e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(2); 1123-1131

Original Research Article

Assessment of Prevalence of Metabolic Syndrome among Patients with Epilepsy on Antiepileptic Drugs: An Observational Study

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Received: 20-12-2022 / Revised: 15-01-2023 / Accepted: 03-02-2023

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to evaluate the prevalence of metabolic syndrome among patients with epilepsy.

Methods: This was a cross-sectional descriptive study conducted at Paras HMRI Hospital, Patna, Bihar, India. The participants were chosen from patients who attended an epilepsy outpatient hospital for 12 months. A total of 200 patients who met the study's inclusion and exclusion criteria were chosen at random.

Results: There were 135 males and 70 females among the subjects. Adults between the ages of 20 and 49 were chosen to represent those with the lowest age-related risk of coronary artery disease and metabolic syndrome. Monotherapy was used by 100 patients (50%). Valproate was the most commonly used monotherapy medication, accounting for 40% of cases. Carbamazepine (25 percent) and phenytoin (18%) were also used as single drugs to control epilepsy in a significant number of patients. Treatment lasted an average of 13.6 years (range 3–48 years).Within one year of onset, 140 patients (70%) began treatment. There was no significant link between the duration of epilepsy and the presence of metabolic syndrome. There was no link between the length of treatment and the number of drugs used and the presence of metabolic syndrome. There was no link found between drug use and cardiovascular risk factors such as diabetes, hypertension, or dyslipidemia.

Conclusion: Antiepileptic medications, especially valproate and carbamazepine have significant effects on the lipid profile and abdominal obesity in patients on treatment. Metabolic syndrome is more prevalent among adult patients <50 years of age with epilepsy compared to the general population in the same age group. This difference could be related to the effect of the antiepileptic medications, especially valproate. There is a need to monitor patients on antiepileptic medications regularly for development of dyslipidemia and obesity.

Keywords: Dyslipidemia, Valproate, Carbamazepine, Metabolic Syndrome.

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Introduction

Epilepsy is characterized by recurrent seizures and is considered to be one of the most common neurological diseases, with significant social and economic impact, being the second most common neurological disorder in the world. [1-3] It is estimated that > 50 million individuals worldwide are affected, with 80% of the burden of epilepsy attributed to the

developing world. [4] The prevalence of epilepsy ranges from 5 to 10 cases per 1,000 inhabitants, and its incidence peaks in the first and seventh decades of one's life. Furthermore, its cumulative annual incidence is estimated to be 67.77 per 100,000 persons. [3,5]

In addition to deaths directly related to epilepsy, such as sudden death, trauma, status epilepticus, and aspiration pneumonia, as well as deaths related to the underlying causes of the seizures, increased mortality has been reported from seemingly unrelated causes such as heart disease and non-cerebral neoplasias. [6] Patients with a history of epilepsy hospitalisation had a worse prognosis when it came to myocardial infarction, according to the researchers. They have proposed a number of explanations for their findings, including the presence of a common underlying pathology for both, such as silent cerebrovascular disease, as well as the presence of common risk factors, such as smoking and alcohol abuse. A negative metabolic profile caused by some commonly used antiepileptic drugs, as well as direct seizure-related myocardial ischemia, were also considered as possible explanations. There are also conflicting reports claiming that epilepsy patients have a lower cardiovascular risk because antiepileptic drugs like carbamazepine raise HDL cholesterol levels in the blood.

Central obesity is an excess accumulation of fat in the abdominal area, particularly due to excess visceral fat. Since visceral fat is supplied by the portal blood system, excess fat in this area can lead to the release of fatty deposits into the bloodstream, causing health-related problems. Central obesity was defined according to the WHO criteria [8] : WC ≥ 94 cm for men and ≥ 80 cm for women or waist-to-hip ratio (WHR) ≥ 0.90 in men and ≥ 0.85 in women and a WHTR of > 0.50. [9] The mortality and morbidity due to sudden cardiac death, myocardial infarction, and angina pectoris were found to be significantly higher in epilepsy patients, especially in symptomatic epilepsy and patients younger than 65 years old, in another study by Anneger's et al. [7] Although some studies have looked into epilepsy mortality due to coronary artery disease, there are few that have looked into epilepsy as a potential risk factor for metabolic syndrome and coronary artery disease. There were no Indian studies on the link between epilepsy and vascular risk factors that could be found. Despite the fact that numerous previous studies have documented the higher risk, susceptibility of the Indian population to metabolic syndrome and coronary artery disease. [10]

The aim of the present study was to investigate the prevalence of metabolic syndrome in epilepsy patients.

Materials and Methods

This was a cross-sectional descriptive study conducted at Paras HMRI Hospital, Patna, Bihar, India. The participants were chosen from patients who attended an epilepsy outpatient hospital for 12 months. A total of 200 patients who met the study's inclusion and exclusion criteria were chosen at random.

Patients who attended the Epilepsy Clinic on a weekly basis were screened for study eligibility. The procedure was explained to those willing to give informed consent and meet the inclusion and exclusion criteria, and they were recruited into the study. The participants were interviewed using a detailed questionnaire to collect demographic information, epilepsy characteristics, and metabolic risk factors. They were given fasting blood samples to determine their fasting blood glucose and lipid profile.

Ethical considerations

The Institute Ethical Committee approved the study. All subjects who took part in the study gave their written informed consent.

The informed consent process was carried out in accordance with the Declaration of Helsinki and the ICH E6 Guideline for Good Clinical Practice.

Inclusion criteria

1. Patients with epilepsy aged 20 to 49 years who consent to participate in the study.
2. Patients who have been taking antiepileptic drugs for at least three years.

Criteria for exclusion

1. Patients with diabetes mellitus, systemic hypertension, dyslipidemia, or other co-morbidities that alter the metabolic profile significantly before the onset of epilepsy.
2. Women who are pregnant or are 6 months postpartum.
3. Patients taking medications that alter the metabolic profile, such as steroids or oral contraceptives.

The Adult Treatment Panel III defines metabolic syndrome (National Institutes of Health, 2004). [11,12] The study used 5 metabolic syndrome criteria that were modified for the Asian Indian population. [13,14]

The presence of three of the five symptoms of metabolic syndrome was defined as

1. Central obesity (defined as a waist circumference of more than 90 cm for men and 80 cm for women).
2. High triglyceride levels (>150 mg/dL or special treatment).
3. Low HDL cholesterol (40 mg/dL in men, 50 mg/dL in women, or a specific treatment for this).
4. Hypertension (systolic blood pressure > 130 or diastolic blood pressure > 85 mm Hg or treatment of previously diagnosed hypertension).
5. High fasting plasma glucose (FPG > 110 mg/dL or type 2 diabetes previously diagnosed).

The Students t-test was used to compare the means of numeric variables between groups. The Chi-square test or Fisher's Exact test were used to compare proportions. For statistical significance, P values of less than 0.05 were used. The statistical analysis was carried out using the SPSS v.20 software.

Results

Table 1: Patient details

Variables	N%
Gender	
Male	130 (65)
Female	70 (35)
Age groups	
20-29	90 (45)
30-39	50 (25)
40-49	60 (30)

There were 130 males and 70 females among the subjects. Adults between the ages of 20 and 49 were chosen to represent those with the lowest age-related risk of coronary artery disease and metabolic syndrome. Almost half of them (45 percent) were between the ages of 20 and 29. Patients aged 30–39 years old made up 25 percent of the total, while those aged 40–49 years old made up 30 percent. The subjects were 32.5 years old on average.

Table 2: Distribution of patients based on monotherapy drug

Drugs	N	% of monotherapy	% of total
Valproate	40	40	20
Carbamazepine	25	25	12.5
Phenytoin	18	18	9
Others	17	17	8.5

Monotherapy was used by 100 patients (50%). Valproate was the most commonly used monotherapy medication, accounting for 40% of cases. Carbamazepine (25 percent) and phenytoin (18%) were also used as single drugs to control epilepsy in a significant number of patients.

Table 3: Duration of epilepsy, Number of drugs and metabolic syndrome

	Duration	Metabolic Syndrome		
		Yes	No	
Type of epilepsy	<5yrs	8	10	15
	5 - 9yrs	20	30	50
	10 - 14yrs	8	35	40
	15 - 19yrs	6	20	30
	>20yrs	18	45	65
P Value	0.220			
Number of drugs	Monotherapy	36	64	100
	Poly therapy	6	24	30
	Dual therapy	18	52	70
Total		60	140	200
P Value	0.212			

Treatment lasted an average of 13.6 years (range 3–48 years).Within one year of onset, 140 patients (70%) began treatment. There was no significant link between the duration of epilepsy and the presence of metabolic syndrome. There was no link between the length of treatment and the number of drugs used and the presence of metabolic syndrome. 70 patients received dual therapy (35 percent). Polytherapy was used by 30 patients (15 percent) who were taking three or more medications.

Table 4: Monotherapy Drugs and vascular risk factors

Drugs	Present	Absent	P Value
Carbamazepine n=25			
Diabetes	8	17	1.00
Hypertension	5	20	0.512
Dyslipidemia	6	19	0.630
Phenytoin n=18			
Diabetes	8	10	0.065
Hypertension	4	14	0.779
Dyslipidemia	9	9	0.250
Valproate n=40			
Diabetes	3	37	0.683
Hypertension	7	33	0.779
Dyslipidemia	24	16	0.250
Others n=17			
Diabetes	2	16	1.00
Hypertension	1	17	0.550
Dyslipidemia	6	11	0.100

There was no link found between drug use and cardiovascular risk factors such as diabetes, hypertension, or dyslipidemia.

Table 5: Monotherapy Drugs and lipid profile

Drugs	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglyceride
Carbamazepine n=25				
Yes	231.8	157.7	49.9	117.8
No	203.8	136.3	43.4	120.1
P Value	<0.001	0.001	0.001	0.841
Phenytoin n=18				
Yes	221.1	147.7	46.3	133.6
No	211.5	142.7	45.5	115.4
P Value	1.291	0.516	0.747	0.177
Valproate n=40				
Yes	192.8	127.1	40.0	127.4
No	220.9	149.7	47.7	116.4
P Value	0.143	0.001	<0.006	0.379
Others n=17				
Yes	213.45	142.13	44.76	124.76
No	213.60	144.03	45.84	118.27
P Value	0.988	0.843	0.679	0.608

Carbamazepine, phenytoin, and clobazam all showed a strong lipid profile association. The use of carbamazepine was linked to higher total cholesterol, LDL, and HDL levels. Valproate use has been linked to lower total cholesterol, LDL cholesterol, and HDL cholesterol. Clobazam use was linked to higher HDL levels.

Discussion

Epilepsy is a chronic neurological disease with two or more unprovoked seizures occurring more than 24 hours apart. It is characterized by recurrent seizures, which are brief episodes of involuntary movement as a result of excessive neural electrical discharges. [15] The epileptic population has a higher risk of non-communicable diseases (NCDs) such as CVDs, the notable culprit for the premature death of this group. [16,17] This is possibly due to the progressive emergence of atherosclerosis accelerating factors like obesity and the profound alterations of metabolic components, often called Metabolic syndrome (MS). [17] A metabolic syndrome is a group of metabolic risk factors, including glucose intolerance, dyslipidemia, hypertension and central obesity which are associated with an increased risk of type 2 diabetes mellitus (T2DM), and CVDs. [18] It is a complex condition and originates primarily from an imbalance of calorie intake as well as energy expenditure but may also be affected by the genetic makeup of an individual, the predominance of a sedentary lifestyle and other factors like dietary patterns. [19]

Males have a higher prevalence of epilepsy than females, according to population-based studies in India, both in urban and rural areas. Men have a prevalence rate of 5.88 per 1000 people, while women10 have a rate of 5.51. [20] The study population had a wide range of epilepsy treatment durations, ranging from 3 to 48 years. Monotherapy was given to 50 percent of the patients. Although carbamazepine was the most commonly used drug, valproate was the most commonly prescribed monotherapy. Other

studies found a similar percentage of patients on monotherapy. In a cohort from an Eastern Indian tertiary centre, 54 percent of patients could be kept on monotherapy. [21] In 2008, phenytoin (31 percent), levetiracetam (25 percent), and carbamazepine (8 percent) were the most commonly used monotherapies in adults in a study conducted by Wang et al [22] in the United States. The medication used depends on the type of epilepsy syndrome being treated, with valproate being preferred in primary generalised epilepsies and carbamazepine being used more frequently in localised epilepsies.

Many studies have shown that traditional anticonvulsant medications, particularly valproate, carbamazepine, and phenytoin, have significant metabolic effects. Anticonvulsants can affect liver function and make the hepatic microsomal enzyme system more active. [23,24] The altered metabolism of various substances such as drugs and lipids is linked to this enzyme induction phenomenon. A significant increase in serum levels of triglyceride, total cholesterol, HDL, and VLDL cholesterol was observed in patients receiving combination therapy of either phenytoin and phenobarbitone or phenytoin and carbamazepine or phenytoin alone in a study conducted in Delhi [25] to establish the relationship between antiepileptic drug use and serum lipid levels. Patients who received carbamazepine alone had significant increases in serum triglyceride and VLDL cholesterol levels, but no significant changes in total cholesterol or HDL cholesterol levels.

Carbamazepine was linked to higher total and HDL cholesterol levels in our study, whereas valproate therapy significantly reduced both. Both had no discernible effect on triglyceride levels. Carbamazepine raised and valproate reduced LDL cholesterol levels to statistically significant levels, indicating that changes in HDL cholesterol profile alone are not responsible for changes in serum total cholesterol. The modifications could be due to the two drugs have different effects on microsomal enzymes. The enzymes are induced by carbamazepine and inhibited by valproate. Carbamazepine stimulates cholesterase synthesis in the liver and increases bile acid formation and pool size, which increases cholesterol absorption in the intestine by facilitating micelle formation. [26] Multiple studies have linked phenytoin to higher serum cholesterol levels. Although our patients showed the same trend, the difference was not statistically significant. To establish the same, a larger study with a greater number of patients taking each antiepileptic medication may be required. Valproate therapy has been linked to an abnormal metabolic profile in the past. Valproate-treated patients had higher circulating insulin concentrations relative to body mass index, higher uric acid and triglyceride levels, and lower high-density lipoprotein cholesterol concentrations, according to Pylvalnen et al. [27]

Ciszowski et al., revealed that carbamazepine could affect different cardiovascular parameters, such as blood pressure in toxic doses 21. Carbamazepine could have an effect on cytochrome p450 and could cause a marked decrease in serum concentrations and efficacies of CYP3A and / or p-gp substrates, resulting in blood pressure changes. [28] Effect of sodium valproate on body fat mass could be explained by these mechanisms. It could dysregulate the hypothalamic system, and affect serum adipokines, hyperinsulinemia and insulin 54 resistant. [29] Effect on hypothalamic system might be explained by valproate effects on the gammaaminobutyric acid (GABA) transmission enhancement in the hypothalamic axis. [30,31] In addition, sodium valproate could increase the expression of adipokines in the brain and pituitary (cephalokines), which regulates

resistin and angiopoietin-like protein 4 (ANGPTL4) that might have a role in obesity and insulin resistance. [32,33]

Conclusion

The patient's gender or epilepsy characteristics had no effect on metabolic syndrome or vascular risk factors. Antiepileptic drugs, particularly valproate and carbamazepine, have a significant impact on lipid profiles and abdominal obesity in patients taking them. Metabolic syndrome is more common in adult epilepsy patients under the age of 50 than in the general population of the same age group. This disparity could be due to the antiepileptic medications' effects, particularly valproate. To figure out the exact mechanism, more large-scale research may be required. The study emphasises the importance of routinely monitoring antiepileptic medication patients for the development of dyslipidemia and obesity.

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