Original Article

Serum Folate Levels in Children with Epilepsy Seen in a Tertiary Health Care Facility in North Central Nigeria

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Abstract

Background: Children suffering from epilepsy are maintained on antiepileptic drugs (AED) to ensure a reasonable quality of life. These drugs, however, are not without side effects. Notable among which is interference with the metabolism of folate with its attendant clinical implications such as megaloblastic anemia and bleeding diathesis. **Aim:** This study was carried out to determine the serum folate levels of children with epilepsy, compare the folate levels of these children with that of controls, the levels in subjects on different AED, and to investigate the possible effect of duration of AED use on serum folate levels. **Patients and Methods:** It was a comparative cross-sectional study involving children with epilepsy aged 2–14 years attending the paediatric neurology clinic of University of Ilorin Teaching Hospital (UITH), Ilorin. A total of 140 epileptic and 140 age-and-sex-matched nonepileptic children as controls were recruited into the study. **Results:** Mean serum folate levels in subjects of 6.3 ± 1.6 ng/mL was significantly lower than 7.5 ± 1.5 ng/mL in controls (P = 0.001). The mean serum folate level in subjects on AED was comparable with the value in AED naïve subjects. The mean serum folate level was also comparable among subjects on carbamazepine, phenobarbitone, and valproate as monotherapy. There was no correlation between the duration of AED use and the mean serum folate levels (r = −0.180; P = 0.069). **Conclusion:** The mean serum folate level in subjects was significantly lower than the value in controls; but was comparable in subjects on carbamazepine, phenobarbitone, and valproate as monotherapy. There was no correlation between the duration of AED use and mean serum folate levels

Keywords: *Antiepileptic drugs, epilepsy, serum folate*

Introduction

According to the International League Against Epilepsy (ILAE), epilepsy is a disease of the brain manifesting in the following ways: (1) At least two seizures, both unprovoked, occurring greater than 24 h apart; (2) one unprovoked seizure and a probability of more seizures similar to the general recurrence risk of individuals who have had two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome.[1] An individual seizure episode on its own is a paroxysmal involuntary brain function disturbance that may manifest as impaired consciousness, abnormal motor activity, abnormal behavior, problems of sensation, or autonomic system abnormalities.[2]

Fifty million people in the world have epilepsy.[3] The prevalence ranges between 2.2 and 58 per 1,000 among African children and 6.2 per 1,000 among Nigerian children.[3,4]

Children suffering from epilepsy are chronically maintained on antiepileptic drugs (AED) to guarantee a reasonable quality of life.[5-7] These drugs are not without side effects. The side effects have been shown to include disturbance in folate metabolism and related/unrelated

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hematologic derangements.[8,9] It has been shown that folate is among other things a cofactor for purine and thymidine synthesis.[10,11] Working in conjunction with vitamin B_{12}, it brings about methylation of homocysteine to methionine, a precursor of *S*-adenosylmethionine, which is a methyl group donor.[10,11] Deficiency of folate can thus lead to a reduction in red blood cell production, problem with chromosome stability, and disturbed deoxyribonucleic acid (DNA) methylation.[10,11] These can lead to clinical conditions like megaloblastic anemia, aplastic anemia, and teratogenesis in women of child-bearing age.[12-14]

It has, thus, been suggested that epileptics on AED receive routine supplemental folic acid to prevent the aforementioned AED side effects.[15] It has also been reported that routine supplementation with folic acid might not necessarily be beneficial.[16] There are even drawbacks to the practice of routine folic acid supplementation. Folate has epileptogenic properties and has been shown to enhance the electrical kindling model of epilepsy.[15] Another drawback is the fact that excessive folate has been linked to increased risk of developing colorectal cancer.[17,18] It has also been reported that epileptic children on AED can have serum folate levels similar to that of the general population.[19]

This work was, therefore, undertaken to investigate the serum folate levels of children with epilepsy in our environment and the relationship with the AED they are on/duration of treatment. This is important because of the need to determine if the serum folate levels of these children are indeed reduced before contemplating correction.

Materials and Methods

The study was a descriptive cross-sectional one. Subjects were children with epilepsy aged 2–14 years attending the paediatric neurology clinic of University of Ilorin Teaching Hospital (UITH), Ilorin. The age range 2–14 years was studied as the upper age limit of children seen in UITH was 14 years and the clinic had no child with epilepsy below 2 years at the time of the study. Controls were apparently healthy children aged 2–14 years attending the General Out-patient or Paediatric Out-patient clinics for routine visits or for minor ailments such as upper respiratory tract infections, functional abdominal pain. The duration of recruitment of the study participants spanned a period of 11 months—August, 2015 to July, 2016.

Sample sizes for subjects and controls were determined using the formula for estimating the minimum sample size for continuous variables.[20,21] One hundred and forty (140) epileptic children attending the paediatric neurology clinic—including those on AED and the newly diagnosed who were yet to commence AED were consecutively recruited into the study following validly obtained written informed consent from the parents/guardians and assent where applicable. Among children on AED, only those who were regular on their drug(s) were recruited. One hundred and forty (140) age-and-sex-matched controls were also recruited from the Out-patient clinics. Children receiving folic acid supplements and other multivitamins were excluded from the study. So were children with nutritional deficiencies.

Information gathered from the study participants, their guardians, and the case notes were entered into the study proformas. Anthropometric measurements were also entered into the study proformas. Blood samples were drawn for serum folate estimation. The samples were allowed to clot for at least 30 min before centrifugation for 5 min. The sera were then removed and stored at a temperature not greater than − 20℃ for analysis at the end of sample collection. Repeated freeze-thaw cycles were avoided. Serum folate was measured using the human folic acid ELISA kit manufactured by Monobind Incorporated, Lake Forest, California, 92630, USA; and marketed by NIMS Diagnostics Nigeria Limited, Suleja, Niger State, Nigeria.

Data obtained were imputed into the computer and analyzed using statistical package for social sciences (SPSS) version 20.0 for windows. Frequency distribution tables of variables were generated. Measures of central tendency and dispersion of quantitative variables were determined. Student's *t*-test was used to compare means of normally distributed continuous variables. Differences between proportions of categorical variables were evaluated using the Chi-square test. Analysis of variance (ANOVA) was used when comparing more than two sets of continuous variables. The Spearman's rank and Pearson's correlating technique was used to estimate correlation between categorical and continuous variables, respectively. The confidence level was set at 95% and level of significance at $P < 0.05$.

Ethical approval for the study was obtained from the Ethical Review Committee (ERC) of the University of Ilorin Teaching Hospital.

Written informed consent for participating in the study was signed by the parents or guardians of children who participated.

Results

Of the 140 epileptic children studied, 77 were males and 63 were females Table 1, giving a male to female

Table 1: Socio-demographic characteristics of the study population

Variables	Study Population		Total *n*=280	χ^2	*P*
	Subject *n*=140 (%)	Control *n*=140 (%)			
Age groups (years)					
2-<5	54 (38.6)	52 (37.1)	106	0.009	0.923
5-<8	23 (16.4)	24 (17.1)	47	0.000	1.000
8-<11	26 (18.6)	23 (16.4)	49	0.082	0.775
11-14	37 (26.4)	41 (29.3)	78	0.115	0.734
Sex					
Male	77 (55.0)	77 (55.0)	154	0.001	0.999
Female	63 (45.0)	63 (45.0)	126	0.001	0.999
Socio-economic class					
Upper (I & II)	91 (65)	64 (45.7)	155	4.361	0.037*
Middle (III)	29 (20.7)	28 (20.0)	57	0.000	1.000
Lower (IV &V)	20 (14.3)	48 (34.3)	68	10.721	0.001*
Age (years)					
Mean	7.2±4.1	7.3±4.2		0.787	0.888

χ^2: Chi square; *Statistically significant (i.e., P<0.05); *t*: Independent samples *t*-test

Table 2: Antiepileptic drug use by children with epilepsy

Variables	Frequency (140)	Percentage
Antiepileptic drugs use		
Yes	104	74.3
No	36	25.7
Number of antiepileptic drugs used (*n*=104)		
Single	84	80.8
Combination	20	19.2
Names of antiepileptics used* (*n*=104)		
Carbamazepine	75	72.1
Phenobarbitone	28	26.9
Sodium Valproate	20	19.2
Prednisolone	1	1.0
Duration of antiepileptic drug use (mo)		
<12	34	32.7
12-24	29	27.9
>24	41	39.4

*Multiple Response

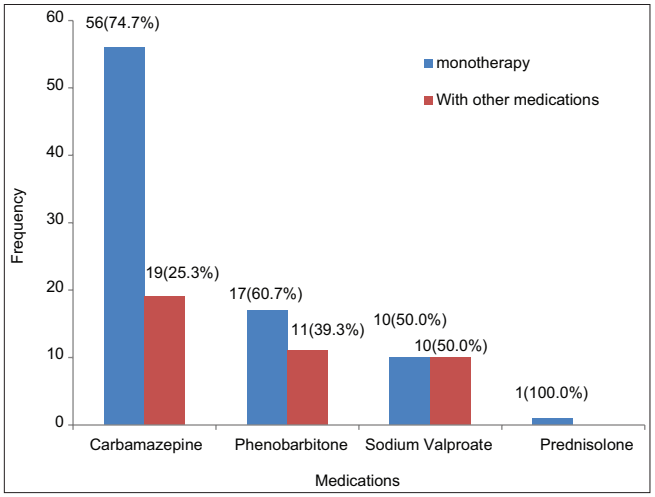

Figure 1: Pattern of AED use amongst subjects

ratio of **1.2:1**. There were also 140 nonepileptic age-and-sex-matched children who served as controls. The mean age of epileptic children was 7.2 ± 4.1 years, which is comparable with 7.3 ± 4.2 years in controls (P = 0.888). The mean weights, heights, body mass indices, weight for age z-scores, height for age z-scores, and weight for height z-scores of the subjects were also comparable with those of controls. The subjects, however, had significantly lower occipitofrontal circumference (OFC) compared with the controls.

Generalized epilepsy accounted for 87.1%, whereas focal epilepsy accounted for 12.9% of the subjects studied. One hundred and four (74.3%) subjects were regular on various AED, whereas 36 (25.7%) were newly diagnosed epileptics who were yet to be commenced on AED. Seventy (67.3%) of the AED users had been on anticonvulsants for 12 mo or more. The remaining 34 (32.7%) had been on AED for less than 12 mo before recruitment. Eighty-four (80.8%) of those on AED were on a single drug and the remaining 20 (19.2%) were on more than one drug combination. Carbamazepine, singly or in combination, was the most frequently used AED – recorded in 75 (72.1%) of the AED users [Table 2].

Fifty-six (74.7%) of the 75 subjects on carbamazepine were on the drug singly, whereas 19 (25.3%) were on carbamazepine combined with other drugs. Only one patient was on prednisolone, and it was not combined with other drugs [Figure 1].

The epileptic children had a significantly lower mean serum folate level of 6.3 ± 1.6 ng/mL compared to

Table 3: Serum folate levels of subjects and controls compared

Variable	Total *n*=280	Patient		*t*	*P*
		Subject *n*=140	Control *n*=140		
Serum Folate (ng/mL)					
Mean±SD		6.3±1.6	7.5±1.5	−6.474	0.001*

t: Independent samples *t*-test; *: Statistically significant (i.e., $P<0.05$)

Table 4: Serum folate levels of subjects and controls compared across age groups

Variable	Total, *n*	Serum Folate (ng/mL) (Mean±SD)		*t*	*P*
		Subject *n*=140	Control *n*=140		
Age group (years)					
2-<5	54	5.9±1.8	7.9±1.5	−3.133	0.002*
5-<8	23	6.9±1.5	7.1±1.3	−0.483	0.631
8-<11	26	6.7±1.5	8.0±1.7	−3.059	0.004*
11-14	37	6.2±1.5	6.8±1.6	−0.893	0.375
Sex					
Male	77	5.8±1.7	7.6±1.5	−3.488	0.001*
Female	63	6.9±1.5	7.3±1.5	−0.899	0.370

t: Independent Samples *t*-test; *$P<0.05$

Table 5: Comparison of serum folate levels of subjects based on AED use

Variable	Total *n*=140	Subjects		*t*	*P*
		AED Users (*n*=104)	Non AED Users (*n*=36)		
Serum Folate (ng/mL)					
Mean±SD		6.9±3.5	7.4±3.0	−0.703	0.483

Table 6: Comparison of serum folate levels based on different monotherapy AED

Variables	Antiepileptic Drugs			*F*	*P*
	Carbamazepine *n*=56	Phenobarbitone *n*=17	Sodium Valproate *n*=10		
Serum Folate (ng/mL)					
Mean±SD	6.2±1.6	6.0±1.7	6.0±1.9	0.133	0.875

F: One-Way Anova; Statistically significant (i.e., $P<0.05$)

Table 7: Serum folate levels correlated with duration on AED

Variables	Serum folate level (ng/mL)		*r*	*P*
	Mean±SD	*n*		
Duration on AED (months)		104	−0.180	0.069
<12	7.8±3.9			
12-24	6.6±3.3			
>24	6.2±3.9			

r: Spearman correlation coefficient

the value 7.5 ± 1.5 ng/mL reported in controls, with a *P* value of 0.001 [Table 3]. Male subjects had [Table 4] on AED, however, had comparable mean serum folate level with newly diagnosed subjects who were yet to be started on AED [Table 5].

The mean serum folate levels of subjects on the different AED as monotherapy were also comparable [Table 6].

There was no correlation between the serum folate level and the duration on AED [Table 7].

Discussion

It had been suggested that AED treatment resulted in lower serum levels of folate with its attendant clinical manifestations.[8,22,23] The AED said to be implicated include carbamazepine, phenobarbitone, gabapentin, oxcarbazepine, phenytoin, primidone, and valproate.[9,10,11,22] The AED used by epileptic children in this study included carbamazepine, phenobarbitone, and valproate among those earlier highlighted.

The mean serum folate level was significantly lower in subjects in this study compared with controls. This finding is similar to what was reported by Labadarios *et al.*,[8] Trimble *et al.*,[24] Schwaninger *et al.*,[25] Kishi *et al.*,[22] Linnebank *et al.*, and Huang *et al.* who published their works between 1978 and 2016.[10,11] A solitary work by Eldeen *et al.*[19] done among Egyptian children with epilepsy in 2012, however, reported no significant difference in the serum folate levels of these epileptic children and selected controls.

The mechanisms by which AED alter folate metabolism are still uncertain. It has been suggested that AED can alter folate metabolism by induction of liver microsomal enzymes; impairment in the absorption of folate; interaction in a competitive manner with folate coenzymes; and increased requirement for folate as a cofactor in the hydroxylation of AED.[22] In a survey of serum folate status of patients with epilepsy the mean serum folate levels were reduced significantly in patients treated with phenobarbitone and carbamazepine.[22] However, treatment with valproate and zonisamide seemed not to affect serum folate level.[22] This suggests that liver enzyme induction may be responsible for the low serum folate levels in patients treated with AED.[8,22] Phenobarbitone and carbamazepine induce hepatic microsomal enzymes, whereas valproate does not.[22] In this study, there was, however, no significant difference in the mean serum folate levels of subjects on valproate monotherapy and the drugs thought to be microsomal enzyme inducers - phenobarbitone and carbamazepine as monotherapy, though the number of subjects on valproate monotherapy was rather small. The relatively fewer number of subjects on valproate monotherapy makes it difficult for strong inferences to be drawn.

It was also observed in this study that the mean serum folate level of subjects on AED was statistically comparable with that of newly diagnosed subjects who were yet to be commenced on AED. This may have been accounted for by the fact that the common AED are readily purchased in our environment as over the counter drugs. Some of these patients with epilepsy who were recruited as AED naïve subjects might have received AED, bought over the counter without disclosing such before recruitment. Eldeen *et al.*[19] who also worked among resource poor African children also found no significant difference in the mean serum folate level of subjects on AED compared with those who were yet to be started on AED.

Though the mean serum folate level appeared to reduce as the duration on AED increased, there was no statistical correlation between these two variables. This observation differs from what was reported by Sener *et al.*,[26] who reported a negative correlation between the duration of AED use and serum folate. The fact that some patients in the present study were on more than one AED combination while the study by Sener *et al.* involved only subjects on AED monotherapy could have been responsible for this difference.

Conclusion and Recommendation

It was revealed in this work that epileptic children had lower mean serum folate levels compared with age-and-sex-matched controls. Serum folate level in subjects on AED was, however, comparable with that in AED naïve subjects. The serum folate level was also comparable among subjects on carbamazepine, phenobarbitone, and valproate as monotherapy. There was no correlation between the duration of AED use and serum folate level.

It is, therefore, recommended that only epileptic children with demonstrable low folate values receive folate supplementation. Routine administration of folic acid to epileptic children on AED may not be justified.

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Conflicts of interest

There are no conflicts of interest.

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