ASSESSMENT OF SERUM LEVEL OF FOLIC ACID AND VITAMIN B12 IN CHILDREN WITH IDIOPATHIC EPILEPSY

By

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ABSTRACT

Background: *The association between elevated levels of Vitamin B12 and folic acid and the occurrence of epileptic seizures in humans is a subject of ongoing debate. The aim of this study to evaluates the influence of blood concentrations of Vitamin B12 and folic acid on children diagnosed with idiopathic epilepsy.*

Method: *Our study was carried out on a sample of 44 youngsters diagnosed with idiopathic epilepsy, along with 11 individuals who were selected as healthy controls. The participants were recruited from Bab El Sharia University Hospital. The research was carried out from November 2022 to July 2023. All the studied were subject to comprehensive medical history, thorough physical examination, and assessing the concentrations vitamin B12 and folic acid. Then the patients' groups were supplemented with vitamin B12 (100mcg/24hour for 14 days then once weekly for 3 months) and folic acid (50mcg/day for 3 months) from November 2022 to July 2023. Lastly. Evaluation of patients' clinical condition and the measurement of vitamin B12 and folic acid levels were done.*

Results: *our study indicates that folic acid and vitamin B12 had favorable results in terms of the clinical neurological status of individuals diagnosed with idiopathic epilepsy. In comparison to the baseline measurements, the administration of vitamin B12 and folic acid supplements resulted in a substantial decrease in both the frequency of seizures per month and the severity score of seizures.*

Conclusion: *Folic acid and vitamin B12 have a positive impact on the neurological results seen in individuals with idiopathic epilepsy. The administration of Vitamin B12 and folic acid resulted in a significant decrease in monthly occurrence of seizures and the severity of seizures in individuals with idiopathic epilepsy.*

Keywords: *Homocysteine; Epilepsy; Folic acid; Vitamin B12; Anti-epileptic drugs.*

INTRODUCTION

Epilepsy is characterized by the development of sudden, involuntary contractions of skeletal muscles, resulting from disruptions in the neuronal activity of the brain **(Trinka et al., 2015)**. This particular ailment is well recognized as being very frequent among children across various age group. The epilepsy prevalence in children is estimated to range from 1% to 2% **(Knupp et al., 2012)**.

According to **Dragoumi et al. (2013)**, who suggested that most of epilepsies seen in children under the age of fifteen are classified as idiopathic, meaning that they lack a clear and identifiable cause.

Nevertheless, epilepsy may manifest as a secondary condition resulting from several factors, including febrile seizures, hereditary disorders, central nervous system infections, electrolyte imbalances, or exposure to toxic substances **(Minardi et al., 2019)**.

Empirical data suggests that a significant proportion, namely about two-thirds, of children diagnosed with both idiopathic and non-idiopathic forms of epilepsy exhibit positive long-term results. Notably, individuals with benign idiopathic childhood epilepsy have been shown to achieve a complete remission rate of 100%. According to a prior investigation, the primary determinant of the ultimate results and clinical trajectory of idiopathic epilepsy was shown to be the first reaction to anti-epileptic treatment. According to **Dragoumi et al. (2013)**, there was a good correlation between prompt treatment response and improved short-term results.

The occurrence of infantile seizures due to vitamin B12 deficiency is regarded as an infrequent and harmless cause. The presence of this insufficiency may lead to a range of symptoms including challenges with eating, megaloblastic anemia, delays in development, decreased muscle tone, inadequate growth, seizures, and perhaps even.

The aim of our study is to evaluate the influence of blood concentrations of folic acid and vitamin B12 on pediatric patients diagnosed with idiopathic epilepsy, as regard frequency and severity.

Sample size calculation:

The following equation was used to calculate the sample size for the two parallel groups included in the study; n = 2(power index) *(pooled SD/Mean difference)2. The pooled SD and mean difference were derived from previously published literature. Using the post hoc data, the equation yields a minimal sample size of 11 patients, and assuming a ratio of unexposed/exposed of 1, the minimal sample was 11 for each group for 80% power and a .05 margin of error.

Ethical Consideration:

- Approval by the ethical committee of the Pediatrics department at the Faculty of Medicine at Al-Azhar University under the registration number: 000458 was obtained before the study.
- Patients were enrolled in the study after taking informed oral and written consent from their parents.
- Patient data confidentiality was preserved during all study procedures.
- The patient and parents have the right to withdraw any time.
- There was no conflict of interest regarding the study or publication.
- There is no financial support or sponsorship.
- We ensure that the participants are not physically or psychologically harmed during the study.

Inclusion Criteria:

1. Children with idiopathic epilepsy.
2. Ages ranging from 2-18 years with both sexes.

Exclusion Criteria:

1. Neurological, endocrinal, or any systemic diseases other than epilepsy.
2. Symptomatic and cryptogenic epilepsy.
3. Nutritional status impairments (Z score ≤ -2SD).
4. Previous treatment with folic acid and Vit B12 in the last 3 months.
5. Drug-induced folate and/or Vit B12 deficiency.

PATIENTS AND METHODS

This study was conducted on 55 children recruited from Bab El Sharia University Hospital. Forty-four children were diagnosed with idiopathic epilepsy with regular follow-up at the Pediatric Neurology Clinic during the period from November 2022 to July 2023.and 11children as control group.

All the studied patients and control group was subjected to the following:

A. Full history taking with stress on developmental history, Perinatal history, social status, Family history of epilepsy, Onset, and duration of epilepsy, Frequency of seizures, Types, number, and doses of anti-epileptic drugs, and Dietetic history.

B. Complete clinical examination on chest, heart and abdomen with stress on anthropometric measurements example: body weight, height, body mass index, head circumference, and complete neurological examination.

C. Lab. evaluated of Serum vitamin B12 and folic acid assessment by Immuoasaay (ELISA and Chemiluminescence).

All the studied patients were evaluated after Supplementation of vitamin B 12 and folic acid for 3 months (for patient group only).

The included participants were divided into five subgroups (each group = 11 patients):

Group A: Children with idiopathic epileptic with folate deficiency only.

Group B: Children with idiopathic epileptic with Vit B12 deficiency only.

Group C: Children with idiopathic epilepsy with both folate and Vit B12 deficiency.

Group D: Children with idiopathic epilepsy with normal folate and Vit B12 serum level.

Control group: Healthy age and sex-matched children.

Lastly as regard patients with decreased folic acid less than 5 ng/ml and vitamin B12 less than 190 pmol/L, will be supplemented with folic acid 50 ug./day for three months and vitamin B12 100ug/day for 14 days then once weekly for two and half months.

Lastly, Frequency and severity of epileptic fits were assessed, together with serum folic acid and vitamin B12.

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student’s t test for independent samples for comparing 2 groups of normally distributed data and/or large enough samples, and one way analysis of variance (ANOVA) test with posthoc multiple 2-group comparisons when comparing more than 2 groups of normally distributed data and/or large enough samples. Kruskal Wallis test was used when comparing not-normal numerical data. For comparing categorical data, Chi-square (x2) test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS

The results of our study summarized in the following tables and figures:

Table (1): Demographic and Anthropometric Data of The Study Participants

Parameter		Group A, n=11	Group B, n=11	Group C, n=11	Group D, n=11	Control group, n=11	p-value
Gender	Male	8	6	6	6	7	0.549
	Females	3	5	5	5	4	
Age, (years)		8 (5-11)	8 (5-11)	8 (5-11)	7 (5-10)	8 (5-11)	0.173
Weight, (kg)		22 (18-25)	23 (18-26)	21 (17-28)	22 (18-26)	24 (18-27)	0.761
Height, (cm)		121 (117-124)	121 (118-123)	119 (117-125)	121 (118-125)	122 (118-125)	0.346
Head Circumference, (cm)		54 (52-55)	54 (53-55)	54 (53-55)	54 (53-55)	55 (53-55)	0.279
BMI, $(kg/m)^2$		14.5 (13-16)	15 (13-17)	14 (12-18)	15 (13-17)	16 (13-17)	0.097

This table shows insignificant difference between the studied group regarding to anthropometrics measurement p-value >0.05.

Table (1): The neurological characteristics of the included participants

Parameters		Group A	Group B	Group C	Group D	p-value
Character of epilepsy	**Generalized**	3	2	4	4	0.143
	Focal	8	9	7	7	
Age of onset		4 (1-6)	4 (1-6)	3 (2-9)	3 (2-7)	0.014
Duration of Epilepsy		4 (2-6)	4 (3-5)	4 (2-6)	4 (3-5)	0.009
Number of AED		2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	1.00
Frequency of seizures/month before treatment		2 (1-3)	2 (1-3)	2 (1-3)	1 (0-2)	0.001
seizure severity score before treatment		51 (47-54)	52 (47-55)	50 (46-57)	10 (7-43)	0.019

This table shows that:

The focal type of seizures was common among all studied groups, with the median age of onset of seizures at 4 (1-9). The baseline frequency of seizures was 2 (0-3) episodes per month with a median seizure severity score of 49 (7-57).

Table (2): Clinical characteristics after folic acid and vitamin b12 treatment courses

Parameters	All patients	Group A	Group B	Group C	p-value
Frequency of seizures/month after treatment	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1.00
seizure severity score after treatment	24 (19-30)	24 (20-27)	25 (20-28)	23 (19-30)	0.041
Level of B12 before treatment	381 (186-397)	387 (375-396)	194 (188-198)	190 (186-202)	0.243
Level of Folic acid before treatment	4 (1.4-4.4)	2 (1.5-2.4)	4 (3.3-4.3)	2 (1.4-2.7)	0.114
Level of B12 after treatment	370 (362-378)	-	370 (364-374)	366 (362-378)	0.007
Level of Folic acid after treatment	3.7 (3.2-4.5)	4 (3.3-4.2)	-	4 (3.2-4.5)	0.001

This table shows that, the seizure frequency and severity score decreased compared with the baseline values, 1 (0-2) and 24 (19-30), respectively. The levels of folic acid and vitamin b12 were elevated compared with the baseline values.

Table (3): Comparison of the frequency of seizures/month before and after folic acid and/or vitamin b12 administration

Groups	Frequency of seizures/month before treatment	Frequency of seizures/month after treatment	P- Value*
Group A	2 (1-3)	1 (0-2)	**0.002**
Group B	2 (1-3)	1 (0-2)	**0.002**
Group C	2 (1-3)	1 (0-2)	**0.004**

Groups A, B, and C showed a statistically significant decrease in the frequency of the seizures per month following the treatment of folic acid and/or vitamin B12; p= 0.002, 0.002, and 0.004 for the three groups respectively.

Table (4): Comparison of the seizure's severity score before and after folic acid and/or vitamin b12 administration (Carpay et al.,1997):

Groups	**seizure** severity **score before treatment**	seizure severity score after treatment	P- Value*
Group A	51 (47-54)	24 (20-27)	**0.001**
Group B	52 (47-55)	25 (20-28)	**0.001**
Group C	50 (46-57)	23 (19-30)	**0.001**

*= Wilcoxon signed ranks test

Similarly, these groups showed a statistically significant decrease in the seizure severity scores after the treatment course; p= 0.001.

Table (5): Compares the levels of vitamin B12 and levels of folic acid before and after treatment

Groups	Level of B12 before treatment	Level of B12 after treatment	P- Value*
Group B	194 (188-198)	370 (364-374)	**0.001**
Group C	190 (186-202)	366 (362-378)	**0.001**
Groups	**Level of Folic acid before treatment**	**Level of Folic acid after treatment**	
Group A	2 (1.5 - 2.4)	4 (3.3-4.2)	**0.003**
Group C	2 (1.4-2.7)	4 (3.2-4.5)	**0.003**

This table shows that, after treatment, the serum levels of folic acid and vitamin B12 significantly increased in patients with folic acid and vitamin b12 deficiency compared with the baseline serum levels; $p<0.05$.

DISCUSSION

It is important to evaluate the influence of folic acid and vitamin B12 on persons with epilepsy in order to better understand of their impacts on the clinical course of patients.

However, there is a scarcity of adequate research in the medical literature that investigates this specific matter in persons who have been diagnosed with idiopathic epilepsy. The research findings indicated a significant discrepancy in the levels of vitamin B12 among children diagnosed with idiopathic epilepsy compared to their peers who did not exhibit symptoms of epilepsy. However, no statistically significant difference in folic acid blood levels was seen between the group of children diagnosed with epilepsy and the group without epilepsy. Based on the research done by **Youness et al. (2022)**, no statistically significant difference was seen in the levels of folic acid between the cohort of patients with epilepsy and the control group. According to the research done by **Eldeen et al. (2012)**.

In contrast to anticipated outcomes, epileptic patients exhibited significantly higher amounts of vitamin B12 in comparison to a control group. The discrepancies reported in the findings might perhaps be ascribed to variances in the exact kind of antiepileptic medication used, as well as inequalities in the nutritional status of participants across various research. Based on the research done by **Tamura et al. (2000)**, The research done by **Eldeen et al. (2012)** revealed that the supplementation of Vitamin B has been shown to effectively reduce the levels of Hcy. This is attributed to the essential role of vitamin B12 and folate as cofactors in the remethylating process of Hcy. Moreover, the use of vitamin supplements into the treatment regimen of anti-epileptic medicine has been shown to reduce drug resistance experienced by patients and enhance the probability of achieving a cure for refractory epilepsy **(Kaiboriboon et al., 2013)**.

In recent result conducted by **Zou et al. (2022)**, it was shown that there exists a positive correlation between the reduction in seizure frequency and the alteration in serum homocysteine (Hcy) levels. This finding suggests that a drop in Hcy levels may contribute to the management of seizure frequency. According to **Zou et al. (2022)**, the use of vitamin B supplements has been shown to decrease levels of homocysteine (Hcy) and improve outcomes in individuals with seizures.

After a period of three months of therapy, a significant reduction was seen in both the occurrence rate of seizures and the duration of each episode, as compared to the initial measurements. Furthermore, it was shown that the serum concentrations of TNF-α and hs-CRP exhibited a notable reduction during a three-month period of therapy. The results of this study indicate a synergistic relationship between vitamin B12 and carbamazepine in the therapy of epilepsy. Nevertheless, the administration of carbamazepine and vitamin B12 supplementation did not result in a reduction in homocysteine levels. The observed values were notably greater in comparison to the control groups and pre-treatment levels **(Zou et al., 2022)**.

Folic acid plays a crucial role in the management of epilepsy in patients. In the case of children with diminished cerebral folate levels, the transport of folate into the brain is hindered, resulting in the manifestation of unmanageable seizures. In their study, **Deopa et al. (2019)** conducted an evaluation on the impact of folic acid supplementation on seizure management among juvenile individuals who were concurrently undergoing treatment with anti-epileptic medications. The researchers discovered that individuals who were given folic acid supplementation had a noteworthy reduction in the average occurrence of seizures following a three-month period, in contrast to the patients who did not get supplementation and did not display any meaningful alteration during the same three-month timeframe.

Furthermore, individuals who received folic acid supplementation exhibited a noteworthy decrease in the length of seizure episodes. However, this reduction was not shown to be statistically significant when compared to patients who did not receive folic acid supplementation. **Deopa et al. (2019)** observed a noteworthy enhancement in folate levels relative to the baseline, in contrast to a considerable decline in folate levels among individuals who did not get folate supplementation. Furthermore, it was observed that the average folate concentration exhibited a statistically significant increase among children who were free from seizures in comparison to those who continued to have seizures. The results of this study demonstrate a clear and direct correlation between levels of folate and the frequency of assaults.

Gibberd et al. (1981) observed a noteworthy reduction in seizure frequency among individuals who received folate supplementation, whereas those who did not get supplementation did not exhibit any substantial improvement in their seizure frequency. Nevertheless, the observed difference between the two groups did not demonstrate statistical significance. The results of this study indicate that the observed reduction in seizure frequency was not solely attributable to the administration of folic acid. The impact of folic acid was investigated by **Grant et al. (1970)** and **Ralston et al. (1970)** in a double-blind, placebo-controlled experiment with epileptic patients exhibiting low blood folate levels (< 3 ng/ml). However, no substantial change in seizure frequency was seen after up to one year of folate administration.

According to a study conducted by **Gutheil et al. (2013)**, it has been shown that juvenile patients with epilepsy have lower Z-scores for height in comparison to age-matched healthy controls. **El-Khayat et al. (2010)** similarly observed similar results in terms of height, but they could not identify a statistically significant difference in weight between individuals with epilepsy and the healthy control group. According to a study conducted by **Rättyä et al. (1999)**, there is no significant impact on the anthropometric measurements of growth in girls with epilepsy while using antiepileptic medicines. Furthermore, the study conducted by **Rogathe et al. (2014)** found no statistically significant differences in BMI between individuals with epilepsy and a control group of healthy individuals.

CONCLUSIONS

The use of folic acid and vitamin B12 has shown positive effects on the clinical neurological outcomes of individuals diagnosed with idiopathic epilepsy. The administration of vitamin B12 (100mcg/24hour for 14 days then once weekly for 3 months) and folic acid (50mcg/day for 3 months) resulted in a significant reduction in monthly occurrence of seizures and the severity of seizures in individuals with deficiencies in Vitamin B12 and/or folic acid. Furthermore, these interventions resulted in a notable elevation in the blood concentrations of Vitamin B12 and folic acid as compared to the initial values.

RECOMMENDATION

It is advisable to carry out multicenter studies with individuals diagnosed with idiopathic epilepsy in order to get robust and dependable data.

Supplementation with vitamin B12 and folic acid in children with idiopathic epilepsy will decrease severity and frequency.

LIMITATIONS

One significant constraint of our research is to the limited sample size within our community. Assessing the clinical implications of our findings is a greater challenge. Additionally, the limited sample size restricts the extent to which the findings may be applied to a larger population and accurately reflect its characteristics.

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