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AMONG CHILDREN FROM 4 YEARS TO 14 YEARS, METABOLIC EFFECTS OF LONG-TERM ANTIEPILEPTIC DRUG THERAPY IN RURAL AREAS OF KUSHINAGAR, UTTAR PRADESH

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Abstract
Long-term antiepileptic drug (AED) therapy is known to have detrimental metabolic consequences. However, nothing is known about this among Indian youngsters. In comparison to healthy controls, this study aimed to examine the effects of long-term AEDs on children's anthropometry, glycaemic parameters, insulin resistance, lipid profile, and hepatic steatosis. This retrospective analysis was conducted at a district hospital paediatric clinic. Children aged **4 to 14 years** with epilepsy who have been on antiepileptic drugs (AEDs) for a minimum of one year were identified. This cohort was separated into monotherapy and polytherapy groups. Age- and gender-matched controls were recruited from healthy youngsters in the neighbourhood. Every case and control had a thorough physical examination and tests, including an abdominal ultrasound and tests for liver transaminases, fasting lipid profiles, fasting insulin, and fasting blood glucose. The study comprised 50 controls and 75 children receiving long-term AED treatment (40 receiving monotherapy and 35 receiving polytherapy). In comparison to controls, children on AED had noticeably greater levels of insulin resistance, fasting blood glucose, and LDL cholesterol. When compared to children on other medications, children on an oxcarbazepine regimen were shown to have a worse metabolic profile. Comparing this group of epileptic children on long-term AED treatment to matched healthy controls revealed a negative metabolic profile. In order to fully define the connection and create effective intervention methods, more extensive community-based research is required. A complete epilepsy care program should include a focus on leading a healthy lifestyle.

Keywords: Antiepileptic drugs, insulin resistance, levetiracetam, non-alcoholic fatty liver disease, oxcarbazepine, sodium valproate

INTRODUCTION

Many epileptic patients on long-term antiepileptic medication (AED) therapy have been shown to have an aberrant metabolic profile[1]. This may be due to the somewhat sedentary lifestyle that many of these individuals lead. But the AEDs' capacity to modify the Cytochrome P450 system's enzymes also appears to be a significant factor[2]. While sodium valproate (VPA) is an enzyme inhibitor, the majority of first-generation AEDs, including carbamazepine (CBZ), phenytoin sodium,

phenobarbital, and primidone, are enzyme inducers[3]. Lamotrigine, levetiracetam, and phenytoin are weight-neutral, whereas felbamate, topiramate, and zonisamide are linked to weight reduction. Traditionally, VPA, CBZ, pregabalin, vigabatrin, and gabapentin have been linked to weight increase[4]. Nevertheless, research on this topic has been inconsistent, and phenytoin has also been linked to insulin resistance and weight gain. The metabolic effects of AEDs have been found to differ by gender in several investigations. AEDs' effects on lipids have likewise been inconsistent[5]. The majority of research has demonstrated that levetiracetam and lamotrigine are lipid neutral, VPA lowers lipid levels, while phenytoin and CBZ raise lipid levels. A few studies have demonstrated that the lipid profile improves when lamotrigine or levetiracetam is substituted for phenytoin and CBZ. Levetiracetam raises LDL cholesterol nevertheless, according to some recent research[6]. It has been demonstrated that phenytoin, CBZ, and VPA raise children's lipoprotein (a) levels. Those on VPA and phenytoin showed signs of insulin resistance (IR) and hyperinsulinemia[7]. Metabolic alterations in oxidative stress and inflammatory indicators, such as matrix metalloproteinase 9, homocysteine, uric acid, and C-reactive protein, have also been seen in epileptic patients receiving long-term AEDs. Adult patients undergoing VPA, CBZ, and lamotrigine monotherapy showed signs of non-alcoholic liver disease (NAFLD), which is thought to be the hepatic manifestation of metabolic syndrome[8]. It has also been demonstrated that long-term VPA therapy causes NAFLD in obese teenagers. Additionally, epilepsy has been linked to increased cardiovascular morbidity and death[9]. All of the negative metabolic anomalies observed in epileptic patients using AEDs may predispose them to atherosclerotic cardiovascular disease, even if direct causation of atherosclerosis has not been shown[10]. Men using carbamazepine, phenytoin, and valproic acid have been shown to have increased carotid intimamedia thickness, a sign of atherosclerosis, but not those receiving lamotrigine monotherapy[11].

Only a small number of studies have shown negative metabolic alterations in children receiving long-term AED medication; the majority of the aforementioned investigations have been conducted in adults[12]. Even fewer works of Indian literature exist. Since these kids may have a lot of other urgent concerns, such as learning difficulties, behavioural abnormalities, personality changes, and hyperactivity, the metabolic adverse effects of AEDs are most frequently disregarded. Premature cardiovascular disease is more common among Southeast Asians and Indians [2,5,8,11]. With an estimated 20% incidence, obesity and metabolic syndrome are becoming epidemics among Indian youngsters. At 5.5 to 10 cases per thousand, epilepsy is also very common in India[11]. As a result, we anticipate that children with epilepsy who use AEDs for an extended period of time may suffer from metabolic side effects, which might cause serious health issues for this group. In order to compare the prevalence of metabolic syndrome components—obesity, dyslipidaemia, hypertension, insulin resistance, and non-alcoholic fatty liver disease (NAFLD)—with normal age- and sex-matched healthy children from the same community, this hospital-based retrospective database was planned to examine a cohort of children with epilepsy receiving long-term AED therapy.

MATERIALS AND METHODS

We conducted a five-year retrospective database review (from 2019-2023) of children from 4 years to 14 years of age attended the OPD or admitted in the combined district hospital with primary complication of epilepsy. The investigation was carried out at combined district hospital, Kushinagar at paediatric epilepsy clinic. The retrospective database included ambulant children with epilepsy, defined by the International League Against Epilepsy[13], who were between 4 and 14 years **old** and receiving monotherapy (one AED) or polytherapy (several AEDs) for at least a year before enrolling.

Selection of study material[14]

The retrospective database excluded children with thyroid disorders or other endocrine diseases, chronic liver, heart, or renal disease, progressive neurological or psychiatric illness, children on medications that could change blood glucose or the lipid profile, such as statins, steroids, or insulin, and children with severe neurodevelopmental disabilities. Children who had no history of epilepsy or other medical, neurodevelopmental, or psychiatric conditions were chosen from the community and

used as controls. They were matched by age, sex, and socioeconomic position. Parents of both cases and controls gave their informed permission. The institutional ethics committee gave its approval to the project.

A thorough medical history was first taken of each kid, and then they were evaluated clinically and anthropometrically (including height, weight, body mass index [BMI], and waist circumference). Following an overnight fast, blood samples were examined for liver function tests (LFT), insulin, lipid profiles, and blood glucose. A sphygmomanometer was used to measure the systolic and diastolic blood pressures using cuff sizes that were appropriate for the patient's age. A single radiologist performed an abdominal ultrasonogram (USG) on each of these patients in order to check for NAFLD. Impairment of fasting glucose (IFG) was defined as blood glucose levels over 100 mg/dl. The criteria for acceptable, borderline, and high lipids were as follows: low-density lipoprotein (LDL) cholesterol less than 110, 110-129, and more than 130 mg/dl; total cholesterol less than 170, 171-199, and more than 200 mg/dl, respectively.[15]

Table 1- Correlation between the children on AEDs vs controls and monotherapy vs polytherapy

	Cases (N75)	**Controls (N50)**	***P*-value**	**Polytherapy (N35)**	**Monotherapy (N40)**	***P*-value**
Age (years)	6.21 ± 4.4	6.54 ± 2.8 years	0.701	6.87 ± 5.50	6.54 ± 5.35	0.745
Mean duration of	4.22 ± 3.54	-	-	3.64 ± 2.14	4.85 ± 3.18	0.521
Height (cm)	136.1 ± 11.4	114.2 ± 17.2	0.521	125.5 ± 18.2	141.2± 17.1	0.345
Weight (kg)	32.1 ± 3.77	29.1. ± 2.02	0.301	34.96 ± 1.79	36.74 ± 1.72	0.514
BMI (kg/m^2)	20.6 ± 3.46	19.7 ± 3.61	0.216	21.9 ± 5.26	22.1 ± 5.43	0.287
Total cholesterol (mg/dl)	178.4 ± 33.7	156.5 ± 25.5	0.04	178.2 ± 36.7	179.6 ± 37.2	0.132
LDL (mg/dl)	112.2 ± 29.6	97.5 ± 18.6	0.006	124.6 ± 28.4	128.9 ± 29.6	0.551
HDL (mg/dl)	42.6 ± 11.6	54.9 ± 15.6	0.301	52.5 ± 19.8	56.9 ± 21.2	0.667
FBS (mg/dl)	94.9 ± 10.8	97.4 ± 13.6	0.011	86.7 ± 14.1	89.8 ± 14.7	0.546
S. Insulin (uIU/	7.6 ± 4.4	5.1 ± 1.2	0.002	7.4 ± 4.2	7.2 ± 3.8	0.487

Note BMI = body mass index, LDL = low density lipoprotein, HDL = high density lipoprotein, HOMA-IR = homeostatic model for assessment of insulin resistance. $P < 0.05$ is significant

Statistical analysis

IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA) was used for statistical analysis. Continuous variables are represented by mean and standard deviation or median with range, whereas categorical variables are represented by frequency and percentage. When comparing means, the Mann-Whitney test was used for non-normalcy and an independent sample t-test for normality. A chi-square test was employed to determine the statistical significance of fatty liver in patients and controls. Analysis of variance (ANOVA) was performed to compare the control, polytherapy, and monotherapy groups.

RESULTS

Seventy-five children were included in the study.40 children on single AEDs and 35 on multiple AEDs served as cases, and 50 healthy children from the community who were not on any AEDs served as controls. Male to female ratio was 40:35among cases and 31:19 among controls. 69% had a diagnosis of epilepsy due to an unknown cause, and the rest had postencephalitis sequelae , cerebral palsy, and febrile illness-related epilepsy syndrome. The AEDs used were Sodium Valproate in 21, Oxcarbezepine in 24, Levetiracetam in 19, Clobazam in 18, Carbamazepine in 7, Phenytoin in 6, and

Phenobarbitone in 3 children. Among the 40 children on polytherapy, 21 were on two drug.

Family history of diabetes and hypertension was present in 36 and 13 out of the 75 cases, respectively, whereas it was present only in 3 of the controls. 21 children on AEDs had a normal BMI, 11 were overweight, and 12 were obese, compared to 16 normal and 8 overweight children in controls. Nine

children on AEDs had IFG, and none had hypertension. 17 children on AEDs had high total and/or LDL cholesterol, and 11 had borderline values, whereas 17 controls had a normal lipid profile.
Comparisons of anthropometric indices, blood glucose levels, insulin levels, and lipid profile in cases and controls and between polytherapy and monotherapy groups are given in table 1. Fasting blood glucose, insulin resistance, and LDL cholesterol were significantly higher in children on AEDs compared to controls in spite of comparable anthropometric indices. Children on polytherapy had higher insulin resistance compared to monotherapy. Blood glucose and LDL cholesterol were significantly higher in monotherapy vs. controls (*P* 0.003 and 0.008), whereas insulin resistance was significantly higher in the polytherapy group vs. controls (*P* 0.004); other differences were not statistically significant. All four of them were on polytherapy, of which three were on oxcarbazepine-based regimens and one was on a valproate-based regimen. Four children were on AED therapy for almost 8 years; however, the other two had a relatively short duration of only one years.

Table 2: Comparison of groups with and with out oxcarbazepine vs vs controls

		Control	With oxcarbazepine	P value with control and oxcarbazepine	Control	Without oxcarbazepine	P value with control and oxcarbazepine
1	Height (cm)	129.1 ± 17.8	144.1 ± 17.4	0.234	129.1 ± 17.8	132.7 ± 18.6	0.301
2	Weight (kg)	29.4 ± 11.2	45.6 ± 13.7	0.011	29.4 ± 11.2	32.9 ± 11.4	0.031
3	BMI (kg/m^2)	19.8 ± 2.9	24.5 ± 3..88	0.004	19.8 ± 2.9	19.7 ± 3.6	0.018
4	T. Cholesterol (mg/dl)	169.1 ± 17.9	198.3 ± 35.7	0.003	169.1 ± 17.9	188.4 ± 31.3	0.004
5	LDL (mg/dl)	78.9 ± 11.6	119.9 ± 22.8	0.004	78.9 ± 11.6	99.8 ± 16.5	0.008
6	HDL (mg/dl)	49.7 ± 5.09	59.2 ± 18.2	0.301	49.7 ± 5.09	54.5 ± 9.1	0.354
7	FBS (mg/dl)	82.52 ± 14.9	111.4 ± 14.9	0.002	82.52 ± 14.9	93.2 ± 14.5	0.003
8	Insulin (uIU/ml)	4.34 ± 2.67	9.42 ± 4.1	0.002	4.34 ± 2.67	5.02 ± 2.06	0.004

Note- BMI = body mass index, LDL = low density lipoprotein, HDL = high density lipoprotein, HOMA-IR = homeostatic model for assessment of insulin resistance. P < 0.05 is significant

The effects of VPA, oxcarbazepine, and levetiracetam on anthropometric indices and metabolic parameters were analysed. Patients on VPA did not show any statistically significant difference in their anthropometric parameters, fasting blood glucose, fasting insulin, insulin resistance levels, total cholesterol, and HDL levels, but the VPA group had significantly lower LDL-cholesterol levels compared to the non-valparin group . Patients in the levetiracetam group did not show any statistically significant difference in any of the parameters when compared to patients in other treatment/control groups. Patients taking oxcarbazepine had a higher mean weight and BMI (*P* value = 0.004 and 0.018, respectively), higher fasting blood glucose and serum insulin (*P* = 0.003 and 0.004 respectively) compared to patients on other AEDs. Compared to controls, the patients who were on oxcarbazepine had significantly higher weight (*P* = 0.031), BMI (*P* = 0.018), fasting blood glucose (0.003), fasting insulin, insulin resistance, and LDL cholesterol (*P* = <0.001).

DISCUSSION

Children on AEDs had a poorer metabolic profile than age- and sex-matched controls, according to this study on a cohort of 72 South Indian children. Of those on AEDs, 64% are overweight or obese, and 14% have IFG. Children using AEDs had substantially greater levels of serum insulin, fasting blood glucose, LDL cholesterol, and IR than controls. The metabolic profile of oxcarbazepine was poorer than that of levetiracetam or VPA among the individual medications.

Despite having similar anthropometric profiles, children on AEDs had a negative metabolic profile when compared to controls, suggesting that weight gain and adiposity are likely not the only factors at play. Although the exact causes of the negative metabolic profile of AEDs in children with epilepsy remain unknown, they may be linked to increased hunger, leptin, ghrelin, and insulin resistance, as well as enzyme changes brought on by AEDs. Frequent seizures and neurohypothalamic changes in the underlying aetiology may also be factors in the brain's abnormal control of metabolism[16,17].
Despite the fact that VPA is traditionally thought of as the AED linked to the greatest metabolic abnormalities, this study found that children using VPA only had decreased LDL cholesterol levels and no differences in obesity, insulin resistance, blood glucose, or total cholesterol levels.

Hypothalamic dysregulation, its impact on adipocytokines, hyperinsulinemia, insulin resistance, and hereditary vulnerability are among the mechanisms linked to VPA-associated metabolic disorders[18,19]. Increased expression of leptin, resistin, and fasting-induced adipose factor has been linked to VPA treatment. VPA treatment may be linked to increased triglyceride and cholesterol levels in children and changed body composition in adults, according to earlier Indian research from North India[20].

The study's most notable conclusion is that, when compared to children taking other medications, children using oxcarbazepine had the highest incidence of obesity, insulin resistance, elevated blood glucose, and elevated total cholesterol. Oxcarbazepine is an antiepileptic medication that shares structural similarities with carbamazepine and is primarily active owing to its monohydroxy derivative metabolite. However, the main distinction is that activation of the cytochrome P450 system has no effect on its metabolism[21]. Oxcarbazepine inhibits CYP2C19 and induces CYP3A4 and CYP3A5, impeding the metabolism of other drugs like phenytoin[22]. There is contradictory research on oxcarbezepine's impact on metabolism. Oxcarbezepine therapy may result in substantial and long-lasting changes to thyroid and lipid profiles, according to some research, while other studies have found that it has no effect on weight loss, serum glucose, insulin, cortisol, leptin, NPY, galanin, and ghrelin levels, or carotid intima-media thickness in children with epilepsy [20,21,22]. It has been demonstrated that substituting oxcarbazepine for CBZ normalises Cyp 450 activity and lowers total cholesterol while raising LDL cholesterol levels. It has been demonstrated that eslicarbazepine acetate, a more recent derivative of oxcarbazepine, has a greater impact on lipid metabolism than traditional carboxamides[23].

It is evident from this study that Indian compared to their age- and sex-matched counterparts from the same community, children with epilepsy who are taking AEDs for an extended period of time have a worse metabolic profile. It also demonstrates a pattern in the negative effects of some medications relative to others. The study's strength is that, as far as we are aware, it is the only one from north India that examines the unfavourable metabolic profile of kids on long-term AEDs and compares it with typical, healthy kids. The reduced sample size and the overlap of individuals using different medications are the limitations. Therefore, more extensive community-based research is required to determine how different medication doses and combinations affect the harmful metabolic characteristics and the processes that underlie them. Till then, monitoring for metabolic complications and emphasis on following a healthy lifestyle to maintain an ideal BMI may be made part of any comprehensive epilepsy care in children.

CONCLUSIONS

Compared to age- and sex-matched healthy children, children on long-term AEDs are more likely to be obese and have higher mean fasting blood glucose levels, insulin resistance, and LDL cholesterol. Children using several AEDs had a greater prevalence of NAFLD. Oxcarbazepine-based regimens were shown to have a considerably poorer metabolic profile among the AEDs, with higher levels of total cholesterol, insulin resistance, and blood glucose.

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