Change in Apo B100/A1 Ratio in Children With Epilepsy on Monotherapy With Sodium Valproate, Oxcarbazepine or Levetiracetam

A prospective longitudinal study was conducted to assess the Apo B100/A1 ratio as a marker of cardiovascular risk in children with epilepsy aged 5-14 years on long-term anti-seizure medication monotherapy with either sodium valproate, oxcarbazepine, or levetiracetam. Apo B100/A1 ratio showed an increase after six months of monotherapy with oxcarbazepine (*P*=0.05).

Keywords: Adverse effect, *Cardiovascular risk, Lipid profile, Outcome.*

Epilepsy in children often require long term anti-seizure medications. Studies have demonstrated that anti-seizure medications including phenobarbitone, carbamazepine, valproate and phenytoin might affect the serum lipid profile including levels of high density lipo-protein (HDL-C), low density lipoprotein (LDL-C) and total cholesterol to HDL (TC/HDL-C) ratio [1,2]. Apo B is a prominent risk factor for atherosclerosis and coronary heart disease (CHD); whereas Apo A manifests anti-atherogenic effects. Studies have shown that the Apo B/A1 ratio is a more reliable and effective predictor of coronary disease than others [3].

The effect of anti-seizure medications on lipid profile may not directly translate into increased risk for cardiovascular morbidity as there is a paucity of literature on Apo B/A1 ratio as a cardiovascular risk for children with epilepsy. Hence, the present study was planned to assess the Apo B100/A1 ratio including lipid profile as a marker of cardiovascular risk in children with epilepsy (CWE) on long-term anti-epileptic monotherapy.

This prospective cohort study was conducted in the department of biochemistry and pediatrics at our tertiary care teaching hospital. An institutional ethics committee approval was sought, and written informed consent was obtained from the caregivers of all participants. Children with epilepsy aged 5-14 years who were planned to be started on monotherapy with either sodium valproate, oxcarbazepine, or levetiracetam were enrolled consecutively. Children with a body mass index of more than the 95th percentile were also excluded. Children with known chronic renal disease, chronic liver disease, progressive neurological disorder, or congenital heart disease were excluded from the study. Children who were receiving any drug that could affect lipid metabolism were also excluded. A convenience sample size of 15 children each planned for sodium valproate, oxcarbazepine and levetiracetam were chosen. The eligible participants were enrolled consecutively till a desired sample size of 15 was achieved for each anti-seizure medication. Baseline demographic and clinical details of the enrolled participants were recorded. Their treatment records were retrieved.

A blood sample (4 mL) was collected twice, once at baseline when AED was commenced and at a six-month follow-up. The serum was separated by centrifugation and was preserved at -20^0C. Baseline hemogram, liver function test, renal function test, random blood sugar and fasting lipid profile were estimated. Serum apolipoprotein B100 and apolipoprotein A1 were analysed by the enzyme-linked immunosorbent assay (ELISA) method [6]. ApoB100/ApoA1 ratio was computed and compared between the baseline and six months in all three groups.

Statistical analysis was performed using the Statistical package for social sciences (SPSS version 21.0). All data were entered in Microsoft Excel (MS Excel).

Table I Demographic and Clinical Profile of Children With Epilepsy

	VPA (n=15)	*OXC (n=15)*	*LEV (n=15)*
Age (y)[a]	10.2 (2.24)	10.3 (2.98)	10.2 (3.02)
Male gender	9 (60)	8 (53.33)	11 (73.33)
BMI (kg/m^2)[a]	16.8 (1.31)	17.0 (2.25)	16.7 (1.95)
Seizure type			
Focal	11 (24.4)	9 (20)	8 (17.8)
Generalized	3 (6.67)	4 (8.89)	6 (13.3)
Unknown	1 (2.22)	2 (4.44)	1 (2.2)
Diagnosis			
Neurocysticercosis	7 (15.6)	5 (11.1)	9 (20)
Post-meningitic sequaelae	1 (2.22)	0	1 (2.2)
Encephalitis sequalae	1 (2.2)	0	0
Tubercular meningitis	3 (6.7)	2 (4.4)	3 (6.7)
Febrile seizures	1 (2.2)	0	1 (2.2)
Idiopathic epilepsy	2 (4.4)	8 (17.8)	1 (2.2)
Abnormal EEG record	1 (2.2)	2 (4.4)	1 (2.2)
Abnormal neuroimaging	4 (8.9)	2 (4.4)	2 (4.4)

All values in no. (%) or [a]mean (SD). VPA: sodium valproate; OXC: oxcarbazepine; LEV:levetiracetam.

Table II Apolipoproteins and Apo B/100/A1 Ratio of Children With Epilepsy (*N*=45)

	At baseline	*At 6-mo follow-up*
Valproate group, n=15		
Apo A1 (ng/mL)[a]	234.5 (137.0)	154.7 (69.37)
Apo B100 (ng/mL)	193.3 (137.73)	152.0 (133.57)
Apo B100/A1 ratio	0.9 (0.89)	1.1 (1.1)
Oxcarbazepine group, *n*=15		
Apo A1 (ng/mL)	182.7 (71.81)	171.1 (70.20)
Apo B100 (ng/mL)[a]	140.8 (89.59)	295.3 (246.47)
Apo B100/A1 ratio	0.9 (0.63)	1.8 (1.11)
Levetiracetam group, n=15		
Apo A1 (ng/mL)	170.0 (64.24)	147.0 (58.12)
Apo B100 (ng/mL)[b]	211.0 (163.15)	218.6 (103.00)
Apo B100/A1 ratio	1.2 (0.87)	2.0 (1.71)

Values in mean (SD). [a]*P<0.05;* [b]*P=0.05.*

Categorical variables were expressed as numbers (percentage) and continuous variables as median (IQR). The ApoB100/ApoA ratio and other continuous variables were compared between the groups and within the group using Wilcoxon signed rank test and paired student *t* test or Kruskal Wallis test. Values of ApoB100 and ApoA were correlated among the three groups using the Spearman correction coefficient. *P* value equal to or less than 0.05 was considered significant.

In the present study, out of the 45 children, 15 children each on monotherapy with valproate, oxcarbazepine, and levetiracetam were enrolled. The baseline demographic profile and disease characteristics were comparable between the groups (**Table I**). Only one child on oxcarbazepine required increase in the dose after one month and was then well controlled on same dose till 6-month follow-up period. No child required addition of new anti-seizure medication or change of medication in the 6-month follow-up period.

The mean serum ApoA1 level decreased significantly after six months of valproate therapy, whereas serum ApoB100 levels had a significant increase in the oxcarbazepine group (**Table II**). Apo B100/A1 ratio increased significantly in oxcarbazepine group. (*P*=0.05) (**Table II**). There was a signi-ficant positive correlation between ApoB100 and ApoA levels among those who received OXC therapy (r=0.74; *P*=0.01). However, the correlation was not significant in the VPA (r=0.17; *P*=0.54) and LEV (r=-0.45; *P*=0.09) groups (**Fig. 1a-c**). There was a significant fall in the HDL levels and a rise in the VLDL level in the valproate group. The rest of the biochemical laboratory parameters did not reveal any significant change before and after the drug administration and were also comparable between the three groups (**Web Table I**).

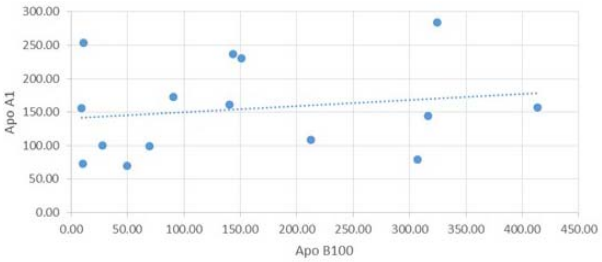

Fig. 1a Correlation of Apo B100 & A1 among group A after six months of VPA monotherapy.

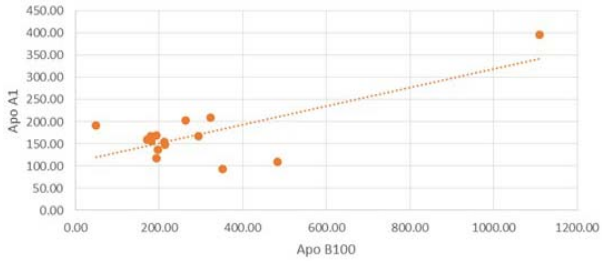

Fig. 1b Correlation of Apo B100 & A1 among group B after six months of OXC monotherapy.

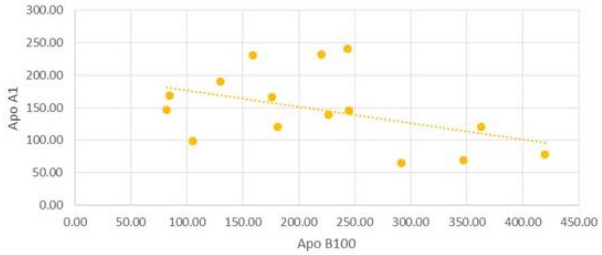

Fig. 1c Correlation of Apo B100 & A1 among group C after six months of LEV monotherapy.

Apo B100/A1 ratio has been reported as a sensitive measure of atherogenicity. Literature reveals that higher the value of Apo B100/A1 ratio, the higher is the risk of future cardiovascular and cerebrovascular disease [3, 5]. The ratio of Apo B100/A1 is considered a better indicator for the new cardiovascular events than the lipid profile [5]. The present study with a limited sample size found a statistically significant increase in Apo B100/A1 ratio among children receiving oxcar-bazepine monotherapy for six months.

The lipid-raising effect of AEDs may be due to the induction of cytochrome enzymes. Cyt p450 enzyme system is involved in the synthesis and metabolism of cholesterol and enzyme-inducing drugs also stimulate the endogenous hepatic synthesis of cholesterol. However, adverse lipid profile has been reported with both enzyme-inducing and enzyme-non-inducing anti-seizure medications [6].

Our findings are consistent with the findings of other authors who have also revealed deranged lipid profiles with the use of oxcarbazepine, even after 3 months of therapy [7]. These findings are in congruence with others, who have demonstrated a neutral effect on Apo B100/A1 in those who were on mono-therapy with levetiracetam [8]. Kim, et al. [9] reported a significant increase in LDL-C, apo B, and Apo B/A1 ratio after six months of monotherapy with levetiracetam, oxcarbazepine and topira-mate. There was no significant increase in Apo ratio in the valproate group, which was consistent with previous literature. Increased total cholesterol, triglyceride, LDL-C and apo B100 have been reported with VPA in epileptic children [10].

The limitations include a small sample size in each group, and limited follow-up till 6 months. The enrolled participants have a wide heterogenicity thus limiting the generalizability of the study results. In addition, dietary pattern of fat intake during the six-month follow-up period was not documented, which could confound the results in all the three groups. Further studies could be planned with a sufficient sample size and a follow-up period of 1-2 years. In the future studies, children with family history of premature cardiac deaths may also be excluded considering its association with mortality related to cardiovascular diseases.

The findings of the present study raise a concern about potential cardiovascular risk in terms of the ApoB100/ApoA level ratio among children receiving oxcarbazepine mono-therapy. Confirmation of these findings from larger, multicentric studies with dietary data will quite further policy regarding monitoring and follow up of children on oxcarbazepine monotherapy.

Ethics clearance; IEC, Pt. BD Sharma PGIMS; No. BREC/Th/19/Bio/02, dated Dec 26, 2019.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Laboratory Parameters of Enrolled Children With Epilepsy

Characteristics	*Sodium Valproate group*		*Oxcarbazepine group*		*At baseline At 6-mo follow-up*	
Hemoglobin (g/dL)	11.55 (0.73)	11.49 (1.14)	11.68 (0.76)	11.39 (0.84)	11.9 (0.90)	11.58 (0.77)
Total leukocyte count (cu mm)	9.09 (1.40)	8.77 (1.65)	9.77 (1.93)	9.41 (0.85)	9.14 (1.83)	8.97 (1.54)
(creatinine (mg/dL)	0.71 (0.1)	0.68 (0.07)	0.61 (0.16)	0.70 (0.13)	0.76 (0.20)	0.75 (0.12)
AST (U/L)	29.13 (8.77)	26.33 (8.03)	35.60 (14.39)	30.80 (23.49)	35.53 (24.12)	27.67 (23.92)
ALP (U/L)	213.07 (51.16)	234.73 (90.50)	226.07 (43.16)	263.80 (140.90)	187.40 (69.46)	225.53 (55.53)
Albumin (gm/dL)	3.25 (0.86)	3.04 (1.06)	3.28 (1.14)	3.13 (1.12)	3.52 (1.17)	3.46 (1.01)
Amylase (mg/dL)	73.8 (28.13)	75.67 (24.22)	78.40 (30.52)	81.13 (23.52)	89.47 (28.68)	80.60 (10.62)
Blood glucose (mg/dL)[a]	92.93 (14.45)	92.67 (13.10)	86.93 (11.11)	88.0 (10.92)	101.73 (23.77)	87.53 (8.77)
Triglycerides (mg/dL)	99.53 (42.63)	100.60 (40.61)	132 (98.48)	136.93 (49.84)	117.33 (59.17)	123.87 (49.87)
Cholesterol (mg/dL)	149.67 (24.27)	159 (41.43)	142.07 (34.34)	159.07 (24.11)	150.27 (26.31)	163 (48.16)
HDL (mg/dL)[b]	57.47 (11.92)	54.13 (11.27)	50.20 (10.29)	44.60 (17.55)	56.83 (13.06)	53.20 (18.57)
LDL (mg/dL)	71.67 (21.76)	84.93 (38.90)	69.33 (25.20)	82.20 (20.80)	70.80 (28.81)	86.27 (32.47)
VLDL (mg/dL)[c]	19.93 (8.45)	20.53 (8.05)	26.67 (19.74)	28.13 (10.58)	23.53 (11.84)	24.67 (9.88)

All values in mean (SD). All between group (VPA-OXC-LEV) P> 0.05; All within group comparison (before-after) P values>0.05 in all groups except in Lev group=0.01; [b]VPA group=0.02; [c]VPA group=0.01$ HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein