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Association of Long Term Sodium Valproate Therapy with Non-Alcoholic Fatty Liver Disease among Epileptic Patients

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Abstract

Objective: *To assess the association of long time sodium valproate therapy with non alcoholic fatty liver disease among epileptic patients.* ***Method:****It was a cross-sectional analytical study. Total 40 epileptic patients who had received valporic acid (VPA) monotherapy for at least one year were taken as case. Another 40 newly diagnosed age and sex matched epileptic patients without any antiepileptic drugs were also taken for comparison. Participants underwent hepatic ultrasound, anthropometric evaluations, and biochemical tests.* ***Result:*** *The occurrence of ultrasound-diagnosed non alcoholic fatty liver disease (NAFLD) was higher (37.5%) in VPA-treated patients than in controls (10%) with significant difference (P=.004). There was no significant difference in serum cholesterol level(165.60± 14.99 mg/dl vs.162.38 ± 11.74 mg/dl, P =.287), HDL level(42.83 ± 2.31mg/dl vs. 43.53 ± 2.51 mg/dl, P = .198), LDL level(99.6±13.43mg/dl vs. 96.65 ± 11.77mg/dl, P=.299) andtriglyceride level(116.9± 14.14 mg/dl vs 113.2 ± 10.32 mg/dl, P =.185) between valproate and non valproate group. The BMI of valproate treated patients were also higher (23.28±2.62) than the mean BMI of control group (21.27± 2.53) with significant difference (P=.001). The waist circumference was also higher in valproate treated patients (83.85±10.01cm vs. 78.55±9.95 cm) with significant difference (P=.020).* ***Conclusion:*** *Sodium valproate mono-therapy is associated with non alcoholic fatty liver disease among epileptic patients , who have typical VPA-related increased body weight.*

Keywords: *Sodium valproate, Non alcoholic fatty liver disease*

Introduction:

Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process..[1] It is considered to *be one of the commonest and frequently encountered neurological* conditions that imposes heavy burden on individuals, families, and also on healthcare systems. The worldwide prevalence of epilepsy is variable and varied among countries. It is estimated that there are at least 1.5 to 2.0 million epilepsy patients in Bangladesh.[2]

Antiepileptic drugs are the simplest and the safest means of controlling epilepsy. There are a number of antiepileptic drugs. Among those some are first line anti epileptics and some are second line anti epileptics according to the types of seizures. Commonly used first line antiepileptics are carbamazepine, valproic acid, lamotrigine, ethosuximide, oxcarbazepine, levetiracetam and commonly used second-line anti epileptic drugs are phenytoin, gabapentin, topiramate,clobazam, phenobarbital, clonazepam, primidone. The choice of anticonvulsant is dependent on seizure type, epilepsy syndrome, co morbidities, other medications used, and the patients' age, lifestyle

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and socioeconomic conditions. Antiepileptic drugs (AED) are frequently used in the treatment of psychiatric diseases and pain syndromes, insomnia apart from seizure. Valporic acid (VPA) is one of the commonest antiepileptic drugs. It has a broad spectrum of anticonvulsant activity. Weight gain is a common side effect of VPA. The increase in body weight is found to be associated with metabolic disorders indicating an increase in insulin resistance during VPA therapy. Insulin resistance is also related to the development of nonalcoholic fatty liver disease.[3]

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease encompassing simple fatty infiltration (steatosis), fat and inflammation (nonalcoholic steatohepatitis, NASH) and cirrhosis, in the absence of excessive alcohol consumption (typically a threshold of <20 g/day for women and <30 g/day for men).The most significant risk factors for NAFLD include the components of metabolic syndrome: obesity, glucose intolerance or diabetes, hypertension, and dyslipidemia, particularly elevated triglycerides and low levels of HDL cholesterol.Studies showed an overall prevalence of NAFLD of approximately 5% in the general population, and a significant increase of up to 25% and even 75% in patients with obesity and type 2 diabetes mellitus.[4]

Study regarding the association of long term sodium valproate therapy with ultrasound diagnosed NAFLD was previously done.[5] outside our country. So far known, no such type study was found to be done in our country. Therefore, the objective of this study was to determine the frequency of NAFLD in patients with epilepsy receiving sodium valproate mono-therapy for long time and its significance.

Method:

This cross sectional analytic study was carried out in the Epilepsy clinic and outdoor of Department of Neurology, BSMMU over a period of two years from July 2014 to June 2016. Forty epileptic patients of age above 18 years who were treated with sodium valproate for at least 12 months were selected as study population (Group I). Another 40 newly diagnosed age and sex matched epileptic patients who yet not started antiepileptic drugs were also taken for comparison (Group II).Known patients with non alcoholoic fatty liver disease, diabetes mellitus, and dyslipidemia were excluded from the study. Detailed history was collected and clinical examination & investigation were done for each patient. Statistical analysis was conducted using SPSS Version 21.The results were expressed as means (SD) for continuous variables and as percentages for categorical variables. Comparisons of continuous data between patients on VPA and control group were performed with unpaired student's t-test, and those of categorical data with the Chi-square test. To study the correlation between NAFLD and BMI and between NAFLD and waist circumference spearman rank order correlation were done. Statistical significance was defined as a P value <0.05.

Result:

Maximum patients were in age group 18-22 years in both groups. Mean age was 23.83 ± 8.46 years in valproate group and 23.58 ± 7.31 years in non valproate group. Males were predominant (65% vs. 35%) in both groups. Male female ratio was 1.85:1 in both groups.

BMI was significantly higher in group I (23.28 ± 2.62) than that of group II (21.27 ± 2.53). Similarly waist circumference was higher in group I (83.85 ± 10.01) than that of group II (78.55 ± 9.95).There was no significant difference in total cholesterol, HDL, LDL and Triglyceride between group I (sodium valproate) and group II (Non valproate) (Table 2).

In group I (valproate), 15 (37.5%) and in group II (non valproate) group 4 (10.0%) patients had fatty liver. There was statistical significant difference between these two groups (Table III).(P value=0.004)

Table-I

Demographic profile of the patients (n=80)

	Group		p value
	Group I*	Group II**	
Age (years)			
18 – 22	26 (65.0)	25 (62.5)	
23 – 27	5 (12.5)	7 (17.5)	
28 – 32	2 (5.0)	2 (5.0)	
33 – 37	3 (7.5)	3 (7.5)	
>37	4 (10)	3 (7.5)	
Mean SD	23.83 ± 8.46	23.58 ± 7.31	0.890
Range (Min-Max)	18 - 50	18 - 45	
Gender			
Male	26 (65.0%)	26 (65.0%)	1.000
Female	14 (35.0%)	14 (35.0%)	

*Valproate group, ** Control group

Table-III

Clinical findings and lipid profile of the patients treated with valproate(Group-I) and control group (Group-II) (n=80)

Clinical and laboratory findings	Group		p value
	Group I	Group II	
Clinical findings			
BMI (kg/m^2)	23.28 ± 2.62	21.27 ± 2.53	0.001
Waist (cm)	83.85 ± 10.01	78.55 ± 9.95	0.020
Lipid profile			
Total Cholesterol (mg/dl)	165.60± 14.99	162.38 ± 11.74	0.287
HDL (mg/dl)	42.83 ± 2.31	43.53 ± 2.51	0.198
LDL (mg/dl)	99.6 ± 13.43	96.65 ± 11.77	0.299
Triglyceride (mg/dl)	116.9± 14.14	113.2 ± 10.32	0.185

Table-III

Frequency of fatty liver in patients treated with valproate (Group-I) and control group (Group-II) (n=80)

Liver	Group		p value***
	Group I	Group II	
Fatty liver	15 (37.5%)	4 (10.0%)	0.004
Normal liver	25 (62.5%)	36 (90.0%)	
Total	40 (100.0)	40 (100.0)	

Discussion:

This cross sectional study was carried out to see whether there is any association between long term sodium valproate therapy and non alcoholic fatty liver disease among epileptic patients.

In this study it was observed that majority patients were in 18-22 years range. The mean age of patients taking sodium valproate was found to be 23.83 ± 8.46years. These findings are compatible with studies performed by Habib et al.[6],Paknahad et al.[7] andSener et al.[8].

In this current study it was observed that male were predominant among the epilepsy patients which

was 65% of the study population.This male predominance is also observed in studies done by Habib et al.[6],Sener et al.[8] and Mian et al.[7].

In this study the mean BMI of valproate treated patients was 23.28±2.62 kg/m^2 and mean BMI of control group was 21.27± 2.53 kg/m^2. The difference between the two groups was significant (P =.001). The mean waist circumference of valproate treated patients was 83.85±10.01 cm and that of control group was 78.55±9.95cm. The difference between the two groups was also significant (P=.02). Both this results showed association of valproate with weight gain. This result supports multiple studies done around the world such as studies done byGaspari et al.[9],Kim & Lee[10]andVerotti et al.[11].

In this study the mean cholesterol level in sodium valproate group was 165.60± 14.99 mg/dl and that of control group was 162.38 ± 11.74 mg/dl. The difference between the two groups was not significant (p=0.287). The HDL level in sodium valproate group was 42.83 ± 2.31mg/dl and that of non valproate group was 43.53 ± 2.51 mg/dl. The difference between the two groups was insignificant (P=0.198). The LDL level in sodium valproate group was 99.6 ± 13.43 mg/dl and that of non valproate group was 96.65 ± 11.77mg/dl. The difference between these two groups was not significant (P=0.299). The triglyceride level in sodium valproate group was 116.9± 14.14 mg/dl and that of non valproate group was 113.2 ± 10.32 mg/dl. The difference between the two groups was not significant (p=.185). All these results showed that there was no significant alteration in lipid profile in valproate therapy. There are multiple studies done worldwide to find out the effects of long term sodium valproate therapy on lipid profile. The result of this study is compatible with studies conducted by Manimekalaiet al.[12], Nikolaos et al.[13], Geda et al.[14], and Yilmaz et al.[15].

This study showed that 37.5% patients taking sodium valproate were affected by fatty liver. This result is compatible with studies conducted by Verrotti et al.[12] and Saleh et al.[17]. Though a study conducted in 2004 showed that 61% patients taking valproate were having NAFLD[18]which is higher than the current study. This study showed that 10% of epileptic newly diagnosed patient were suffering from NAFLD. The prevalence of NAFLD in normal population is 10-15%.[19]The difference between these two groups was significant proving the fact that valproate therapy is associated with fatty liver. This result is line with the study done by Verrottiet al.[11],Saleh et al.[16],Luef et al.[17], Luef et al.[19] and Hamed et al.[20].

Conclusion:

This study showed that long term sodium valproate therapy is strongly associated with increased body weight, abdominal obesity and non alcoholic fatty liver disease.

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