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# ATHEROSCLEROTIC RISK AMONG EPILEPTIC PATIENTS TAKING CARBAMAZEPINE, PHENYTOIN TREATMENT: BRIEF REVIEW

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**ABSTRACT**: Epilepsy is a common chronic neurological disorder that requires long-term or sometimes lifetime therapy. Anticonvulsant drugs are used in large quantities during long-term antiepileptic therapy and the treatment may be associated with various metabolic abnormalities in connective tissues, endocrine system and the liver. Recent evidence indicates that prolonged use of antiepileptic drugs (AEDs) particularly carbamazepine (CBZ), phenytoin (PHT) might modify some vascular risk factors; however, the influence of AED therapy on the development of atherosclerosis has been the subject of controversy and pretty unclear. Some epidemiological studies have reported a higher prevalence of ischemic vascular disease among epileptic patients on AEDs, while in other studies the mortality due to atherosclerosis-related cardiovascular disease in treated epileptics has been observed to be lower than in the general population. The etiology of atherosclerosis-related vascular diseases in epileptic patients has not been fully clarified. Atherosclerotic vascular alterations may start early in life, this review focuses on major atherogenic risk, including disordered lipid profiles, and increased lipoprotein (a) serum levels among epileptic patients.

**INTRODUCTION:** Epilepsy is the most common serious neurological condition and approximately 50 million people worldwide have it. This neurological disease account 1% of global burden of disease (WHO). This equals lung cancer in men and breast cancer in women. In India it is estimated to have 60-80 lakhs of people with epilepsy [1, 2].

In the US, about 100,000 new cases of epilepsy are diagnosed [3, 4]. In the UK, between 1 in 140 and 1 in 200 people (at least 300,000 people) are currently being treated for epilepsy [5]. Epidemiological studies suggest that between 70 and 80% of people developing epilepsy will go into remission, while the remaining patients continue to have seizures and are refractory to treatment with the currently available therapies [6, 7].

The most common risk factors for epilepsy are cerebrovascular disease, brain tumours, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance, and infections of the central nervous system. In resource-poor countries, endemic infections, such as malaria and neurocysticercosis, seem to be major risk factors [8].

Multiple epidemiologic studies have shown positive correlations between epilepsy and comorbid vascular disease. Patients with epilepsy suffer mildly increased mortality from ischemic heart disease, with standardized mortality ratios (SMRs) between 1.2 and 2.5 in several studies in developed countries [9, 10]. One Chinese study demonstrated an SMR of 10.7 for myocardial infarction [11] and comorbid myocardial

ischemia as reported on death certificates was positively correlated with epilepsy with an odds ratio of 16 [12]. Nonfatal ischemic heart disease is also significantly elevated 34% to 63% above controls [13]. Stronger correlations between epilepsy and cerebrovascular disease are seen, with mortality ratios 3.7 to 5.3 [14] and morbidity close to 7 in one study. The latter correlation is to be expected, as stroke is a known causative factor for epilepsy. Whether having epilepsy increases subsequent cerebrovascular risk is more difficult to demonstrate in the literature, as the crosssectional nature of most studies makes it difficult to infer causation.

Very little data exist regarding the effects of specific AEDs on the incidence of vascular events. One Finnish study found a lower prevalence of ischemic heart disease in epilepsy patients, and furthermore found that patients who were on enzyme-inducing AEDs had 29% lower mortality due to heart disease [15]. When a Norwegian group performed a survey of coronary risk profiles on patients with epilepsy and controls, however, they found no significant differences [16].

It is possible that the Finnish study reflects genetic variants in the isolated, homogeneous Finnish population, as Finnish studies of serologic risk factors also yield different results than those in other populations. This review focuses on risk of atherogenic metabolic alterations, disordered lipid profiles, and increased lipoprotein (a) serum levels among epileptic patients on phenytoin, carbamazepine treatment.

**Mechanism of Enzyme induction effects on Serum Cholesterol:** The enzyme-inducing AEDs phenytoin (PHT), carbamazepine (CBZ), increase the activity of the hepatic cytochrome P450 system, which is involved in synthesis of serum cholesterol. Animal data show that a particular enzyme, CYP51A1, catalyzes the conversion of lanosterol into cholesterol intermediates [17]. When these intermediates build up through inhibition of the enzyme, they in turn inhibit the rate-limiting step of cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and slow the synthesis of cholesterol [18].

It follows that induction of CYP51A1 should therefore increase cholesterol production through metabolism of these intermediates and reduced feedback inhibition. While the pathway has not been explicitly studied in humans to our knowledge, this mechanism engenders some predictions regarding the effects of certain AEDs in patients. For example, an enzyme-inducing AED such as PHT , CBZ should increase serum cholesterol.

On the other hand, valproic acid (VPA), an enzyme-inhibiting medication, should decrease metabolism of inter- mediates and increase feedback inhibition, thereby decreasing production of cholesterol. One might also conjecture that pharmacogenetic heterogeneity of these effects could result in varying effects of a given AED on lipids in different patients [19].

**AED and Atherosclerosis risk:** Atherosclerosis is the leading cause of death in the developed world, although the true frequency is difficult to accurately determine because it is a predominantly asymptomatic condition [20]. It is a disease of large and medium-sized arteries, and is characterized by endothelial dys-function, vascular inflammation, and the presence of buildup (fatty streaks) consisting of lipids, calcium, and cellular debris within the intima of the vessel wall.

Some epidemiological studies have indicated that the prevalence and death rates from atherosclerosis related cardiovascular disease (CVD) are slightly elevated in adult epileptic patients taking antiepileptic drugs (AEDs) [21]. However, other studies have come to the contrasting conclusion that mortality due to ischemic heart disease appears to be lower in treated epileptics than in the general population [22].

Epidemiological studies in adults with epilepsy have found that the risk for ischemic heart disease is increased by 34%, and the risk for fetal CVD is increased by 68% . In a cohort of 9000 patients, once hospitalized for epilepsy, a cause-specific mortality assessment found a standardized mortality ratio of 2.5 for ischemic heart disease and 3.5 for stroke. However, in a study of 30–50 year old males, no difference was found in the total coronary risk profile between those with epilepsy and controls.

Thus, the influence of AED therapy on the development of atherosclerosis has been the subject of controversy, although recent evidence indicates that prolonged antiepileptic treatment might modify some vascular risk factors [23].

It has been well documented that atherosclerotic vascular alterations may start early in life and progress with age. The first signs of hyperlipidemia can be detected in childhood [24] and fatty streaks, which are the earliest pathologic lesions of the atherogenic process, can be observed in the aorta and coronary arteries of individuals by the age of 20. Thus, recent studies have focused on the incidence of vascular risk factors and a higher risk of atherosclerosis development among children with epilepsy; however, this link has not yet been firmly established and remains controversial [25, 26, 27, 28].

Epilepsy is a relatively frequent chronic disorder in childhood and often requires lifelong therapy. It is widely suggested that either epilepsy itself or the prolonged administration of some AEDs is associated with the undesirable metabolic side effects implicated in dysfunction of the vessel wall.

This dysfunction can promote atherogenesis and ultimately result in occlusive vascular diseases such as stroke, myocardial infarction, and peripheral arterial disease [29, 30, 31]. The study conducted by Dechadarevian et al. demonstrated the presence of atherosclerotic changes at autopsy of an 11-year-old child who died following a status epilepticus who had been treated with carbamazepine (CBZ) for long-standing epilepsy. The child had hypercholesterolemia and an over 40% reduction in the vessel lumen diameter due to marked intimal proliferation and accumulation of foam cells in the coronary arteries [32] .

1. **Carbamazepine:** Carbamazepine (CBZ) is widely used as an anticonvulsant drug in adults and children. The drug is known to cause multiple metabolic alterations, among them changes in serum lipoprotein concentrations. The precise frequency and nature of these changes are unclear as are the underlying mechanisms of action. In many studies increased total and/or low-density lipoprotein cholesterol (LDL-C) concentrations were found, and elevated high-density lipoprotein cholesterol (HDL-C) is also frequently reported [33-43]. The interpretation of most studies is limited due to unsatisfactory study designs; there are very few prospective studies [44, 45, 46] whereas all other studies were cross-sectional and a variety of different control groups were used for comparison. In many studies there were antiepileptic comedications. Studies in children are difficult to interpret because lipoprotein profiles change with increasing age. In addition, it cannot be completely ruled out that epilepsy itself can lead to changes in lipoprotein profiles.

Cholesterol concentrations and especially the ratio of LDL-C to HDL-C are relevant determinants for the incidence and mortality from coronary heart disease [47, 48]. There is some evidence that coronary heart disease is less common in patients with epilepsy [49] although these data are still uncertain. CBZ is known to be a powerful inducing agent of cytochrome *P*-450 enzymes [50, 51] and its effects on lipoproteins have been largely attributed to its enzyme-inducing action. Overall, however, there is very little information about the metabolic changes that are responsible for the effects of CBZ on lipids and no study controlled for confounding factors such as diet.

CBZ also induces liver microsomal enzymes, thereby altering the metabolism of lipids, bile acids and bilirubin [52]. This leads to alteration in serum lipid levels and thus affects the development of atherosclerosis. Some serum lipids and apoproteins are atherogenic while others seem to have an anti-atherogenic effect. Subjects with high serum HDL-C levels have a low risk of coronary heart disease, whereas those with high serum TC and LDL-C have increased risk. However the ratio between the cholesterol fractions (TC/HDL-C; HDL-C/ LDL-C) is a better predictor for the development of atherosclerosis. Increased HDL-C/ TC and HDL-C/LDL-C is a powerful protective factor against atherosclerosis while the reverse increases the risk.

There are contradictory reports on the relationship of antiepileptic drugs to serum lipids. CBZ therapy leads to increased serum HDL-C levels, and HDL-C/TC ratio also tends to be increased. Muuronen, *et al.* reported that the mortality related to atherosclerotic heart disease was lower among patients treated with antiepileptic drugs than in the general population. They related this finding to the increased levels of HDL-C in these patients.

Some studies have failed to demonstrate a significant change in serum lipids in patients receiving CBZ monotherapy[53]. However most workers have shown significant increase in TC and other lipid fractions in epileptic children receiving CBZ [54, 55, 56] Franzoni, et al. showed that rise in TC was a result of increased LDL-C levels only. Others have suggested that the increase in TC is due to increase in both LDL-C and HDL-C [57]. Similarly, there are contradictory reports on the effects of anticonvulsants on atherogenic ratio (TC/HDL and LDL/HDL ratio). Increased TC/HDL and LDL/HDL ratio indicate a higher risk of atherosclerosis.

It is suggested that an increase in this ratio, following CBZ therapy might increase the risk of atherosclerosis. Aggarwal et al., does not show a significant alteration in TC/HDL and LDL/HDL ratio. This result matches with the results of others [38] showing no significant difference in TC/HDL-C and LDL-C/HDL-C ratio in children receiving CBZ. LDL-C levels were 33.3% higher in cases compared to controls whereas HDL-C levels were 53.3% higher. Since HDL-C levels are supposed to be protective, significance of these changes needs to be studied further [33].

Some investigators reported a significant decrease in TC/HDL ratios during the CBZ treatment [19] and some reported a slight increase during the first year of treatment followed by an insignificant decrease [46]. This ratio was reported to be increased 18 and 6 months after the onset of CBZ treatment in two studies performed in adult and pediatric patients, respectively [35, 43] Similarly, there are contradictory reports on the LDL/HDL ratio in the studies performed in adults[45]. However, the results of the studies performed in the children revealed an increase in this ratio, similar to the results in our CBZ group. In the CBZ group, TC/HDL and LDL/HDL ratios greater than the upper limit of normal were more frequent in the second and sixth months, respectively, as were the levels of TC and LDL.

In conclusion, these studies demonstrated that TC, LDL, and the atherogenic ratios increase during treatment with CBZ. In addition, the increase in the level of GGT is thought to be related to the inductive effect of CBZ. The National Child Education Program in the United States dictates that some preventive measures should be taken in childhood to prevent premature atherosclerosis.

Furthermore, some investigators have recommended avoiding a diet with high cholesterol levels in children treated with CBZ [36, 39]. The published data related to the alterations of serum lipids resulting from antiepileptic treatment inducing microsomal enzyme activation, suggest that the changes in the serum lipids beyond 3 months of treatment could be more significant.

However, larger populations are needed to assess the relative risk of atherosclerosis caused by the alterations observed during treatment with CBZ. Further studies are required to examine the implication of these changes and the need for preventive measures. Long term prospective studies are required to evaluate the risk of atherosclerosis caused by alteration in serum lipid levels in epileptic patients receiving therapy with CBZ.

2. **Phenytoin:** Phenytoin (PHT) is used as an anticonvulsant drug in adults and children. The drug is known to cause multiple metabolic alterations, among them changes in serum lipoprotein concentrations. The precise frequency and nature of these changes are unclear as are the underlying mechanisms of action. In many studies increased total and/or low-density lipoprotein cholesterol (LDL-C) concentrations were found, and elevated high-density lipoprotein cholesterol (HDL-C) is also frequently reported [58, 59].

   In particular growing evidence suggests that the older generation AEDs that are commonly used for treatment of epilepsy including phenytoin exert prominent effects on the hepatic enzyme system and may alter metabolic pathways that are related to increased vascular risk. Recent studies [60, 61] indicated that PHT is the potent inducer of the cytochrome P450 (CYP450) system, which exerts strong effects on serum lipid profile. It follows that this enzyme inducing drug may substantially increase the risk of atherosclerosis.

Emerging evidence further showed that treatment with PHT is significantly associated with increased blood levels of total cholesterol, atherogenic (non HDL) cholesterol and triglycerides [62]. Chaung *et al*., showed that the increase in thickness of CCA IMT in monotherapy with PHT may be related to total cholesterol and LDL-C [63]. Close monitoring of serum lipid levels and and long-term follow up of patients receiving phenytoin to observe the incidence of ischemic heart disease is needed to obtained clinically significant results.

**Effects of AEDs on Carotid Intima-media thickness:** Although enzyme-inducing medications appear to increase lipids and other serologic markers of vascular risk, the question remains as to whether these changes in risk markers actually increase the incidence of ischemic events in treated patients. Ischemic vascular disease can have many causes, but if inducer-treated epilepsy patients were truly subject to higher rates of myocardial infarction and stroke from the aforementioned serologic alterations, one would expect that vascular disease in these patients would have an atherosclerotic etiology.

Carotid intima-media thickness (CA-IMT) as assessed by ultrasound is considered to be a surrogate measure of atherogenesis and has been strongly correlated with risk of both stroke and myocardial infarction in several prospective studies [64, 65, 66]. One study of patients treated mainly with enzyme-inducing drugs showed higher CA-IMT relative to controls [67].

Chaung *et al.,* also demonstrated that the duration of monotherapy with CBZ & PHT is significantly associated with acceleration of atherosclerosis in patients with epilepsy, via different underlying mechanism. Dyslipidemia has long long been known to be important risk factors for atherosclerosis.

LDL-C plays an important role in the atherosclerotic process by increasing endothelial permeability, retention of lipoproteins within the intima of blood vessel, recruitment of inflammatory cells and formation of foam cells. Emerging evidence further showed that treatment with enzyme inducing AED's such as CBZ and PHT, is significantly associated with increased blood levels of total cholesterol, atherogenic cholesterol, triglyceride and tHCY.

It is therefore of interest that increase in thickness of CCA IMT in monotherapy with PHT and CBZ may be related to total cholesterol and LDL-C [63].

Another investigation found that CBZ-treated patients had higher CA-IMT than VPA-treated patients, who in turn had higher CA-IMT than untreated patients with epilepsy. When carotid thickness was studied in children treated with VPA alone, treated patients had significantly higher CA-IMT without a difference in serum lipids [68]. CA-IMT in epilepsy patients appears to be positively correlated with duration of AED therapy [69] though these investigators did not separate their findings according to different groups of AEDs.

These data confirm that enzyme-inducing AEDs may be associated with increased vascular risk over time, consistent with their effects on serologsic markers. However, they also suggest that VPA might increase vascular risk through mechanisms unknown. It is possible that epilepsy itself might increase vascular risk, which might then be further exacerbated by enzymatically active AEDs.

Future studies are needed to compare CA-IMT between those treated with newer-generation non-enzyme-inducing agents such as levetiracetam, lamotrigine, and topiramate.

**CONCLUSION:** The risk of vascular complications from AED therapy is an area of legitimate concern in need of further study. Enzyme-inducing AEDs in particular may pose a risk by increasing atherogenic serum cholesterol fractions. AED may also have adverse long-term metabolic consequences, including obesity, insulin resistance, and the metabolic syndrome.

Pharmacoepidemiologic studies are needed to determine the long-term vascular effects of carbamazepine and phenytoin. Because patients with epilepsy require medication for years, and often for life, it is difficult to justify the long-term use of these agents when there are capable alternatives. Many of the adverse effects of the older drugs appear to be rapidly reversible, prompting consideration of whether patients who are currently treated with these agents should be switched to alternative therapies, even in the absence of obvious side effects.

Newer medications without effects on hepatic enzymes likely do not have these chronic metabolic consequences, and we recommend their use over older-generation drugs whenever possible.

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