Effect of Carbamazepine on Serum Lipids and Liver Function Tests

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We prospectively studied the effect of carbamazepine (CBZ) therapy on serum lipids and liver function tests in 28 patients and 28 age and sex matched controls. The mean age of patients was 8.29 years, duration of therapy with CBZ 10.3 months and dose of CBZ 13.1 mg/dL. The patients and controls were comparable in weight, height and BMI. Mean ± SD of cholesterol 162 ± 25.8 mg/dL in patients was significantly more (P<0.001) than controls 131±25.2 mg/dL. Mean LDL cholesterol and HDL cholesterol were also significantly raised in patients. Values of mean VLDL, triglycerides, ratio of LDL/HDL, TC/HDL-C bilirubin and SGPT were not significantly different in two groups. Blood Levels of alkaline phosphatase were significantly more in patients compared to controls. The long term implications of these findings need to be studied.

Key words: *Alkaline phosphatase, Carbamazepine, Cholesterol, Lipids.*

EPIDEMIOLOGICAL, clinical and experimental investigations have shown that alteration in serum lipids predisposes to atherosclerosis(1,2). There are contradictory reports on the influence of antiepileptic drugs on serum lipids and their influence on atherosclerosis(3-9). Risk of atherosclerosis is directly related to increase in serum concentration of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C); and inversely related to increase in high-density lipoprotein cholesterol (HDL-C)(10,11). Alteration in lipid profile may vary in different populations. This is one of the first studies on Indian children that aimed to evaluate the effect of carbamazepine (CBZ) on serum lipids and liver function tests.

Subjects and Methods

This prospective study was conducted in Pediatric outpatients department of a tertiary care hospital. The patients who were on CBZ monotherapy for at least three months were included in the study. Patients who had received any other anticonvulsant before CBZ therapy or were receiving two or more anticonvulsants or had a family history of atherosclerosis or metabolic disease or any other hepatic, renal or cardiac disease requiring long term therapy were excluded from the study. Patients with gross developmental delay or congenital abnormalities were also excluded from the study. Detailed family and developmental history and history regarding type of seizure, diagnosis, dose, dosing schedule was recorded. Weight and height were recorded as per standard techniques and body mass index (BMI) was calculated. The control group consisted of 28 healthy age and sex-matched children. Those who fulfilled these criteria were enrolled for this study after written consent from their parents.

Venous blood sample (2 mL) was drawn from antecubital vein and serum was

separated stored at 2ºC-8ºC. Sample was collected in the morning after a fasting period of 8-12 hours in both cases and controls. Serum was analyzed for lipid profile by autoanalyzer using colorimetric method for triglycerides and total cholesterol (ENZOKIT Ranbaxy). High-density lipoprotein was determined using AutoZyme HDL-cholesterol precipitating reagent (Accurex Biomedical). Very low density lipoproteins (VLDL) and LDL-C were calculated using Friedewald formula *i.e.*, LDL cholesterol = Total cholesterol–(HDL cholesterol × 0.2 Triglycerides).

Statistical analysis

Based on previous study(8) a sample size of 27 was calculated to detect a difference of 22 mg/dL in mean total cholesterol with a power of 80% and α of 0.05. Data was analyzed using SPSS version 6.0. Unpaired (2-tailed) Student *t* test was applied to difference in means of various parameters in the two groups (significance of $P < 0.05$). Number of patients with higher than normal blood levels were compared in patients and controls using Chi-square test. Fisher test was applied for values <5. Effect of diet, dose and duration of treatment on various parameters were analyzed using Anova test within as well as between groups using multiple comparisons.

Results

A total of 56 subjects were included (28 cases and 28 controls). Mean age was 8.3 ± 2.8 years in patients and 8.4 ± 2.6 years in controls (range 3-12 years). There were 18 females and 10 males in each group. Mean duration of therapy was 10.3 ± 6.9 months. Mean dose of CBZ was 13.1 ± 3.5 mg/kg/day. Type of seizure was partial with secondary generalization in 43% (n = 12), complex partial seizure in 46% (n = 13) and simple partial seizure in 11% (n = 3). Clinical characteristics of the two groups are shown in *Table I.* There was no difference in weight, height, BMI, and type of diet among the two groups. *Table II* depicts mean levels of lipid profile and liver function tests in cases and controls. There was significant increase in TC, LDL-C and HDL-C level in cases in comparison to controls ($P < 0.001$). There was also significant increase in serum alkaline phosphatase in cases ($P < 0.03$) in comparison to controls. However levels of VLDL, triglycerides (TG), LDL/HDL, TC/HDL, total bilirubin and SGPT were not altered significantly. Diet, duration of therapy, doses and dosing schedule did not alter the lipid profile and liver function test ($P > 0.05$).

Patients were divided in groups according to lipid levels above or below a clinically significant level (*Table III*). There were significantly more children with HDL >35 mg/dL and alkaline phosphatase >300 IU/L among those receiving carbamazepine compared to controls ($P<0.05$). Children with VLDL >30 mg/dL, TG >100 mg/dL, Cholesterol >170 mg/dL, LDL >110 mg/dL, SGPT >40 IU/L

TABLE I– *Clinical Characteristics of Cases and Controls.*

Parameter	Cases (n = 28)	Controls (n = 28)
Age (yr)	8.29 ± 2.8	8.36 ± 2.64
Sex		
Male	10	10
Female	18	18
Weight (kg)	21.7 ± 8.0	20.9 ± 5.6
Height (cm)	120.3 ± 18.0	118.0 ± 13.2
Body mass index	14.5 ± 2.0	14.8 ± 2.0
Diet		
Vegetarian	15	18
Nonvegetarian	13	10

P > 0.05. * Values represent mean ± SD.

TABLE II–*Lipid Profile and Liver Function Tests.*

Parameter	Cases (n = 28)	Controls (n = 28)	P value
Cholesterol (TC)	162.8 ± 25.8	131 ± 25.2	0.001
HDL	49.0 ± 9.16	32.9 ± 11.5	<0.001
VLDL	17.0 ± 7.2	21.8 ± 10.6	0.5
LDL	96.7 ± 22	72.5 ± 21.4	<0.001
Triglycerides	84.8 ± 36.3	108.7 ± 52.3	0.5
Bilirubin	0.52 ± 0.13	0.66 ± 0.7	0.3
SGPT	31.1 ± 28.9	30.6 ± 11.1	0.4
Alkaline phosphatase	398.7 ± 242.1	219.7 ± 175.3	0.003
TC/HDL-C	3.41 ± 0.74	3.74 ± 1.0	0.2
LDL-C/HDL-C	2.04 ± 0.6	2.07 ± 0.7	0.9

* Values represent mean ± SD

and serum bilirubin >1 mg/dL were not significantly different in two groups. If TC of >150 mg/dL or more was compared with 150 mg/dL in the two groups there was a significant difference (P <0.001)

Discussion

CBZ is a commonly used antiepileptic drug in children. It also induces liver microsomal enzymes, thereby altering the metabolism of lipids, bile acids and bilirubin(12). 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(6). 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(6). 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(2). Some studies have failed to demonstrate a significant change in serum lipids in patients receiving CBZ monotherapy(6,13). However most workers have shown significant increase in TC and other lipid fractions in epileptic children receiving CBZ(7-10,14). This fact matches with the results of our study as well where we have found significantly increased levels of TC, HDL-C and LDL-C. Franzoni, *et al.* showed that rise in TC was a result of increased LDL-C levels only(10). Others have suggested that the increase in TC is due to increase in both LDL-C and HDL-C(11), as seen in the present study. 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

TABLE III–*Subjects with Abnormal Lipids and Liver Function Tests.*

Parameters	Cases n (%)	Controls n (%)	P value
LDL (mg/dL)			
<110	20 (71.5%)	26(92%)	0.08
≥110	8 (28.5%)	2(8%)	
Cholesterol (mg/dL)			
<170	17 (60.71)	25 (89.28)	0.1
≥170	11 (39.28)	3 (10.71)	
VLDL (mg/dL)			
<30	27 (96)	24 (86)	0.2
≥30	1 (4)	4 (14)	
HDL (mg/dL)			
<35	2 (7)	13 (46.5)	0.001*
≥35	26 (93)	15 (53.5)	
TG (mg/dL)			
<100	18 (64)	11 (39)	0.06
≥100	10 (36)	17 (61)	
Bilirubin (mg/dL)			
<1	28 (100)	27 (96)	0.3
≥1	0	1 (4)	
SGPT (IU/L)			
<40	22 (78.5)	23 (82)	0.7
≥40	6 (21.5)	5 (18)	
Alkaline phosphatase (IU/L)			
<300	13 (46.5)	25 (89)	0.001
≥300	15 (43.5)	3 (11)	

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(5). The present study does not show a significant alteration in TC/HDL and LDL/HDL ratio. This result matches with the results of others(7), showing no significant difference in TC/HDL-C and LDL-C/HDL-C ratio in children receiving CBZ. In our study 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.

The Committee on Nutrition of American Academy of Pediatrics (AAP) has classified serum cholesterol levels in the range of 170 to 199 mg/dL as "borderline" and levels in excess of 200 mg/dL "high"(15). Nine (32%) patients on CBZ in its study showed serum TC level in the range of 170 to 199 mg/dL as opposed to 3 (10%) in control group (P not significant). Only 2 cases (7%) had TC in excess of 200 mg/dL, compared to none in controls. The AAP defines LDL-C level in the range of 110 to 129 mg/dL "borderline" and in excess of 129 mg/dL "high". Eight (28.5%) patients on CBZ showed LDL-C in the range of 110 to 129mg/dL, compared to one in control group.

Results of liver function tests did not differ significantly in patients except for raised

Key Messages

- Carbamazepine alters lipid levels in children.
- Long-term implication of such alterations in terms of atherosclerosis and dietary intervention needs to be studied

alkaline phosphatase. CBZ is considered to increase vitamin D metabolism, and risk of bone disease. Decreased vitamin D levels in subjects on CBZ might result in increased blood levels of alkaline phosphatase(16) as seen in this study.

This study shows that blood level of TC, LDL-C, HDL-C and alkaline phosphatase were increased during CBZ treatment. 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 children receiving therapy with CBZ.

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Cardiovascular Involvement in Kawasaki Disease

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We report 72 patients with Kawasaki disease seen at this Centre over 7 years. Cardiac involvement in the form of mild pancarditis was seen in 28% patients, but disappeared subsequently. Thirteen (18.5%) children developed coronary artery disease, out of which 4 resolved by the end of two months and another 6 after one year; 3 patients continued to show coronary artery dilatation and aneurysm formation. Children who received IV gammaglobulin in full dose within 10 days of onset of illness, showed no evidence of coronary artery disease during follow up.

Key words: *Coronary aneurysm, IV gammaglobulin, Pancarditis.*

KAWASAKI disease (KD) is considered a rare disease in the Indian subcontinent(1). During the last decade an increased incidence is being seen in Kerala(2). Since its original description by Kawasaki in Japan, KD has been reported from all parts of the world. The basic pathology is a vasculitis involving all blood vessels, predominantly the coronary arteries. The diagnosis is based on easily recognizable clinical features. Five days of fever and at least 4 of the following 5 principal clinical features should be present to make a diagnosis of KD(3). These include cervical lymphadenopathy, a polymorphous