N-Terminal pro-Brain Natriuretic Peptide, Homocysteine and Methylenetetrahydrofolate Reductase Gene Polymorphism in Elderly Depressed and Mild Cognitive Impairment Patients

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ABSTRACT

There is increasing evidence that vascular disease contributes to cognitive impairment and depression. Secretion of N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) increases in several cardiac illnesses, making this neurohormone a reliable diagnostic and prognostic biomarker of cardiovascular risk. Homocysteine (Hcy) is harmful to neurons and blood vessels, including the cerebral microvasculature. It is possible that such effects contribute to the cascade of events that leads to cognitive decline, dementia, and depression in later life. Hcy is produced during the metabolism of the essential amino-acid methionine, its plasma level can be influenced by factors such as vitamin deficiency, renal function, and a common mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, where cytosine is replaced by thymine (C→T) at nucleotide position 677. The aim of the present study was to evaluate the role of NT-proBNP, Hcy, folate , and MTHFR gene polymorphism in late life mild cognitive impairment (MCI) and depression, and to determine the association between homozygous carriers of the TT genotype and Hcy and NT-proBNP on one-hand and depressive and cognitive scores on other-hand. The study included 60 elderly patients, they attended the Outpatient Clinic for treatment of depression (group I, n=32) and/or MCI (group II, n=28). In addition to a control group (group III, n=20) which matched to the patients with respect to age and gender with no previous history of psychiatric diseases. Both plasma NT-proBNP and Hcy levels were assayed by ELISA and folate levels were assayed by electrochemiluminescene immunoassay, in addition MTHFR C677T gene polymorphism was evaluated using PCR and restriction fragment length polymorphism (RFLP) using HinfI restriction enzyme. Both NT-proBNP and Hcy were significantly increased but folate was significantly decreased in the patients groups as compared to the control subjects. Both Hcy and NT-proBNP were significantly positively correlated with depression scores assessed by Hamilton Rating Scale of Depression (HRSD), but significantly negatively correlated with cognitive impairment assessed by Mini-mental state examination (MMSE) score. The carriers of MTHFR, TT genotypes had an increased risk of developing depression and had significantly higher plasma level of both and NT-proBNP and Hcy than CT or CC patients genotypes ($p<0.001$).

***In conclusion**: the MTHFR C677T gene variation may play an important role in the modulation of mood but does not contribute to genetic susceptibility to cognitive performance in later life. The MTHFR C677T mutation is associated with plasma Hcy and NT-proBNP levels. Elevated NT-proBNP and Hcy levels may play a role in linking depression and /or MCI with increased cerebrovascular and/or cardio-vascular risk.*

INTRODUCTION

The pathological mechanisms that lead to the expression of depression and dementia in later life remain largely unknown. At present, the treatment for dementia do not provide cure, only slight delays in the progression, therefore, many researchers have turned their attention to the prevention of dementia[1]. Clarification of the role of vascular risk factors in dementia is important because most are modifiable, in contrast to other risk factors such as age and genetics. Thus, vascular risk factors may serve as targets for strategies of prevention[2].

Secretion of N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) increases in several cardiac illnesses, making this neurohormone a reliable diagnostic and prognostic biomarker of cardiovascular risk [3, 4].Brain natriuretic peptide (BNP) is produced as a prohormone (pro-BNP) comprising of 108 amino acids and is enzymatically cleaved into physiologically active BNP (77–108) and the amino-terminal portion of the prohormone (1–76) (N terminal (NT)-proBNP)[5]. By means of its natriuretic and diuretic properties, as well as its action as antagonist of renin-angiotensin-aldosterone system, that neurohormone produces a myriad of biological effects, such as vasodilatation, changes in electrolyte and fluid balances, and inhibition of the sympathetic nervous system[6].

Homocysteine (Hcy) is a thiol-containing amino acid that is produced during the metabolism of methionine. By receiving a methyl group from 5-methyltetrahydrofolate, Hcy can be re-methylated to methionine, which, is also, the immediate precursor of S-adenosylmethionine (SAM). In the brain, SAM is directly involved in the synthesis and metabolism of dopamine, norepinephrine and serotonin, which are neurotransmitters postulated to play an important role in the pathogenesis of depression and anxiety[7].

The plasma level of Hcy can be influenced by factors such as vitamin deficiency, renal function, and a common mutation in the methylenetetrahydrofolate reductase (MTHFR) gene[8].

MTHFR is the crucial enzyme in folate-mediated one-carbon transfer reactions. MTHFR gene is localized in the short arm of chromosome 1 (1p36.3)[9]. MTHFR catalyses the NADPH- dependent reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.That molecule functions as a cofactor for methylation of Hcy to methionine[10].Frosst et al[11] found a MTHFR gene polymorphism 677C→T (a cytosine to thymine substitution at nucleotide 677, also called the thermo-labile variant), which substituted alanine with valine (A222V)[11]. This polymorphism may be associated with decreased MTHFR activity, mild-to-moderate hyperhomocysteinemia, premature cardiovascular disease and neural tube defects[12]. Severe deficiency of MTHFR leads to mental and vascular disorders[13]. It is conceivable, however that the MTHFR genotype may play an important role in the modulation of mood and cognitive

function in humans. Therefore the aim of the present study was to evaluate the changes of NT-proBNP, Hcy, folate , and MTHFR C677T gene polymorphism in late life MCI and depression, and to determine the association between the MTHFR C677T gene polymorphism and plasma concentration of both Hcy and NT-proBNP on one-hand and with depression and cognitive impairment scores on other-hand.

SUBJECTS & METHODS

The current study was conducted in the Neuropsychiatry Department, Tanta University Hospital in the period from the 1st of January 2007 to the 31st of December 2007. It included 60 elderly patients, with a mean age of 62.25 ± 6.28 years; 33 were females and 27 were males. They attended the Outpatient Clinic for treatment of depression (group I, n=32) and/ or MCI (group II, n=28). In addition, a control group (group III) consisted of 20 healthy volunteers of 15 females and 5 males, with a mean age of 60.25±4.98 years, matched to the patients with respect to age and gender with no previous history of psychiatric diseases were included. All controls were free of chronic and acute physical illness. Control group was assessed for cognitive impairment using the Mini-mental state examination (MMSE) and only those with a score greater than 26 entered the study. Exclusion criteria for all patients included: severe cognitive impairment, dementia, severe sensory impairment, history of strokes, history of current or previous hazardous drinking, used hormone replacement therapy during the six months prior to assessment, patients with drug abuse or past history of drug abuse, smoking, renal insufficiency, cardiovascular, liver diseases and other psychiatric disorders were excluded from the present study. Also, patients on any kind of vitamin substitution were excluded from the study[(2)]. All participants signed informed consent before testing. All patients were subjected to the following:

1. **Diagnosis of major depressive disorder** using semi-structured clinical interview of DSM-IV-TR (American Psychiatric Association[(14)].
2. **Assessment of severity of depression** using the 16- item Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1960) [(15)].
3. **Assessment of the cognitive function** using the following measures [(16)]:
   a. **MMSE:** It is a screening test that can be used to track the changes in the patient's cognitive state[(17)] .
   b. **Faces memory (FM):** immediate and delayed memory for faces.
   c. **Word lists (WL):** measures immediate and delayed memory for verbal material.
   d. **Verbal Paired Associates (VPA):** uses the same test procedures described for WL and produces measures of immediate and delayed cued recall for semantically unrelated pairs of words.
   e. **Block design (BD):** is a constructional test in which the

subject is presented with four or nine colored blocks. This is a sensitive test of visuo-spatial organization.

f. **Verbal fluency (VF):** ***Part 1:*** was investigated by asking subjects to name as many words as possible rhyming with the word (dog) within 3 minutes and many words as possible rhyming with the word (key) within 3 minutes. ***Part 2:*** was investigated by asking subjects to name as many words as possible derived from the word (cupboard) and to name as many words as possible derived from the word (balcony) within 3 minutes. The VF total score represents the sum of the number of words produced for each one of the two parts.

4. **Biochemical and genetic analysis:** Blood samples were collected in vacuum tubes containing EDTA in the morning after an overnight fast and is centrifuged within one hour of collection at 1500×g for 20 min at room temperature. Plasma was separated, stored in aliquots, and kept frozen at −70 °C until analysis for determination of:

a. ***NT-proBNP*** was measured using a competitive enzyme linked immunosorbent assay (ELISA) (Biomedica Laboratories, Vienna, Austria) according to the manufacturer's protocol[4].

b. ***Total plasma Hcy*** was measured using EIA kit supplied by Axis-Shield Diagnostics Ltd. The technology Park Dundee DD2 1XA United Kingdom, according to **Frantzen et al.**[18].

c. ***Plasma folate*** was measured by using the electrochemiluminescene immunoassay according to **Ng et al.,**[19]. Electro-chemiluminescene immunoassay of folate assays employ a competitive test principle using natural folate binding protein (FBP) specific for folate. Folate in the sample competes with the added folate (labeled with biotin) for the binding sites on FBP (labeled with ruthenium complex).

d. ***Genotype analysis for MTHFR C677T polymorphism:*** DNA was extracted from buffy coat layer of blood cells by using Qiagen Kits according to the manufacturer's recommendations (Qiagen-France, Courtaboeuf, France) and the 677 C→T mutation was determined by use of the polymerase chain reaction (PCR) and *HinfI* restriction enzyme digestion as described by **Frosst et al.,1995**[11]. Briefly, PCR amplification of a 198-bp segment containing nucleotide 677 was done using two specific primers, the sense primer, 5`-TGAAGGAGAAGGTGTCTGC GGGA-3`(exonic) and antisense primer 5`- AGGACGGTGCG GTGAGAGTG-3` (intronic) were used. DNA was amplified by using a PCR thermal cycler (Perkin-Elmer, Cetus, Norwalk, CT). PCR reaction was carried out in a total volume of 50 µL contained about 200 ng DNA template, 0.5 µM of each primer, 200 µM each dNTP, 10 mM Tris-HCl (pH 8.3), 1.5 mM $MgCl_2$, 50 mM KCl and 1.25 U of Taq

DNA polymerase (Amersham, Bioscience). The reaction conditions were as follows: initial heat activation at 95°C for 4 min and 35 subsequent cycles of denaturation at 94°C for 60 s, annealing at 61°C for 60 s, and extension at 72°C for 2 min. PCR product (198 bp fragment) was digested with *HinfI* restriction endonuclease (MBI Fermentas) for 12 h at 37°C.When a C to T substitution is present, *HinfI* restriction site is created. The restriction enzyme digests the 198-bp fragment into a 175-bp and a 23-bp fragment and the amplified product derived from the wild-type allele was not affected. These fragments were separated by electrophoresis on a 2% agarose gel and visualized with ethidium bromide (Fig.1).

Statistical analysis

The raw data were fed to the computer program Minitab software release 13.1, copyright © 2000. Descriptive statistics were used to determine frequencies, means and 95% confidence intervals of the mean (CI). Quantitative data was presented as mean ± SD. Qualitative data was presented as number and percentage. Chi-Square test ($\chi 2$) was used for comparison between two groups as regards qualitative data and the odds ratio (OR) estimated for 2 × 2 tables. One way analysis of variance (ANOVA) is used for comparison between more than two means of more than two different groups, and if there is significant difference, post hoc Scheffe test is done. Pearson correlation test was used to test correlation between different variables. Results were considered significant at $p \leq 0.05$.

RESULTS

Table (1) shows comparison between the studied groups as regards age and different biochemical parameters in which there was a significant increase in both NT-proBNP and Hcy but significant decrease in folate in the patients groups as compared to the control with no significant difference between both patients groups and no significant differences as regards age in all the studied groups. Both Hcy and NT-proBNP were significantly positively correlated with each other (r=0.46 p<0.001)and with depression scores assessed by HRSD (r= 0.49, r= 0.40, p=0.001 respectively), but significantly negatively correlated with cognitive impairment assessed by MMSE (r=-0.52, r=-0.39, p<0.001 respectively), face memory (r=-0.50, -0.42, p<0.001 respectively), verbal fluency part 1 (r=-0.45, -0.32, p<0.001), and verbal fluency part 2 (r= 0.39,-0.35, p< 0.001 respectively) so that the higher the plasma Hcy, the NT-proBNP, the more the scores of HRSD and the lower the scores of cognition assessed by MMSE, FM test and VF-parts 1 and 2, so the more the cognitive impairment. No significant correlation was detected between both plasma Hcy, NT-proBNP and scores of WL, VPA, and BD. (Table 2)

By using chi-square, table (3) shows no significant differences between the studied groups as regards gender, but significant difference as regards family history of psychiatric disorders (p=0.004) and MTHFR

genotypes (p=0.04). In (table 4) there was, a significant increase in percentages of MTHFR genotypes TT and T allele among depression group as compared to control group (p=0.04,0.005 respectively) (tables 3,4). The carriers of MTHFR, TT, TC genotypes and T allele had an increased risk of developing depression (OR = 0.1, 95% CI: 0.01-0.8, p=0.04, OR=0.26, 95% CI: 0.07-0.9, p=0.07, OR = 0.24, 95% CI: 0.1-0.62, p=0.005 respectively) on comparing depression with controls and using normal MTHFR CC genotype and C allele as referent respectively. There were no statistically significant differences in the MTHFR genotype and allele distributions in MCI patients compared with controls (table 4). Upon classification of the patients groups according to MTHFR genotypes no significant difference between the 3 genotypes regarding age but plasma level of both and NT. Pro.BNP and Hcy were found to be significantly higher (p<0.001) and plasma folate was non-significantly lower in TT carrier patients than CT or CC patients. (Table 5).TT patients have significantly higher scores of depression assessed by HRSD (p=0.008), were more to suffer from significant cognitive impairment as assessed by MMSE (p=0.001), FM (p=0.002), WL (p=0.008), and VF- 2 (p=0.001) than CT and CC carrier patients. However, no significant difference was detected between TT patients and the other 2 genotypes regarding VPA, BD, VF-1. (Table 5)
MTHFR gene polymorphisms (TT), (TC) and (CC) were represented in (fig 1).

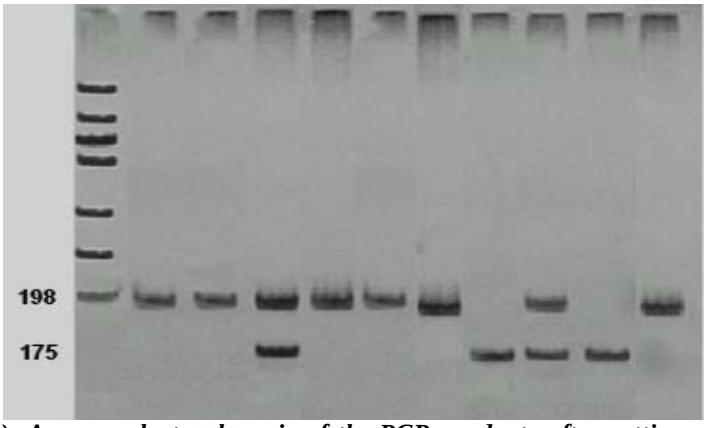

Figure (1): Agarose electrophoresis of the PCR products after cutting with Hinf1 restriction endonuclease. The bands were visualized using ethidium bromide and 2 % agarose (lanes 1,2,4,5,6 and 10 represent normal homozygote (677CC), lane 7 and 9 represents homozygote (677TT) and lane 3 and 8 represents the heterozygote (C677T).

Table (1): Age and laboratory parameters in the studied groups

	Depression (group I) (no= 32)	MCI(group II) (no=28)	Control (group III) (no=20)	F	P
	Mean ±SD	Mean ±SD	Mean ±SD		
Age (years)	61.72±5.65	62.86± 6.97	60.25±4.98	1.4	0.34
NT-proBNP (pmol/l)	135±76	120±55	36.5±6.7	18.9	<0.001* all are significant except I vs. II
Hcy (µmol/l)	13.06±2.95	12.43±3.52	10.30±1.72	5.66	0.005*all are significant except I vs. II
Folate (ng/ml)	4.5±3.01	4.7±2.25	6.6±2.56	4.33	0.02* all are significant except I vs. II

Mild cognitive impairment (MCI) N-terminal pro-B-type natriuretic peptide (NT. ProBNP), Homocysteine (Hcy)

Table (2): Pearson correlation between Hcy, NT-proBNP and both depression and cognitive scores in the patients groups (N=60):

	Hcy (µmol/l)		NT-proBNP (pmol/l)	
	r	p	r	p
HRSD	0.49	<0.001*	0.40	<0.001*
MMSE	-0.52	<0.001*	-0.39	<0.001*
FM	-0.50	<0.001*	-0.42	<0.001*
WL	-0.23	>0.05	-0.18	>0.05
VPA	0.19	>0.05	0.13	>0.05
B D	0.17	>0.05	0.15	>0.05
VF-1	-0.45	<0.001*	-0.32	<0.001*
VF-2	-0.39	<0.001*	-0.35	<0.001*
NT. Pro. BNP (pmol/l)	0.46	<0.001*	------	-------

*Hamilton Rating Scale of Depression (HRSD), Mini Mental State Examination (MMSE), Faces memory (FM), Word lists (WL),verbal paired associates (VPA), Block design (BD), verbal fluency part 1 (VF-1), verbal fluency part 2 (VF-2). *Significant at $p \leq 0.05$*

Table (3): Gender, Family history and MTHFR genotypes in the studied groups

	Depression (group I) (no= 32)		**MCI(group II) (no=28)**		**Control (group III) (no=20)**			
Gender	No	%	No	%	No	%	χ^2	p
Females	20	62.50	13	46.43	15	75		
Males	12	37.50	15	53.57	5	25	4.1	0.13
Family history:								
+ve	9	28.13	12	42.86	0	0	11.2	0.004*
-ve	23	71.87	16	57.14	20	100		
CC	10	31.25	11	39.29	14	70		
CT	14	43.75	14	50	5	25	10.08	0.04*
TT	8	25.00	3	10.71	1	5		

*methylenetetrahydrofolate reductase (MTHFR). *Significant at $p \leq 0.05$*

Table (4): MTHFR genotypes and alleles distribution in the studied groups

MTHFR genotypes	**Control (group III) (no=20)**	**Depression (group I) (no= 32)**	**OR (95%CI)**	**P depression group vs. Control group**	**MCI (group II) (no=28)**	**OR (95%CI)**	**P MCI group vs. Control group**
CC	14	10	1.00(referent)		11	1.00(referent)	
CT	5	14	0.26(0.07-0.9) (CT vs. CC)	0.07	14	0.28(0.08-1.02) (CT vs. CC)	0.09
TT	1	8	0.1(0.01-0.8) (TT vs. CC)	0.04*	3	0.26(0.02-2.9) (TT vs. CC)	0.54
MTHFR Allele							
C	33	34	1.00(referent)		36	1.00(referent)	
T	7	30	0.24(0.1-0.62)	0.005*	20	0.38(0.14-1.02)	0.08

**Significant at $p \leq 0.05$*

Table (5): Age, laboratory parameters, HRSD, MMSE, FM, WL, VPA, BD, VF-1, and VF-2 in studied patients according to MTHFR genotype:

	TT (N=15)		CT (N=27)		CC (N=18)		F	P	Scheffe test
	Mean	±SD	Mean	±SD	Mean	±SD			
Age(years)	62.27	8.01	62.81	5.78	62.85	6.79	0.06	0.496	-
NT-proBNP (pmol/l)	170	40	110	30	80	20	36.9	0.001*	TT>CT>CC
Hcy(μmol/l)	14.31	1.79	12.15	2.28	11.1	1.01	12.5	0.001*	TT>CT=CC
Folate(ng/ml)	5.1	2.4	4.5	1.05	4.4	3.1	0.5	0.6	-
HRSD	22.13	3.23	17.74	5.84	17.28	3.89	5.26	0.008*	TT>CT=CC
MMSE	17.00	3.57	21.07	2.88	19.89	3.50	7.63	0.001*	TT<CT=CC
FM	22.67	4.79	27.85	8.97	32.72	7.33	7.10	0.002*	TT<CT=CC
WL	23.93	6.08	25.33	6.26	30.78	7.62	5.24	0.008*	TT=CT<CC
VPA	8.27	3.33	10.00	2.48	10.00	2.72	2.18	0.122	-
BD	16.13	3.40	14.56	5.29	14.17	4.99	0.77	0.469	-
VF-1	16.47	3.52	17.26	4.20	16.11	3.95	0.49	0.614	-
VF-2	15.40	2.99	19.15	2.81	19.56	2.90	10.47	0.001*	TT<CT=CC

N-terminal pro-B-type natriuretic peptide (NT. ProBNP), Homocysteine (Hcy)Hamilton Rating Scale of Depression (HRSD), Mini Mental State Examination (MMSE), Faces memory (FM), Word lists (WL),verbal paired associates (VPA), Block design (BD), verbal fluency part 1 (VF-1), verbal fluency part 2 (VF-2)

DISCUSSION

There is increasing evidence that vascular disease contributes to cognitive impairment and depression. There is some evidence that controlling vascular factors can prevent or postpone dementia.[1] In the present study, NT proBNP, Hcy and MTHFR gene (C677T) polymorphism were investigated as possible risk markers for vascular disease in elderly patients (depression and MCI). Although natriuretic peptides have been suggested to exert significant behavioral effects so far few data are available on their circulating levels in relation to negative mood states. Specifically, while atrial natriuretic peptide (ANP) may display significant anxiolytic effects, the role of B-type natriuretic peptide (BNP) and NT-proBNP in psychiatric conditions remains largely unexplored[20]. In the present study, higher level of plasma NT-proBNP levels was detected in patients with depression and / or MCI as compared with the control group and it was significantly positively correlated with the severity of depressive symptoms and cognitive impairment, as measured by the HRSD score and MMSE respectively. The mechanisms underlying the NT-proBNP elevation in depressed patients are not clear. It is possible; however, that endothelium dysfunction, which has been reported in patients with major depressive disorder (MDD), could also be involved in the elevation of NT-proBNP levels[4,21]. An alternative pathway whereby NT-proBNP values may be altered in depression could be mediated by sex steroid hormones that coordinately influence natriuretic peptide synthesis[22]. It is intriguing that patients with depression may

show patterns of androgen deficiency, and that androgens can suppress natriuretic peptide release. However, the possible influence of sex hormones on plasma NT-proBNP values warrants further investigation since no significant effect of gender on the levels of that neuro-hormone was found[4]. It was suggested that increased plasma NT-proBNP may be one of the links between MDD and the increased risk for adverse cardiac events[4]. The mechanism by which BNP is related to cognitive dysfunction is unclear.

Endothelial abnormalities have recently been linked to cerebrovascular disease and reduced cognitive function[23,24]. **Nilsson et al.**[2] found NT-proBNP was associated with the presence of vascular disease, pathological computer tomography scan (CT) findings and age, and they stated that patients with any form of vascular disease or with pathological CT findings might be regarded as patients with increased risk of a rapid progression of their vascular disease and consequently, also, their mental illness. Thus, these patients might be selected for increased control of vascular risk factors. So, they concluded that the control of conventional vascular risk factors and therapy could be guided by the level of plasma Hcy and serum NT-proBNP. Also, **Silbert et al.,**[25] reported that, it is possible that cognitive impairment may result from the vascular disease rather than a direct association with either Hcy or CRP. In addition, **Nilsson et al.,**[26] observed elevated serum concentrations of NT-proBNP in patients with dementia or vascular disease as a sign of poorer cardiovascular status, and concluded that routine determination of NT-proBNP is valuable for obtaining information about cardiovascular status. Further-more, **Yip et al.**[6] found that National Institutes of Health Stroke Scale (NIHSS) was strongly and independently associated with the increased plasma NT-proBNP levels and suggested that such relationship may be explained by an increased sensitivity of NT-proBNP secretion in response to enhanced sympathetic activity, reflecting the severity of neurological impairment in which **Sander et al.,**[27] have demonstrated that a higher level of NT-proBNP in stroke patients is associated with increased sympathetic activation after stroke. So, in their study, they encourage the use of that peptide as a novel biochemical marker for risk stratification in patients after ischemic stroke.

The link between elevated plasma Hcy and vascular disease is well established with numerous studies confirming that hyperhomo-cysteinemia is a risk factor for atherosclerosis. **Nilsson et al.**[2] stated that the findings of elevation of plasma Hcy in elderly patients with mental disease (both organic dementia and affective disorders) and vascular disease support the hypothesis that hyperhomocysteinemia might play a role in the pathogenesis of mental disease and cognitive impairment through cerebrovascular injury **Seshadri et al.,**[28] stated that Hcy is harmful to neurons and blood vessels, including the cerebral microvasculature so that such effects

may contribute to the cascade of events that leads to cognitive decline, dementia, and depression in later life. In the present study higher levels of plasma Hcy and low level of plasma folate were detected in patients with depression and/or MCI as compared with the control group. These results came in accordance with several studies which revealed that late life depression is associated with high plasma Hcy. **Kim et al.[29]**, **Tiemeier et al.[30]** and **Bottiglieri et al.[31]** had previously shown that older adults with depression have higher Hcy levels than normal controls or patients with neurological illnesses. A large cross-sectional Norwegian study has also found that subjects with depression were more likely to have high plasma Hcy, but not low plasma B_{12} or folate[32].The mechanisms that underlie the association between plasma Hcy and depression remain largely unknown, but it is possible that such an association is at least partly mediated by cerebrovascular illness in the form of strokes or white matter disease[33]. The latter could include mechanisms involving disturbed cellular methylation, which are critical to the synthesis and metabolism of norepinephrine, serotonin and dopamine which may be related to depression of mood. The Hcy depression hypothesis, if true, would mandate inclusions of imaging studies for cerebrovascular disease and measures of Hcy, folate, and B_{12} and B_6 vitamins in the clinical evaluation of older depressed patients[17]. Furthermore, it has been suggested that homocysteic acid and cysteine sulfinic acid, as metabolites of Hcy, may have an excitotoxic effect on the *N*-methyl-D aspartate receptors in the CNS. They may also inhibit the *S*-adenosylmethionine–dependent methylation of biogenic amines and phospholipids[34,35]. Thus, although Hcy could theoretically cause depression via direct neurotoxicity, an elevated plasma Hcy concentration may merely be a marker of impaired monoamine metabolism, which causes depression through reduced CNS methylation.

The atherosclerotic and thrombogenic promoting effect of Hcy may also increase the risk for stroke and cerebrovascular disease, which in turn are related to cognitive impairment and dementia[36]. Several mechanisms for the effects of Hcy on cognitive decline have been proposed. Hcy might influence cognition through a direct toxicity on glutamate neurotransmission and cerebrovascular endothelium, an indirect inhibition of transmethylation reactions in brain, potentiation of amyloid neurotoxicity and promotion of tau phosphorylation[37]. It has been hypothesized that inadequate B vitamin status and high Hcy concentrations may contribute to cognitive decline through silent brain infarction[38]. In vivo studies using animal models of Alzheimer disease (AD) showed that hippocampal neurons cultured without folate, or with added Hcy, undergo increases in reactive oxygen species, phospho-tau immunoreactivity, and other indicators of apoptosis[39]. The results of the present study came in accordance with those of **Russo et al.[40]**, **Vidal et al.[41]** and **Kim et al.[42]** who stated that hyperhomocysteinemia has been

associated with cognitive impairment in various neurological diseases. **Haan et al.**[43], **Troen and Rosenberg**[36] added that if elevated Hcy promotes cognitive dysfunction, then lowering Hcy by means of B-vitamin supplementation may protect cognitive function by arresting or slowing the disease process. In contrast, the results from the Rotterdam Study showed that plasma Hcy is not associated with either cognitive impairment or decline.[44] In the present study, it was observed that the severity of cognitive decline assessed by the MMSE was significantly negatively correlated with hyperhomocysteinemia. Similar associations between plasma Hcy and the MMSE have been reported by other investigators studying patients with dementia.[45,46] However, **Kalmijn et al.**[44] failed to confirm such association between plasma Hcy and cognitive decline. Various possible explanations for the lack of an association have been offered based largely on methodological differences.

Both MDD and MCI are complex disorders that thought to result from multiple genes in combination with environmental and developmental components[47]. A common missense mutation of the MTHFR gene (C677T) has been shown to be a risk factor for premature cardiovascular disease and neural tube defect. Deficient activity of MTHFR has also been implicated in the pathogenesis of psychiatric conditions such as schizophrenia and affective disorders[48]. In the present study, MTHFR TT homozygous was significantly more common among depression patients groups as compared with control. Elderly people carrying TT genotype of MTHFR gene had higher serum level of Hcy and NT-proBNP as compared with CT and CC genotypes. Moreover, TT genotype subjects are more depressed and had higher scores on HRSD than those carrying CT or CC genotypes. The results of the present study came in accordance with those of **Gilbody et al.**[49] and **Kempisty et al.**[48] who demonstrated an association between the MTHFR C677T variant and depression, schizophrenia, and bipolar disorder (BD). The association of 677TT genotypes with BD and schizophrenia may be linked to the excitatory amino-acids hypothesis and/or decreased SAM concentration of blood plasma in neuropsychiatric disorders. Such association may suggest the shared genetic defects in these disorders. **Gaysina et al.**[47], **Almeida et al.**[8] and **Bjelland et al.**[32] reported that the MTHFR 677TT genotype, is associated with a significant elevation in the circulating concentrations of Hcy and a decrease in serum folate concentrations. This may parallel a similar reduction in 5-methyltetrahydrofolate in the CNS, leading to a potential reduction in monoamine neurotransmitter function and an elevated risk of depressive disorder but **Gaysina et al.,**[47] found no significant differences in genotype or allele frequencies between depressive patients and controls. So, they suggested that the MTHFR C677T polymorphism is not involved in the etiology of clinically significant recurrent unipolar MDD. In contrast **Kunugi et al.**[50], **Arinami et al.**[51] suggested that homozygosity for the

T677 allele of the MTHFR gene is unlikely to play a major role in the pathogenesis of schizophrenia or affective disorders in their samples. Such discrepancies between different reports describing the contribution of MTHFR polymorphism to BD and schizophrenia may be partially due to socio-economic status. Also, it could be explained by low statistical power due to the limited number of cases, combined with the low frequency of MTHFR T/T homozygosity. So that a further exploration of the involvement of the MTHFR gene in the susceptibility to affective disorders, with larger sample sizes, are needed to fully establish the role of the MTHFR gene.

The present data do not provide evidence for an association between the MTHFR C677T mutation and MCI which did not coincide with the results of **McIlroy et al.,**[52] who stated in their study that possession of the T allele of the MTHFR C677T polymorphism significantly increases risk for vascular dementia (VaD). When the VaD group was compared with the nondemented stroke patients group, the T allele was significantly overrepresented in the former, leading to the possibility that this allele confers increased risk for dementia after stroke. It is feasible that this increased risk could be mediated by the effect of the reduction in activity of the enzyme associated with the substitution of valine for an alanine residue, leading to an increase in Hcy levels. But the present study came in accordance with the results of **Almeida et al.**[8], **Religa et al.**[53], **Brunelli et al.,**[13], **Gussekloo et al.**[54], **Chapman et al.**[55] who found no relation between the common mutation in the MTHFR gene and cognitive impairment in older persons.

Therefore, their data showed that homozygosity for the C677T mutation in the MTHFR gene is not a genetic risk factor for cognitive impairment in the oldest old. A possible explanation of increased plasma concentrations of Hcy are associated with cognitive impairment in older persons, whereas there is no association with the common MTHFR mutation is that the increased plasma concentration of Hcy is a phenomenon associated with cognitive impairment or its treatment, instead of being part of the causal mechanism. Another possibility could be that the number of persons was too small to find significant differences between the MTHFR genotypes and the cognitive measurements.[54] Conflicting results between the outcomes of studies that used plasma concentrations of Hcy and studies that used the MTHFR polymorphism have been reported for other diseases also. Increased plasma concentrations of Hcy were associated with the occurrence of stroke, however, no association was found between the various MTHFR genotypes and the risk of stroke[56]. In the present study an association between the C677T mutation and plasma Hcy levels, regardless of folate status, was shown. That result suggested that the C677T mutation and Hcy concentrations are so closely associated that folate levels cannot compensate for the reduced activity of the MTHFR enzyme and hyperhomocysteinemia. These data are supported by the results of the study of **Husemoen et al.**[57] in which plasma Hcy levels were significantly

higher in TT individuals compared to CC and CT individuals with normal folate status. **Religa et al.**[53] stated that moderate homocysteinaemia was found in subjects with the TT genotype when the level of folic acid was low ,suggesting that individuals having the TT genotype should obtain higher folate intake to minimize the risk of developing dementia. In contrast **Kim et al.**[58] found no association between C677T polymorphism and Hcy levels. Finally in the present study, NT-proBNP concentrations were significantly higher in patients with the C677T mutation compared to patients without the mutation. This is supported by the results of **Cho et al.**[9] and **Pathare et al.**[59] study who found an association between the CT genotype and vascular disease in mild hyperhomocysteinemia

Conclusion

It has been shown that increased Hcy and NT-proBNP are frequently present in elderly patients with depression and/or MCI. Fully elucidating the link between depression and/or MCI and elevated levels of both Hcy and NT-proBNP concentrations may prove an important step toward understanding the association between major depression and/or MCI with either cerebrovascular or cardiovascular upsets. The MTHFR C677T gene variation may play an important role in the modulation of mood but does not contribute to genetic susceptibility to cognitive performance in later life. The MTHFR C677T mutation is associated with both plasma Hcy and NT-proBNP levels. In depression and/or MCI patients with MTHFR C677T mutation, prospective observation of the development of cerebrovascular or cardiovascular upsets, involving periodic repeated measurement of Hcy and NT-proBNP concentrations may be needed.

Recommendations: whether the elevated levels in Hcy and NT-proBNP in both depression and MCI may be due to vascular pathogenesis of both disease entities or it may be due to accompanying silent cardiovascular disease, needs further investigations with further performing a correlation between both Hcy and NT-proBNP with routine markers for cardiac injury. Also, as a continuation of that study it remains to be shown if supplementation with B vitamins and/or homocysteine lowering therapy, could influence the rate of cognitive decline and/or depression.

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الجزء النهائى ناحية N من الناتروريتك من النوع B، الهوموسيستيين والطرز الجينية لجين التتراهيدروفولات ريدكتيز فى الإكتئاب والإضطراب المعرفي البسيط في آخر العمر

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يعتبرالجزء النهائى ناحية N من الناتروريتك من النوع B من عوامل الخطر لامراض القلب أما الهوموسيستين فهو ينتج عن أيض الحمض الأميني الميثيونين وإن أحد العوامل التي تؤثر في ذلك هو تغير الطرز الجينية لجين التتراهيدروفولات ريدكتيز. و قد وجد أن الأشخاص الذين يحملون الطراز الجيني (تي-تي) يكون مستوي الهوموسيستين لديهم في الدم مرتفع و لذلك يصبحون أكثر عرضة للإصابة بأمراض الاكتئاب و العته و الاضطراب المعرفي البسيط.ويهدف البحث الىتقييم دور تغير الطرز الجينية لجين التتراهيدروفولات ريدكتيز والهوموسيستين و الفولات بلاضافة الى الجزء النهائى ناحية N من الناتروريتك من النوع B في المرضى المصابين بالاكتئاب و الاضطراب المعرفي البسيط ذو البداية المتأخرة. وقد شملت هذه الدراسة60 مريضا (32 مريضا بالاكتئاب و28 يعانون من الاضطراب المعرفي البسيط) و متوسط أعمارهم 62.25± 6.28 (33 إناث و27 ذكور) بالإضافة إلى 20 من الأصحاء كعينة ضابطة ملائمة للمرضى في العمر و الجنس. وقد قمنا بدراسة أنواع الطرز الجينية لجين التتراهيدروفولات ريدكتيز و مستوى الهوموسيستين و الفولات و الجزء النهائى ناحية N من الناتروريتك من النوع B في الدم لجميع المرضى والأصحاء و قمنا بتشخيص مرض الاكتئاب و قياس شدته باستخدام مقياس هاملتون للاكتئاب و قياس الوظائف المعرفية باسخدام مقاييس فحص الحالة الذهنية القصير، ذاكرة الوجوه، قائمة الكلمات، أزواج الكلمات المرتبطة، تصميم المكعبات ، و الطلاقة اللفظية الجزئين الأول و الثاني. وقد أظهرت الدراسةأن مرضى الاكتئاب و مرضى الاضطراب المعرفي البسيط يكون مستوي الهوموسيستينو الجزء النهائى ناحية N من الناتروريتك من النوع B لديهم أعلى و مستوى الفولات أقل من العينة الضابطة و أن الفرق ذو دلالة إحصائية. و قد وجد أن المرضى الذين يحملون الطراز الجيني (تي-تي) يكون مستوي الهوموسيستين و الجزء النهائى ناحيةN من الناتروريتك من النوع B لديهم في الدم أكثر ارتفاعا من المرضى الذين يحملون الطراز الجيني (تي-سي أو سي-سي) و أن الفرق ذو دلالة إحصائية وكذلك اكتئابا أشد و لكن ليس اضطرابا معرفيا أكثرمن المرضى الذين يحملون الطراز الجيني (تي-سي أو سي-سي) و قد وجد أنه كلما ارتفعت نسبة الهوموسيستين في الدم كلما زادت شدة الاكتئاب والاضطراب المعرفي.
الخلاصة: من هذا يمكن أن نستخلص ان ارتفاع مستوى الهوموسيستيين و الجزء النهائى ناحيةN من الناتروريتك من النوع B فى الدم يمكن أن تشكل عوامل خطورة مع غيرها من العوامل الأخرى فى الإصابة بمرض الاكتئاب و الاضطراب المعرفي البسيط في أواخر العمر و أن المرضى الذين يحملون الطراز الجينى (تى-تى) هم أكثر عرضة للإصابة بالاكتئاب و ليس الاضطراب المعرفي البسيط في أواخر العمر. و أن ارتفاع نسبة الجزء النهائى ناحية N من الناتروريتك من النوع B فى الدم تحتاج الى دراسة أخرى لمعرفة علاقتة السببية بمرض الاكتئاب و الاضطراب المعرفي البسيط في أواخر العمر