Relationship between blood-level folic acid deficiency and depression in patients with refractory epilepsy

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Introduction

Depression is common in patients with epilepsy, resulting in lack of response to antiepileptic drugs. Antiepileptic drugs are found to reduce folic acid level. Depression is a common symptom of folate deficiency. This study was undertaken to assess the relationship between serum folate levels and depression in patients with refractory epilepsy.

Patients and Methods

The study included 37 patients with refractory epilepsy, attending the neuropsychiatric outpatient clinic in the Suez Canal University hospital after giving written informed consent. We included adult male and female patients with age ranging from 18–40 years. Patients were subjected to clinical history, examination, serum folate level, and Hamilton Depression Rating Scale.

Results

According to the Hamilton Depression Scale, 62.2% were estimated to have mild, moderate, and severe depression. Half of the patients (48.7%) were estimated to have low levels of folic acid, with nine of them (24.3%) were having low normal values. There was significant association between severe depression and low folic acid level (<3.5). Longer duration of the disease was found to be associated with lower folic acid levels and higher depression scale score with significant difference. There was no significant association between received drugs and the severity of depression or low serum folic acid.

Conclusion

Depression was higher in patients with refractory epilepsy. Low serum folic acid was considered as a risk factor for depression and its severity in patients with refractory epilepsy, particularly in patients receiving polytherapy.

Keywords:
depression, folic acid, refractory epilepsy

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Introduction

Depression is the most common psychiatric disease in patients with epilepsy with average incidence of 30–40% [1]. Depression has been associated with lack of response to AEDs, and thereby with the likelihood of developing pharmacoresistant or intractable epilepsy [2]. Refractory epilepsy is defined as two or more seizures per month for a period of 2 years or more despite supervised trials (6 months each twice with monotherapy and once with polytherapy) [3].

Several antiepileptic drugs (AEDs), such as carbamazepine, valproic acid, phenytoin, oxcarbazepine, and lamotrigine have been reported to reduce folic acid absorption in humans [4,5]. Serum and red blood cell folate are reduced in up to 90% patients receiving phenytoin, carbamazepine, or barbiturates [6]. Depression is a common symptom of folate deficiency [7].

The aim of this study was to assess the relationship between serum folate levels and depression in patients with refractory epilepsy attending the neuropsychiatry outpatient clinic in the Suez Canal University hospital.

Patients and methods

The study included 37 patients with refractory epilepsy attending the neuropsychiatric outpatient clinic in Suez Canal University hospital after giving written informed consent. Both adult male and female patients with age ranging from 18 to 40 years old were included. We excluded patients who did not experience epileptic seizures for at least 2 weeks, patients receiving folic acid supplementation, patients known to be mentally retarded, patients with psychotic symptoms, patients with chronic organic diseases, patients with family history of depression, patients with substance abuse, and female patients in premenstrual or postmenopausal periods.

Patients fulfilling the inclusion and exclusion criteria were subjected to clinical history, examination, serum

folate level in which the normal range of folate levels is 3.5–16.1 ng/ml (3.5 ng/ml–7.7 ng/ml will be considered to be in the low normal range) [8], and the Hamilton Depression Rating Scale in which a multiple-choice questionnaire was used to detect and to rate the severity of a patient's depression [9].

Data were imported into the Statistical Package for the Social Sciences (latest available version of SPSS, SPSS Inc., Chicago, Illinois, USA) software for analysis. According to the type of data, the following tests were used to test differences for significance: χ^2 and paired *t*-test. The assessment of odds ratio was used to test the relationship between different dependent and independent variables. *P* value was set at a value of less than 0.05 for significant results and less than 0.01 for highly significant results. An informed consent was taken from all the patients before taking any data or conducting any investigations.

Results

Of the 37 patients, 20 of them (54.1%) were women and 17 of them (45.9%) were men. The age of the studied patients was found to be ranging from 22 to 38 years.

According to the received medications and duration of disease, no monotherapy was received, most commonly drugs were used in combination (polytherapy) of two or three drugs. Carbamezapine and phenytoin were received by 28 patients for each drug (75.7%). Valporic acid was received by 24 patients (64.86%). The mean duration of the disease was 12.1 years with most of the patients (56.8%) having been diagnosed for 10–15 years.

According to the Hamilton Depression Scale, 14 patients (37.8%) were not depressed. Ten patients (27.1%) were estimated to have mild depression, whereas eight (21.6%) had severe depression (Table 1).

Approximately half of the patients (48.7%) were estimated to have low levels of folic acid, with nine of them (24.3%) having low normal values (Table 2). There was significant association between severe depression and low folic acid level (< 3.5). There is significant association between patients with no depression (13.5%) and high normal level of folic acid (Table 3).

Longer duration of the disease was found to be associated with lower folic acid levels with significant difference (Table 4). There was significant difference between longer duration of the disease and higher depression scale score (Table 5).

Table 1 Severity of depression according to Hamilton Depression Scale

Depression scale	Number	Percentage (%)
No depression (0–6)	14	37.8
Mild depression (7–17)	10	27.1
Moderate depression (18–24)	5	13.5
Severe depression (>24)	8	21.6
Total	37	100

Table 2 Folic acid level among the studied patients

Folic acid level	Number	Percentage (%)
Low (<3.5)	18	48.7
Low normal (3.5–7.7)	9	24.3
Medium normal (7.8–11.9)	5	13.5
High normal (12–16)	5	13.5
Total	37	100

There was no significant association between received drugs and the severity of depression. However, most of the patients with severe depression were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valporic acid (Table 6). There was also no significant association between received drugs and low serum folic acid, although most of the patients with low serum folic acid were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valporic acid (Table 7).

Discussion

Depression is the most common psychiatric disease in patients with epilepsy [1]. An average incidence of 30–40% is, however, assumed [10]. Hitiris *et al.* [2] reported that depression due to the reduction in serum folate, which is associated with the induction of enzymes by AEDs, has been associated with lack of response to AEDs and thereby with the likelihood of developing pharmacoresistant epilepsy.

Hence, more important is that if the depression is not detected the epilepsy is actually harder to control, again probably for biological reasons [11]. Schuele and Lüders [12] found that emotional and psychosocial difficulties are disproportionately high in people with refractory epilepsy.

In this study, the prevalence of depression among the studied patients with refractory epilepsy was found to be 62.2%. This finding agrees with the findings by Gilliam *et al.* [13], Victoroff *et al.* [14], and Jones *et al.* [15], as they reported that 50–58% of the patients with refractory epilepsy were identified as having depression. O'Donoghue *et al.* [16] also noted that depression occurred more frequently in patients with higher seizure frequency compared with seizure-free patients.

In contrast, Attarian *et al.* [17] reported that patients with epilepsy have a higher prevalence of depression than the general population, but the intractability of the seizure disorder does not seem to be an independent risk factor for the occurrence of depression. This contrast may be due to using of the Beck Depression Inventory in that study to evaluate depressive symptoms. Depression in epilepsy is multifactorial in nature and has been shown to be influenced by a number of factors, which includes neurobiological, psychosocial, and pharmacological factors [18].

In this study, 48.7% were estimated to have low levels of folic acid (< 3.5), in addition to 24.3% having low normal values (3.5–7.7 ng/ml). This finding is agreed with Hermann *et al.* [19] as they found in 46 patients with chronic epilepsy,

Table 3 Relationship between folic acid level and depression scale

Folic acid level	No depression (0–6)	Mild depression (7–17)	Moderate depression (18–24)	Severe depression (>24)	*P* value
Low (<3.5)	3 (8.1%)	4 (10.8%)	4 (10.8%)	7 (18.9%)	0.01[a]
Low normal (3.5–7.7)	3 (8.1%)	4 (10.8%)	1 (2.7%)	1 (2.7%)	0.6 (NS)
Medium normal (7.8–11.9)	3 (8.1%)	2 (5.4%)	0 (0%)	0 (0%)	0.4 (NS)
High normal (12–16)	5 (13.5%)	0 (0%)	0 (0%)	0 (0%)	0.02[a]

NS, not significant.
[a]Statistically significant difference (*P* value <0.05).

Table 4 Relationship between folic acid level and duration of disease

	Low (<3.5)	Low normal (3.5–7.7)	Medium normal (7.8–11.9)	High normal (12–16)	*P* value
Mean ± SD	16.89 ± 2.3	13.6 ± 4.1	12.5 ± 5.3	11.8 ± 3.9	0.01[a]

SD, standard deviation.
[a]Statistically significant difference (*P* value <0.05).

Table 5 Relationship between depression scale and duration of disease

	No depression (0–6)	Mild depression (7–17)	Moderate depression (18–24)	Severe depression (>24)	*P* value
Mean ± SD	9.1 ± 2.9	11.6 ± 3.4	13.6 ± 4.9	17.5 ± 7.6	0.02[a]

SD, standard deviation.
[a]Statistically significant difference (*P* value <0.05).

Table 6 Relationship between combination therapy and depression

Drugs	No depression (0–6)	Mild depression (7–17)	Moderate depression (18–24)	Severe depression (>24)	*P* value
Valporic acid, carbamezapine, phenytoin	0 (0%)	1 (2.7%)	2 (5.4%)	3 (8.1%)	0.05 (NS)
Carbamezapine, valporic acid	5 (13.5%)	4 (10.8%)	0 (0%)	0 (0%)	0.1 (NS)
Phenytoin, valporic acid	5 (13.5%)	2 (5.4%)	1 (2.7%)	1 (2.7%)	0.8 (NS)
Carbamezapine, phenytoin	4 (10.8%)	3 (8.1%)	2 (5.4%)	4 (10.8%)	0.6 (NS)

NS, no statistically significant difference (*P* value >0.05).

Table 7 Relationship between combination therapy and folic acid level

Drugs	Low (<3.5)	Low normal (3.5–7.7)	Medium normal (7.8–11.9)	High normal (12–16)	*P* value
Valporic acid, carbamezapine, phenytoin	4 (10.8%)	1 (2.7%)	1 (2.7%)	0 (0%)	0.6 (NS)
Carbamezapine, valporic acid	2 (5.4%)	3 (8.1%)	2 (5.4%)	2 (5.4%)	0.3 (NS)
Phenytoin, valporic acid	2 (5.4%)	3 (8.1%)	1 (2.7%)	3 (8.1%)	0.1 (NS)
Carbamezapine, phenytoin	10 (32.4%)	2 (5.4%)	1 (2.7%)	0 (0%)	0.07 (NS)

NS, no statistically significant difference (*P* value >0.05).

folate serum level was below the normal range limit in 21.7% of patients with chronic epilepsy, of the remaining patients 45.6% had a low normal folate level.

In this study, there was significant association between depression and low serum folic acid level. Fifteen (40.5%) of the studied patients were found to have depression (ranging from mild, moderate, and severe depression) and low folic acid level (< 3.5). Seven (18.9%) of the studied patients were found to have severe depression and low folic acid level (< 3.5). Most of the patients with no depression (29.7%) were estimated to have normal levels of folic acid (ranging from low normal to high normal levels) and 13.5% of the patients with no depression were estimated to have high normal level of folic acid, which was a statistically significant difference.

This agreed with the findings by and Froscher *et al.* [20], who reported that in patients with psychiatric disorders, patients with epilepsy have a lower folate serum level than controls, and Kishi *et al.* [21] found that the reduction in serum folate is associated with the induction of enzymes by AEDs. Hermann and Whitman [22] in their study found that patients with minor depression had a significantly lower serum folate level than patients without depression. A serum folate level below 7.5 ng/ml was significantly associated with a pathological score on the Self-Rating Depression Scale.

In this study, longer duration of the disease was found to be associated with higher depression scale score. The mean duration of the disease was 12.1 years with most of the patients having been diagnosed for 10–15 years now (56.8%). This finding is consistent with most of the studies that found correlation between seizure frequency, longer duration of epilepsy, and depression [17,23]. This is in contrast with Glosser *et al.* [24], Oguz *et al.* [25], Baki *et al.* [26], and Kim *et al.* [27] who found that, however, the age, age of onset, duration of illness, religion, education, and multidrug therapy were not related to the severity of depression. The reasons for inconsistencies between these results and other studies are possibly due to difference in study groups, as other studies evaluate temporal lobe epileptic patients with hippocampal atrophy or hippocampal sclerosis, whereas this study evaluated patients with refractory epilepsy and used a different scale for evaluating depression.

In present study, there is no monotherapy was received, most commonly drugs were used in combination (polytherapy) of two or three of drugs among the studied patients, were carbamezapine and phenytoin were received by twenty eight of the patients for each drug (75.7%). Valporic acid was received by 24 patients (54.1%). This finding is nearly similar to the study conducted by Meneses *et al.* [28], who found that the most frequently used AEDs were phenytoin, valproic acid, carbamazepine, clobazam, and primidone.

In this study, there was no significant association between received drugs and the severity of depression. However, most of the patients with severe depression were receiving carbamezapine and phenytoin as part of their therapy either alone or in combination with valporic acid. This finding agrees with the study by Meneses *et al.* [28] and Mensah *et al.* [29], as they reported that depression was not associated with monotherapy or polytherapy. In contrast, Nemeroff and Owens [4] reported that carbamazepine, phenobarbital, phenytoin, and vigabatrin can contribute to depression and memory impairment.

Ogawa *et al.* [6] found that some AEDs are at risk for low levels of serum and red blood cell folic acid. This finding is in contrast to this study as there was no significant association between received drugs and the low serum folic acid. However, most of the patients with low serum folic acid were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valporic acid.

There is no conflict of interest to declare.

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الملخص العربي

العلاقة ما بين نقص مستوى حمض الفوليك بالدم و مرض الاكتئاب فى مرضى الصرع المستعصي

هدف البحث: إن مرض الاكتئاب هو من أكثر الأمراض شيوعا بين مرضي الصرع. و قد وجدت الأبحاث أن 30-40% من مرضي الصرع غير المستجبين للعلاج والذي يسمي في هذه الحالة مرض الصرع المستعصي. كما أشارت الأبحاث أن نسبة الاكتئاب بين مرضي الصرع المستعصي تتراوح من 50-58%. وأثبتت الدراسات أن التشنجات الصرعية ذاتها تقلل من نسبة حمض الفوليك في الدم و يعد الاكتئاب من أكثر الأمراض شيوعا في حالات نقص حمض الفوليك بالجسم. تهدف هذه الدراسة إلي تحديد العلاقة بين نسبة حمض الفوليك بالدم وظهور الاكتئاب بين مرضي الصرع المستعصي. **طريقة البحث:** و قد تمت الدراسة على سبعة و ثلاثون مريضا يعانون من الصرع المستعصي ويتعرضون لعدد من النوبات الصرعية لا تقل عن نوبة صرعية بالشهر في خلال سنتين بالرغم من انتظامهم علي أكثر من نوعين من الأدوية المضادة للصرع التقليدية. وتم أخذ التاريخ المرضي والفحص الإكلينيكي الشامل وتم عمل رسم مخ و أخذ عينة من الدم لتحديد نسبة حمض الفوليك, كما خضعت لتطبيق سلم هاملتون لتقييم الاكتئاب. **نتائج البحث:** وجدت الدراسة أن معدل انتشار الاكتئاب بين مرض الصرع المستعصي 62.2% و معدل نقص نسبة حمض الفوليك بالدم 48.7%, و قد تبين أن هناك علاقة قوية بين نقص نسبة حمض الفوليك بالدم و بين ظهور الاكتئاب بل وحدته أيضا. كما أثبتت هذه الدراسة أن هناك علاقة قوية بين عدم وجود تغيرات أو بؤر صرعية في رسم المخ وعدم ظهور الاكتئاب بين مرضي الصرع. **الاستنتاج:** معظم المرضي المستخدمين لعقار الكاربامازبين وعقار الفينيتوين معا يعانون من اكتئاب و نقص نسبة حمض الفوليك إلا أن هذه النسبة ليست ذات قيمة إحصائية.