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ORIGINAL RESEARCH OPEN ACCESS

Effects of long term antiseizure medications on atherosclerosis

Surendra Babu B[1], Prasanth Varghese C[1,*] and Gilvaz PC[1]

[1]Department of Neurology, Jubilee Mission Medical College & research Institute, Thrissur, Kerala - 680005, India

Abstract

Long-term therapy with antiseizure medications (ASMs) has been associated with metabolic consequences that lead to an increase in the risk of atherosclerosis in patients with epilepsy. This study was conducted to assess the effects of ASMs on vascular risk factors namely, serum Lipid profile and C-reactive protein (CRP) in epileptic patients and to assess the correlation between the duration of the ASMs, and carotid intima media thickness (IMT). Forty three adult patient participants who were receiving ASM monotherapy for more than 2 years and 43 control patients were enrolled in this study. All participants received measurement of common carotid artery (CCA) and IMT by B-mode ultrasonography to assess the extent of atherosclerosis. Other measurements included body mass index (BMI), serum lipid profile and CRP. The correlation between duration of ASM and average carotid IMT was calculated by using the Pearson's correlation coefficient method. The majority of subjects on phenytoin 8 (66.7%) were positive for CRP. There was an equal proportion of patients on carbamazepine who were equally positive 5(50%) and negative 5(50%) for CRP. There was a statistically significant association between phenytoin consumption and CRP positivity. There was positive correlation between duration of phenytoin consumption and average IMT. There was a strong positive correlation between duration of phenobarbitone consumption and average IMT and was statistically significant. Our results also suggest that long-term use of ASMs with prominent effects on the enzyme system, including Carbamazepine, phenytoin, sodium valproate or phenobarbitone may contribute to the progression of atherosclerosis in patients with epilepsy.

Keywords: epilepsy; ASMs; IMT; CRP; phenytoin; carbamazepine; sodium valproate; phenobarbitone

Introduction

Epilepsy is a chronic disabling disease with propensity for recurrent seizures. Epilepsy affects around 50 million people worldwide. People with epilepsy have increased mortality compared to general population with cardiovascular disease as a significant risk factor for death as suggested by epidemiological studies.

Epilepsy can be controlled with antiseizure medications (ASMs) [1]. More than 30% of epileptic patients have to undergo long term therapy with ASMs [2].

However, one of the concerns with long term ASMs is their potential to influence cardiovascular health due to various mechanisms, such as metabolic effects, alterations in lipid profiles, and effects on endothelial function. Of note, seizures may occur following cerebrovascular events and especially after major strokes and venous sinus thrombosis [3]. In addition, patients with autoimmune diseases such as Systemic lupus erythematosus, Sjogren's syndrome, Crohn's and Behcet's disease, which have been also linked to increased CVD risk can present with epilepsy [4-6]. Seizures may also be the first clinical manifestation of brain arteriovenous malformations, especially when they are located in the frontal and temporal lobes [5]. The most used treatments for epilepsy worldwide are older generation drugs such as phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), and valproic acid (VPA), which have prominent enzymatic effects.

***Corresponding author:** Dr. Prasanth Varghese C, Asst. Professor, Department of Neurology, Jubilee Mission Medical College & research Institute, Thrissur, Kerala - 680005, India. Email: prasanthneuro@gmail.com

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The association between ASM and CVD morbidity and mortality is not clearly defined. This study was conducted to evaluate the vascular risk factors and carotid atherosclerosis in epileptics who are on long term anti-epileptic therapy.

Materials and methods

This cross-sectional study was conducted at the Department of Neurology, Jubilee Mission Medical College & Research Institute, Thrissur, following approval from institutional ethical committee. The study was conducted for a period of 18 months from July 2020 to January 2022 and was carried out for 86 participants i.e., 43 epilepsy patients and 43 controls after categorizing each variable. Epilepsy patients aged between 18 and 65, receiving ASM monotherapy for more than 2 years were included in the study. Patients who discontinued ASM for more than 2 weeks, patients with Nephrotic syndrome, diabetes mellitus, thyroid and liver disorders were excluded from the study. Common carotid artery IMT (intima media thickness) is measured by B-mode ultrasound system to assess the extent of atherosclerosis. Scanning was done for both the left and right Common carotid artery, defined as the 1 cm vascular wall segment of the carotid artery immediately proximal to the dilation of the bifurcation plane. An optimal longitudinal image was saved and the IMT is analyzed using a computerized image analysis system

Statistical analysis

Statistical analysis was carried out for 86 participants i.e., 43 epilepsy patients and 43 controls after categorizing each variable. Base line data was collected from patients *viz* age, sex, ASM, dosage duration of ASM, carotid IMT, Lipid profile, BMI, CRP and was analyzed. The significance of difference in mean between two groups was analyzed by student t-test. The correlation between duration of ASM and average carotid IMT was calculated by using the Pearson's correlation coefficient method

Results

This cross-sectional study was conducted to evaluate the vascular risk factors and carotid atherosclerosis in epileptics who are on long term anti-epileptic therapy. The study subjects were divided in to two groups involving 43 patients as cases and 43 participants as control.

Age wise distribution of participants

It was observed that majority of subjects were in the age group of 25 to 34 years and 35 to 44 years in cases and controls. The distribution of age among cases and control is presented in table 1.

Table 1: Age wise distribution of cases and controls.

Age group	*Group*		*Total*	*Chi square*	*p value*
	Cases	*Controls*			
<14	6 (14.0)	3 (7.0)	9 (10.5)		
15-24	8 (18.6)	9 (20.9)	17 (19.8)		
25-34	10 (23.3)	11 (25.6)	21 (24.4)		
35-44	10 (23.3)	11 (25.6)	21 (24.4)	3.303	0.688
45-54	2 (4.7)	5 (11.6)	7 (8.1)		
55-64	7 (16.3)	4 (9.3)	11 (12.8)		
Total	43	43	86		

The mean age of the cases and control was found to be 33.30 ± 15.9 in cases and 34.07 ± 14.2 in control.

Duration and dosage of ASMs in study group

The mean duration of treatment with phenytoin was 6.42 ± 4.69 years with dosage range of 200 – 300mg, carbamazepine was 8.60 ± 4.97 years with dosage range of 400-800mg, sodium valproate was 5.91 ± 3.17 years with dosage range of 400-600mg and phenobarbitone was 8.50 ± 5.12 years with dosage range of 30-60mg (Table 2).

Table 2: Duration and dosage of ASMs in study group.

Drug	*N*	*Mean*	*Dosage range*
Phenytoin (PHT)	12	6.42 ± 4.69	200-300
Carbamazepine (CBZ)	10	8.60 ± 4.97	400-800
Sodium valproate (VPT)	11	5.91 ± 3.17	400-600
Phenobarbitone (PB)	10	8.50 ± 5.12	30-60

Effect of phenytoin on atherosclerosis risk factors

The mean BMI value was higher among subjects on phenytoin compared to controls. This difference was found to be statistically significant. The comparison of mean BMI values among control and Phenytoin group is plotted in figure 1.

The mean total cholesterol, HDL levels were slightly higher among subjects consuming phenytoin. Whereas, mean LDL and TGL were slightly higher among controls. The differences were not found to be statistically significant (Table 3).

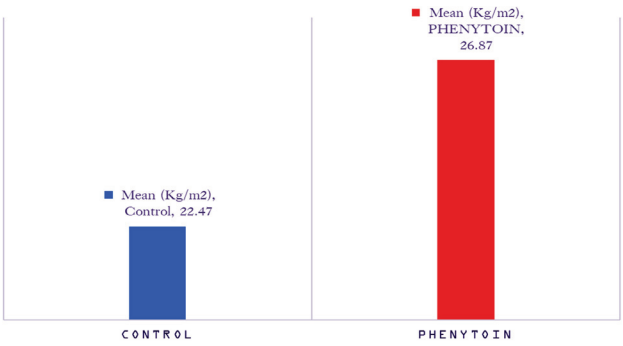

Figure 1: Comparison of mean BMI values of control and phenytoin group.

The mean Intima media thickness (IMT) levels on right side and average levels were slightly lower subjects who were consuming phenytoin compared to the controls. On the other hand, mean IMT levels on left side was slightly higher among subjects consuming phenytoin. The differences were not found to be statistically significant (Table 4).

Effect of carbamazepine on atherosclerosis risk factors

The mean BMI value was higher among subjects on carbamazepine compared to controls. This difference was not statistically significant.

The mean total cholesterol, LDL, HDL, TGL levels were higher among subjects taking carbamazepine compared to controls. The differences in levels of TC and TGL were found to be statistically significant (Table 5).

The mean IMT levels on right and left side and average levels were slightly lower among subjects who were taking carbamazepine compared to controls. The differences were not found to be statistically significant (Table 6).

Effect of sodium valproate on atherosclerosis risk factors

The mean BMI value was higher among patients on sodium valproate compared to controls. This difference was not statistically significant. Among the lipid profile only triglyceride was found to be higher in the valproate group (p value 0.008) compared to controls. There was no significant difference in carotid IMT between the groups (Table 7).

Effect of phenobarbitone on atherosclerosis risk factors

The mean BMI value was lower among subjects on phenobarbitone compared to controls and difference was not statistically significant. The mean total cholesterol, LDL, HDL, TGL levels were higher among subjects taking phenobarbitone. The differences in mean TC, HDL and TGL levels were found to be statistically significant. There was no significant difference in carotid IMT between the groups (Table 8).

Table 3: Comparison of mean lipid levels of control and phenytoin group.

Lipid level	*Drug*	*N*	*Mean*	*Std. Deviation*	*t*	*p value*
TC mg%	Control	43	154.58	12.955	0.348	0.729
	Phenytoin	12	155.92	4.795		
LDL mg%	Control	43	99.60	11.009	0.330	0.743
	Phenytoin	12	98.50	6.613		
HDL mg%	Control	43	31.98	3.299	0.337	0.737
	Phenytoin	12	32.33	2.995		
TGL mg%	Control	43	142.21	20.160	0.059	0.954

Table 4: Comparison of IMT values between control and phenytoin group in right and left.

IMT	*Drug*	*N*	*Mean*	*Std. Deviation*	*t*	*p value*
IMT-Right	Control	43	1.974	0.874	0.460	0.647
	Phenytoin	12	0.805	0.197		
IMT-Left	Control	43	0.735	0.670	0.046	0.963
	Phenytoin	12	0.744	0.098		
IMT- Average	Control	43	1.354	0.437	0.456	0.650
	Phenytoin	12	0.774	0.114		

Table 5: Comparison of means lipid levels of control and carbamazepine group.

Lipid levels	*Drug*	*N*	*Mean*	*Std. Deviation*	*t*	*p value*
TC mg%	Control	43	154.58	12.955	2.93	0.005
	Carbamazepine	10	170.10	22.383		
LDL mg%	Control	43	99.60	11.009	0.751	0.456
	Carbamazepine	10	103.20	22.070		
HDL mg%	Control	43	31.98	3.299	0.450	0.655
	Carbamazepine	10	32.50	3.375		
TGL mg%	Control	43	142.21	20.160	2.519	0.015
	Carbamazepine	10	159.60	17.167		

Table 6: Comparison of means IMT values of control and carbamazepine group.

IMT	*Drug*	*N*	*Mean*	*Std. Deviation*	*t*	*p value*
IMT-Right	Control	43	1.974	0.874	0.463	0.645
	Carbamazepine	10	0.684	0.117		
IMT-Left	Control	43	0.735	0.670	0.304	0.763
	Carbamazepine	10	0.670	0.129		
IMT- Average	Control	43	1.354	0.437	0.486	0.629
	Carbamazepine	10	0.677	0.086		

Table 7: Comparison of means lipid levels of control and valproate group.

Lipid levels	*Drug*	*N*	*Mean*	*Std. Deviation*	*t*	*p value*
TC mg%	Control	43	154.58	12.955	1.327	0.190
	Sodium valproate	11	160.18	10.323		
LDL mg%	Control	43	99.60	11.009	0.567	0.573
	Sodium valproate	11	97.64	6.265		
HDL mg%	Control	43	31.98	3.299	1.393	0.170
	Sodium valproate	11	33.55	3.475		
TGL mg%	Control	43	142.21	20.160	2.754	0.008
	Sodium valproate	11	160.27	15.875		

Table 8: Comparison of mean lipid levels of control and phenobarbitone group.

Lipid levels	*Drug*	*N*	*Mean*	*Std. Deviation*	*t*	*p value*
TC mg%	Control	43	154.58	12.955	4.432	0.001
	Phenobarbitone	10	176.40	18.198		
LDL mg%	Control	43	99.60	11.009	1.286	0.204
	Phenobarbitone	10	106.10	24.637		
HDL mg%	Control	43	31.98	3.299	2.462	0.017
	Phenobarbitone	10	35.50	6.587		
TGL mg%	Control	43	142.21	20.160	1.898	0.020
	Phenobarbitone	10	154.90	12.635		

The mean IMT levels on right, left side and average levels were slightly lower subjects who were consuming phenobarbitone compared to the controls. The differences were not found to be statistically significant. (Table 9)

Table 9: Comparison of mean IMT values of control and phenobarbitone group.

IMT	*Drug*	*N*	*Mean*	*Std. Deviation*	*T*	*p value*
IMT-Right	Control	43	1.974	0.874	0.451	0.645
	Phenobarbitone	10	0.718	0.116		
IMT-Left	Control	43	0.735	0.670	0.295	0.769
	Phenobarbitone	10	0.672	0.096		
IMT- Average	Control	43	1.354	0.437	0.473	0.638
	Phenobarbitone	10	0.695	0.089		

Antiseizure medications and CRP

The majority of subjects on phenytoin 8 (66.7%) were positive for CRP. There was equal proportion of subjects on carbamazepine were positive and negative for CRP. In rest of the drugs and controls, proportion of subjects with negative CRP were more than positives. There was a statistically significant association between phenytoin consumption and CRP positivity.

Table 10: CRP level between control and ASM group.

Drug	*Group*	*CRP*		*Chi square*	*p value*
		Positive	*Negative*		
Phenytoin	Control	12 (27.9)	31 (72.1)	6.0909	0.013
	Cases	8 (66.7)	4 (33.3)		
Carbamazepine	Control	12 (27.9)	31 (72.1)	1.8176	0.177
	Cases	5 (50.0)	5 (50.0)		
Sodium valproate	Control	12 (27.9)	31 (72.1)	0.1124	0.737
	Cases	3 (27.3)	8 (72.7)		
Phenobarbitone	Control	12 (27.9)	31 (72.1)	0.1353	0.712
	Cases	4 (40.0)	6 (60.0)		

Correlation between duration of ASM and average IMT

There was positive correlation between duration of phenytoin consumption and average IMT. This correlation was not statistically significant. There was a strong positive correlation between duration of phenobarbitone consumption and average IMT, this correlation was statistically significant (Table 11).

Table 11: Correlation between duration of ASM and average IMT.

Drug	*Pearson's correlation*	*p value*
Phenytoin	0.462	0.130
Carbamazepine	0.167	0.644
Sodium valproate	0.180	0.597
Phenobarbitone	0.682	0.030

Discussion

Cardiac morbidity and mortality are known to be higher in epilepsy, the exact cause for this association is unknown. The causal role of ASM in cardiac morbidity and mortality of people with epilepsy remains controversial. This cross-sectional study was carried out with an aim to investigate the effects of long-term ASMs on vascular risk factors and atherosclerosis.

The study subjects were divided in to two groups involving 43 participants as control and 43 patients as cases. The mean age of the cases and control was found to be 33.30 ± 15.896 in cases and 34.07 ± 14.155 in control, age range was similar in previously conducted studies. [7-8].

Long-term ASM therapy may result in low-grade systemic inflammation and increase in oxidative stress, as manifested by higher concentrations of hs-CRP and

TBARS [9-10]. Chronic production of reactive oxygen species may exceed the capacity of cellular antioxidants, resulting in oxidative modification of LDL-C, promotion of proinflammatory responses, recruitment of macrophage, and development of atherosclerotic lesion [11]. Moreover, hs-CRP has been found to induce the expression of cytokines and cell adhesion molecules, which are recognized activators of the extrinsic pathway of the coagulation system [12-13]. In the present study the majority of subjects on phenytoin 8 (66.7%) were positive for CRP, but a similar effect was not observed with other antiepileptic medications tested.

There was positive correlation between duration of phenytoin consumption and average IMT. There was a strong positive correlation between duration of phenobarbitone consumption and average IMT, this correlation was statistically significant.

In our study, the mean BMI value was significantly higher among subjects on phenytoin only. Dyslipidemia has long been known to be an important risk factor for atherosclerosis [13]. In the study of Chuang et al the body mass index (BMI) was significantly higher in the PHT and VPA groups when compared with controls, but insignificant in the LTG and CBZ groups [8].

LDL-C increase atherosclerosis by multiple mechanism including changing endothelial permeability, accumulation of lipoproteins within the intima of blood vessels, increase in inflammatory cells, and formation of foam cells.

Emerging evidence further showed that treatment with enzyme-inducing ASMs, such as CBZ and PHT, is significantly associated with increased blood levels of total cholesterol, atherogenic (non-HDL) cholesterol, triglycerides, and tHcy [9, 14, 15]. In the current study there was no definite relation between LDL-C and ASMs, however Total cholesterol and triglyceride shows statistically significant association with CBZ and phenobarbitone. Triglyceride alone was high in patients on sodium valproate. In previous studies effects of VPA on changes in lipid profiles and lipoproteins remains controversial [15-18].

Prospective and retrospective incidence cohort studies have established that patients with epilepsy carry a significantly higher mortality rate than the general population [19-21]. Whereas cardiovascular disease is not considered a contributing factor [19-21]. A number of studies reported an elevated standardized mortality ratio for patients with epilepsy to die of cerebrovascular diseases that are related to atherosclerosis [20-22]. However, few data exist regarding the long-term effects of specific ASMs on vascular events. One previous study revealed that the IMT of CCA was significantly increased in patients with long-term ASM therapy [10]. In the present study there was a positive correlation between IMT and duration of intake of phenobarbitone, such an effect was not noted for other ASMs.

Limitations: The study was conducted in a tertiary referral centre which may not reflect the general population. This is a single centre study with limited number of patients, multicentric study with a greater number of patients would have given more robust data. The study did not include newer ASM

Conclusion

ASMs like phenytoin causes inflammatory milieu as evidenced by increased CRP, which increases the chance for atherosclerosis. There was positive correlation between duration of phenytoin consumption and average IMT. There was a strong significant positive correlation between duration of phenobarbitone consumption and average IMT. Our results also suggest that long-term use of older-generation ASMs with prominent effects on the enzyme system, like phenytoin and phenobarbitone may contribute to the progression of atherosclerosis in patients with epilepsy. This information offers a guide for the choice of drug for patients with epilepsy who require long-term ASM therapy, particularly in aged and high-risk individuals.

Conflicts of interest

Authors declare no conflicts of interest.

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