ORIGINAL RESEARCH

A prospective observational study of the metabolic syndrome in antiepileptic drug-treated epileptic patients

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Received: 08Dec, 2023 Accepted: 22Jan, 2024

ABSTRACT

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

Methods: This was a prospective study conducted and the participants were chosen from patients who attended an epilepsy outpatient clinic for 10 months. A total of 100 patients who met the study's inclusion and exclusion criteria were chosen randomly.

Results: The subjects consisted of 64 men and 36 women. Individuals aged 20 to 49 were selected as representatives of the demographic group with the least susceptibility to coronary artery disease and metabolic syndrome associated with ageing. 46% of the individuals fell between the age range of 20 to 29. Individuals in the age range of 30-39 accounted for 24% of the overall population, whilst those in the age range of 40-49 accounted for 30%. The average age of the participants was 33.7 years. Fifty patients (50%) were treated with monotherapy. Valproate was the predominant monotherapy treatment, representing 40% of patients. A substantial proportion of individuals with epilepsy were administered carbamazepine (24%) and phenytoin (18%) as monotherapy for seizure management. There was no discernible correlation between the length of time a person had epilepsy and the occurrence of metabolic syndrome. There was no correlation seen between the duration of therapy and the quantity of medications administered, as well as the occurrence of metabolic syndrome. A total of 40 patients were administered dual treatment. Ten individuals used polytherapy, which included the concurrent use of three or more drugs.

Conclusion: Antiepileptic medicines, particularly valproate and carbamazepine, have notable impacts on the lipid profile and abdominal obesity in individuals undergoing therapy.

Key words: Dyslipidemia, valproate, carbamazepine, metabolic syndrome

INTRODUCTION

Epilepsy is a common neurological disorder that is not caused by infection and affects both adults and children, leading to considerable impairment and death.[1] Children with a high prevalence of epilepsy may have metabolic difficulties at a young age due to the need of long-term antiepileptic therapy. Multiple studies have proven the impact of AEDs on various lipid markers, including total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and apolipoprotein levels. However, most of these studies have focused on adults, with little research conducted on children.[2] Disruption of lipid profile and other metabolic irregularities may result in the development of metabolic syndrome in children. Childhood start of Paediatric Metabolic Syndrome (PMS) might result in the premature development of diabetes mellitus and cardiovascular problems throughout adulthood.[3] Metabolic syndrome adversely affects mental health and cognitive function in children and adolescents.[4]

Although several treatment techniques have been developed and implemented, the incidence of metabolic syndrome remains high in most high-income countries[5], with notable differences across nations.[6] Primary research have confirmed this discovery by showing that the occurrence in the overall population varies from 0.4% to 24%, and in the population of obese individuals it ranges from 6% to 55.8%.[7-10] Furthermore, there is a lack of universally accepted protocols or benchmarks for

diagnosing metabolic syndrome in children, leading to considerable disparity in the diagnostic approaches documented in the literature reveal metabolic adverse effects associated with first-generation anticonvulsants in paediatric patients.[11-13]

Currently, while the utilisation of second-generation anticonvulsants is on the rise owing to their improved pharmacological characteristics, the metabolic side effects of these medications in children remain uninvestigated. As doctors are administering combination therapy using medications from different generations to address resistance to single-agent treatment, the negative effects of these drug combinations have not yet been described.

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

MATERIALS AND METHODS

This research was a cross-sectional descriptive study that specifically targeted individuals who visited an epilepsy outpatient hospital during a period of 10 months. One hundred patients who satisfied the study's criteria for inclusion and exclusion were randomly selected.

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 6 months postpartum.
3. Patients taking medications that alter the metabolic profile, such as steroids or oral contraceptives.

METHODOLOGY

Patients who visited the Epilepsy Clinic every week underwent a screening process to determine their eligibility for the research. The protocol was elucidated to those who expressed their willingness to provide informed permission and fulfilled the specified criteria for inclusion and exclusion. Subsequently, they were enrolled as participants in the research. The individuals had interviews using an elaborate questionnaire to gather demographic data, epilepsy characteristics, and metabolic risk factors. The participants were provided with fasting blood samples in order to assess their fasting blood glucose and lipid profile.

The definition of metabolic syndrome is provided by the Adult Treatment Panel III, as stated by the National Institutes of Health in 2004.[14,15] The research included 5 metabolic syndrome criteria that were adapted for the Asian Indian population.[16,17]

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

1. Central obesity (defined as a waist circumference of less 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).

STATISTICAL ANALYSIS

For statistical significance, P values of less than 0.05 were used. The statistical analysis was carried out using the SPSS v.22 software.

RESULTS

Table 1: Patient details

Variables	N%
Gender	
Male	64 (64)
Female	36 (36)
Age groups	
20-29	46 (46)
30-39	24 (24)
40-49	30 (30)

The subjects consisted of 64 men and 36 girls. Individuals aged 20 to 49 were selected as representatives of the demographic group with the least susceptibility to coronary artery disease and metabolic syndrome associated with ageing. 46% were between the age range of 20 to 29. Individuals in the age range of 30-39 accounted for 24% of the overall population, whilst those in the age range of 40-49 accounted for 30%. The average age of the participants was 33.7 years.

Table 2: Distribution of patients based on monotherapy drug

Drugs	N	% of monotherapy	% of total
Valproate	20	40	20
Carbamazepine	12	24	12
Phenytoin	9	18	9
Others	8	16	8

Fifty patients (50%) used monotherapy. Valproate was the predominant monotherapy treatment, representing 40% of patients. A substantial proportion of patients were administered carbamazepine (24%) and phenytoin (18%) as monotherapy for the management of epilepsy.

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

	Duration	Metabolic Syndrome		
		Yes	No	
Type of epilepsy	<5yrs	4	5	9
	5 - 9yrs	10	15	25
	10 - 14yrs	4	17	21
	15 - 19yrs	3	10	13
	>20yrs	9	23	32
P Value	0.280			
Number of drugs	Monotherapy	18	32	50
	Poly therapy	3	7	10
	Dual therapy	9	31	40
Total		30	70	100
P Value	0.232			

There was no discernible correlation between the length of time a person had epilepsy and the occurrence of metabolic syndrome. There was no correlation seen between the duration of therapy and the number of medications administered, and the development of metabolic syndrome. A total of 40 patients were administered dual treatment. Ten individuals used polytherapy, which included the administration of three or more drugs.

Table 4: Drugs and vascular risk factors

Drugs	Present	Absent	P Value
Carbamazepine n=30			
Diabetes	2	30	1.00
Hypertension	3	25	0.512
Dyslipidemia	5	16	0.630
Clobazam n=27			
Diabetes	1	25	1.00
Hypertension	2	23	0.543
Dyslipidemia	11	15	0.160
Phenytoin n=25			
Diabetes	2	18	0.065
Hypertension	2	16	0.779
Dyslipidemia	10	8	0.250
Valproate n=20			
Diabetes	1	18	0.683
Hypertension	3	16	0.779
Dyslipidemia	12	10	0.250
Phenobarbitone n=10			
Diabetes	1	9	1.00
Hypertension	1	10	0.550
Dyslipidemia	4	7	0.100

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

Table 5: Drugs and lipid profile

Drugs	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglyceride
Carbamazepine n=30				
Yes	221.3	158.5	48.6	115.3
No	202.4	137.2	42.2	119.1
P Value	<0.021	0.011	0.001	0.731
Clobazam n=27				
Yes	220.9	148.1	48.6	116.7
No	211.7	142.0	43.0	117.5
P Value	0.123	0.217	0.012	0.737
Phenytoin n=25				
Yes	220.1	146.5	45.3	132.3
No	210.3	141.5	44.5	114.2
P Value	1.181	0.413	0.636	0.166
Valproate n=20				
Yes	191.4	128.1	41.0	127.4
No	219.5	148.6	48.4	116.4
P Value	0.121	0.011	0.026	0.245
Phenobarbitone n=10				
Yes	212.15	143.23	43.83	123.43
No	212.30	145.13	44.72	117.14
P Value	0.544	0.421	0.345	0.304

Carbamazepine, phenytoin, and clobazam all had a significant correlation with lipid profiles. Carbamazepine use was associated with elevated levels of total cholesterol, LDLand HDL. The use of valproate has been associated with a decrease in overall cholesterol levels, as well as a reduction in levels of LDL cholesterol (often known as "bad" cholesterol) and HDL cholesterol (commonly known as "good" cholesterol). The usage of clobazam was associated with elevated levels of high-density lipoprotein (HDL).

DISCUSSION

Epilepsy is a persistent neurological disorder characterized by the occurrence of two or more unprovoked seizures that are separated by more than 24 hours. It is defined by recurring seizures, which are short periods of uncontrollable movement caused by excessive brain electrical discharges.[18] Individuals with epilepsy are at an elevated risk of developing non-communicable diseases (NCDs), particularly cardiovascular diseases (CVDs), which are a significant cause of early mortality in this population.[19,20] This phenomenon may be attributed to the gradual development of variables that accelerate the progression of atherosclerosis, such as obesity and significant changes in metabolic components, often referred to as Metabolic Syndrome (MS).Twenty A metabolic syndrome refers to a cluster of metabolic risk factors, such as glucose intolerance, dyslipidemia, hypertension, and central obesity, that are linked to a higher likelihood of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs).[21] Obesity is a multifaceted disorder that largely arises from an imbalance between calorie consumption and energy expenditure. However, it may also be influenced by an individual's genetic composition, a mostly inactive lifestyle, and dietary habits.[22]

The subjects consisted of 64 men and 36 girls. Individuals aged 20 to 49 were selected as representatives of the demographic group with the least susceptibility to coronary artery disease and metabolic syndrome associated with ageing. 46% of the individuals fell between the age range of 20 to 29. The proportion of patients in the age group of 30-39 years was 24% of the total, while the age group of 40-49 years accounted for 30%. The average age of the participants was 33.7 years. Population-based research in India have shown that men have a greater incidence of epilepsy compared to females, regardless of whether they reside in urban or rural settings. The prevalence rate for males is 5.88 per 1000 individuals, whilst women have a rate of 5.51.[23] The research cohort exhibited a diverse spectrum of epilepsy treatment durations, spanning from 3 to 48 years. Monotherapy was administered to 50 percent of the patients. While carbamazepine was often used, valproate was the predominant choice for monotherapy prescriptions. Subsequent investigations revealed a comparable proportion of individuals receiving just one kind of treatment. Within a cohort originating from a tertiary hospital in Eastern India, a notable 54 percent of patients were able to be maintained on a single therapeutic regimen.[24] According to a research done by Wang *et al.*[25] in the United States, phenytoin, levetiracetam, and carbamazepine were the most frequently prescribed monotherapies for adults in 2008, accounting for 31 percent, 25 percent, and 8 percent respectively. Fifty patients (50%) received monotherapy. Valproate was the predominant monotherapy treatment, representing

40% of patients. A substantial proportion of patients were administered carbamazepine (24%) and phenytoin (18%) as monotherapy for the management of epilepsy. The choice of medicine depends on the specific epileptic condition being treated, with valproate being the preferred option for primary generalized epilepsies and carbamazepine being more often used for localized epilepsies.

There was no discernible correlation between the length of time a person had epilepsy and the occurrence of metabolic syndrome. There was no correlation seen between the duration of therapy and the quantity of medications administered, as well as the occurrence of metabolic syndrome. A total of 40 patients were administered dual treatment. Ten individuals who were taking three or more drugs used polytherapy. No correlation was seen between drug usage and cardiovascular risk factors, including diabetes, hypertension, or dyslipidemia. Multiple investigations have shown that conventional anticonvulsant drugs, including valproate, carbamazepine, and phenytoin, have significant metabolic impacts. Anticonvulsants may impact liver function and enhance the activity of the hepatic microsomal enzyme system.[26,27] This enzyme induction process is associated with the modified metabolism of several compounds, including medicines and lipids. The study conducted in Delhi[28] aimed to establish the correlation between the use of antiepileptic drugs and serum lipid levels. It observed a notable rise in the serum levels of triglyceride, total cholesterol, HDL, and VLDL cholesterol in patients who received combination therapy of phenytoin and phenobarbitone, phenytoin and carbamazepine, or phenytoin alone. Patients administered carbamazepine as a standalone treatment saw notable elevations in blood triglyceride and VLDL cholesterol levels, whereas there were no significant alterations in total cholesterol or HDL cholesterol levels.

Carbamazepine, phenytoin, and clobazam had a significant correlation with lipid profiles. Carbamazepine use was associated with elevated levels of total cholesterol, LDL, and HDL. The use of valproate has been associated with decreased levels of total cholesterol, LDL cholesterol, and HDL cholesterol. The usage of clobazam was associated with elevated levels of high-density lipoprotein (HDL). In our investigation, we found that the use of carbamazepine was associated with elevated levels of total and HDL cholesterol. Conversely, valproate medication was shown to dramatically decrease both total and HDL cholesterol levels. Neither had any noticeable impact on triglyceride levels. Carbamazepine elevated and valproate lowered LDL cholesterol levels to statistically significant levels, demonstrating that changes in HDL cholesterol profile alone are not responsible for changes in blood total cholesterol. The alterations may be attributed to the disparate impacts of the two medications on microsomal enzymes. Carbamazepine induces the enzymes, whereas valproate inhibits them. Carbamazepine enhances the production of cholesterase in the liver, leading to an increase in the creation and size of bile acids. This, in turn, promotes the absorption of cholesterol in the gut by increasing the development of micelles.[29] Various investigations have shown a correlation between phenytoin and elevated levels of cholesterol in the bloodstream. While our patients exhibited a similar pattern, the disparity did not reach statistical significance. In order to confirm this, a more extensive investigation including a bigger sample size of individuals using each antiepileptic drug may be necessary. Prior research has shown a connection between valproate medication and an atypical metabolic profile. According to Pylvalnen *et al.*, individuals who were treated with valproate had elevated levels of insulin in their bloodstream in relation to their body mass index. They also had greater levels of uric acid and triglycerides, and lower concentrations of high-density lipoprotein cholesterol.[30]

CONCLUSION

Neither the patient's gender nor their epilepsy features had any influence on metabolic syndrome or vascular risk factors. Antiepileptic medicines, including valproate and carbamazepine, have a substantial influence on lipid profiles and abdominal obesity in people who use them. Metabolic syndrome has a higher prevalence among adult epilepsy patients compared to the general population within the same age bracket. The difference in outcomes may be attributed to the impact of antiepileptic medicines, including valproate. In order to determine the precise process, more extensive study may be necessary.

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