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Original Article

Pharmacology Section

Metabolic Derangements with Anticonvulsants in Children with Generalised Tonic-clonic Epilepsy: A Cross-sectional Study

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ABSTRACT

Introduction: Epilepsy is one of the most prevalent non-communicable neurologic conditions, accounting for significant disability and mortality. The effects of Antiepileptic Drugs (AEDs) on total cholesterol, triglycerides, High-Density Lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and apolipoprotein levels have been demonstrated in many studies, mainly conducted with adults. However, there have been very few studies in children. Derangement of lipid profile and other metabolic abnormalities could lead to the development of metabolic syndrome in children. The adverse metabolic effects of anti-epileptics are underestimated, as only a few studies have been done in this area, which is a legitimate concern.

Aim: To assess the impact of AEDs on metabolic parameters in children with epilepsy.

Materials and Methods: This was a descriptive, cross-sectional study conducted in the Department of Paediatrics and Pharmacology at Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India. The study included 100 children with epilepsy from May 2022 to October 2022. A predefined case record form, including demographic and clinical characteristics, was filled for each participant. The parameters recorded were age, gender, outpatient number, type of epilepsy, history of duration of epilepsy, current AED history, and seizure frequency over the preceding six months, as per the case record form. Guidelines from the International Diabetes Federation were used for diagnosing metabolic syndrome in children. The data was entered into Microsoft excel and presented using descriptive statistics. The chi-square test was used to differentiate between categorical variables.

Results: The mean age of the study participants was 10.2±2.97 years. There were more males (62%) than females (38%). A 48% of the patients received monotherapy, while 52% received polytherapy. A total of 24% of the patients had derangement in lipid profile (increased triglycerides and decreased HDL), with 14% of patients on monotherapy and 10% on polytherapy. The difference in metabolic derangements between monotherapy and polytherapy was not statistically significant (p=0.25). Out of 100 participants, 3% fulfilled the criteria for metabolic syndrome, with a predominance in males.

Conclusion: Metabolic derangements are known with 1st generation AEDs, but 2nd generation AEDs can also lead to significant metabolic abnormalities.

Keywords: Child, Combination drug therapy, Metabolic syndrome

INTRODUCTION

Epilepsy is one of the most prevalent non-communicable neurological conditions, accounting for significant disability and mortality in adults as well as children [1]. The high incidence of epilepsy in children, coupled with the need for long-term antiepileptic treatment, could lead to the development of metabolic complications at an early age. The effect of AEDs on total cholesterol, triglycerides, HDL cholesterol, low-density lipoprotein cholesterol, and apolipoprotein levels has been demonstrated in many studies, mainly performed with adults, but very few in children [2]. Derangement of lipid profile and other metabolic abnormalities could lead to the development of metabolic syndrome in children. Paediatric Metabolic Syndrome (PMS) in childhood can lead to the early onset of diabetes mellitus and cardiovascular diseases in adulthood [3]. Metabolic syndrome also has a negative impact on mental health and overall cognitive performance in children and adolescents [4].

Despite the development and implementation of multiple treatment strategies, the prevalence of metabolic syndrome remained high in the majority of high-income countries [5], with significant variations across countries [6]. Primary studies supported this finding by demonstrating that the prevalence in the general population ranges from [7] (0.4%) to [8] (24%), and in the obese population ranges from [9] (6%) to [10] (55.8%). Moreover, there are no standard guidelines or criteria for metabolic syndrome, with significant variation in the diagnostic methods in children [11]. Various studies [12,13] found in the literature show metabolic side effects with first-generation anticonvulsants in children. Now-a-days, with the increasing use of second-generation anticonvulsants due to their better pharmacological profile, the metabolic adverse effect profile with these drugs in children is still unexplored. Since clinicians are following treatment with combination therapy of both generation drugs due to resistance with a single agent, their combination side effects are still not documented. The present study is being undertaken to assess the impact of AEDs on metabolic parameters in children with epilepsy. The objective of the study was to compare the effect of monotherapy and polytherapy in children with epilepsy.

MATERIALS AND METHODS

This was a descriptive and cross-sectional study conducted in the Department of Paediatrics and Pharmacology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India, on 100 children with epilepsy between May 2022 and October 2022. Written informed consent was obtained from the parents before enrollment, and assent was obtained from children above seven years of age. Approval was obtained from the Institutional Ethics Committee (IEC/19/71) before the study commenced.

A total of 130 patients between 5 and 18 years of age with a history of epilepsy, presenting at the paediatric outpatient clinic, were screened using a simple random sampling technique.

Sample size calculation: was done using the formula:

$$N=4pq/d^2$$

N=sample size, p=prevalence, q=1-p, d=precision

A sample size of 104 patients was required to achieve 5% precision at a 95% confidence level, assuming a prevalence rate of metabolic syndrome with AEDs to be 7% [14].

Inclusion criteria: The study included children between the ages of 5-18 years, of either gender, diagnosed with generalised epilepsy and who had been stable on anti-convulsants (monotherapy or combination) for at least three months were included in the study after their parents provided written informed consent.

Exclusion criteria: Those with psychogenic/Non-Epileptic Seizures (NES), a history of focal brain pathology/lesions, co-existing diabetes mellitus, dyslipidemia already on lipid-lowering agents, taking medications known to interfere with body weight status (such as antidepressants, corticosteroids, etc.,), co-morbid neurodevelopmental conditions (mental retardation, developmental delay, cerebral palsy, autism, attention deficit hyperactivity disorder), and chronic medical conditions (asthma, hypertension, chronic renal failure, chronic lung disease, thalassaemia, hypothyroidism, etc.,) were excluded from the study.

Procedure

A pre-defined case record form was used for each participant, which included demographic and clinical characteristics. The recorded parameters were age, gender, outpatient number, type of epilepsy, history and duration of epilepsy, current Anti Epilepsy Drugs (AED) history, and seizure frequency over the preceding six months.

Anthropometric data were obtained for each child. Standing height (cm) was measured to the nearest 0.1 cm with a standard calibrated stadiometer, and body weight (kg) was noted on a standard weighing scale to the nearest 0.1 kg, with children dressed in minimal clothing. Waist circumference was measured using a constant tension flexible tape at the midpoint between the lower part of the lowest rib and the highest point of the hip on the mid-axillary line [15]. Blood pressure was measured twice using a sphygmomanometer and stethoscope, and the lower reading was utilised for analysis. Fasting blood sugar, total cholesterol, High Density Lipoprotein (HDL), and triglyceride levels were recorded from laboratory data.

In the present study, guidelines from the International Diabetes Federation were used for diagnosing metabolic syndrome in children [Table/Fig-1] [3]. According to these guidelines, paediatric metabolic syndrome is defined as the presence of any two of the following parameters along with abdominal obesity.

Parameter	Levels
Central obesity	>90th percentile or adult cut-offs
Triglycerides	≥150 mg/dL
HDL cholesterol	<40 mg/dL
Blood pressure	Systolic BP ≥130 or diastolic BP ≥85 mmHg
Fasting blood glucose	≥100 mg/dL

[Table/Fig-1]: Metabolic syndrome in children (International Diabetes Federation).

STATISTICAL ANALYSIS

The data was tabulated in a Microsoft excel sheet and analysed using SPSS version 23.0 software. The results of the descriptive analysis will be presented as proportions (percentages) with 95% confidence intervals. The Chi-square (χ^2) test will be used to analyse differences between categorical variables. A p-value <0.05 will be considered statistically significant.

RESULTS

A total of 100 patients were analysed for the study. Out of these, four patients were lost to follow-up due to the COVID-19 pandemic outbreak. The mean age of the study participants was 10.2±2.97 years. Males constituted the majority (62%) while females accounted for 38%. The mean duration of treatment in years was 2.75±2.07.

To facilitate assessment, the patients were categorised based on the AEDs prescribed by the clinician. They were divided into two groups: the monotherapy group (receiving only one AED) and the polytherapy group (receiving a combination of two or more AEDs). The monotherapy group was further subcategorised into first-generation AEDs {Valproate (VPA), Phenytoin (PHT), Carbamazepine (CBZ), Ethosuximide (ESM)} and second-generation AEDs {Levetiracetam (LEV) and Oxcarbazepine (OXC)}.

Similarly, the polytherapy group was further divided into combinations of only first-generation AEDs, combinations of first and second-generation AEDs, combinations of first and third-generation AEDs, combinations of second and third-generation AEDs, and combinations of first, second, and third-generation AEDs. Out of the total patients, 48 received monotherapy, while 52 received polytherapy [Table/Fig-2]. The distribution of prescribed drugs in the study population is shown in [Table/Fig-2].

Drug therapy	Generation	Drug prescribed	No of patients (N=100) n (%)
Monotherapy (n=48)	1st generation	VPA	20 (20)
		PHT	8 (8)
		CBZ	3 (3)
		ESM	1 (1)
	2nd generation	LEV	11 (11)
		OXC	5 (5)
Polytherapy (n=52)	1st G	VPA+PHT CBZ+VPA	7 (7)
	1st+2nd G	VPA+LEV	5 (5)
	1st+3rd G	VPA+CLB VPA+PHT+CLB	15 (15)
	2nd+3rd G	LEV+CLB	8 (8)
	1st+2nd+3rd G	VPA+LEV+CLB	17 (17)

[Table/Fig-2]: AEDs prescribed in study population.
N: Total no of participants; n: Number of patients taking the drug; VPA: Valproate; PHT: Phenytoin; CBZ: Carbamazepine; ESM: Ethosuximide; LEV: Levetiracetam: OXC: Oxcarbazepine; CLB: Clobazam

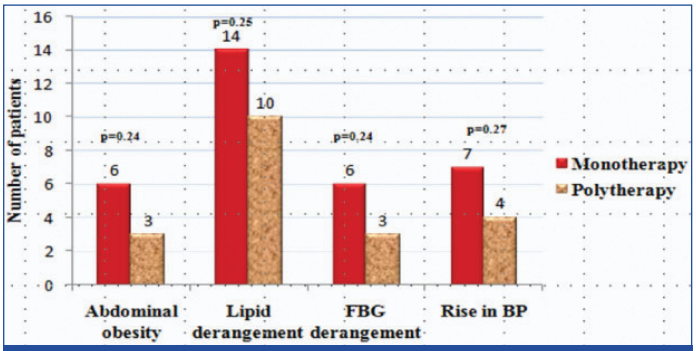
The study included 33 participants (33%) who had alterations in any of the metabolic parameters while taking long-term monotherapy or polytherapy with AEDs. Among those on monotherapy, abdominal obesity was observed in six patients (6%), out of which four patients (4%) had abdominal obesity while taking the first-generation drug, VPA. Additionally, three patients (3%) were on triple therapy with VPA+LEV+CLB (p-value- 0.24). A total of 24 patients (24%) showed derangement in their lipid profiles, characterised by increased triglyceride levels and decreased HDL.

Out of these, 14 patients (14%) were on monotherapy, while 10 patients (10%) were on polytherapy (p-value-0.25). The maximum lipid derangement was observed in patients taking VPA (7%) and triple therapy with VPA+LEV+CLB (5%). An increase in Fasting Blood Glucose (FBG) was more common in patients on monotherapy compared to polytherapy. Specifically, six patients (6%) on monotherapy and three patients (3%) on polytherapy experienced derangement in FBG (p-value- 0.24). Among those on monotherapy, the highest increase in FBG was seen in patients taking valproate (4%). Raised blood pressure was observed in seven patients (7%) on monotherapy and four patients (4%) on polytherapy (p-value- 0.27). However, the difference in metabolic derangements between monotherapy and polytherapy was not statistically significant [Table/Fig-3,4].

Out of 100 participants, three fulfilled the criteria for metabolic syndrome. One participant was on monotherapy with Valproate, another was on levetiracetam, and the third one was on polytherapy with valproate+ levetiracetam + clobazam. All patients had abdominal obesity above the 90th percentile, as per guidelines from IDF.

Drug therapy	Drug prescribed	Abdominal obesity n (%)	Lipid derangement n (%)	FBG derangement n (%)	Rise in BP n (%)
Monotherapy	VPA	4 (4)	7 (7)	4 (4)	3 (3)
	PHT	1 (1)	2 (2)	0	0
	CBZ	0	1 (1)	0	1 (1)
	ESM	0	0	0	0
	LEV	1 (1)	4 (4)	1 (1)	2 (2)
	OXC	0	0	1 (1)	1 (1)
Polytherapy	VPA+PHT CBZ+VPA	0	2 (2)	0	1 (1)
	VPA+LEV	0	1 (1)	0	0
	VPA+CLB VPA+PHT+CLB	0 0	2 (2) 0	1 (1) 1 (1)	2 (2) 0
	LEV+CLB	1 (1)	0	0	1 (1)
	VPA+LEV+CLB	2 (2)	5 (5)	1 (1)	0
Total		9	24	9	11

[Table/Fig-3]: Metabolic derangement in study population.
N: Total no of participants; n: Number of patients taking the drug; VPA: Valproate; PHT: Phenytoin; CBZ: Carbamazepine; ESM: Ethosuximide; LEV: Levetiracetam; OXC: Oxcarbazepine; CLB: Clobazam; monotherapy (n=48), Polytherapy (n=52); Total number of participants- N=100



[Table/Fig-4]: Association between the drug therapy and metabolic derangement in the study populations.

Additionally, the patient on levetiracetam had been on the therapy for the past one and a half years and experienced derangements in HDL, triglyceride cholesterol, and blood pressure. The patients on valproate and triple therapy showed derangements in FBS, TGs, HDL cholesterol, along with abdominal obesity. Both patients had been under treatment for six months [Table/Fig-5].

S. No.	Drug therapy	TG (mg/dL)	HDL (mg/dL)	FBS (mg/dL)	Blood pressure (mmHg)	Abdominal obesity (cm)
1.	Valproate+clobazam +levetiracetam	180	34	102	140/88	105
2.	Valproate	210	38	108	138/84	116
3.	Levetiracetam	355	45	92	146/94	110

[Table/Fig-5]: Metabolic parameters of patients diagnosed with metabolic syndrome.
TG: Triglycerides; HDL: High density lipoprotein; FBS: Fasting blood sugar

DISCUSSION

Epilepsy in children is one of the most common non-communicable neurological conditions, leading to morbidity and affecting their quality of life. The need for long-term antiepileptic treatment in children can result in the development of metabolic complications at an early age. Metabolic derangements have a slow onset, insidious progression, and manifest gradually. Definitions of metabolic syndrome in adults have been published by many organisations, including the World Health Organisation (WHO) [16], NCEP III [17], International Diabetes Foundation (IDF) [18], and the National Heart, Lung, and Blood Institute (NHLBI) [19]. However, there are no consensus guidelines for diagnosing metabolic syndrome in the paediatric population. This study followed the guidelines provided by the International Diabetes Federation for diagnosing metabolic syndrome in children [3].

In this cross-sectional study, various metabolic parameters were found to be altered in 33% of children receiving long-term monotherapy as well as polytherapy with AEDs. There was a higher incidence of derangement in metabolic parameters such as FBG, lipid profile, and blood pressure with monotherapy, especially with the 1st generation AED, VPA. An increase in FBS was more common with valproate compared to polytherapy. Similarly, derangement in the lipid profile was more prevalent with valproate compared to 2nd generation drugs. However, a few patients were also found to have deranged lipid parameters with polytherapy involving a combination of 1st, 2nd, and 3rd generation AEDs. Changes in waist circumference, i.e., abdominal obesity, were also more pronounced in children who received a combination of 1st, 2nd, and 3rd generation AEDs, but the incidence was lower than in children who received monotherapy, especially valproate. The increase in blood pressure was also higher with monotherapy. A study conducted by Dhir A et al., also reported a higher incidence of deranged lipid profiles (24.6%) with valproate monotherapy [20].

In this study, significant derangement in lipid profile was observed in 24.3% of patients who received 2nd generation AED, levetiracetam, as monotherapy or in combination. Approximately, 72% of children receiving levetiracetam monotherapy showed overall derangement in one or more metabolic parameters. However, studies conducted by Nishiyama M et al., and Attilakos A et al., found no significant derangements in lipid parameters in epileptic children treated with levetiracetam monotherapy [21,22].

The definition of metabolic syndrome in children is still evolving. Only a few studies have reported metabolic syndrome in children receiving antiepileptics [14,23]. Inaloo S et al., showed that the prevalence of metabolic syndrome in children with seizure disorder taking AEDs (sodium valproate and Carbamezipine) was higher than in healthy children (7.8% vs 1.1%, p-value=0.032) [14]. Verrotti A et al., reported metabolic syndrome in 46.5% of obese older children on valproate monotherapy [24]. In this study, 3% of children were found to have metabolic syndrome with AEDs.

This cross-sectional study clearly indicates that children with epilepsy on long-term AEDs have derangements in metabolic parameters compared to their healthy peers of the same age. The study also suggests a trend regarding the adverse effects of certain drugs, especially 2nd generation AEDs, compared to other drugs. Appropriate and careful selection of AEDs, without compromising therapeutic efficacy, supplemented by lifestyle counseling for exercise and diet, along with routine monitoring, should be practiced to avoid metabolic derangements in children taking long-term AEDs.

Limitation(s)

The main limitations of this cross-sectional study include the unavailability of baseline lipid profiles and anthropometric parameters, the lack of serial measurements, and the absence of standard definitions for paediatric metabolic syndrome. This study demonstrated derangement in metabolic parameters in children on long-term AEDs. However, various studies in the literature altered metabolic parameters with 1st generation AEDs, which is also observed in the present study. Additionally, this study found derangements in various metabolic parameters with levetiracetam when given as monotherapy or in combination therapy with other drugs. Therefore, it is necessary to confirm the results of this study with better-designed cohort studies to ascertain the metabolic abnormalities and underlying mechanisms observed in children on levetiracetam.

CONCLUSION(S)

Long-term therapy with anticonvulsants in children can lead to metabolic derangements, which could increase their susceptibility to metabolic syndrome. Clinicians should actively monitor for

metabolic side effects, particularly with 2nd generation AEDs, as observed in the present study. The definition of metabolic syndrome in children needs to be properly established, and further analytical studies are required in this direction to confirm the findings of the present study.

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