

# Nonalcoholic Fatty Liver Disease, Carotid Intima-Media Thickness and Lipid Profile in Epileptic Children

Mahsa Ghajarzadeh<sup>a, e</sup>, Soheila Borji<sup>b</sup>, Sarvenaz Pourjabbar<sup>c</sup>,  
Mehdi Mohammadifar<sup>b</sup>, Mahmoud Reza Ashrafi<sup>d</sup>

## Abstract

**Background:** Sodium valproate and carbamazepine are among frequent medications utilized for seizure control in children. Several adverse effects such as fatty liver disease, lipid profile changes and increased Intima-Media Thickness (IMT) were reported among cases who were treated with these medications.

**Methods:** Here we assessed 38 children (under 18) who were treated by sodium valproate and carbamazepine for at least six months for developing adverse effects including fatty liver disease, lipid profile changes and increased IMT. Cases who were treated with two or more antiepileptic-drugs or treated less than six months with each of drugs were excluded. Fasting venous blood sample drawn and radiologic evaluation of liver and both carotid arteries by two independent individuals performed.

**Results:** We found fatty liver disease in five patients who were treated with sodium valproate and lower White Blood Cell (WBC) count in carbamazepine group. Lipid profiles and IMT of both carotid arteries were not significantly different between groups.

**Conclusions:** Children who are treated with sodium valproate would be better to be carefully assessed by sonographic modalities for developing fatty liver as an adverse effect of the drug.

**Keywords:** Seizure; Children; Fatty liver; IMT; Lipid profile

## Introduction

Seizure is a chronic neurologic condition which makes a lot of troubles for children and their families. Seizure control with suitable drugs is critical to achieve seizure-free condition during treatment and after treatment withdrawal. Sodium valproate and carbamazepine are among frequent medications utilized for seizure control in children.

Sodium valproate is a first-line anticonvulsive agent used in epileptic children because of its broad spectrum of activity and tolerability. Weight gain, fatty liver disease, hematological and cardiovascular disorders have been reported as side effects of this widely prescribed medication [1].

Carbamazepine is another drug of choice for seizure control; lipid profile changes; aplastic anemia, nausea and vomiting are among frequent complications of carbamazepine custom in epileptic cases [2].

Total cholesterol (TC) and low-density lipoprotein (LDL) have been identified as risk factors for atherosclerosis along with changes in anatomy and function of great vessels. A previous study suggested that LDL level in childhood is a predictive factor of carotid intima-media thickness (IMT) in young adults and IMT has positive association with chronic heart diseases [3].

The aim of this study was to determine fatty Liver Disease, Carotid IMT and lipid profile in epileptic children who are under treatment.

## Materials and Methods

This prospective study was conducted in Children Medical Center (Affiliated hospital of Tehran University of Medical Sciences) between September 2010 and May 2011 while 38 epileptic children enrolled in this cross-sectional study. Patients who were on carbamazepine or sodium valproate mono-therapy for at least six months were included. Cases

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<sup>a</sup>Student Scientific Research Center (SSRC), Tehran University of Medical Sciences, TUMS, Iran

<sup>b</sup>Radiology, Medical Imaging Center, Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Imam Khomeini Hospital, Tehran University of Medical Sciences, Iran

<sup>c</sup>Tehran University of Medical Sciences, TUMS, Iran

<sup>d</sup>Tehran University of Medical Sciences, Children Medical Center, TUMS, Iran

<sup>e</sup>Corresponding author: Mahsa Ghajarzadeh, No 45, 32th Street, Gisha Avenue, Tehran, Iran. Email: mahsa\_blue719@yahoo.com

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**Table 1.** Baseline Characteristics of Patients

	Number of Cases (%)	Age*(mean ± SD) (Year)	Sex** (F / M)	BMI*** (kg/m <sup>2</sup> )
Carbamazepine	13 (34.2%)	11 ± 3.5	3 / 10	22.1 ± 16.6
Sodium valporate	25 (65.8%)	9 ± 3.7	5 / 20	17.8 ± 5.1

\*P-value = 0.1; \*\*P-value = 0.5; \*\*\*P-value = 0.2.

who were treated with two or more antiepileptic-drugs or treated less than six months with each of drugs were excluded. Demographic characteristics, height and weight were recorded and body mass index (BMI) calculated; Fasting venous blood sample (2 mL) drawn from antecubital vein and serum separated. Autoanalyser by colometric method applied for triglycetides and cholesterol measurements (EN-ZOKIT Ranbaxy).

AtouZyme high-density lipoprotein (HDL) cholesterol reagent used for HDL determination while LDL calculated by

Freidwald formula:  $LDL = TC - (HDL \times 0.2 \text{ Triglycerides})$ .

Two independent radiology residents performed B-mode ultrasound examinations with a Toshiba Sonolayer SSH160A (Toshiba Medical, Tokyo, Japan) equipped with a 7.5 MHz linear array transducer on subjects in the supine position.

Images of maximum far wall Carotid IMT were recorded at both right and left common carotid arteries. Images were recorded on super-VHS videotapes and read by both independent residents. For each subject the mean IMT was

**Table 2.** Laboratory Findings of Two Groups

	Carbamazepine Group	Sodium Valporate Group	P-value
WBC (White blood cells)	5715.3 ± 841.4	7362.4 ± 2067.2	0.001
RBC (Red blood cells)	4.8 ± 0.4	4.5 ± 0.8	0.3
Hemoglobin (g/dL)	13.4 ± 1.7	12.9 ± 1.2	0.3
Plt (Platelete)	104328.2 ± 139881.4	135275.7 ± 163220	0.5
ALT (Alanine aminotransferase) (U/L)	17.9 ± 10.1	16.9 ± 7.1	0.7
AST (Aspartate aminotransferase) (U/L)	22.4 ± 7.9	24.7 ± 6.2	0.3
ALP(Alkaline phosphatase) (U/L)	591 ± 130.7	524.6 ± 244.4	0.5
TG (Triglyceride) (mg/dL)	71.2 ± 20.5	80.7 ± 31.02s	0.2
Total cholesterol (mg/dL)	156.2 ± 33	149.4 ± 24.6	0.3
HDL (High-density lipoprotein) (mg/dL)	53.2 ± 9.7	54.3 ± 13.9	0.8
LDL(Low-density lipoprotein) (mg/dL)	92.9 ± 23.1	79 ± 26.1	0.1
Calcium(mmol/L)	9.4 ± 0.6	9.7 ± 0.4	0.1
Phosphorous (mmol/L)	5 ± 0.9	5.4 ± 1.1	0.9

**Table 3.** Radiologic Findings of Patients

	Carbamazepine	Sodium Valproate	P-value
Right carotid IMT (mm)	0.46 ± 0.09	0.44 ± 0.06	0.4
Left carotid IMT (mm)	0.43 ± 0.07	0.42 ± 0.06	0.9
Number of cases with fatty liver disease	0	5	0.02

calculated as the average of all mean IMT measurements.

Liver sonography performed by both residents and results were checked for agreement between them for Non-alcoholic Fatty Liver Disease determination. SPSS version 13 (SPSS Inc., Chicago, USA) used for data analysis. Data are presented as mean ± SDs, frequency and valid percent. Student t test for continuous variables and the Pearson  $\chi^2$  test with the Fisher exact test applied for categorical variables assessment. P value less than 0.05 was considered statistically significant.

## Results

Thirty-eight epileptic children participated in this study. Thirteen three were on carbamazepine and 24 were on sodium valproate treatment. Twenty two children in valproic group and three in carbamazepine group presented with generalised tonic-clonic seizure and others (three in valproic group and ten in carbamazepine group) presented with partial seizures. Table 1 shows baseline characteristics of patients. Table 2 shows laboratory findings of two groups presented in mean ± SDs. Table 3 shows radiologic findings of patients.

Both sonographers detected grade one fatty liver disease in 5 children in sodium valproate group (agreement 100%).

## Discussion

To our knowledge this is the first study which evaluates liver changes, carotid IMT and lipid profile in epileptic children who are under treatment by sodium valproate or carbamazepine. Sodium valproate is a well-tolerated anti-epileptic drug that has been widely used for epileptic children.

One of its well-established adverse effects is weight gain which leads to nonalcoholic fatty liver disease, insulin resistance and cardiovascular disorders as consequences [4-8].

Our study showed no significant difference of BMI between two groups; however Grosso et al. found that treatment by sodium valproate for at least three months is associated with weight gain in children. In a study by Wirrel et al., they found that 58% of teenagers who are under treatment with valproic acid get mild to moderate weight gain [9].

We did not observe any differences regarding serum lipid profiles in two groups, which is against findings of Demircioglu et al.. They have found higher total amounts of cholesterol, LDL, TC/HDL in 31 children who were under treatment with carbamazepine than 7 cases who were treated by sodium valproate [10]. By evaluating epileptic children receiving Phenobarbital/sodium valproate/carbamazepine, Eiris et al. reported higher levels of TC, HDL and LDL in children received carbamazepine than other two groups [11].

There were no significant differences in laboratory findings between two groups except in white blood cell count (WBC), which was significantly lower in carbamazepine group. Aplastic anemia is regarded as a considerable adverse effect of carbamazepine; hence all cases who are treated with this medication should be evaluated regularly by CBC test [2]. Although there are studies that reported thrombocytopenia as a main adverse effect of valproic acid [12]; in this study PLT level was higher in valproic than carbamazepine group.

In the current study five cases in sodium valproate group had fatty liver disease in liver sonographic assessment while there was no evidence of this finding in carbamazepine group. Non-alcoholic fatty liver has a wide spectrum from simple steatosis to non-alcoholic steatohepatitis with necroinflammation and fibrosis that may progress to cirrhosis an irreversible liver damages.

Valproate and its metabolites interfere with mitochondrial function and fatty acid oxidation which result in induction of micro vesicular hepatic steatosis. This has been believed as the mechanism of fatty liver development in cases treated with sodium valproate [13].

In a previous study, Luefa et al. reported fatty liver in 60.9% of patient under Valproate treatment while this figure was 22.7% in patients under carbamazepine; higher lipid profile level was reported in carbamazepine group [14].

We found no statistically significant difference between carotid IMTs in two groups while in a study by Erdemir A et al. they found increased intima media thickness of common carotid arteries in children under sodium valproate therapy in comparison with healthy ones [15]. Intima media thickness is a simple, quick, non invasive and cost-effective method that that can show atherosclerosis in middle-aged and older adults. It has positive association with chronic heart diseases

[3].

Our study includes some limitations. First of all, our sample size was small because Children Medical Center is the main referral center for children care in Iran and most patients who refer to this center are cases with refractory seizure under treatment with multi-drug anti-epileptic regimen. Second, our study lacked a comparison with healthy group due to ethical issues such as blood sampling in healthy individuals and the fact that parents in our culture are so strict to let their healthy children to be entered in studies with no gain for them.

To come to a conclusion we cannot define anything about carbamazepine lipid profile changes while we may suggest that children who are treated with sodium valproate would be better to be carefully assessed by sonographic modalities for developing fatty liver as an adverse effect of the drug.

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