Methyltetrahydrofolate reductase polymorphism, folic acid, and B12 in a sample of patients with depressive and anxiety symptoms

Heba Fathy[a], Sherine Mohamed Abd El-Mawella[a], Hoda Abdou[a], Ashraf Adel[a] and Amal Abdou[b]

Departments of [a]Psychiatry and [b]Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Egypt

Correspondence to Heba Fathy, Department of Psychiatry, Faculty of Medicine, Cairo University, Cairo, Egypt
Tel: +010 1404826;
e-mail: heba_eid666@yahoo.com

Received 22 October 2010
Accepted 23 November 2010

Middle East Current Psychiatry 2011, 18:118–125

Introduction
Both anxiety and depression are common symptoms or disorders with a major impact on public health. There are several theories regarding potential associations between depression and levels of vitamin B12 and folate. Vitamin B12 and folate are associated with the synthesis of monoamines and are involved in single carbon transfer methylation reactions associated with the production of monoamine neurotransmitters. This study was conducted to investigate the relationship between depression and other components of 1-carbon metabolism, such as vitamin B12, folate, and the methylenetetrahydrofolate reductase 677C→T polymorphism, and to compare the associations among folate, vitamin B12, and the methylenetetrahydrofolate reductase C677T polymorphism, in anxiety and depression.
Methods
After obtaining approval from the ethics committee in Kasr El Aini hospital, 90 participants were randomly selected in a comparative cross-sectional study. The sample consists of three groups: a group of depressive disorders without psychotic symptoms ($n=30$), a group of anxiety disorders ($n=30$), and a control group ($n=30$). The patients were recruited from the psychiatric out-patient clinic. Patients were diagnosed by a lecturer of psychiatry according to *DSM-IV* criteria. Psychometric procedure: Beck depression Inventory for severity of depression, Hamilton rating scale of depression, and Hamilton rating scale of anxiety. Laboratory: simultaneous assay of vitamin B12 and folic acid by radioimmune assay technique and analysis of methylenetetrahydrofolate reductase (C677T) by means of PCR and RFLP.
Results
Both anxiety and depression groups have the same percentage of gene mutation (33.3%). Folic acid and vitamin B12 mean values were the highest in the control group, followed by the anxiety group; the least was in the depression group. Within the depression group, there is a negative correlation between the severity of depression and folic acid. Within the depression group, patients with mutant gene have lower levels of both folic acid and vitamin B12 than patients with nonmutant gene. Within the anxiety group, patients with mutant gene have lower levels of both folic acid and vitamin B12 than patients with nonmutant gene.
Conclusion
Folic acid and vitamin B12 were lower than normal in both patients with anxiety and with depression and this was combined with gene mutation.

Keywords:
anxiety, depression, folic acid, vitamin B12

Middle East Curr Psychiatry 18:118–125

2090-5408

Introduction

Both anxiety and depression are common symptoms or disorders with a major impact on public health [1]. A possible role of nutritional factors in the pathogenesis of neuropsychiatric disorders has long been debated [2]. There are several theories regarding potential associations between depression and levels of vitamin B12 and folate. Vitamin B12 and folate are associated with the synthesis of monoamines and are involved in single carbon transfer methylation reactions associated with the production of monoamine neurotransmitters. Low levels of 5-hydroxyindole acetic acid in cerebrospinal fluid have been found in patients with depression with folate deficiency [3]. Clinical studies have shown an inverse relationship between folate status and depression [4]. Such a relationship has been inferred from studies showing an increased frequency of folate deficiency among patients with depression [5]. More severe and

prolonged depressive episodes and weaker treatment response to antidepressants in patients with low folate status and enhanced antidepressant response with folic acid supplementation have been observed [6]. In contrast, the possible role of vitamin B12 status in neuropsychiatric disorders has been motivated by the central nervous system damage caused by overt or subtle vitamin B12 deficiency. Data regarding the association between vitamin B12 status and depression are scarce [7]. Vitamin B12 is also required in the synthesis of S-adenosylmethionine, which is needed as a methyl donor in many methylation reactions in the brain. It has also been suggested to have antidepressant properties. The action of methyltetrahydrofolate reductase (MTHFR) is associated with the formation of tetrahydrobiopterin. This compound is an important enzyme cofactor for tryptophan hydroxylase, the rate-limiting enzyme for the synthesis of 5-hydroxytryptamine (serotonin). Similarly, tetrahydrobiopterin is a cofactor for the rate-limiting enzyme tyrosine hydroxylase (tyrosine 3-monooxygenase) for the synthesis of dopamine and norepinephrine. The three monoamines, dopamine, norepinephrine, and serotonin are neurotransmitters. It is generally accepted that boosting the synthesis or the availability of these compounds results in an antidepressant effect. Thus, MTHFR plays a crucial role in neurotransmitter biosynthesis and in the concentration of monoamines in the synaptic cleft [8]. Single nucleotide polymorphisms in MTHFR have been reported, including a C→T transition at nucleotide 677 in exon 4. For the C677T polymorphism, homozygote variants have 30% enzyme activity in comparison with homozygotes for the wild-type C allele, whereas heterozygotes retain 65% of wild-type MTHFR enzyme activity. Both of these polymorphisms are functional and result in diminished enzyme activity. The consequences of the C677T polymorphism have been demonstrated in population studies, in which lower levels of red blood cell folate, plasma folate, and vitamin B12 have been reported among nondiseased individuals with the 677 TT genotype in comparison with individuals with other genotypes [9].

The aim of this study is to examine the associations among folate, vitamin B12, and the MTHFR C677T polymorphism in anxiety and depression.

Patients and methods

After obtaining approval from Research Ethics Committee Review in Kasr El Aini hospital, 90 patients were randomly selected in a comparative cross-sectional study. All patients gave consent to participate in the study after full explanation of procedures was provided. The sample consists of three groups: a group of major depressive disorders (MDDs) without psychotic symptoms ($n = 30$), a group of generalized anxiety disorders ($n = 30$), and a control group ($n = 30$). The patients were recruited from a psychiatric outpatient clinic. Control cases (healthy volunteers among medical and paramedical personnel staff of Kasr El Aini university hospital) were chosen from an alphabetical computer list of employees of the hospital. All the scales showed an absence of psychopathology in the control group. They were matched in age and sex. This was conducted over 6 months. Patients were diagnosed by a lecturer of psychiatry according to *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (*DSM-IV*) [10] criteria. Both sexes were included and the age limit was 20–50 years. We excluded patients with other psychiatric disorders such as mixed anxiety–depressive disorder, mental retardation, organic brain disorders, and substance-induced psychiatric disorders, in addition to general medical condition (any condition affecting folic acid or vitamin B12 levels).

Psychometric tools

Semi-structured interview

A specially designed semi-structural interview derived from the Kasr El Aini psychiatric sheet was used to cover demographic data, personal data, history, and family history.

Structured Clinical Interview for DSM Axis of Disorders: it provides broad coverage of axis-I psychiatric diagnosis according to DSM-IV [11].

Hamilton depression rating scale [12]

This scale was designed by Hamilton [12,13]. The original version consisted of 17 items and was later increased to 24 items by Klerman *et al.* [14]. The scale is not meant to be a diagnostic instrument [15]. Hamilton depression rating scale was found to distinguish between different groups of patients drawn from general practice, day-patient care, and in-patients [16]. The concurrent validity is high [17]. The interrater reliability of Hamilton depression rating scale is also consistently high [12]. This is an objective test.

Hamilton anxiety rating scale [18]

Similar to the depression rating scale by the same investigator, the anxiety rating scale was specially developed to rate clinical anxiety in patients already diagnosed as suffering from an anxiety state (it is for use by a trained rater after an ordinary clinical interview). Hamilton took 12 groups of symptoms that were regularly observed in anxiety states as his starting point. The addition of a rating of behavior at an interview made 13 items. Each was rated on a five-point scale from 0 to 4 in an ascending order of severity [16].

Beck depression inventory [19] (Arabic version)

It is a self-report scale designed to assess DSM-IV-defined symptoms of depression such as sadness, guilt, loss of interest, social withdrawal, increase and decrease in appetite or sleep, suicidal ideation, and other behavioral manifestations of depression over the previous 2 weeks. It can also be used over time to monitor symptoms and to assess response to therapeutic interventions. The inventory is composed of 21 groups of statements on a 4-point scale with the patient selecting the one that best matches his or her current state. Each statement group corresponds to specific behavioral manifestation responses and is scored 0–3, corresponding to no, mild, moderate, or severe depressive symptoms. The score range varies from 0 to 63 in which higher score indicates greater depression severity. Score in the range of

0–13 indicates no or minimal depression; 14–19, mild depression; 20–28, moderate depression; and 29–63 indicates severe depression. It is translated into Arabic by Gharib Abdel Fattah and is used in many studies. We used this test for severity ranking and it is a subjective test.

Laboratory

(1) Fasting samples were collected on plain tubes for the assay of serum vitamin B12 and folic acid. Serum was separated and frozen at −20°C until time of analysis. Simultaneous assay of vitamin B12 and folic acid by the radioimmune assay technique was carried out using SimulTRAC-SNB supplied by MP Biomedicals (Diagnostics Division Orangeburg, New York, USA) [20].

(2) Three milliliter of blood was collected using sterile EDTA vaccutainer tubes for DNA extraction and analysis. Samples were stored at −70°C until the assay date. Genomic DNA for MTHFR C677T gene polymorphism was analyzed using PCR, followed by restriction fragment length polymorphism analysis [21].

Genomic DNA was extracted from whole blood by the standard salting-out technique [22].

In brief, the forward and reverse primers supplied by (Fermentas, USA) were used in the following sequence:

5′-TGAAGGAGAAGGTGTCTGCGGGA- 3′ (forward)
5′-AGGACGGTGCGGTGAGAGTG-3′ (reverse).

Amplification was performed using Master Taq polymerase enzyme and a hybaid thermal cycler (Promega Corporation, USA). The mixture was denatured at 95°C for 10 min, and the PCR reaction was performed for 35 cycles under the following conditions: denaturation at 95°C for 1 min, annealing at 65°C for 30 s, and extension at 72°C for 1 min and a final extension cycle of 72°C was for 7 min. Amplified bands were detected by electrophoresis on 1.5% agarose gel containing ethidium bromide. Amplified PCR products were digested with HinfI (Fermentas, USA) and analyzed on agarose gel (3.5%) for the identification of the point mutation in the MTHFR gene. A single fragment of 198 bp was identified as homozygous (CC); a single fragment of 175 bp was identified as homozygous (TT) genotype, and two fragments of 198 and 175 bp were identified as heterozygous (CT).

Statistical methods

Data were statistically described in terms of range, mean ± standard deviation, median, frequencies (number of cases), and percentages when appropriate. Comparison of quantitative variables between the study groups was carried out using the Student *t*-test for independent samples for comparing two groups when normally distributed and using the Mann–Whitney *U*-test for independent samples when not normally distributed. Comparison of quantitative variables between more than two groups of normally distributed data was carried out using the one-way analysis of variance test with posthoc multiple two-group comparisons, whereas non-normal data were compared using the Kruskal–Wallis analysis of variance test with the Mann–Whitney *U*-test for independent samples as posthoc multiple two-group comparisons. For comparing categorical data, the χ^2 test was performed; the exact test was used instead when the expected frequency is less than 5. Correlation between various variables was carried out using the Spearman rank correlation equation for non-normal. A probability value (*P* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows.

Results

Sociodemographic data (Tables 1 and 2)

Table 1 Mean age in the three groups

	Depression (*N*=30)		Anxiety (*N*=30)		Control (*N*=30)	
Age	Mean	SD	Mean	SD	Mean	SD
	32.1	7.7	32.33	7.7	31.2	5.7

SD, standard deviation.

Table 2 Sex and family history of depression or anxiety disorders

	Depression		Anxiety		Control		
	N	Percentage	*N*	Percentage	*N*	Percentage	*P*
Sex							
Male	13	43.3	15	50	17	56.7	0.587
Female	17	56.7	15	50	13	43.3	
Total	30	100	30	100	30	100	
Family history of depression or anxiety disorder							
Positive	9	30	8	26.7	4	13.3	0.271
Negative	21	70	22	73.3	26	86.7	
Total	30	100	30	100	30	100	

N, number.
P<0.05 is statistically significant.

Beck depression inventory (Table 3)

Table 3 Severity of depression in the three groups

	Depression		Anxiety		Control		
	N	Percentage	*N*	Percentage	*N*	Percentage	*P*
Beck depression inventory							
No	0	0	19	63.3	30	100	0.000
Minimum-to-mild	17	56.7	11	36.7	0	0	
Moderate-to-severe	13	43.3	0	0	0	0	
Total	30	100	30	100	30	100	

N, number; No, no depression.
P<0.05 is statistically significant.

Methylenetetrahydrofolate reductase *C677T* polymorphism (Table 4)

Table 4 Methylenetetrahydrofolate reductase *C677T* polymorphism

	Depression		Anxiety		Control		
	N	Percentage	*N*	Percentage	*N*	Percentage	*P*
Gene							
Mutant	10	33.3	10	33.3	6	20	0.42
Nonmutant	20	66.6	20	66.7	24	80	
Total	30	100	30	100	30	100	

N, number.
$P<0.05$ is statistically significant.

Clinical variables among depression, anxiety, and control groups (Table 5–7)

Table 5 Clinical variables between depression and control groups

	Depression (30)		Control (30)		
	Mean	SD	Mean	SD	*P*
Folic acid	5.8	4.5	9.8	4.9	0.003
Vit B12	439.5	189.2	512.4	216.2	0.189
Hamilton depression	27.2	6.9	1.07	1.4	0.000
Hamilton anxiety	4.9	4.1	0.5	0.8	0.000

SD, standard deviation; Vit, vitamin.

Table 6 Clinical variables between anxiety and control groups

	Anxiety (30)		Control (30)		
	Mean	SD	Mean	SD	*P*
Folic acid	8	5.5	9.8	4.9	0.166
Vit B12	504.9	231.9	512.4	216.2	0.89
Hamilton depression	15	5.1	1.07	1.4	0.000
Hamilton anxiety	34	4	0.5	0.8	0.000

SD, standard deviation; Vit, vitamin.

Table 7 Clinical variables between depression and anxiety groups

	Depression (30)		Anxiety (30)		
	Mean	SD	Mean	SD	*P*
Folic acid	5.8	4.5	8	5.5	0.09
Vit B12	439.5	189.2	504.9	231.9	0.23
Hamilton depression	27.2	6.9	15	5.1	0.000
Hamilton anxiety	4.9	4.1	34	4	0.000

SD, standard deviation; Vit, vitamin.
$P<0.05$ is statistically significant.

Correlations within the depression group

Within the depression group (Table 8), there is a negative correlation between the severity of depression and folic acid, which was just statistically significant. There is also a negative correlation between depression severity and vitamin B12, which was statistically significant. Furthermore, there is a positive correlation between the level of folic acid and vitamin B12, which was statistically significant.

Table 8 Correlation between folic acid and vitamin B12 with depression and anxiety

	Beck depression		Vit B12		Hamilton depression		Hamilton anxiety	
	P	*R*	*P*	*R*	*P*	*R*	*P*	*R*
Folic acid	0.05	−0.35	0.02	0.3	0.11	−0.29	0.92	0.019
Vit B12	0.03	−0.38			0.104	−0.302	0.87	−0.03

R, correlation coefficient; Vit, vitamin.
$P<0.05$ is statistically significant.

Within the depression group (Table 9), patients with mutant gene have lower levels of both folic acid and vitamin B12 than patients with nonmutant gene and this difference was statistically significant.

Table 9 Correlation between the folic acid and vitamin B12 and gene mutation within the depression group

	Mutant gene		Nonmutant		
	Mean	SD	Mean	SD	*P*
Folic acid	2	1.8	7.7	4.2	0.000
Vit B12	310	150	504	175	0.002

SD, standard deviation; Vit, vitamin.
$P<0.05$ is statistically significant.

Within the depression group (Table 10), patients with more severe depression have lower levels of folic acid and vitamin B12 than patients with minimal-to-mild depression. This was statistically significant with the vitamin B12 level and did not reach a statistically significant difference with the folic acid level (Table 11).

Table 10 Correlation between the folic acid and vitamin B12 and severity of depression within the depression group

	Minimum-to-mild		Moderate-to-severe		
	Mean	SD	Mean	SD	*P*
Folic acid	6.8	3.9	4.5	5	0.06
Vit B12	484.9	174.4	504	175	0.04

SD, standard deviation; Vit, vitamin.
$P<0.05$ is statistically significant.

Table 11 Correlation between gene mutation and family history in depression group

	Positive FH		Negative FH		Total		
	N	Percentage	*N*	Percentage	*N*	Percentage	*P*
Gene mutation							
Mutant	7	77.8	3	14.3	10	33.3	0.001
Nonmutant	2	22.2	18	85.7	20	66.7	
Total	9	100	21	100	30	100	

FH, family history; *N*, number.
$P<0.05$ is statistically significant.

Correlations within the anxiety group (Tables 12–14)

Table 12 Correlation between folic acid and vitamin B12 with depression and anxiety

	Beck depression		Vit B12		Hamilton depression		Hamilton anxiety	
	P	*R*	*P*	*R*	*P*	*R*	*P*	*R*
Folic acid	0.02	−0.399	0.001	0.57	0.15	−0.026	0.76	−0.05
Vit B12	0.33	−0.181			0.56	−0.11	0.59	0.100

R, correlation coefficient; Vit, vitamin.

Table 13 Correlation between the folic acid and vitamin B12 and gene mutation within the anxiety group

	Mutant gene		Non mutant		
	Mean	SD	Mean	SD	*P*
Folic acid	3.4	3.7	10.3	4.9	0.000
Vit B12	421.3	205	546.7	238	0.183

SD, standard deviation; Vit, vitamin.
$P<0.05$ is statistically significant.

Table 14 Correlation between gene mutation and family history in anxiety group

	Positive FH		Negative FH		Total		
	N	Percentage	*N*	Percentage	*N*	Percentage	*P*
Gene mutation							
Mutant	7	87.5	3	13.6	10	33.3	0.000
Nonmutant	1	12.5	19	86.4	20	66.7	
Total	8	100	22	100	30	100	

FH, family history; *N*, number.

Discussion

An association between depression and folate status has been demonstrated in clinical studies, whereas data are sparse on the relationship between depression and other components of 1-carbon metabolism, such as vitamin B12, homocysteine, and the MTHFR 677C→T polymorphism. The relationship between anxiety and these components is less well known [6]. Hence, this study was conducted to examine the associations among folate, vitamin B12, and the MTHFR 677C→T polymorphism, and anxiety and depression in a case–control comparative study.

As regards vitamin B12, mean value was highest in the control group followed by the anxiety group; the least was in the depression group and the difference did not reach statistical significance between all groups. As regards folic acid, mean value was highest in the control group followed by the anxiety group; the least was in the depression group and the difference did not reach statistical significance, except between the depression and the control group.

Our finding was proved by the finding of Coppen and Bolander Gouaille [23] who reported that both low folate and low vitamin B12 have been found in studies of patients with depressive disorders. An association between depression and low levels of the two vitamins is found in studies of the general population. Low plasma or serum folate has also been found in patients with recurrent mood disorders treated by lithium. A link between depression and low folate has similarly been found in patients with alcoholism.

Our results were consistent with the results of Alpert and Fava [24], who reported that a low folate level was relatively common (18%) among patients with MDD. Recently, it was reported that low dietary folate and depressive symptoms are associated in middle-aged Finnish men [25].

Nevertheless, a low folate level was not detected in German or Chinese patients with major depression. Hong Kong and Taiwan populations with traditional Chinese diets (rich in folate), including patients with major depression, have high serum folate concentrations. However, these countries have very low life-time rates of major depression and the low folate levels are linked [23]. This contradiction in the previous results could be explained by the fact that culturally defined dietary habits influence the relationship between the folate status and depression in different societies [26]. In addition, sex, smoking, and creatinine could cause this contradiction [27].

We also detected that both anxiety and depression groups have the same percentage of gene mutation (33.3%), whereas the control group reported 20% mutation, and the differences were not significant.

Absence of significant differences between both groups of depression and anxiety may be explained by the high degree of comorbidity between both disorders. Physicians often attempt to separate depression from anxiety. Unfortunately, such distinctions are often challenging and artificial as anxiety symptoms are common in patients with major depression. Moreover, the National Comorbidity Survey indicates that comorbid depression and anxiety is the rule rather than the exception in up to 60% of patients with MDD [28].

In addition, in our study the control group reported 20% with gene mutation; this can be explained by the fact that approximately 10% of the population is homozygous for the 677 C→T polymorphism of the MTHFR gene. In a meta-analysis of studies investigating the association between depression and MTHFR genotype, overall TT carriers had a 22% increase in the odds of depression compared with CC carriers [29]. Another study conducted by Bjelland *et al.* [6] from 1996 to 1997 on a large population group found a strong relationship between the T/T MTHFR genotype and depression, and the association was present for both cutoff levels of depression. Associations were observed between the lowest level of vitamin B12 [< 230.0 pmol/l (< 312 pg/ml)] and depression with high cutoff (HADS-D score ≥11).

Our results show that within the depression group there is a negative correlation between the severity of depression and

folic acid and this was just statistically significant. Moreover, there is a negative correlation between depression severity and vitamin B12, which was statistically significant. There is also a negative correlation between Hamilton depression and both folic acid and vitamin B12, which was statistically significant. Our findings agree with Penninx *et al.* [30] who found that older, physically disabled women with metabolically significant vitamin B12 deficiency have been found to have a two-fold higher risk of depression than women with normal plasma levels of vitamin B12.

However, our study disagrees with the finding of Hintikka *et al.* [3] who detected no correlation between the severity of depression and the level of vitamin B12 at baseline. Furthermore, Bjelland *et al.* [6] failed to detect a relationship between depression and folate.

Only a weak relationship or no relationship was seen between anxiety disorder and folate or vitamin B12 level or MTHFR genotype. In contrast, an inverse relationship between the level of folate and severity of depression has been reported in some other studies [31].

Finally, one of the important factors to be considered is that, whether the deficiencies in B12 and folate are primary and have a role in depression and anxiety or are secondary because both depression and anxiety affect the diet intake through loss of appetite, it is possible that safe augmentation strategies for antidepressive treatments could be advised. It is proved by Hintikka *et al.* [3] who applied his study by the determination of hematological indices, erythrocyte folate, and serum vitamin B12 levels at baseline and again at the 6-month follow-up in 115 outpatients with *DSM third edition, revised* MDD. They found that higher vitamin B12 levels were significantly associated with a better outcome. Finally, increasing dietary intake of B12 and folic acid is a simple, safe, and inexpensive method to improve mood, to fight stress, and to increase mental energy [7]. It is hypothesized that folate augmentation can be used to boost antidepressant efficacy, although further studies are necessary [8].

Conclusion

There is a negative correlation between serum level of vitamin B12, folic acid, and severity of depression in depression and anxiety groups. The levels of folate and vitamin B12 were lower in the depression group than the anxiety group, but the differences were not statistically significant. We detected gene mutation in 33.3% of both anxiety and depression groups. It was found that patients with mutant gene have lower levels of both folic acid and vitamin B12 in both depression and anxiety groups. From the above, we concluded that correction in the level of vitamin B12 and folic acid may lead to improvement of the severity of depression.

Study limitation

(1) The research was financed by the researcher, which limited the size of the sample.
(2) We did not investigate different types of depressive disorders and anxiety disorders.
(3) The sample size was small.

There is no conflict of interest to declare.

References

1 Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, *et al.* The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry 1999; 60:427–435.

2 Fernstrom JD. Can nutrient supplements modify brain function? Am J Clin Nutr 2000; 71 (**6 Suppl**):1669S–1675S.

3 Hintikka J, Tolmunen T, Tanskanen A, Viinamaki H. High vitamin B12 level and good treatment outcome may be associated in major depressive disorder. BMC Psychiatry 2003; 3:17.

4 Bottiglieri T, Crellin R, Reynolds EH. Folate and neuropsychiatry. In: Bailey LB, editor. *Folate in health and disease*. New York: Marcel Dekker; 1995. pp. 435–462.

5 Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. Folate, vitamin B12 and homocysteine in major depressive disorder. Am J Psychiatry 1997; 154:426–428.

6 Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. Folate, vitamin B12, homocysteine and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. Arch Gen Psychiatry 2003; 60:618–626.

7 Tiemeier H, Van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. Vitamin B12, folate and homocysteine in depression: the Rotterdam Study. Am J Psychiatry 2002; 159:2099–2101.

8 Pauwels EKJ. The folate puzzle. Part IV: folate and depression. Drugs Future 2008; 33:591–595.

9 Gilbody S, Lewis S, Lightfoot T. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review. Am J Epidemiol 2007; 165:1–13.

10 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders DSM-IV-TR*. 4th ed. Washington: American Psychiatric Publishing, Inc.; 2000.

11 First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured clinical interview for DSM-IV, axis I disorders (SCID-I)*. Washington, DC: American Psychiatric Association, Inc.; 1997.

12 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62.

13 Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6:278–296.

14 Klerman GL, Lavori PW, Rice J, Reich T, Endicott J, Andreasen NC, *et al.* Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. Arch Gen Psychiatry 1985; 42:689–693.

15 Preskorn SH, Fast GA. Beyond signs and symptoms: the case against a mixed anxiety and depression category. J Clin Psychiatry 1993; 54 (**Suppl**): 24–32.

16 Carroll BJ, Fielding JM, Blashki TG. Depression rating scales. A critical review. Arch Gen Psychiatry 1973; 28:361–366.

17 Kearns NP, Cruickshank CA, McGuigan KJ, Riley SA, Shaw SP, Snaith RP. A comparison of depression rating scales. Br J Psychiatry 1982; 141: 45–49.

18 Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55.

19 Beck AT, Steer RA, Brown GK. *Manual for the beck depression inventory*. 2nd ed. San Antonio, TX: Psychological Corporation; 1996.

20 Garcia Casal MN, Osorio C, Landaeta M, Leets I, Matus P, Fazzino F, *et al.* High prevalence of folic acid and vitamin B12 deficiencies in infants, children, adolescents and pregnant women in Venezuela. Eur J Clin Nutr 2005; 59:1064–1070.

21 Jaaskelainen E, Keski Nisula L, Toivonen S, Romppanen EL, Helisalmi S, Punnonen K, *et al.* MTHFR C677T polymorphism is not associated with placental abruption or preeclampsia in Finnish women. Hypertens Pregnancy 2006; 25:73–80.

22 Trowsdale J. Genomic structure and function in the MHC. Trends Genet 1993; 9:117–122.

23 Coppen A, Bolander Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol 2005; 19:59–65.

24 Alpert JE, Fava M. Nutrition and depression: the role of folate. Nutr Rev 1997; 55:145–149.

25 Tolmunen T, Voutilainen S, Hintikka J, Rissanen T, Tanskanen A, Viinamaki H, *et al.* Dietary folate and depressive symptoms are associated in middle-aged Finnish men. J Nutr 2003; 133:3233–3236.

26 Lee S, Wing YK, Fong S. A controlled study of folate levels in Chinese inpatients with major depression in Hong Kong. J Affect Disord 1998; 49:73–77.

27 Sachdev PS, Parslow RA, Lux O, Salonikas C, Wen W, Naidoo D, *et al.* Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample. Psychol Med 2005; 35:529–538.

28 Aina Y, Susman JL. Understanding comorbidity with depression and anxiety disorders. J Am Osteopath Assoc 2006; 106 (**5 Suppl 2**): S9–S14.

29 Ford AH, Flicker L, McCaul K, Van Bockxmeer F, Hegarty S, Hirani V, *et al.* The B-VITAGE trial: a randomized trial of homocysteine lowering treatment of depression in later life. Trials 2010; 11:8. doi:10.1186/1745-6215-11-8.

30 Penninx BW, Guralnik JM, Ferrucci L, Fried LP, Allen RH, Stabler SP. Vitamin B(12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. Am J Psychiatry 2000; 157:715–721.

31 Carney MW, Chary TK, Laundy M, Bottiglieri T, Chanarin I, Reynolds EH, *et al.* Red cell folate concentrations in psychiatric patients. J Affect Disord 1990; 19:207–213.

الملخص العربى

دراسة مقارنة لفيتامين ب وحمض الفوليك وتعدد الشكل لجين الميثيلين تيتراهيدرو فولات

في عينة من مرضى الاكتئاب والقلق

هبة فتحى*- شيرين عبد المولى*- هدى عبدة*-اشرف عادل*- امال عبدة**

*** قسم الطب النفسى- ** قسم الباثولوجيا الكيميائية و الاكلينيكية**

كلية الطب- جامعة القاهرة

الهدف

دراسة دور نقص فيتامين ب وحمض الفوليك **وتعدد الشكل لجين الميثيلين تيتراهيدرو فولات** فى عينة من مرضى الاكتئاب والقلق في مقارنة لمعرفة اذا كان لهم دور فى مسببات المرض ا لاستفادة من ذلك فى الخطة العلاجية.

طريقة وأدوات البحث

طبقت هذه الدراسة على30 من مرضى الاكتئاب و من 30 من مرضى القلق المترددين على العيادة النفسية بكلية طب القصر العينى وعلى المرضى المحجوزين فى القسم الداخلى. ومقارنتهم30 من عينة قياسية. وقد تم تطبيق مقياس بك للاكتئاب ومقياس هاملتون للاكتئاب والقلق. كما تم قياس مستوى فيتامين ب وحمض الفوليك فى الدم . ودرجة **تعدد الشكل لجين الميثيلين تيتراهيدرو فولات في** مرضى الاكتئاب والقلق كل على حدى.

وجد أن مستوى فيتامين ب وحمض الفوليك اكثر فى العينة الضابطة يليه مرضى القلق ثم أقل مستوى فى مرضى الاكتئاب ولا توجد دلالات احصائية ايجابية الا بين مرضى الاكتئاب والعينة الضابطة . كما وجد أن هناك علاقة عكسية ايجابية بين شدة الاكتئاب والقلق ومستوى فيتامين ب وحمض الفوليك فى كل من مرضى الاكتئاب و مرضى القلق . وهذه العلاقة تبدو اكثر فى مرضى الاكتئاب يليه القلق يليه العينة الضابطة.

وبالنسبة الي **تعدد الشكل لجين الميثيلين تيتراهيدرو فولات** وجد أن هناك تحور عند 33.5 % من مرضى الاكتئاب والقلق كلا على حدة مقارنة ب 20% من العينة الضابطة. و لايوجد اى فروق ايجابية بين القلق والاكتئاب و العينة الضابطة.

الخلاصة:

ان هناك نقص فى مستوي نقص فيتامين ب وحمض الفوليك و **وتعدد الشكل لجين الميثيلين تيتراهيدرو فولات** فى مرضى الاكتئاب يليه القلق يليه العينة الضابطة وان هذه العلاقة عكسية بمعنى نقص فيتامين ب وحمض الفوليك يصاحبه زيادة فى شدة الاكتئاب والقلق. وهذا يدفعنا الى ضرورة اضافة فيتامين ب وحمض الفوليك مع مضادات الاكتئاب والقلق .كما يتطرق بنا الى مزيد من الابحاث فى مجال الجينات لفتح مجال العلاج بالجينات.