Original Research Article

International Journal of Neurology and Neurosurgery
Volume 10 Number 1, January - March 2018
DOI: http://dx.doi.org/10.21088/ijnns.0975.0223.10118.5

Analysis of the Effects of Longterm Antiepileptic Drugs on Vascular Risk Factors and Atherosclerosis

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Abstract

One of the most common disorders that affect brain is epilepsy. More than 30% of epileptic patients have to undergo long term therapy with antiepileptic drugs (AED). Studies show an increase in mortality in symptomatic epileptic patients due to ischemic heart disease and acute cardiac failure. The mechanism behind the role of AEDs on cardiovascular diseases needs investigation. Hence the present study was designed to study the long term effect of AEDs on vascular risk factors like serum lipid profile, C-reactive protein (CRP), carotid intima media thickness (CIMT) in epileptic patients in comparison with control subjects. The study also correlated duration of the AEDs with CIMT. The results showed that carbamazepine and phenobarbitone therapies significantly increased serum total cholesterol, LDL-cholesterol and CRP but not HDL-cholesterol, Triglyceride and BMI. Patients on phenytoin and sodium valproate increased BMI but no significant change on lipid and CRP levels were observed. All the antiepileptic drugs in this study significantly increased CIMT.

Keywords: Epilepsy; Antiepileptic Drugs; Atherosclerosis; Lipids; CIMT.

Introduction

Epilepsy is the tendency to have recurrent, unprovoked seizures resulting from the synchronous and excessive discharge of a group of neurons in the cerebral cortex. Worldwide, approximately 50 million people are affected by epilepsy, which accounts to 1% of the global burden of disease [38]. Several studies demonstrated positive correlations between epilepsy and vascular diseases. Mortality ratio due to ischemic heart disease in epilepsy patients is 1.2 to 2.5 [1,23], while other studies reported a mortality ratio of 10.7 due to myocardial infarction [9,28].

Cardiovascular disease is the most frequent cause of premature death in both developed and in developing countries. Atherosclerosis is a focal, inflammatory fibro proliferative response to endothelial injury and is characterised by carotid intima medial wall thickness (CIMT) [17,24,30]. C-reactive protein (CRP) is a marker of systemic inflammation, which predicts cardiovascular events such as ischemic stroke and myocardial infarction [25-27,32,37,49-52].

Enzyme-inducing antiepileptic drugs (AEDs) carbamazepine (CBZ), phenytoin (PHT), primidone (PRM) and phenobarbital (PB), induces the cytochrome P450 system which play a role in the synthesis of cholesterol and increase it. When metabolism of the cholesterol intermediates is inhibited, these intermediates increase and inhibit the rate-limiting step of cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase and decrease the synthesis of cholesterol [15]. Valproate (VPA), an enzyme-inhibiting drug, decreases the production of cholesterol.

Various studies showed that CBZ or PHT significantly elevates total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) [6,8,10,11,13,19,22,33,34,36]. VPA is associated with lower serum LDL and/or TC in children and adults in many studies [4,5,10,22,33, 34]. Moreover, patients treated with enzyme-inducing AEDs like CBZ and

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Received on 30.11.2017, **Accepted on** 18.01.2018

valproate showed increased CIMT when compared to controls [12,14,29]. There is positive correlation between duration of AEDs and CIMT [32]. There was a significant reduction of CRP, when patients on enzyme-inducing AEDs were changed to nonenzyme-inducing agents [19]. The mechanism by which enzyme-inducing AEDs increase CRP is not known.

The above studies indicate that enzyme-inducing AEDs is significantly associated with vascular risk factors but the mechanism behind this action remains unclear. Hence the present study was designed to study the effect of AEDs on vascular risk factors like serum lipid profile and CRP in epileptic patients in comparison with control subjects. The study is also focussed onto analyse the effect of AEDs on CIMT, a marker of atherosclerosis in epileptic patients and also to correlate duration of the AEDs with CIMT.

Methods

Experimental Design

Patients (N=100) attending epilepsy clinic over a period of 12 months from april 2014 to march 2015 in neurology department, Madras Medical College and Rajiv Gandhi Government general hospital, Chennai - 600 003 were included in the study. Inclusion criterion includes patients receiving AED monotherapy for more than 2 years. Sex matched healthy volunteers were considered as control subjects (N=100). The study was approved by institution ethical committee.

Study Design

Cross sectional study

Collection of Serum

After ensuring 12 hours overnight fasting, normal diet (without any fat restriction) for previous two weeks, and abstinence from alcohol, the blood was collected from epilepsy patients and healthy controls, serum was separated and stored at 4^0C.

Measurement of Lipid Profile

Concentration of total cholesterol, HDL-cholesterol, and triglycerides were assessed enzymatically with commercially available reagents. Concentration of LDL-cholesterol was calculated by use of the Friedewald equation for participants who had triglycerides (< 400 mg/dl).

Common Carotid Artery Intima Media Thickness (CCA IMT)

To assess the extent of atherosclerosis, CCA IMT (bilateral) was measured by B-mode ultrasound System. An optimal longitudinal image was saved and the IMT was analyzed using a computerized image analysis system.

Measurement of C-Reactive Protein (CRP)

The vascular risk marker CRP was measured by latex agglutination method. The CRP was determined using a Dimension® RxL clinical chemistry analyzer in a serum specimen with CRP FlexTM reagent cartridges.

A concentration more than 6 mg/L was defined as elevated according to the reference values of our laboratory.

Statistics

Statistical analysis was carried out for 200 participants [100 epilespy patients, 100 controls] after categorizing each variable. Base line data collected from patients age, sex, AED, dosage duration of AED, carotid intima media thickness, Lipid profile, BMI, CRP were analyzed.

The significance of difference in means between two groups was analyzed by student t-test. The correlation between duration of AED and average CIMT was calculated by Pearson's correlation coefficient method. Statistical analysis was carried out using SPSS (statistical package for social sciences) version 20 software. Statistical significance was taken when p value was < 0.05.

Results

In our study, 100 epileptic patients matched with 100 healthy controls were studied for cardiovascular risk factors namely lipid profile (TC, LDL, HDL,TGL), body mass index (BMI), CRP and CIMT and the following observation were made.

Comparison of age group in control and epileptic patients

Patients with age group ranging from 10 to 90 years were studied.

From the above data (Figure 1, Tables 1 & 2), it is clear that the distribution of age between control and AED study group is not statistically different.

Table 1: Statistical analysis of age difference

	Group	N	Mean	SD (SD)	SEM (SEM)
Age (in years)	Control	100	30.65	13.497	1.350
	Study	100	31.68	14.466	1.447

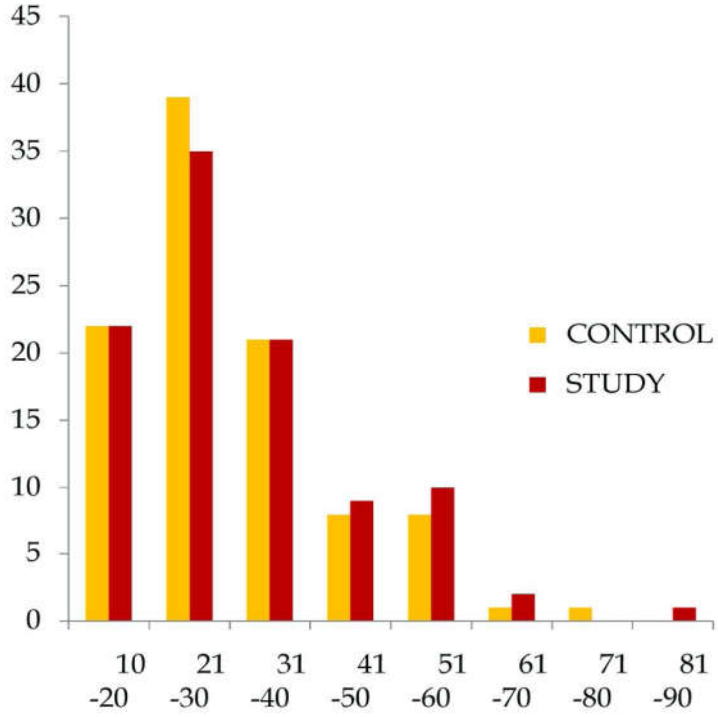

Fig. 1: Age distribution in control and study grou

Comparison of sex difference in control and epileptic patients

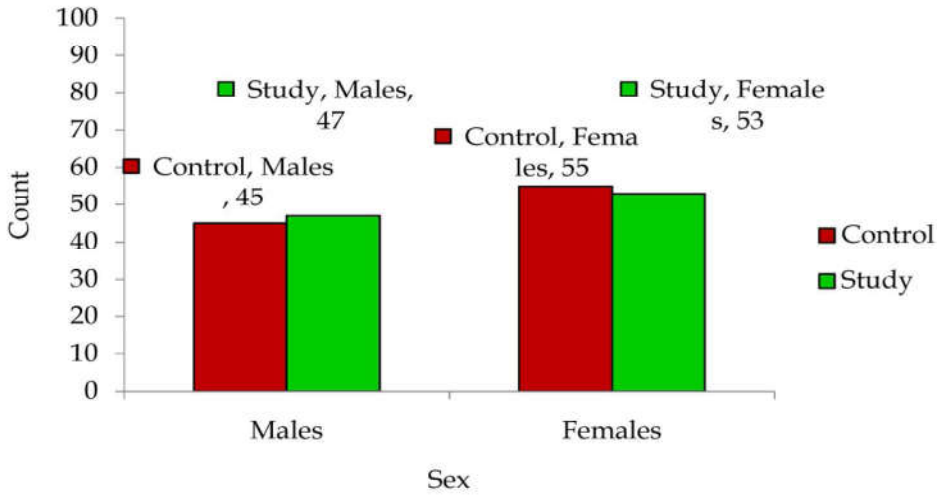

Fig. 2: Sex distribution in control and study group

Table 2: Comparison of mean age of study and control group

	t-test value	DF	p value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Age (in years)	-.521	198	.603	-1.03	1.978	-4.932	2.872

Table 3: Statistical analysis (Chi Square Test) of sex between control and study group

	Value	DF	Asymp. Sig. (2-sided) p value
Pearson Chi-Square	.081(b)	1	.777

The Figure 2 and Table 3 shows no significant difference between control and epileptic groups although females show preponderance when compared to males.

Duration and dosage of antiepileptic drugs in epileptic patients

Table 4: Duration and dosage of AEDs in study group

AED	No. of patients	Mean duration of AEDs (Years) with SD	Dosage Range in mg/day
Phenytoin	32	5.09 ±3.59	200-400
Carbamazepine	28	8.35 ±4.49	400-1200
Valproate	21	6.43±3.21	400-1600
Phenobarbitone	19	8.37 ±4.03	15-60

Effect of phenytoin on atherosclerosis risk factors

Table 5: Comparison of mean BMI values of control and phenytoin group

	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed) p value
BMI kg/m²	Control	100	22.747	2.6520	.2652	-5.852	.000
	Phenytoin	32	26.241	3.7119	.6562	-4.936	.000

Table 6: Comparison of mean lipid levels of control and phenytoin group

Lipids in mgs%	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed) p value
TC	Control	100	158.77	9.700	.970	.721	.472
	Phenytoin	32	157.47	5.542	.980	.944	.348
LDL-C	Control	100	95.88	9.213	.921	-.465	.642
	Phenytoin	32	96.69	5.905	1.044	-.580	.563
HDL-C	Control	100	32.38	3.966	.397	-1.801	.074
	Phenytoin	32	33.75	2.929	.518	-2.100	.039
TGL	Control	100	148.69	17.904	1.790	.148	.883
	Phenytoin	32	148.16	17.428	3.081	.150	.881

Table 7: Comparision of means IMT values of control andphenytoin group

CCA- IMT (mm)	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed) p value
IMT- Right	Control	100	.6175	.07120	.00712	-6.548	.000
	Phenytoin	32	.7544	.16800	.02970	-4.482	.000
IMT- Left	Control	100	.6254	.07656	.00766	-6.785	.000
	Phenytoin	32	.7409	.10375	.01834	-5.813	.000
IMT – Average	Control	100	.6215	.05114	.00511	-9.550	.000
	Phenytoin	32	.7477	.09696	.01714	-7.056	.000

The results (Tables 5-7) depicts that epileptic patients on phenytoin treatment have significantly high BMI and IMT (average) values when compared to control subjects.

Effect of carbamzepineon atherosclerosis risk factors

Table 8: Comparison of mean BMI values of control andcarbamzepinegroup

	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed) p value
BMI kg/m²	Control	100	22.747	2.6520	.2652	-.993	.323
	Carbamzepine	28	23.289	2.1605	.4083	-1.114	.270

Table 9: Comparison of means lipid levels of control and carbamzepine group

Lipids in mgs%	Sub Group	N	Mean	SD	SEM	T	Sig. (2-tailed) p value
TC	Control	100	158.77	9.700	.970	-6.128	.000
	Carbamzepine	28	173.93	16.720	3.160	-4.586	.000
LDL-C	Control	100	95.88	9.213	.921	-4.981	.000
	Carbamzepine	28	107.68	16.171	3.056	-3.697	.001
HDL-C	Control	100	32.38	3.966	.397	.226	.822
	Carbamzepine	28	32.18	4.839	.914	.202	.841
TGL	Control	100	148.69	17.904	1.790	-1.509	.134
	Carbamzepine	28	154.07	11.062	2.090	-1.955	.055

Table 10: Comparison of mean IMT values of control and carbamzepine group

CCA- IMT (mm)	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
IMT- Right	Control	100	.6175	.07120	.00712	-3.993	.000
	Carbamzepine	28	.6914	.12808	.02421	-2.930	.006
IMT- Left	Control	100	.6254	.07656	.00766	-4.955	.000
	Carbamzepine	28	.7196	.12426	.02348	-3.816	.001
IMT – Average	Control	100	.6215	.05114	.00511	-6.376	.000
	Carbamzepine	28	.7055	.09035	.01708	-4.717	.000

This study shows epileptic patients on carbamazepine has significantly raised TC, LDL-C and IMT (average) values in comparison with control subjects.

Effect of Valproate on atherosclerosis risk factors

Table 11: Comparison of mean BMI values of control andvalproate group

	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
BMI kg/m^2	Control	100	22.747	2.6520	.2652	-2.006	.047
	Sodium Valproate	21	24.095	3.4379	.7502	-1.694	.103

Table 12: Comparison of mean lipid levels of control andvalproate group

Lipids in mgs%	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
TC	Control	100	158.77	9.700	.970	-.018	.986
	Sodium Valproate	21	158.81	5.980	1.305	-.024	.981
LDL-C	Control	100	95.88	9.213	.921	-1.185	.238
	Sodium Valproate	21	98.38	6.305	1.376	-1.510	.139
HDL-C	Control	100	32.38	3.966	.397	-1.758	.081
	Sodium Valproate	21	34.00	3.130	.683	-2.051	.048
TGL	Control	100	148.69	17.904	1.790	-1.302	.195
	Sodium Valproate	21	154.05	12.690	2.769	-1.625	.112

Table 13: Comparison of mean IMT values of control and valproate group

CCA- IMT (mm)	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
IMT- Right	Control	100	.6175	.07120	.00712	-5.203	.000
	Sodium Valproate	21	.7157	.10815	.02360	-3.984	.001
IMT- Left	Control	100	.6254	.07656	.00766	-3.618	.000
	Sodium Valproate	21	.6924	.07987	.01743	-3.519	.001
IMT – Average	Control	100	.6215	.05114	.00511	-6.248	.000
	Sodium Valproate	21	.7040	.07143	.01559	-5.035	.000

The data shown above (Tables 11-13) shows that sodium valproate treatment increases BMI and IMT (average) values in epileptic patients when compared to control.

Effect of Phenobarbitone on atherosclerosis risk factors

Table 14: Comparison of mean BMI values of control and phenobarbitone group

	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
BMI kg/m^2	Control	100	22.747	2.6520	.2652	1.695	.093
	Phenobarbitone	19	21.642	2.3253	.5335	1.855	.074

Table 15: Comparison of mean lipid levels of control andphenobarbitone group

Lipids in mgs%	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
TC	Control	100	158.77	9.700	.970	-5.523	.000
	Phenobarbitone	19	174.11	16.806	3.856	-3.857	.001
LDL-C	Control	100	95.88	9.213	.921	-4.212	.000
	Phenobarbitone	19	107.89	19.430	4.458	-2.640	.016
HDL-C	Control	100	32.38	3.966	.397	-.821	.413
	Phenobarbitone	19	33.26	5.801	1.331	-.636	.532
TGL	Control	100	148.69	17.904	1.790	-.573	.567
	Phenobarbitone	19	151.16	12.619	2.895	-.725	.473

Table 16: Comparison of mean IMT values of control andphenobarbitone group

CCA- IMT (mm)	Sub Group	N	Mean	SD	SEM	t	Sig. (2-tailed)p value
IMT- Right	Control	100	.6175	.07120	.00712	-4.842	.000
	Phenobarbitone	19	.7126	.11035	.02531	-3.618	.002
IMT- Left	Control	100	.6254	.07656	.00766	-2.154	.033
	Phenobarbitone	19	.6674	.08458	.01940	-2.012	.056
IMT - Average	Control	100	.6215	.05114	.00511	-4.802	.000
	Phenobarbitone	19	.6900	.08223	.01886	-3.507	.002

These results (Tables 14-16) show epileptic patients on Phenobarbitone has significantly higher TC, LDL-C and IMT (average) values when compared to controls.

Table 17: Correlation between duration of AED and average IMT

Drug	Phenytoin	Carbamazepine	Valproate	Phenobarbitone
Pearson correlation	.446	.115	.405	.597
p value	.011	.56	.068	.007

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

By pearson correlation, Phenytoin and phenobarbitone shows significant positive correlation between duration of AED and Average IMT. After adjusting for age and sex by regression analysis, effect of phenytoin on average CCA-IMT did not show any significant difference whereas duration of phenobarbitone therapy showed a significant effect on CCA-IMT.

Comparison of C-reactive protein between control and study group

Table 18: Comparison of CRP between control and AED group

CRP mg/l	Phenytoin		Carbamazepine		Valproate		Phenobarbitone	
	Control	Study	Control	Study	Control	Study	Control	Study
Positive >6mg/l	23	18	23	16	23	6	23	5
Negative <6 mg/l	77	14	77	12	77	15	77	14
Positive % within subgroup	23%	56.3%	23%	57.1%	23%	28.6%	23%	26.3%
Negative % within subgroup	77%	43.8%	77%	42.9%	77%	71.4%	77%	73.7%

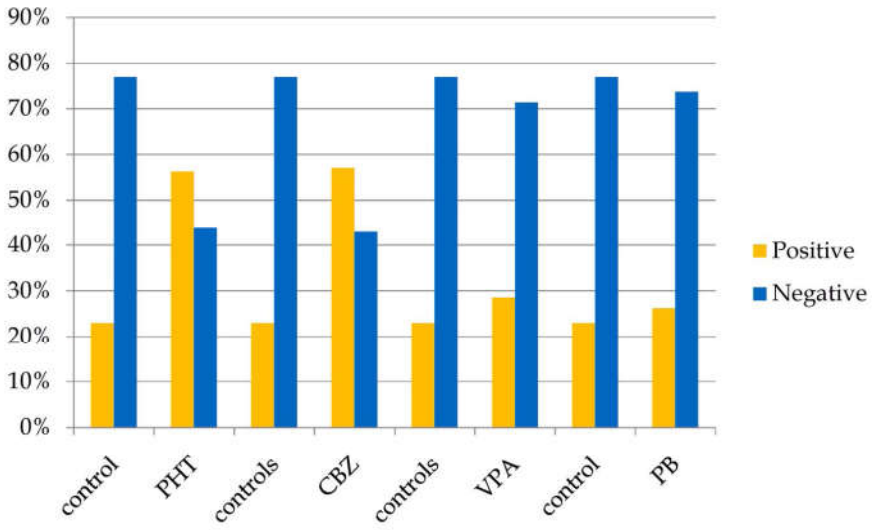

Fig. 3: Comparison of CRP between control and AED group

Table 19: Statistical analysis comparing CRP between control and AED group

	Pearson Chi-Square Value	DF	Asymp. Sig. (2-sided) P value
Phenytoin	12.516(b)	1	.000
Carbamazepine	12.037(b)	1	.001
Valproate	.296(b)	1	.587
Phenobarbitone	.098(b	1	.755

These results (Figure 3; Tables 18 & 19) show that CRP is significantly positive in phenytoin and carbamazepine groups.

Table 20: Summary of observations

Risk factors	Phenytoin	Carbamazepine	Valproate	Phenobarbitone
BMI	↑**(S)**	NS	↑**(S)**	NS
TC, LDL-C	NS	↑**(S)**	NS	↑**(S)**
HDL-C, TGL	NS	NS	NS	NS
CCA-IMT	↑**(S)**	↑**(S)**	↑**(S)**	↑**(S)**
Correlation between duration of AEDs and average CCA-IMT	Insignificant Positive correlation	Insignificant Positive correlation	Insignificant Positive correlation	Significant Positive correlation
CRP	↑**(S)**	↑**(S)**	↑NS	↑NS

S – Significant; NS – Not Significant; ↑ - Increased

Discussion

Patients with epilepsy have to undergo chronic treatment with AEDs. It is not only important that their epileptic seizures have to be under control but also adverse effects due to long term antiepileptic drugs (AED) intake have to be minimal. In this context, there have been few studies that have indicated that long term AED intake has been associated with increased vascular risk factors. In contrast, a Finnish study [20] had shown that the mortality due to cardiovascular risk in patients taking long term AEDs was significantly lower. Another Norwegian study [21] showed that the risk for coronary events in patient with epilepsy versus controls was not significantly different.

A large majority of our patients are mostly taking long term AEDs. As only old generation AEDs are provided in our hospital, it is useful to study the long term effects of old generation AED's especially on cardiovascular system. Taking this into consideration, we analysed patients taking AED monotherapy more than two years with age and sex

matched controls. We analysed the effects of AED on BMI, cardiovascular risk factors like lipid profile, CRP and CIMT.

In our study, chronic intake of phenytoin increased BMI. Very few studies are available regarding phenytoin intake and lipid levels. Some studies showed nonsignificant elevations in total cholesterol and HDL-C [5,18]. Mintzer et al [19] showed a significant increase in TC, LDL cholesterol levels on long term phenytoin intake, which was not observed in the present study. Despite the chronic intake of phenytoin elevated LDL cholesterol levels in the current study, this difference was not statistically significant. This may be due to lower average dose prescribed to our patients when compared to western population.

Our results showed that carbamazepine significantly increased TC, LDL cholesterol. Bramswig et al., [3] has shown that TC, LDL cholesterol and CIMT significantly correlated to carbamazepine intake. Similarly, Mintzer et al. [19]; Belcastro et al. [2]; Svalheim et al. [34] have shown that carbamazepine is significantly associated with increased TC and atherogenic (Non HDL) cholesterol. These effects of carbamazepine may be due to enzyme inducing effects of the drug.

Long term intake with Valproate had been associated with increased BMI, which is a independent risk factor for cardiovascular disease. In the present study, chronic valproate intake was not significantly associated with elevations of TC and LDL-C. In support to the concept, other studies also showed that chronic valproate intake was not associated with significant elevation in TC, LDL and TGL in children and adults [5,10,33,34]. These effects of valproate may be because it displays non enzyme inducing effect.

A significantly large number of epileptic patients are on phenobarbitone monotherapy in developing countries like India, primarily due to its cost factor [28]. Phenobarbitone did not affect the BMI. Interestingly, our results showed that a significant elevation of levels of TC and LDL-C, in accordance with other previous studies [6,10,11,31,33,34]. This effect of phenobarbitone could be explained due to its enzyme inducing effects. Hence this finding is of great importance as phenobarbitone could contribute to cardiovascular defects when given for a long time as it increased serum lipid levels.

Chuang et al. [7] have shown positive correlation of vascular risk factors with duration of AED in the CBZ, PH and VPA treatment groups. In contrast, in the present study, the duration of Valproate, phenytoin or carbamazepine therapy was not significantly associated with increased CCA IMT. The reason for this could be due to different mechanism of action and dosage of each drug given to our population.

CRP has been found to be an independent risk factor for vascular disease [25-27]. Moreover, the effect of AEDs on CRP level is elusive. Mintzer et al. [19] found that CRP level was reduced when patients were changed from enzyme inducing to non enzyme inducing drugs. In our study also, we found out that patients on carbamazepine and phenytoin (enzyme inducing drugs) had significantly elevated levels of CRP, while patients on valproate (non enzyme inducing drug) did not. On the contrary, phenobarbitone (an enzyme inducer) did not alter levels of CRP. Eventhough this observation correlated with a previous study [32], the reason for CRP levels not being elevated in patients on Phenobarbitone therapy is not clear. The limitation of this study was that the quantification of CRP using various dilutions was not done. Though Valproate effect on BMI is well established, the role of other AEDs on BMI is not well known. A larger sample size might be needed to study the effect of AED monotherapy on BMI. The sample size was likely to be insufficient and hence a type II error in these results cannot be ruled out.

From the above observations, it is vivid that AEDs have variable effects on each of the vascular risk factors, probably due to different modes of action. These effects have to be analyzed on a larger sample size to consider the long term effect of AEDs on vascular risk factors.

Conclusion

Epileptic patients on carbamazepine and phenobarbitone had significantly elevated levels of serum TC, LDL-cholesterol. HDL-cholesterol level, Triglyceride and BMI remain unaltered in these groups. Patients on phenytoin and sodium valproate had significantly elevated BMI but no significant change on lipid levels was observed. Patients on phenytoin and carbamazepine had significantly elevated level of CRP in this study. All the antiepileptic drugs in this study significantly increased the common carotid artery intima media thickness. It is observed that there is significant positive correlation between duration of phenobarbitone therapy and average CCA IMT, which was not noted with carbamazepine, phenytoin and sodium valproate. This study of antiepileptic drugs on vascular risk factors will have a bearing on the selection of AEDs

in refractory epileptic patients and elderly patients. Hence a longterm study with a large sample size is needed to clearly assess the effects of AEDs on vascular risk factors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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