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Effect of Antiepileptic Drugs on Liver Function Tests and Lipid Profile in Paediatric Age Group in Okhla Industrial Area.

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ABSTRACT

Background: Epilepsy is the fourth most common neurological disease and affects people of all ages. There are 150,000 new cases of epilepsy every year.The highest incidence of epilepsy in children coupled with the need of long-term antiepileptic treatment could lead to alterations in haemato-biochemical parameters at an early age. Phenytoin and valproic acid are commonly used antiepileptic drugs in children. This study was aimed to assess the serum lipid profile and liver function tests in children with epilepsy on phenytoin or valproic acid monotherapy for 6 months and their control counter-parts. **Methods:** This case control study recruited children from the pediatric outpatient department of Esic Hospital, Okhla. All consecutive children diagnosed with epilepsy as per International League against Epilepsy definition on phenytoin or valproic acid monotherapy for 6 months were enrolled along with the percentage distribution of type of seizures they were suffering. After baseline clinical and anthropometric evaluation (including body mass index [BMI]), the fasting blood samples were analyzed for serum lipid profile and liver function changes. **Results:** Total of 133 children were enrolled. There were 42 and 36 patients in phenytoin and valproic acid groups respectively and 55 in normal healthy control group. We observed statistically significant high mean total cholesterol and alkaline phosphatase levels in group receiving phenytoin when compared with valproic acid or control group. **Conclusion:** The lipid and liver enzyme abnormalities may be observed in children on phenytoin or valproic acid therapy, which warrants careful screening and monitoring as young children have immature detoxification mechanisms and a greater variability in dosing owing to a wider range of body size and weight. New epilepsy research should be integrated in areas i.e. Genomics, neuroimaging, neuropsychology and neuropathology for better understanding of the disease and to improve the global health outcomes.

Keywords: epilepsy, seizure, valproic acid, phenytoin, lipid profile, liver function test.

INTRODUCTION

Epilepsy is a disrupt systematic functioning of brain characterised by the periodic and unpredictable occurrence of seizure. The word 'Seizure' refers to a transient alteration of action, behaviour and performance due to the disordered, synchronous, and rhythmic firing of populations of brain neuron. The episodes of seizures are unpredictable or uncertain and their frequency is highly variable.[1]

As per WHO, epilepsy is one of the most common serious brain disorder that affects not only the individual, but also disturbs the family and the society in general. WHO estimates that 8 per 1000 population worldwide have epilepsy, with higher prevalence in developing countries as compared to developed countries. Further, there are approximately around 10 million people estimated to be with epilepsy in India accounting for 1/5th of the global burden. The main causes of epilepsy under consideration are head injuries, cerebrovascular disease, CNS infections, Cerebral malformations, degenerative brain diseases and birth trauma.[2]

Most children with epilepsy are treated with medication. Doctors will not usually prescribe medicine until after a child has had more than one seizure and been diagnosed with epilepsy. They often need to try a few different antiepileptic (seizure-preventing) drugs before the right one is found.[3]

For drug metabolism and elimination of many antiepilectic drugs (AEDs), liver is the primary organ and thus is subjected to drug-induced toxicity. There is a wide range of hepatotoxic reactions, from mild and transient increase of hepatic enzymes to fatal hepatic failure.[4]

Conventional AEDs as monotherapy are commonly adviced to use in developing countries with limited resources .Though most prefer phenytoin (PHT) as

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initial monotherapy followed by carbamazepine (CBZ) and sodium valproate (VPA) based on the type of seizure , this behaviour is highly variable in different countries and as well as primary and tertiary care hospital set ups within a country. Local socio-economic, cultural and ethnic factors, geneticprofile of an individual and availability of drugs also affect the patient treatment regimens. Moreover, basic differences in patient's demographic, seizure frequency and severity of seizure limit the direct comparison of individual trials.[5]

The eminence of life in patients with epilepsy (PWE) is compromised not only due to sequelae of seizures but also the adverse effects (AEs) of medication. Prescription of AEDs needs consideration of both drug efficacy and possible AEs in each patient. The relation between neurological AEs and epilepsy is not clearly understood, and also it is difficult to know whether AEs are a consequence of epilepsy, a reaction to epilepsy or an AE of treatment. The presence of various neurological AEs may heighten sensitivity to general symptoms. Therefore, any measure of adverse events must have the ability to differentiate successfully between symptoms caused by AED use and those that are directly related to epilepsy or mood.[6]

Phenytoin and valproic acid are the broad spectrum antiepileptic drugs commonly used for most paediatric epilepsies. The lipid abnormalities with phenytoin have been described infrequently.[7] Many other studies have described the lipid abnormalities in children with valproic acid.[8] The results are conflicting with regard to the variable trends observed in the lipid parameters and liver enzymes.

Increase level of serum concentration of certain lipids and lipoproteins in children such as total cholesterol (TC), elevated triglyceride (TG) concentrations, increased low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) are common and important risk factors for the development of coronary heart disease in later life. Thus, increased changes in serum lipid levels and liver function tests (LFT) following antiepileptic drugs may be very useful to choose the safest drug and prevention of cardiovascular complications in later life.[9] Also, lowering of bone mineral density was observed with long term treatment with antiepileptic agents.[10]

Phenytoin is metabolized in liver by hydroxylation and glucuronide conjugation. The kinetics of metabolism capacity limited; and its changes from first order to zero order over therapeutic range, thus small increments in dose, produce disproportionately increases plasma concentrations. Valproic acid is completely metabolized in liver by oxidation and glucuronide conjugation. Valproic acid causes a decrease in serum free carnitine levels by inhibition of plasma level carnitine uptake having concerns particularly in children younger than 2 years for developing an idiosyncratic potentially fatal hepatotoxic syndrome. Children are likely to be more vulnerable to any potential factor unfavourably affecting to metabolic status. As the lipid abnormalities may be encountered in children on phenytoin or valproic acid therapy, periodic monitoring and counselling for lifestyle modifications may be warranted. These should be used cautiously in those with pre-existing risk factors for metabolic syndrome such as family history, obesity, dyslipidemia, hypertension and insulin resistance.[11]

Thus, the present study was conducted to explore any adverse effects on liver function tests and lipid profile in children showing seizure disorder who received the treatment of two commonly used antiepileptic drugs viz. phenytoin and valproic acid.

MATERIALS AND METHODS

This study was conducted in the Department of Biochemistry, Esic Hospital, Okhla. It comprised of total 133 children on anticonvulsant monotherapy for at least 3 months.

An informed written consent was obtained from parent of each child enrolled in the study after explaining about the study. Age and sex-matched healthy controls were enrolled from the outpatient department.

Children on combination antiepileptic drug therapy, thyroid disorder or other endocrinopathies, chronic liver, heart or renal disease, progressive neurological or psychiatric illness and guardians who refused to give consent on drugs which may alter the lipid profile or liver enzymes such as steroids, insulin, statins were excluded. A detailed clinical history including age,sex, occupation, socio-economic status, duration of illness and any associated risk factor contributing for the illness was elicited from the subjects. The information regarding the age, sex, type of seizures, duration and dose of the antiepileptic therapy, any family history of stroke or cardiovascular disease were collected followed by a detailed systemic examination.

The study population were divided into three groups: cases which include children receiving AEDs: phenytoin and valproic acid monotherapy for 3 months and controls as healthy children.

Height and weight was calculated as per the standard procedure. Anthropometry measurements were taken for each child. Standing height(cm) was measured with a standard calibrated stadiometer, and the body weight (kg) was noted on a standard weighing scale with children dressed in appropriate clothing. With all aseptic precautions and overnight fasting blood samples (3 ml) were drawn by venipuncture and collected to measure serum total cholesterol, HDL-C, LDL-C, TG and liver enzymes (SGPT and SGOT), Alkaline phosphatase and bilirubin. All these parameters were assessed by the COBAS C311

analyzer. Very low density cholesterol and low density lipoprotein cholesterol were calculated using Friedewald formula.

Statistical Analysis

All data were entered in Microsoft excel sheet and was imported to SPSS software. All the analysis were performed using SPSS, Version 20.0. Chi square test was performed to find out the significance of correlation between the data and p value of < 0.05 was considered statistically significant.

RESULTS

Table 1: Socio- Demographic parameters of Cases and Controls

S. No	Parameters	Cases		Controls N=55
		Valproicacid N=36	Phenytoin N=42	
1	Age (yrs)	7.25±2.4	7.63±1.8	7.41±2.5
2	Sex			
-	Male	22	22	28
-	Female	14	20	27
3	Weight (kg)	20.9±4.3	19.6±3.0	22.4±3.5
4	Height(cms)	118.2±9.4	116±8.8	121±8.3
5	BMI (kg/m2)	16.8±3.3	15.4±2.8	17.2±3.9
6	DIET			
	Vegetarian	16	17	31
	Non-Vegetarian	20	25	24
7	Types Of Seizures			
	GCT	25	33	-
	MC	8	9	-
	AS	3	0	-

GCT-Generalized tonic clonic seizures, MC-Monoclonic seizures, AS- Absence seizures

Table 2: Biochemical parameters to asses Lipid Profile and LFT in Cases and Controls

Parameters	Cases		Control N=55	P-Value
	Valproicacid N=42	Phenytoin N=36		
TC (mg/dl)	158.5±34.1	169.4±33.2	154±29.2	0.03
HDL (mg/dl)	48.9±10.2	46.9±9.5	42.2±12.5	0.52
LDL (mg/dl)	87.9±20.2	100.1±31.3	91.3±22.4	0.11
VLDL (mg/dl)	21.8±7.42	22.4±8.2	20.7±6.99	0.21
TG (mg/dl)	108.7±21.7	112±36.4	102.3±19.3	0.68
BILIRUBIN(mg/dl)	0.79±0.39	0.65±0.32	0.62±0.78	0.14
SGPT (U/L)	34.3±9.1	40.4±8.6	32.6±8.4	0.12
SGOT (U/L)	23.2±7.7	28.1±5.9	25.4±8.7	0.45
ALP (U/L)	463±261.2	561±184.3	395±201.3	0.04

A total of 133 children were enrolled in this study. There were 42 and 36 patients with phenytoin and valproic acid monotherapy respectively for at least 3 months and 55 children in the control group. The Socio- Demographic characteristics of study population are shown in [Table 1]. Generalized tonic clonic seizures were the commonest type of seizures noted in children with mean age 7.54±3.65. Most of the children with epilepsy in our study belonged to low socioeconomic income group with limited access to education. The type of diet does not posed any significant criteria for the development of seizures.

Serum levels of lipids and liver function tests are shown in [Table 2]. Statistically significant high mean of TC and ALP levels are observed in phenytoin when compared with valproic acid or control group. Mean cholesterol in children receiving phenytoin was higher as compared to children receiving valproic acid (P=0.03). Children receiving phenytoin had higher LDL-C level, than the control and valproic acid group. TC, TC/HDL-C and HDL-C/TC were comparable for all the three groups. Statistically significant correlation was obtained between serum alkaline phosphatase levels in children in the phenytoin than control group (P=0.04). However, there was no statistically significant difference among mean HDL-C, TG and LFT levels except ALP in the group receiving phenytoin and valproic acid when compared with control group.

DISCUSSION

In a population based study in 2002[12] showed that valproic acid therapy did not change serum lipids, vitamin B12 and folic acid concentrations in epileptic children. In the study conducted by Yalçin[13] it was observed that patients receiving carbamazepine showed increased serum high density lipoprotein cholesterol (HDLC), apolipoprotein A (Apo A) and apolipoprotein B (Apo B). Patients receiving valproic acid showed increased Apo□B levels only. Study carried out by Bhosale UA it was found that all the antiepileptics were potentially toxic drugs and monotherapy should be considered as gold standard in antiepileptic therapy.[14]

In a study conducted on 49 epileptic patients it was indicated that patients using carbamazepine have significantly higher ALP than those using phenytoin and patients using sodium valproate have significantly higher ALP than those using phenytoin.[15] In a total of 40 freshly diagnosed epileptic children, suffering from idiopathic generalized tonic-clonic or partial seizures it was demonstrated that children receiving VPA for 6 months had lower serum levels of TC, triglycerides, LDL-C, VLDL-C, LDL-C / HDL-C ratio and higher HDL-C levels than controls. Hepatic enzyme inducing drugs such as carbamazepine may have adverse effect on serum lipid profile. This alteration of serum lipids may have clinical relevance with

regard to the incidence of atherosclerosis with antiepilectic drugs.[16]

Pelkonen R showed that the serum cholesterol levels increased by 6 to 48% in patients during the first three months on phenytoin.[17] The mechanism by which phenytoin increases the serum cholesterol level can be explained by two theories. Phenytoin decreases the level of circulating thyroid hormones including free thyroxine and triiodothyronine, and the increase in serum cholesterol could be due to subclinical hypothyroidism.[18] Second theory is based on the phenobarbitone-like effect of phenytoin on hepatic microsomal enzymes. Phenobarbitone stimulates the hepatic synthesis of cholesterol and also increase the intestinal absorption of cholesterol.[19]

In a study by HodaYahyaTomoum et al,[20] which comprised of 22 children with idiopathic epilepsy were on either carbamazepine or valproate. Patients on carbamazepine showed increase in total cholesterol, low-density and high-density lipoproteins cholesterol, and decrease in apolipoprotein AI levels compared with controls.

In a cross-sectional study by Aditi Dhar et al it was found that children on valproate had significantly higher mean serum triglyceride and total cholesterol levels as compared to children on phenytoin monotherapy.[21] Dewan et al,[22] in 79 epileptic patients reported higher total cholesterol in children on phenytoin when compared to valproate and controls.

The present study was designed to investigate the effect of conventional antiepileptic drugs phenytoin and valproic acid on lipid profile parameters and liver function tests. The limitations of this study included lack of serial measurements, the unavailability of sibling's data, and long term follow up of the enrolled children.

CONCLUSION

Evaluation of this prevalence study indicates that more case-control studies should be conducted in paediatric age group to formulate the guidelines for safe drug usage and it's long term effect on the deranged parameters. Parents and doctors should work together to not only find the best treatment, but to keep checking to make sure it continues to be the best option. There is an urgent need of the hour to develop affordable drug delivery system of these antiepilectic drugs for general public and to diversify our interests towards mass health education to dispel the social stigma attached to the disease. New treatments are continually being developed. Hence, it's important to be an active partner in your child's care. Screening for neurobehavioral co morbidities should be an integral part of management in children with “active” epilepsy.

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