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Association of Insulin Resistance with Sodium Valproate Therapy among Epileptic Patient

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Abstract:

Background: *Epilepsy is a common neurological disorder. Sodium valproate is one of the commonest broad spectrum antiepileptic drugs and it is used worldwide. Weight gain is the common side effect which is known to be associated with insulin resistance. The aim of this study was to see the association of sodium valproate therapy with insulin resistance among epileptic patients.* ***Methods:*** *It was a cross-sectional analytical study. Total 102 patients (51 epileptic patients with valproate monotherapy for at least one year and another 51 age and sex matched newly diagnosed epileptic patients without any anti-epileptic drugs) were selected in this study. The study was carried out from March 2016 to April 2017 for one year in the epilepsy clinic and outpatient Department of Neurology at Bangabandhu Sheikh Mujib Medical University, Dhaka. Participants underwent anthropometric evaluations and biochemical tests including fasting blood sugar and fasting insulin level. Insulin resistance (IR) index was calculated.* ***Result:*** *In this study mean duration of valproate treatment was 3.12±1.26 years and mean sodium valproate dose was 1133±440.5 mg/day (17.7±6.65 mg/kg/day). This study revealed serum fasting insulin level in valproate group and non-valproate group was 11.05±4.86 (¡U/ml) and 7.39±2.01 (¡U/ml) respectively. Fasting blood glucose was 4.71±0.79 (mmol/L) in valproate group and 4.41±0.62 (mmol/L) in non- valproate group. Calculated IR index in valproate group and non-valproate group was 2.17±0.55 and 1.46±0.39 respectively. IR index, fasting insulin and blood glucose all were significantly higher in valproate group than non- valproate group. This study also revealed mild positive correlation of IR index with dose and duration of valproate treatment.* ***Conclusion:*** *Sodium valproate treated patient had significantly higher IR index than control group.*

Key words: *Insulin Resistance, Valproate, Epileptic patients etc.*

Introduction:

Valproic acid (N-dipropylacetic acid, or 2-propylpentanoic acid) is a simple branched-chain carboxylic acid[1]. Sodium valproate is the sodium salt of valproic acid. It is one of the commonest 1st line antiepileptic drug used for all kind of seizure[1]. It is also used as a major treatment in bipolar disorder[2] and a prophylactic drug for migraine[3]. The underlying mechanism of action is increment of concentration of GABA in brain, inhibition of neuronal firing inactivation of voltage sensitive sodium channels and t type calcium channels[1]. Continuous use of valproic acid is associated with several side effects. Weight gain is a common side effect of VPA[4]. The increase in body weight is found to be associated with metabolic disorders indicating an increase in

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insulin resistance (IR) during VPA therapy[5]. Sodium valproate causes hyper insulinemia both in obese and lean patient[6]. Insulin resistance is a pathological state characterized by a lack of physiological response of peripheral tissues to insulin action[7]. It is related to obesity, non-insulin dependent diabetes mellitus, hypertension, atherosclerotic cardiovascular disease, dyslipidemia, hyperinsulinemia[8]. Insulin resistance is also related to the development of nonalcoholic fatty liver disease[9]. The exact pathogenesis of valproate induced insulin resistance is still not fully clarified. One hypothesis is valproic acid induced elevation of free fatty acid level which has role in impairment of action of insulin. As valproic acid is branched chain fatty acid and highly protein bound drug, it competes with free fatty acid for protein binding[10]. Beta oxidation of fatty acids may also be inhibited by valproic acid which causes increased level of non-esterified fatty acid in blood[11]. Other hypotheses are valproate induced direct toxicity on pancreatic beta cell[12], defective sympathetic neuronal activity[13], impairment of insulin signal transduction pathway[14]. Insulin resistance can be measured by several methods like homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI) etc.[15]. Homeostasis model assessment was first developed by Matthews et al.[16]. It is derived from the use of the insulin glucose product, divided by a constant.

Although studies regarding the association of long term sodium valproate therapy with insulin resistance were done previously in other countries, so far it is known, no such study was found to be done in this country. Therefore, the objective of this study was to determine the insulin resistance (IR) index in patients with epilepsy receiving VPA mono therapy for long time.

Materials and Methods:

This cross sectional analytic study was carried out in the Epilepsy clinic and outpatient Department of Neurology at Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2016 to April 2017 for a period of one year. Total 102 epileptic patients of both sexes and age >18 years having focal or generalized epilepsy were selected. Among them 51 patients were with sodium valproate therapy for at least 12 months and another 51 patients were newly diagnosed epileptic on arrival without any antiepileptic drug for comparison. Patients were excluded from this study who were diabetic, obese, hypertensive, noncompliant, had neurological disease other than epilepsy, and took antiepileptic other than sodium valproate or any drug causing insulin resistance. Patients and controls were selected by purposive sampling. Detailed history and clinical examination were carried out for each patient and control using especially prepared proforma. Previous records and data were reviewed. Structured questionnaire were used to collect the necessary information. Each participant was undergone measurements of height, weight, waist circumference and blood pressure. BMI was calculated as weight (kg) divided by height (m). After 8 to 12-hours fast, a venous blood sample was withdrawn and analyzed for fasting plasma insulin (FI) and fasting glucose (FG).Test is carried out by automated analyzer: Dimension EXL with LM, Architect Plus ci8200 in the department of Biochemistry, BSMMU. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as proposed by Mathews et al.[16] as follows: Fasting insulin (μU/ml) x Fasting glucose (mmol/L)/22.5.

Data Analysis: Statistical analysis was conducted using SPSS Version 22. The results were expressed as means ± SD for continuous variables and as frequency & percentages for categorical variables. Comparisons of continuous data between patients on VPA and non-valproate group were performed with unpaired student's t-test, and those of categorical data, with the Chi-square test. For comparison of more than two mean group ANOVA test were used. For correlation, Pearson's correlation coefficient test was used. P value <0.05 were taken as statistically significant at 95% confidence interval.

Operational definitions

Long term sodium valproate therapy: Those patients taking sodium valproate for at least 12 months.

Obesity: Defined as BMI ≥30kg/m^2, where BMI is weight in KG/square meters of height [17].

Hypertension: Systolic Blood pressure ≥140 mm of Hg and/ or Diastolic Blood pressure ≥90 mm of Hg after sitting quietly in a chair for at least 5 minutes with feet on the floor[18].

Diabetes mellitus: Defined as

Fasting plasma glucose ≥ 7.0 mmol/L

Plasma glucose in random sample or 2 hrs after 75 mg glucose load ≥11.1 mmol/L[19].

Ethical consideration: Approval was obtained from the Department of Neurology, BSMMU and Institutional Review Board of BSMMU prior to the commencement of this study. The aims and objectives of the study were explained to the patients and/or attendants in easily understandable local language and then informed consent was taken. It was assured that all information and records would be kept confidential and the procedure was helpful for both the physician and the patients in making rational approach of the case management.

Results:

All 102 participants were separated into two groups. First group comprised epileptic patients being treated with VPA(n=51, mean age 23±7.01 years, age range 18-45 years, 32 male, 19 female).. The second group comprised newly diagnosed epileptic patients on arrival who did not take any antiepileptic drug(n=51, mean age 24.8±3.7 years, age range 18-43 years, 34 male, 17 female).

Mean duration of treatment with valproic acid was 3.12±1.26 years and mean drug dose was 1133.12 ± 440.5 mg/day range (400-2000), 17.7± 6.65 mg/kg/day range (7-32). Mean BMI of valproate and non-valproate group were 23.4±1.22(kg/m^2) and 22.63±1.59 (kg/m^2) respectively.

The fasting insulin level in valproate and non - valproate group was 11.05±4.86µU/ml and 7.39±2.01µU/ml with significantly higher in valproate group. The fasting blood glucose in valproate group and non-valproate group was 4.71±0.79mmol/L and 4.41±0.62mmol/L respectively. The blood glucose was significantly higher in valproate group. Calculated insulin resistance index from HOMA-IR formula in valproate and non -valproate group was 2.17± 0.55 and 1.46±0.39 respectively. IR index was significantly higher in valproate group.

Table-I

Participants demographic and clinical characteristics

Characteristics	Valproate group	Non-valproate group	P value
Age (years)	23±7.0 (18-45)	24.8±3.7(18-43)	
Sex			
Male (n)	32	34	
Female(n)	19	17	
Mean duration of treatment (years)	3.12±1.26		
Drug dose (mg/day)	1133.12±440.5		
(mg/kg/day)	17.7± 6.65		
BMI (kg/m^2)	23.4±1.22	22.63±1.59	0.081

Table-II

Comparison of laboratory data between two groups

Variables	Valproate group (n=51) Mean ±SD	Non valproate group (n=51) Mean ±SD	P value
Serum fasting insulin level (µU/ml)	11.05±4.86 (5.10-39.4)	7.39±2.01 (2.80-12.0)	<0.05*
Blood glucose-Fasting (mmol/L)	4.71±0.79 (3.4-6.1)	4.41±0.62 (3.5-5.7)	<0.05*
IR index	2.17±0.55 (1.02-4.70)	1.46±0.39 (0.46-2.75)	<0.05*

Data were analyzed using Student's t-test and were presented as mean ±SD, parenthesis figure indicate range
*significant

There was moderate positive correlation of IR index with duration and dose of valproic acid treatment.

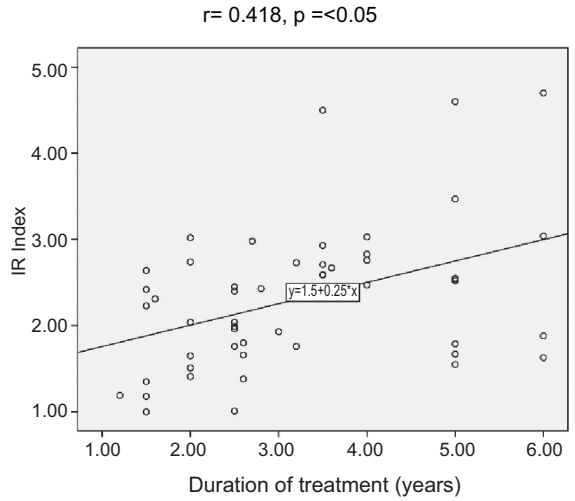

Fig.-1: *Scatter diagram showing moderate positive correlation of IR index with duration of treatment(r=0.418; p = < 0.05).This test was done by Pearson's correlation coefficient test.*

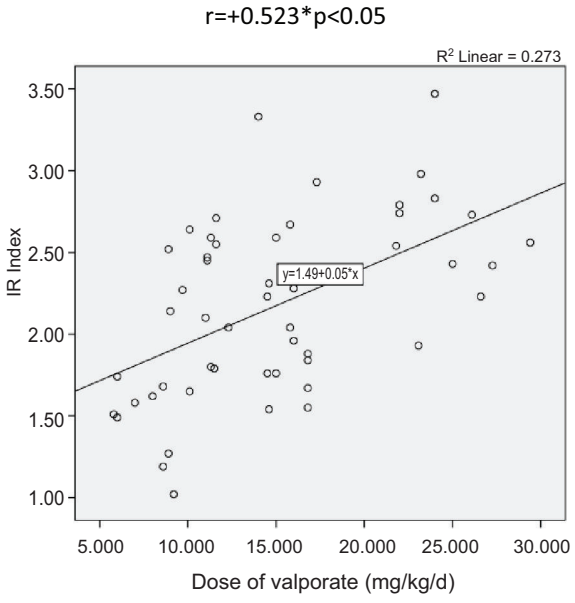

Fig.-2: *Scattered diagram showing moderate positive correlation of IR index with dose of sodium valproate. In this diagram r = +0.523 and p = < 0 .05 which indicates moderately positive. This test was done by Pearson's correlation coefficient test*

Table-III

Comparison of IR index (> 2.6) between valproate group and control group (n=102)

IR index	Valproate group (n=51) No. (%)	Non-Valproate group (n=51) No. (%)	P value
> 2.6	18(35.3)	4(7.8)	<0.05*
<2.6	33(64.7)	47(92.2)	
Total	51(100)	51(100)	

Data were analyzed using Chi-square-test and were presented as frequency and percentage, *significant

35.3% patients in valproate group and 7.8% patients in non-valproate group had IR index > 2.6 which was significantly higher in valproate group.

Discussion:

This cross sectional study was carried out to see the association of insulin resistance in sodium valproate therapy among epileptic patients. In this study it was observed that majority patients were in 19-30 years range. The mean age of patients taking sodium valproate was found to be 23.6 ± 7.01 years. These findings are compatible with studies[20, 21].

In this current study it was observed that male were predominant among the epilepsy patients which was 62.7% of the study population. This male predominance was also observed in studies[20,22]. In this study the mean sodium valproate dose was 1133±440.5 mg/day and mean duration of treatment was 3.12±1.26 years. This present study's dose was compatible to study[6]. In this study the mean BMI of valproate treated patients was 23.4±1.22 kg/m^2 and mean BMI of control group was 22.63± 1.59 kg/m^2. The difference between the two groups was not significant.

In this study IR index, fasting insulin and fasting blood glucose all were significantly higher in valproate group than non-valproate group. Several study shows significantly higher IR index and insulin level in valproate treated patients[6,16].Pylvanen et al.[6] reported hyper insulinemia and higher insulin resistance index both in both obese and non obese patients with equal BMI. Keskin et al.[23] conducted a study with 111 participants (80 epileptic, 31

healthy volunteers) and found that valproate treated patients had higher insulin resistance index than volunteer group with same BMI. The present study showed moderate positive correlation with dose of sodium valproate with fasting insulin level and IR index. Moderate positive correlation of IR index was also seen with duration of treatment. This study is compatible with study[24].

Several study reported valproate induced weight gain [,25,26,27] The causes of increased body weight may be due to valproate induced raised proinsulin and insulin secretion, increased appetite for carbohydrate, reduction of beta oxidation of leptin level due to carnitine deficiency and restricted energy expenditure.[28] In the present study we could not give comment about weight gain because we had no previous records of weight during starting of treatment. There were debate in case of valproate induced weight gain either insulin resistance induced obesity or obesity induced insulin resistance responsible but Pylvanen[6] asserted that obesity was not the cause it was insulin resistance.

Although there was no clean cut reference cut off value in this country for insulin resistance Bhowmik et al.[29] set a cut off value of 2.6 for non-diabetic Bangladeshi population. The present study showed the mean IR index in valproate and non-valproate group were 2.17 and 1.46 respectively. Considering the cut off value of 2.6, in this present study 35.3% patient had IR index> 2.6 in valproate group and 7.8% patient had IR index> 2.6 in control group. The differences between these two groups were significant. It revealed that valproate treated patient were more insulin resistant than non-valproate group.

The optimal method of insulin resistance measurement is hyperinsulinemic-euglycemic clump test. It is costly and time consuming. HOMA-IR calculation is easy to apply and correlates highly with the hyperinsulinemic-euglycemic clump test. That is why HOMA-IR is applied in this study[16].

Limitation

This study was a cross sectional study, the results of this study would have been more reliable if it was a longitudinal study. The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not be reflect the exact picture of the country.

Conclusion:

This study revealed that patients with long term sodium valproate therapy had significantly higher IR index than non-valproate group and there was moderate positive correlation of insulin resistance with dose and duration of valproate treatment. So those patients who are taking sodium valproate both in high dose and long duration are more prone to develop insulin resistance.

Recommendation:

Patients taking sodium valproate for long duration should be warned about the possible weight gain. Adequate dietary advice and exercise advice can be given. Those patients who are taking sodium valproate of long duration and higher dose may be followed up with IR index. Further studies can be undertaken by large number of patients and adequate time.

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