Original Research

Effects of anti-epileptic drugs on lipid profile and lipoprotein (A)

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ABSTRACT
A seizure is a sudden, uncontrolled electrical disturbance in the brain. It can cause changes in behaviour, movements or feelings, and in level of consciousnessThe high incidence of epilepsy in children coupled with the need of long-term antiepileptic treatment could lead to development of metabolic complications at an early age and hence the risk of atherosclerosis. This study was conducted on 38 children in Department of Paediatrics at Soban Singh Jeena Government Institute of Medical Sciences and Research, Almora, Uttarakhand for one and a half year. Biochemical parameters like lipid profile, Lipoprotein a, liver enzymes along with relevant investigations were done before starting anti-epileptic monotherapy and were followed up after 6 months of treatment. Result shows among the antiepileptic drugs carbamazepine and phenytoin had statistically significant changes in lipid profile and lipoprotein (a) results while Phenobarbitone and Valproate didn't show significant increase in lipid profile and lipoprotein (a) on follow up. The study shows several antiepileptic drugs with CYP450 enzyme inducers activity may cause significant rise in levels of lipids and lipoprotein a, hence causing a potent risk factor for atherosclerosis and cardiovascular complications in long term antiepileptic therapy.

Key words: Lipoprotein a, Lipid profile, Seizure, Epilepsy, Antiepileptic drugs

INTRODUCTION

The term *seizure* (from the Latin *sacire*meaning "to take possession of ") refers to a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neurons. The term *epilepsy* refers to a disorder of brain function characterized by the risk of periodic and unpredictable occurrence of seizures[1]. Epilepsy is a neurological disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behaviour, sensations and sometimes loss of awareness. At least two unprovoked seizures more than 24 hr apart are generally required for diagnosis of epilepsy [2]. Sir Charles Locock in 1857 introduced Bromide as the first effective antiepileptic drug and was then used in North America and Europe, thereafter came Phenobarbitone which was discovered in 1912 by German chemist Emil Fischer and is the oldest antiepileptic drug which is still in use. In 1908 (which is earliest check) German chemist named Heinrich Blitz discovered Phenytoin, later in 1953 Carbamazepine was discovered by Swiss chemist Walter Schindler. Valproic acid was discovered by Pierre Emymard (date) during a study of anti-seizure compound. There are 50 million people living with epilepsy worldwide, and most of them reside in developing countries.It is estimated that more than 10 million people with epilepsy live in India. The prevalence is about 1% in our population [3]. The prevalence rate in India varies according to age and place, a rate of 22.2 per 1000 population has been noted in children aging from 8-12 yr with rate of 1.2 to 11.9 per 1000 population [4]. In the past 20 year as per ILAE definitions prevalence rate is 3 to 11.9 per 1000 population. Incidence rate of epilepsy in India is 0.2 to 0.6 per 1000 population per year. The incidence rate of urban population came out to be higher i.e. 0.6 per 1000 population per year than rural rate of 0.4 per 1000 population per year [5]. The modern understanding is now enhanced by organisations like International League against Epilepsy (ILAE) which was founded in 1909. According to ILAE older classification, epilepsy was divided in 3 groups of partial, generalized, unclassified respectively which was modified by ILAE in 2017 and divides epilepsy into four basic groups: focal, generalized, generalized and focal and unknown. Lipoprotein(a) is a very potent atherogenic factor and also an independent risk factor for vascular disease[7]. Lp(a) was identified as LDL variant with additional structural protein named

apo(a) which is covalently bounded [8]. Also there is conclusion of high LDL and low HDL with high levels of Lipoprotein (a) [9] . Increase in concentration of lipoprotein (a) and lipids like total cholesterol, triglyceride, LDL with decrease in HDL are likely to be risk factor for coronary artery disease, thus choice of appropriate anti-epileptic drug is very important [10]. Exercise, diet, and family history generally affects LDL and genetics typically determines Lp(a). Lp(a) levels remain nearly constant throughout one´s life [11]. Liver is the major site for metabolism with little accumulation in spleen and muscle [12], although kidney also play some role in Lp(a) clearance [13]. Phenobarbitone acts on GABA (A) receptor subunit and increases duration of chloride channel which results in depressed CNS by hyperpolarizing the cell and increasing the threshold of action potential. Phenytoin was first used for seizure in 1936, it acts by blocking voltage gated sodium channel thus responsible for increasing the threshold of action potential and prevent spread of seizure. It is used in complex partial seizure, GTCS and status epilepticus. It was in 1968 when carbamazepine was first approved for partialand generalized tonic- clonic seizures. It acts by inhibiting inactivated voltage dependent sodium channel and thus limiting high frequency neuronal firing. CBZ generates active metabolite, carbamazepine-10,11-epoxide and autoinduction enzyme which cause drug-drug interaction. Valproic acid is active against voltage dependent sodium and calcium channel, it also acts on enzyme involved in GABA metabolism and downregulates phospholipase A2 [14].Valproate is metabolised in liver by glucuronide conjugation, it causes reduced concentration of serum carnitine levels by inhibiting activity of plasmalemmal carnitine uptake [15][16]. Usually antiepileptic drugs are required lifelong, thus increasing risk of adverse effects and toxicity. Studies have shown varied effect of these drugs on lipid levels [11]. In study by Manimekalai et al (2014) drugs like phenytoin and carbamazepine significantly raised lipid profile whereas in contrary study by Rakesh et al (2011) showed that not all the lipid parameters get affected by antiepileptic drugs. Valproate and Phenytoin are broad spectrum anti-epileptics which are most commonly used drugs in paediatric epilepsy. Phenytoin has shown lipid alteration sometime [17], valproate also has also shown some lipid abnormalities [18]. The high incidence of epilepsy in children coupled with the need of long term anti-epileptic treatment could lead to development of metabolic complications at an early age and hence the risk of atherosclerosis [11]. The changes in serum lipid and lipoprotein (a) levels do play an important role in atherosclerosis and cardiovascular complications in later life. As per the Expert Panel on Blood Cholesterol Levels on Children and Adolescent of National Educational Cholesterol Program (NCEP, 1992) prevention of premature atherosclerosis should begin early in the childhood [16]. In view of the above facts the present study aims to evaluate the changes in the level of lipids and lipoprotein (a) during the course of treatment of epilepsy with different antiepileptic drugs.

MATERIAL AND METHODS

This prospective follow up study was conducted on 38 children aged 1 to 18 yearadmitted as new cases of seizures during a period of one and half years as Inpatient in Department of Paediatrics, SSJGIMSR, Almora. For every case included in, the study was detailed for their history and clinical examination and relevant examination. Blood samples was collected from patients for lipid profile and lipoprotein a before starting of antiepileptic therapy and the same was followed up after 6 months. Other blood tests such as complete blood count, renal function test, liver function test, C reactive protein, blood culture was done as and when required. A written informed consent was taken from all newly diagnosed cases of seizure. Statistical analysis was done. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median.Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using independent t test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups and ANOVA/Kruskal Wallis test between four groups.Paired t test/Wilcoxon signed rank test was used for comparison between pre and post. A p value of <0.05 was considered statistically significant.The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Table: 4 Age wise disribution of seizure

	AGE	
AGE	**Frequency**	**Percentage**
1-5 years	10	26.32%
5-10 years	13	34.21%
10-18 years	15	39.47%
Total	38	100.00%

Out of 38 patients 10 children were between 1 to 5 yr of age with 26.32 %, 13 were between 5 to 10 year of age with 34.21% and 15 children were above 10-18 yr with 39.47%..

SEX

Table 5: Gender wise distribution of seizure

SEX	Frequency	Percentage
Female	15	39.47%
Male	23	60.53%
Total	38	100.00%

Out of 38 cases there is male predominance of 60.53% with strength of 23 and female with percentage of 39.47% with strength of 15.

TYPE OF SEIZURE

Table 6: Distribution according to type of seizure

Seizure	percentage	number
Focal	13.16 %	5
Gen. & Focal	23.68 %	9
Generalized	63.16 %	24
Total	100 %	38

The above table depicts that Generalized seizure is the most common type of seizure with 63.16% followed by generalized and focal and focal with 23.68% and 13.16% respectively.

ANTIEPILEPTIC DRUGS

Table 7: Distribution according to Antiepileptic drug

	Frequency	Percentage
Carbamazepine	10	26.32%
Phenobarbitone	7	18.42%
Phenytoin	12	31.58%
Valproate	9	23.68%
Total	38	100.00%

The above table shows that out of 38 patients 10 were on Carbamazepine, 7 were on phenobarbitone, 12 were on phenytion and 9 were on valprote.

Table 8: Comparision of Lipoprotein (a) with various antiepileptic drugs

AED	Lipoprotein a (pre-AED)	Lipoprotein a (post-AED)
Carbamazepine	108.75 mg/dl	121.47 mg/dl
Phenobarbitone	109.21	114.77
Phenytoin	112.62	124.23
Valproate	118.74	126.73

Comparing mean Lipoprotein a levels in children on monotherapy of AED concluded that enzyme inducer drugs like Carbamazepine and Phenytion has significant change in levels of Lipoprotein a.

Table 9: Comparision of Triglycerides with various antiepileptic drugs

AED	Triglyceride (pre-AED)	Trigylceride (post-AED)
Carbamazepine	97 mg/dl	103.2 mg/dl
Phenobarbitone	111.86	108.86
Phenytoin	88.75	100.5
Valproate	96.67	96

The above table depicts that there is significant rise in level of mean trigycerides in children on Carbamazepine and Phenytion. No significant change was noted in patients on Phenobarbitone and valproate.

Table 10: Comparision of Cholesterol with various antiepileptic drugs

AED	Cholesterol (pre-AED)	Cholesterol (post-AED)
Carbamazepine	127.2 mg/dl	135.4 mg/dl
Phenobarbitone	123.29	123.71
Phenytoin	133.42	139.92
Valproate	134	136

Children on Carbamazepine shows statistical significant change in cholesterol levels post 6 month of monotherapy, with significant p value of 0.049 in comparing post therapy between phenobarbitone and phenytion.

Table 11: Comparision of LDL with various antiepileptic drugs

AED	LDL (pre-AED)	LDL (post-AED)
Carbamazepine	73 mg/dl	79.1 mg/dl
Phenobarbitone	77.29	81.43
Phenytoin	74.08	78.5
Valproate	76.44	78

When LDL levels were compared, children taking Carbamaepine were found to have significantly elevated LDL.

Table 12: Comparision of HDL with various antiepileptic drugs

AED	HDL (per--AED)	HDL (post-AED)
Carbamazepine	57.7 mg/dl	60.4 mg/dl
Phenobarbitone	59.14	62.29
Phenytoin	53.83	59.33
Valproate	59.78	62.67

The above table shows that there is significant change in mean levels of HDL in patients on Phenytion.

Table 13: Comparision of VLDL with various antiepileptic drugs

AED	VLDL (pre-AED)	VLDL (post-AED)
Carbamazepine	46.2 mg/dl	52.5 mg/dl
Phenobarbitone	47.57	47.14
Phenytoin	35.33	46.83
Valproate	42.22	43

Comparing mean VLDL levels in children on monotherapy of AED concluded that enzyme inducer drugs like Carbamazepine and Phenytion has significant change in levels of VLDL.

Table 14: Comparision of SGOT with various antiepileptic drugs

AED	SGOT (pre-AED)	SGOT (post-AED)
Carbamazepine	56.6 U/L	54.8 U/L
Phenobarbitone	57	56.57
Phenytoin	48.58	55.58
Valproate	46.78	51.78

The above table depicts that there is nostatistical significant change in mean SGOT levels after 6 month of AED monotherapy.

Table 15: Comparision of SGPT with various antiepileptic drugs

AED	SGPT (pre-AED)	SGPT (post-AED)
Carbamazepine	68 U/L	70 U/L
Phenobarbitone	69.43	71.14
Phenytoin	54.67	68.33
Valproate	57.56	69.78

On comparing mean levels of SGPT in children on AED monotherapy, there was statistical significant change in SGPT levels in group recieving Valproate and phenytion.

CARBAMAZEPINE

Table 16: Comparision of variables in Carbamazepine group

carbamazepine	Sample size	Mean ± SD	Median	Min-Max	Inter quartile Range	P value
triglycerides pre-AED	10	97 ± 27.01	91	68-166	86 - 102	0.041
triglycerides post-AED	10	103.2 ± 27.2	96	72-172	89 - 110	
cholesterol pre-AED	10	127.2 ± 13.34	122	110-150	118 - 140	0.005
cholesterol post-AED	10	135.4 ± 15.46	131	116-166	124 - 144	
LDL pre-AED	10	73 ± 9.15	72	62-88	66 - 78	0.017
LDL post-AED	10	79.1 ± 12.81	82	57-94	70 - 88	
HDL pre-AED	10	57.7 ± 7.86	57.5	46-68	52 - 64	0.171
HDL post-AED	10	60.4 ± 9.56	57	50-78	54 - 68	
VLDL pre-AED	10	46.2 ± 10.22	48	32-60	36 - 54	0.024
VLDL post-AED	10	52.5 ± 10.66	57	36-68	46 - 60	
RBS pre-AED	10	94 ± 16.73	92	74-122	78 - 108	0.735
RBS post-AED	10	92.5 ± 12.29	90	72-112	85 - 98	
Lipoprotein a pre-AED	10	108.75 ± 8.7	106.5	102.4-132.4	104.500 - 107.800	0.001
Lipoprotein a post-AED	10	121.47 ± 13.53	123	100.5-149.5	115.200 - 125.600	
SGOT pre-AED	10	56.6 ± 15.38	57	30-78	46 - 68	0.798
SGOT post-AED	10	54.8 ± 11.94	53	40-80	46 - 56	
SGPT pre-AED	10	68 ± 17.05	69	32-98	62 - 78	0.959
SGPT post-AED	10	70 ± 9.38	68	50-86	68 - 76	

The above table shows that 10 patients who were started on Carbamazepine had significant change in Lipoprotein a, triglycerides, chloesterol, LDL, VLDL when followed up after 6 months of monotherapy.
where as no significant change was observed on follow up in levels of HDL, SGOT, SGPT levels.

PHENOBARBITONE

Table 17: Comparision of variables in Phenobarbitone group

phenobarbitone	Sample size	Mean ± SD	Median	Min-Max	Inter quartile Range	P value
triglycerides pre-AED	7	111.86 ± 60.71	92	74-248	86 - 101.250	0.344
triglycerides post-AED	7	108.86 ± 52.01	88	84-226	85 - 99	
cholesterol pre-AED	7	123.29 ± 17.29	118	112-161	112.500 - 123.500	0.932
cholesterol post-AED	7	123.71 ± 17.07	116	108-156	111.500 - 133	
LDL pre-AED	7	77.29 ± 19.84	82	38-98	71.500 - 91.250	0.209
LDL post-AED	7	81.43 ± 17.31	88	46-98	78 - 92.500	
HDL pre-AED	7	59.14 ± 16.85	66	30-76	47 - 71.500	0.274
HDL post-AED	7	62.29 ± 15.72	70	34-78	53 - 73.500	
VLDL pre-AED	7	47.57 ± 6.92	49	34-54	45 - 53	0.805
VLDL post-AED	7	47.14 ± 10.25	52	26-56	44.500 - 53.500	
RBS pre-AED	7	95.14 ± 19	90	74-124	77.500 - 110	0.518
RBS post-AED	7	92.29 ± 19.81	86	70-122	77.500 - 110.500	
Lipoprotein a pre-AED	7	109.21 ± 4.8	108.5	103.7-116.4	105.025 - 113.300	0.256
Lipoprotein a post-AED	7	114.77 ± 13.52	109.4	100.8-134.5	104.100 - 127.875	
SGOT pre-AED	7	57 ± 12.66	56	42-75	45.500 - 68	0.498
SGOT post-AED	7	56.57 ± 15.85	50	41-88	46.250 - 62.500	
SGPT pre-AED	7	69.43 ± 29.99	70	36-124	43 - 79	0.498
SGPT post-AED	7	71.14 ± 16.61	70	40-94	68 - 80.500	

The above table concludes that 7 patients on monotherapy of phenobarbitone for 6 months were followed up and no significant change were noted in triglyceride, cholesterol, LDL, HDL, VLDL, Lipoprotein a, SGOT, SGPT.

PHENYTOIN

Table 18: Comparision of variables in Phenytoin group

Phenytoin	Sample size	Mean ± SD	Median	Min-Max	Inter quartile Range	P value
triglycerides pre-AED	12	88.75 ± 17.09	85	59-122	78 - 100	0.005
triglycerides post-AED	12	100.5 ± 19.93	94	76-138	87 - 110	
cholesterol pre-AED	12	133.42 ± 12.92	130	116-156	123.500 - 141.500	0.116
cholesterol post-AED	12	139.92 ± 16.54	139	114-164	127 - 155.500	
LDL pre-AED	12	74.08 ± 10.43	76.5	56-88	68 - 81	0.356
LDL post-AED	12	78.5 ± 14.3	78	50-96	71 - 92	
HDL pre-AED	12	53.83 ± 6.97	53.5	45-68	49 - 56	0.029
HDL post-AED	12	59.33 ± 10.97	62	40-72	50 - 69	
VLDL pre-AED	12	35.33 ± 14.23	32.5	11-72	29 - 39	0.007
VLDL post-AED	12	46.83 ± 13.6	46	28-82	40 - 50	
RBS pre-AED	12	90.42 ± 14.77	94	66-116	76.500 - 100	0.708
RBS post-AED	12	93 ± 17.38	91	72-124	77 - 103	
Lipoprotein a pre-AED	12	112.62 ± 9.18	111.55	98.4-127.8	104.500 - 119.500	0.019
Lipoprotein a post-AED	12	124.23 ± 15.26	127.6	94.6-148.7	112.600 - 134.050	
SGOT pre-AED	12	48.58 ± 11.67	45.5	36-72	39 - 54	0.289
SGOT post-AED	12	55.58 ± 15.94	56	37-96	44 - 62	
SGPT pre-AED	12	54.67 ± 17.92	51	34-82	39 - 73	0.007
SGPT post-AED	12	68.33 ± 16.06	70	40-88	61 - 82	

The above table shows staistical significant change in triglyceride, HDL, VLDL, SGPT, Lipoprotein a in paients on Phenytion monotherapy for 6 months. Whereas no significant change in levels of cholesterol, LDL, SGOT.

VALPROATE

Table 19: Comparision of variables in Valproate group

Valproate	Sample size	Mean ± SD	Median	Min-Max	Inter quartile Range	P value
triglycerides pre-AED	9	96.67 ± 17.51	96	72-131	87.250 - 103.500	0.439
triglycerides post-AED	9	96 ± 16.58	98	70-120	83 - 107	
cholesterol pre-AED	9	134 ± 16.37	136	112-164	121.500 - 143	0.905
cholesterol post-AED	9	136 ± 24.45	142	106-166	113.500 - 156	
LDL pre-AED	9	76.44 ± 10.09	78	62-90	67 - 85	0.48
LDL post-AED	9	78 ± 8.25	78	66-90	71.500 - 82.500	
HDL pre-AED	9	59.78 ± 8.87	64	48-71	51.500 - 66.500	0.355
HDL post-AED	9	62.67 ± 11.49	62	46-88	57 - 65	
VLDL pre-AED	9	42.22 ± 14.85	40	22-76	35 - 46.500	0.695
VLDL post-AED	9	43 ± 14.32	44	26-74	31.500 - 47.750	
RBS pre-AED	9	86.44 ± 6.31	86	76-98	84.500 - 89	0.481
RBS post-AED	9	89.78 ± 15.67	88	68-122	80 - 97	
Lipoprotein a pre-AED	9	118.74 ± 7.93	120.5	103.6-131.6	115.025 - 122.425	0.09
Lipoprotein a post-AED	9	126.73 ± 12.4	120.4	109.4-144.7	118.525 - 136.925	
SGOT pre-AED	9	46.78 ± 12.42	47	21-64	42.500 - 55.250	0.26
SGOT post-AED	9	51.78 ± 8.91	52	40-68	43.500 - 55.500	
SGPT pre-AED	9	57.56 ± 23	58	17-86	40.500 - 76.500	0.038
SGPT post-AED	9	69.78 ± 10.79	68	52-88	65 - 77.500	

The above table concluded that there is no staistically significant change in patients on Valproate monoterapy for 6 months. Only change seen was in levels of SGPT post therapy with p value of 0.038

DISCUSSION

The results and observation in our study were compared with similar studies done in past by other authors

In our study children who received carbamazepine the mean level of pre-treatment TC, LDL,VLDLand TG were 127.2±13.3 mg/dl, 73±9.1mg/dl, 46.2±10.2mg/dl, 97±27mg/dl respectively. The followup serum levels of TC, LDL,VLDLand TG

after six month of treatment were 135.4±15.4 mg/dl, 79.1±12.8mg/dl, 52.5±10.6 mg/dl, 103.2±27.2mg/dl respectively and the difference among the two was statistically significant (i.e. p value <0.05) whereas the level of HDL, SGPT and SGOT were not significantly altered after six month of treatment (p value > 0.05). the result were similar to the study done by Kantoush et al (1998) [1]. In study done by Manimekalai et al (2014) between control and cases with 20 subject in each group receiving carbamazepine for six month showed significant rise in the TC, HDL and TG post treatment (p value < 0.05)[2]. The study done by Rakesh et al [5] depicts higher levels of cholesterol with mean 160.6±19.17 mg/dl (p value 0.008) in children on carbamazepine whereas other parameters of lipid profile were not altered significantly. In the present study, children on carbamazepine had statistically significant ((p value 0.001). increase levels of Lipoprotein (a) .The results were similar to study conducted by Fatmamujgam et al (2006) [4] where they found signficant increase (p value of <0.05) in serum levels of Lipoprotein (a) in cases receiving carbamazepine. In our study children who recieved Phenobarbitone the mean level of pre-treatment TG, TC, LDL, HDL and VLDL were 111.86±60.71 mg/dl, 123.29±17.29mg/dl, 77.29 ± 19.84mg/dl, 59.14 ± 16.85mg/dl and 47.57 ± 6.92mg/dl respectively. The followup serum levels of TG, TC, LDL, HDL and VLDL after six month of treatment was 108.86±52.01mg/dl, 123.71±17.07mg/dl, 81.43 ± 17.31mg/dl, 62.29 ± 15.72mg/dl and 47.14 ± 10.25mg/dl respectively and the difference among the two had no significant change in lipid profile and lipoprotein (a) on follow up after 6 month of monotherapy, this result is supported by Yilmaz et al (2001) [6] who too found no significant change in levels of TC, HDL, LDL, SGOT, SGPT while serum triglyceride showed some statistical change. In study done by J.M eiris[7] children on Phenobarbitone had increased levels of TC, HDL, LDL when compared to control with significant p value of <0.05. In our study there was no significant increase in Lipoprotein (a) levels after Phenobarbitone monotherapy for 6 months whereas study by Fatma et al concluded significant change in Lipoprotein (a) levels when on Phenobarbitone for 6 months with p value of 0.05 In our study children who recieved phenytoin the mean level of pre-treatment TG, VLDL, HDL were 88.75±17.09mg/dl, 35.33±14.23mg/dl, 53.83±6.97mg/dl respectively. The followup serum levels of TG, VLDL, HDL after six month of treatment were 100.5±19.93mg/dl, 46.83±13.6mg/dl, 52.93±4.35 respectively showed statistical significant change in Triglyceride, VLDL, HDLwith p value of <0.05 whereas no significant change was seen in levels of TC and LDL. In a study by Kantoush et at[1] there was statistical significant change in values of LDL, HDL similar to our study whereas insignificant change was seen in TG and VLDL.

A study by Manimekalai et al (2014) [2] between control and cases with 20 subject in each group recieving Phenytion for 6 month depicted that it has strong association with increased levels of TC, LDL, HDL, TG with 0.0001, 0.029, 0.001, 0.0001 respectively. P kumar et al (2010) [8] in their study on 120 patients with epilepsy on various antiepileptic dugs concluded significant rise in levels of TG, VLDL with minor changes in Cholesterol and HDL when on monotherapy or combined therapy with Phenytion. The results were also supported by study by Pooja et al (2008) Seventy-nine children receiving at least 6 months of antiepileptic monotherapy were categorized into two groups, depending on whether they were receiving phenytoin or valproic acid. Age matched healthy controls were also included, which concluded significant change in TC, HDL, LDL, in children on Phenytion with p value of <0.05 Markus schwaninger et al (2000) [9]in their study on 51 epileptic patients depicted statistical significant effect of Phenytion on Lipoprotein a which is an independent risk factor for atherosclerosis. In another study on Phenytoin study conducted by Rakesh et al [5] depicts that higher levels of only cholesterol were observed in children on Carbamazepine while other parameters of lipid profile were not altered In our study children who recieved Valproate the mean level of pre-treatment SGPTwas 57.56±23 U/L. The followup serum levels of SGPT after six month of treatment was 69.78±10.79 U/L whereas, TC, TG, LDL, VLDL, HDL, SGOT levels were insignificant with p value of >0.05. The results were supported by study done by Muzamil m mugloo et al (2017) [10]which was a case vs control study with 25 patients on Valproate and concluded insignificant change in lipid profile Manimekalai et al(2014) [2] in their study on 20 patients on Valproate for 6 months when copared to control group concluded no statistical change in lipid profile with p value of > 0.05 when on valproate In follow up study by Kantoush et al (1998) [1] on 10 patients on valproate monotherapy for 6 months stated that there is significant decrease in levels of TC, TG, LDL and statistical significant rise in HDL levels after 6 month of monotherapy of Valproate with p value <0.05 Study by Fatmamujgan et al (2006) [4] concluded that there is statistical significant rise in levels of Lipoprotein a when followed at 3,6,12 month of monotherapy which is contrasting to my study with insignificant p value of 0.09 , though there was a rise The effects of hepatic enzyme-inducing AEDs on serum lipid profile (and thus on risk of atherosclerosis) seem to be accurately evaluated only with reference to pre-treatment levels in specific patients. Long-term prospective studies are required to clarify the effects of hepatic-enzyme-inducing AEDs on lipid metabolism in children. Despite the need for longer-term research, the results of the present study clearly indicate that serum lipid profiles and lipoprotein (a) should be carefully monitored in children receiving AED for long term therapy. Other

important issue is antiepileptic drugs may cause hepatoxicity, Main reason of liver injury appears to be due to a hypersensitivity reaction and resembles typical cases of immunoallergic hepatotoxicity (29). Antiepileptic drugs are metabolized by CYP 450 system to drug oxides, which may represent the toxic intermediate or metabolite that binds to tissue macromolecules.

CONCLUSION

From the present study we can conclude that CYP enzyme inducer anti epileptic medicines like phenytoin and carbazepine has association with increased levels of Lipid profile and Lipoprotein (a) where as valproate and levetiracetam showed insignificant change. Therefore, the serum cholesterol level should be regularly monitored in patients undergoing antiepileptic therapy as the need of long term antiepileptic treatment could lead to development of metabolic complications at an early age and hence the risk of atherosclerosis

LIMITATIONS OF THE STUDY

1. Sample size is small.
2. Due to limited time, follow up changes are compared for a span of 6 month which shows lesser variability of changes.
3. Compliance of antiepileptic drug coudn’t be confirmed accurately.

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