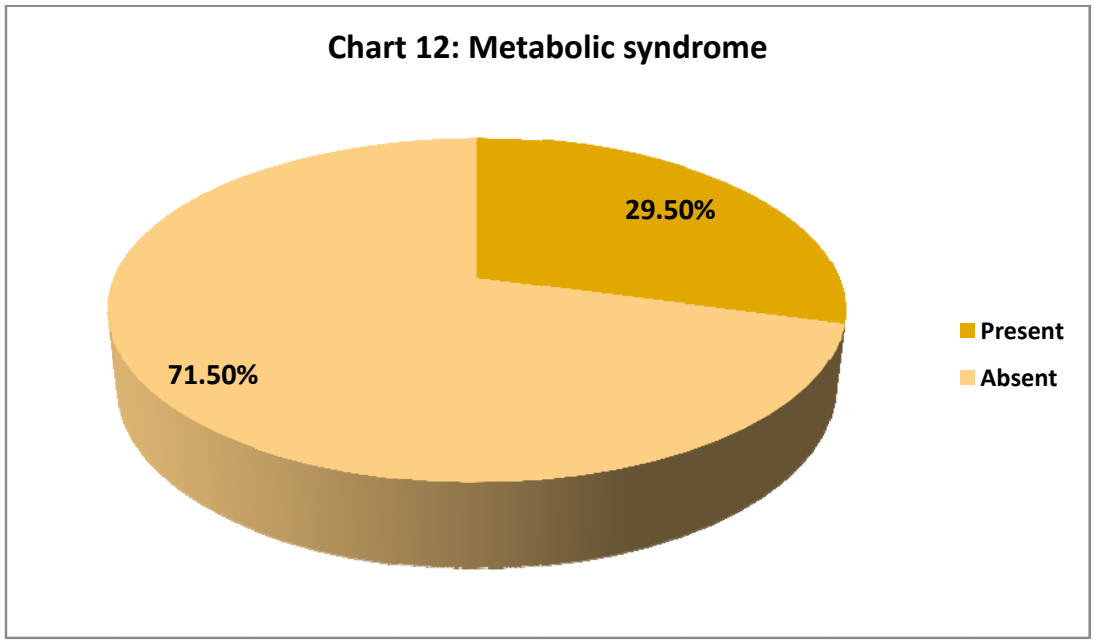


Table 4 : Fasting blood glucose and lipid levels in persons with metabolic syndrome

Metabolic syndrome	FBS (mg/dL)	Total cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Triglycerides (mg/dL)
Present Mean (std deviation)	100.44 (24.32)	224.30 (54.60)	148.57 (43.90)	39.67 (11.01)	179.00 999.30)
Absent Mean (std deviation)	89.57 (10.05)	209.09 (47.31)	141.78 (42.177)	48.18 (48.18)	94.30 (40.76)

Coronary artery disease

Six patients reported dyspnea on exertion; all but one had class II dyspnea while one had class III dyspnea. Abnormal ECGs were noted in twenty four patients. ECG showed ischemic abnormalities in 10 patients. Other ECGs showed left ventricular hypertrophy, chamber enlargement, bundle branch blocks and non-specific ST-T wave abnormalities.

Echocardiogram was performed in 54 patients (29.51 %). Seven patients had abnormal echocardiogram. One patient had regional wall motion abnormality suggestive of previous myocardial infarction. Five patients were detected to have valvular heart diseases for the first time during the study. One patient had rheumatic heart disease – moderate mitral stenosis, two patients had mitral valve prolapse with mitral regurgitation, one had age related aortic sclerosis and one had mild tricuspid regurgitation. All were asymptomatic for their valvular heart disease.

Definite coronary artery disease could be diagnosed in two patients. Both the patients had past history of acute myocardial infarction and coronary angiogram showed triple vessel disease in both the patients. One of the patients underwent coronary artery bypass grafting, whereas the other patient with severe left ventricular dysfunction and left atrial clot with embolic stroke is on conservative management. A diagnosis of likely coronary artery disease was put for three patients in view of suggestive ECG abnormalities. The echocardiogram of these patients were normal.

Table 5: Coronary artery disease in study cohort

Coronary artery disease	Number	Percent
Definite	2	1.1 %
Likely	3	1.64 %
Any CAD	5	2.73 %

COMPARATIVE ANALYSIS OF METABOLIC SYNDROME AND CORONARY ARTERY DISEASE WITH OTHER VARIABLES

Demographic variables and metabolic syndrome

Sex and metabolic syndrome:

Table 6: Sex and metabolic syndrome

Sex		Metabolic syndrome		
		Yes	No	Total
Male	Count	39	81	120
	% within Sex	32.5%	67.5%	100.0%
Female	Count	15	48	63
	% within Sex	23.8%	76.2%	100.0%
Total	Count	54	129	183
	% within Sex	29.5%	70.5%	100.0%
P value - 0.221				

Among the males, 32.5% and among females 23.8% had metabolic syndrome. The difference between the groups was not significant.

Age and metabolic syndrome:

Table 7: Age and metabolic syndrome

			Metabolic syndrome		
			Yes	No	Total
Age group	20-29 yrs	Count	14	67	81
		% within age group	17.3%	82.7%	100.0%
	30-39 yrs	Count	19	31	50
		% within age group	38.0%	62.0%	100.0%
	40-49 yrs	Count	21	31	52
		% within age group	40.4%	59.6%	100.0%
	Total	Count	54	129	183
		% within age group	29.5%	70.5%	100.0%
P value - 0.005					

The prevalence of metabolic syndrome is higher in older age groups with a very significant p value.

Characteristics of epilepsy and metabolic syndrome

Type of epilepsy and metabolic syndrome:

Table 8: Type of epilepsy and metabolic syndrome

			Metabolic syndrome		
			Yes	No	Total
Type of epilepsy	Generalized	Count	16	29	45
		% within type of epilepsy	35.6%	64.4%	100.0%
	Partial	Count	36	90	126
		% within type of epilepsy	28.6%	71.4%	100.0%
	Unclassified	Count	2	9	11
		% within type of epilepsy	18.2%	81.8%	100.0%
	Total	Count	54	128	182
		% within type of epilepsy	29.7%	70.3%	100.0%
P value = 0.469					

There was no significant difference in the presence of metabolic syndrome between the types of epilepsy.

Duration of epilepsy and metabolic syndrome:

Table 9: Duration of epilepsy and metabolic syndrome

			Metabolic syndrome		
			Yes	No	Total
Epilepsy duration group	<5 yrs	Count	8	8	16
		% within group	50.0%	50.0%	100.0%
	5-9 yrs	Count	16	33	49
		% within group	32.7%	67.3%	100.0%
	10-14 yrs	Count	8	29	37
		% within group	21.6%	78.4%	100.0%
	15-19 yrs	Count	5	20	25
		% within group	20.0%	80.0%	100.0%
	≥ 20 yrs	Count	17	39	56
		% within group	30.4%	69.6%	100.0%
	Total	Count	54	129	183
		% within group	29.5%	70.5%	100.0%
P value - 0.225					

The duration of epilepsy was not found to have any significant association with the presence of metabolic syndrome.

Severity of epilepsy and metabolic syndrome:

Table 10: Severity of epilepsy and metabolic syndrome

	Metabolic syndrome		P value
	Present	**Absent**	
Clustering	13 (33.3 %)	26 (66.7 %)	0.319
Status epilepticus	2 (20.0 %)	8 (80.0 %)	0.729
Hospitalization	12 (41.4 %)	17 (58.6 %)	0.124

None of the factors implying more severe seizures like history of clustering of seizures and status epilepticus and requirement of hospitalization for control of seizures were significant for presence of metabolic syndrome.

Treatment of epilepsy

Duration of treatment and metabolic syndrome:

Table 11: Duration of treatment and metabolic syndrome

			Metabolic syndrome		
			Yes	No	Total
Duration of treatment	<10 yrs	Count	26	44	70
		% within group	37.1%	62.9%	100.0%
	10-19 yrs	Count	13	51	64
		% within group	20.3%	79.7%	100.0%
	≥20 yrs	Count	15	32	47
		% within group	31.9%	68.1%	100.0%
	Total	Count	54	127	181
		% within group	29.8%	70.2%	100.0%
P value = 0.098					

Number of drugs and metabolic syndrome:

Table 12: Number of drugs and metabolic syndrome

			Metabolic syndrome		
			Yes	No	Total
Number of drugs	Monotherapy	Count	33	62	95
		% within group	34.7%	65.3%	100.0%
	Dual therapy	Count	15	53	68
		% within group	22.1%	77.9%	100.0%
	Polytherapy	Count	6	14	20
		% within group	30.0%	70.0%	100.0%
Total		Count	54	129	183
		% within group	29.5%	70.5%	100.0%
P value - 0.216					

The duration of treatment and number of drugs used did not show any significant association with the presence of metabolic syndrome.

Type of drugs and metabolic syndrome:

Sufficient numbers to reliably assess significance was available only for five of the drugs – carbamazepine, phenytoin, valproate, clobazam and phenobarbitone.

Current drug use and metabolic syndrome:

Table 13: Current drug use and metabolic syndrome

Drug		Metabolic syndrome		P value
		Present	Absent	
Carbamazepine	**Yes**	16 (25.0 %)	48 (75.0%)	0.327
	No	38 (31.9 %)	81 (68.1 %)	
Phenytoin	**Yes**	14 (35.9 %)	25 (64.1 %)	0.324
	No	40 (27.8 %)	104 (72.2 %)	
Valproate	**Yes**	21 (43. 8 %)	27 (56.3 %)	**0.012**
	No	33 (24.4 %)	102 (75.6 %)	
Clobazam	**Yes**	15 (27.8 %)	39 (72.2 %)	0.110
	No	39 (30.2 %)	90 (69.8 %)	
Phenobarbitone	**Yes**	3 (13.0 %)	20 (87.0 %)	0.064
	No	51 (31.9 %)	109 (68.1 %)	

Metabolic syndrome was significantly more in patients currently on valproate compared to those not on valproate. None of the other drugs showed any significant association with metabolic syndrome.

Valproate and metabolic syndrome:

Valproate was the only antiepileptic medication demonstrated to be significantly related to metabolic syndrome.

Table 14: Relationship between valproate dose and duration and metabolic syndrome

Metabolic syndrome	Present	Absent	P value
Valpraote dose (mg)	386.11	177.52	0.005
Valproate duration (years)	2.88	1.95	0.246

A higher dose of valproate was significantly associated with increased risk of metabolic syndrome. However, the duration of use of valproate was not significant. No significant difference in blood sugar or blood pressure values among patients on valproate. The drug had mixed effect on the lipid profile, producing reduction of LDL cholesterol on the one hand and increase in triglycerides with reduction in HDL cholesterol on the other. Abdominal obesity significantly more in patients on valproate (52.1 % vs 40.0 %)

Drugs used in the last five years:

Table 15: Drug use in the last five years and metabolic syndrome:

	Metabolic syndrome		P value
	Present	**Absent**	
Carbamazepine	20 (25.3 %)	59 (74.7 %)	0.279
Phenytoin	18 (36.0 %)	32 (64.0 %)	0.238
Valproate	27 (34.6 %)	51 (65.4 %)	0.192
Clobazam	17 (25.4 %)	50 (74.6 %)	0.351
Phenobarbitone	4 (13.8 %)	25 (86.2 %)	0.043

There was no significant association between metabolic syndrome and use of valproate in the last five years. However, the association between phenobarbitone use and metabolic syndrome reached significance in this analysis.

Drugs and vascular risk factors:

Table 16: Drugs and vascular risk factors

Drug	Present	Absent	P value
Carbamazepine (n = 63)			
Diabetes	3 (4.7 %)	61 (95.3%)	1.00
Hypertension	6 (9.4 %)	58 (90.6 %)	0.513
Dyslipidemia	31 (48.4 %)	33 (51.6 50	0.636
Phenytoin (n = 48)			
Diabetes	4 (10.3 %)	35 (89.7 %)	0.065
Hypertension	5 (12.8 %)	34 (87.2 %)	0.779
Dyslipidemia	23 (59.0 %)	16 (41.0 %)	0.251
Valproate (n = 39)			
Diabetes	1 (2.1 %)	47 (97.9 %)	0.683
Hypertension	5 (10.4 %)	43 (89.6 %)	0.789
Dyslipidemia	28 (58.3 %)	20 (41.7 5)	0.225
Clobazam (n= 54)			
Diabetes	2 (3.7 %)	57 (96.3 %)	1.00
Hypertension	5 (9.3 %)	49 (90.7 %)	0.543
Dyslipidemia	23 (42.6 %)	31 (57.4 %)	0.150
Phenobarbitone (n=23)			
Diabetes	2 (8.69%)	21 (91.31%)	1.00
Hypertension	1 (4.35 %)	22 (95.65%)	0.543
Dyslipidemia	8 (34.8 %)	15 (65.2 %)	0.100

No significant association was noted between drug use and cardiovascular risk factors – diabetes mellitus, hypertension or dyslipidemia.

Effects of drugs on lipid profile:

Table 17: Drugs and lipid profile

Drug	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglyceride
Carbamazepine (n= 63)				
Yes	231.8	157.7	49.9	117.8
No	203.8	136.3	43.4	120.1
p value	<0.001	0.001	0.001	0.841
Phenytoin (n=48)				
Yes	221.1	147.7	46.3	133.6
No	211.5	142.7	45.5	115.4
p value	0.291	0.516	0.747	0.177
Valproate (n= 39)				
Yes	192.8	127.1	40.0	127.4
No	220.9	149.7	47.7	116.4
p value	0.001	0.001	<0.001	0.379
Clobazam (n= 54)				
Yes	221.9	148.1	49.6	118.7
No	210.7	142.0	44.0	119.5
p Value	0.143	0.377	0.006	0.948
Phenobarbitone (n= 23)				
Yes	213.45	142.13	44.76	124.76
No	213.60	144.03	45.84	118.27
p Value	0.988	0.843	0.679	0.608

Very significant association was noted on lipid profile for carbamzepine, phenytoin and clobazam. Carbamazepine use was associated with increased total cholesterol, increased

LDL and increased HDL. Valproate use was noted to be significantly associated with decreased total cholesterol, LDL and HDL. Clobazam use was associated with increased HDL.

Coronary artery disease

The number of patients with definite coronary artery disease was only two and those with probable coronary artery disease were 3. The number was too low to give meaningful results in multivariate analysis.

Outcome of patients on follow up

The patients were followed up by telephonic interview at the end of the study with a follow up period of six months to two years based on the time of recruitment. One patient died during the course of follow up. The patient was documented to have sudden death due to presumed cardiac cause (autopsy was not performed). This patient's cardiac evaluation done previously was normal.

DISCUSSION

The present study is a prospective cross sectional study to assess the prevalence of metabolic syndrome and coronary heart disease in a group of 183 patients with epilepsy randomly selected from among the patients attending the Epilepsy Clinic in out institute. The study has looked in to the prevalence of cardiovascular risk factors and coronary heart disease specifically at a younger age group where the risk is relatively low. To ensure that the effect of antiepileptic medications is uniform, a minimum period of three years on medications was taken as a mandatory inclusion criterion. To our knowledge, this is the first study is India which has looked into the metabolic and cardiovascular risk profile of patients with epilepsy.

Demographic characteristics of the population

In the present study two thirds of the subjects were males. The prevalence of epilepsy in population base studies in India has shown higher prevalence in males compared to females, both in urban and rural population. The reported prevalence rates are 5.88 per 1000 population in men and 5.51 in women [15]. The difference in the gender distribution is accounted by the type of epilepsy – hormonal differences in prevalence of certain epilepsy syndromes, increased occurrence of certain risk factors like head injury in males etc.

Majority of the patients in this group belong to the southern region of Kerala, which is attributable to the proximity to the institute and increased number of hospital visits compared to those from northern parts of the state who are usually advised to follow up less for their convenience.

Type of epilepsy

In the present data, the percentage of localization related epilepsy was approximately 70% with primary generalized epilepsy accounting for only 25 % of the cases. Another six percent of the patients presented with generalized seizures alone and could not be classified into primary or secondary based on clinical history, EEG or imaging data. Patients with symptomatic generalized epilepsy are not represented in this study as most of them have associated mental sub-normality making the process of giving informed consent difficult. In an analysis by Sridharan et al [(5)], the range for the type of seizures in the population was very wide with primary generalized seizures accounting for 45.45 - 86% of all reported seizures, while partial seizures with or without generalization forming 11.45 -54.54%. In the western literature about 60% of patients attending tertiary centres have localization related epilepsy. The relatively low number of patients with generalized epilepsy in our group could be because the cohort is taken from a tertiary reference centre where more of treatment resistant cases are referred.

Epilepsy was controlled in about 50% cases which is comparable to the general population data where 50 – 60% is noted to achieve remission [(92)].

Therapy of epilepsy

A wide range of duration of epilepsy treatment was noted in the study population ranging from 3 to 48 years. Fifty two percent of the patients were receiving monotherapy. Although carbamazepine was the commonest drug to be used, valproate was the commonest monotherapy. The percentage of patients on monotherapy was comparable to other studies. In a cohort from a tertiary centre in Eastern India, 54% of the patients could be maintained in monotherapy [(93)]. In a study conducted by Wang et al [(94)] in the United States, the most

common monotherapies used in adults were phenytoin (31%), levetiracetam (25%), and carbamazepine (8%) in 2008. The choice of medication reflects the type of epilepsy syndrome being treated – valproate being the preferred drug in primary generalized epilepsies and carbamazepine more commonly used in localization related epilepsies.

Cardiovascular risk factors and metabolic syndrome

The only study systematically looking into the prevalence of cardiovascular risk factor profile in the State was published by Thankappan et al [(95)] in 2010. This study studied the age and gender wise prevalence of the cardiovascular risk factors and the rural- urban variation in the risk factor profile among population selected from Thiruvananthapuram. The study however looks into a wider range of age group of 15 - 64 years than the one covered in our present study. In the study by Thankappan et al [(95)], among adults 15 – 64 years of age in Thiruvananthapuram, prevalence of diabetes mellitus was 14.3% in men and 17.8% in women with an overall figure of 16.2 %. However, looking at a subgroup of the population from 15 to 45 years of age, the prevalence is 7.3 %. This is considerably higher than that of the epilepsy patients which was 4.4%.

Prevalence of hypertension was 28.8% among adults in the age group 15 – 64 years [(95)] and 21.2% in the age group 15 to 45 years. This is almost double the prevalence in our study population.

The lower prevalence of diabetes mellitus and systemic hypertension is attributable to the fact that about 50 % of the study cohort is below 30 years of age in whom the prevalence is shown to be very low. In the population study, less than one third of the study group belonged to the age below 30 years.

Obesity is a significant problem in the state. 30.8 % of adults in the state have a BMI >25. This is considerably more for women than for men. In our study also more of abdominal obesity was noted among female patients compared to males. The prevalence of abdominal obesity was higher in our group compared to the similar age group in the population based study (44.3 % vs 30.03 % respectively). Dyslipidemia was also as common in group compared to the general population in a similar age group.

In the Norwegian HUNT 2 [96] study by Hildrum et al, the prevalence of diabetes mellitus and systemic hypertension was very high compared to the general population in Kerala and our study population. The prevalence of dyslipidemia was not assessed in this population. The prevalence of abdominal obesity was lower than our group.

Both the studies show that patients with epilepsy on treatment tend to have higher prevalence of dyslipidemia and central obesity in spite of including a higher percentage of younger patients.

The levels of physical activity may be different in epileptic patients although there is no data to prove the same. The higher prevalence could also be contributed by the effect of the antiepileptic medications. Most of the patients were on treatment with the older antiepileptics known to produce significant changes in metabolic profile.

The prevalence of metabolic syndrome in the age group 20 to 49 years in a study conducted in an urban population in Rajasthan was 21.9 % [97]. In the Norwegian study, the prevalence of metabolic syndrome was 17.43 %. Epilepsy patients in our group had a higher prevalence of 29.5% indicating that epilepsy or treatment of the condition is associated with a higher risk of metabolic syndrome and the increased risk is attributable to the effect on the lipid profile and central obesity.

Table 18: Comparison of prevalence of vascular risk factors and metabolic syndrome in different studies

Study	Age group	Diabetes mellitus	Systemic hypertension	Dyslipidemia	Abdominal obesity	Metabolic syndrome
Current study	20 – 49 years	4.4 %	11.5 %	50.8 %	44.3 %	29.5%
Thankappan et al (Trivandrum) [95]	15 – 45 years	7.3 %	21.2 %	48.03 %	30.03 %	---
Hildrum et al (Norway) [96]	20 – 49 years	18.1 %	47. 77 %	----	35.67 %	17.43 %
Gupta et al (Jaipur) [97]	20 – 49 years	8.57 %	29.58 %	----	27.18 %	21.93 %

Effect of antiepileptic drugs on the metabolic profile

Classic anticonvulsant medications, especially valproate, carbamazepine and phenytoin have been shown in many studies to have significant effects on the metabolic profile. Anticonvulsants may alter liver function and increase the activity of hepatic microsomal enzyme system [55, 56]. This enzyme induction phenomenon is associated with an altered metabolism of various substances such as drugs and lipids.

In a study conducted in Delhi [60] to establish the relationship between antiepileptic drug use and serum lipid levels, a significant increase in serum levels of triglyceride, total cholesterol, HDL and VLDL cholesterol was noted in patients receiving combination therapy of either phenytoin and phenobarbitone or phenytoin and carbamazepine or phenytoin alone. Patients receiving carbamazepine alone had significant increase in serum levels of triglyceride and VLDL cholesterol, but no significant changes in serum levels of total cholesterol and HDL cholesterol was noted in this group.

In our group, carbamazepine was noted to be associated with raised total cholesterol and HDL cholesterol whereas valproate therapy significantly reduced both. Neither had a

significant effect on the triglyceride levels. The level of LDL cholesterol (which is derived from the values of serum total cholesterol, HDL cholesterol, and triglyceride) was raised with carbamazepine and reduced with valproate to levels attaining statistical significance indicating that the changes in HDL cholesterol profile alone are not responsible for the changes in serum total cholesterol. The changes may reflect the difference in the action on the microsomal enzymes by the two drugs. Carbamazepine induces the enzymes whereas valproate inhibits the enzymes. Carbamazepine stimulates the hepatic synthesis of cholesterase and increase the formation and pool size of bile acids, which in turn raise the level of intestinal absorption of cholesterol by facilitating micelle formation [(63)]. Phenytoin has been shown in multiple studies to be associated with raised serum cholesterol levels. Although the same trend was noted in our patients, the difference did not reach statistical significance. A study including a higher number of patients with each individual antiepileptic medication may be required to establish the same.

Valproate therapy has been previously shown to be associated with adverse metabolic profile. In a study by Pylvalnen et al. [(69)], valproate treated patients were shown to have higher circulating insulin concentrations relative to body mass index, higher uric acid and triglyceride levels, and lower high-density lipoprotein cholesterol concentration. Many of the metabolic effects of valproate are probably related to the increase in body weight associated with its use. Verrotti et al [(63)] showed that up to 40 % patients developed obesity while on valproate therapy. Body mass index at initiation of valproate therapy was not a predictor of the development of obesity or metabolic syndrome [(98, 99)].

Coronary heart disease in epilepsy

Only two of the patients in the cohort had definite coronary heart disease so that association with other factors related to epilepsy and drug therapy could not be performed.

However both the affected patients had severe heart disease with both having left main stem disease and one having significant left ventricular dysfunction. Both had other risk factors – smoking in one and smoking and hypertension in the other.

One of the patients had sudden death not related to an epileptic attack. Although the patient was not clinically symptomatic for a cardiac disease and his baseline cardiac evaluation was normal, the possibility of a cardiac etiology is likely in this patient.

The dyslipidemia of the metabolic syndrome may increase cardiovascular disease risk through different mechanisms from those associated with high total or LDL cholesterol [(84)].

CONCLUSIONS

1. Metabolic syndrome is more prevalent among adult patients below 50 years of age with epilepsy compared to general population
2. This difference is contributed by increased prevalence of abdominal obesity and dyslipidemia in epilepsy patients
3. There is no increase in the prevalence of diabetes mellitus and systemic hypertension between persons with epilepsy and general population.
4. Among the antiepileptic drugs, valproate use was found to have significant association with the presence of metabolic syndrome
5. The higher the dose of valproate, higher the risk of development of metabolic syndrome; the duration of treatment of valproate was not significant
6. Valproate and carbamazepine have significant effects on the lipid profile and abdominal obesity in patients on treatment.
7. Antiepileptic medications produce variable effects on the lipid profile. Carbamazepine use was associated with increased total cholesterol, increased LDL and increased HDL. Valproate use is significantly associated with decreased total cholesterol, LDL and HDL. Clobazam use was associated with increased HDL.
8. The sex of the patient and characteristics of epilepsy did not influence metabolic syndrome or vascular risk factors.
9. The number of patients with coronary artery disease was too few to determine the statistical associations.

SUMMARY

Antiepileptic medications, especially valproate and carbamazepine have significant effects on the lipid profile and abdominal obesity in patients on treatment. Metabolic syndrome is more prevalent among adult patients below 50 years of age with epilepsy compared to the general population in the same age group. This difference could be related to the effect of the antiepileptic medications, especially valproate. Further larger scale studies may be required to elucidate the exact mechanism. The study definitely confirms the need to monitor patients on antiepileptic medications regularly for development of dyslipidemia and obesity.

LIMITATIONS OF THE STUDY

1. Patients on all medications were considered for the study thereby resulting in a smaller number in subgroup analysis
2. Almost half the patients were on more than one antiepileptic medication.
3. An internal control population was not selected
4. The number of cases of coronary artery disease detected were very few in the study. A more rigorous assessment for detection of CAD and more number of patients will be required in future studies.

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ANNEXURE

PROFORMA OF THESIS

1. Identification information

1.1 Serial number ----------

1.2 Hospital number ----------

1.3 Name ----------

1.4 Residential address ----------

1.5 Phone number ----------

2. Demographic data

2.1 Age ---------- years

2.2 Sex ---------- 1. Male 2. Female

2.3 Occupation ----------

2.4 Education status ----------

3. Details of epilepsy (1 = Yes, 0 = No)

3.1 Subtype ----------

1. Generalized 2. Partial 3. Unclassified

3.2 Duration of epilepsy ---------- years

3.3 Total duration of treatment ---------- years

3.4 Present antiepileptic drugs ----------

3.5 Previous antiepileptic drugs ----------

3.6 History of hospitalization for epilepsy ----------

4. Vascular risk factors (1= Yes, 0 = No)

4.1 Current smoker ---------- Smoking index ----------

4.2 Ex- smoker ---------- Stopped since ----------years

4.3 Alcohol consumption ---------- Units/ week ----------

4.4 Physical exercise ----------

1. Aerobic activity for 30 minutes on at least 3 days a week
2. No regular exercise

4.5. Family history of premature coronary artery disease in first degree relatives (Males below 55 years, females below 65 years)

4.6 Family history of stroke ----------

4.7 Diabetes mellitus ---------- Duration ---------- years

4.8 Systemic hypertension ---------- Duration ---------- years

4.9 Dyslipidemia ---------- Duration ---------- years

5. Coronary artery disease (1 = Yes, 0 = No)

5.1 Stable angina ---------- Duration ---------- years

5.2 Unstable angina ---------- Duration ---------- years

5.3 Myocardial infarction ---------- Duration ---------- years

5.4 Hospitalization for acute coronary syndrome ----------

5.5 Special procedures for treatment of CAD ----------

1. PTCA 2. CABG 3. Thrombolysis

6. Physical measurements

6.1 Height ---------- cm

6.2 Weight ---------- kg

6.3 Waist circumference ---------- cm

6.4 Blood pressure 1. Systolic ---------- mm Hg

2. Diastolic ---------- mm Hg

7. Investigations

7.1 Fasting plasma glucose ---------- mg/dl

7.2 HbA1c ----------

7.3 Total Cholesterol ---------- mg/dl

7.4 LDL ---------- mg/dl

7.5 HDL ---------- mg/dl

7.6 Triglyceride ---------- mg/dl

7.7 ECG ----------

7.8 Transthoracic echocardiogram ----------

1. Normal 2. Regional wall motion abnormality 3. Left ventricular hypertrophy 4. Left ventricular dysfunction