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Article

Evaluating homocysteine as a biomarker for bipolar disorder

Hoda Gamaleldeen*, Dalia Elneily, Tarek Molokhia, Adel Elsheshai

Department of Psychiatry, Faculty of Medicine, Alexandria University, Egypt

*Correspondence: Hoda Gamaleldeen, Assistant Lecturer of Psychiatry, Department of Psychiatry, Faculty of Medicine, Alexandria University, Egypt. E-mail: hoda.gamal@alexmed.edu.eg.

Abstract

*Background***:** Bipolar disorder (BD) is a serious mental health disease that affects both men and women. The main objectives for this study were evaluating the level of homocysteine in bipolar patients, and clarification the association between Hyperhomocystinemia (HHcy) and clinical variables and disease severity among psychiatric inpatients in El-Hadara Alexandria university hospital psychiatric wards. *Method:* 60 subjects (30 healthy control, 30 bipolar cases) Homocysteine levels was measured by chemiluminescence technique, then the cases group had been assessed by obtaining detailed clinical data concerning any change in disease severity and its correlation with homocysteine level *Results:* homocysteine level was significantly higher in cases group (25.25 ± 12.93) than control group (9.88 ± 3.89),homocystiene level was positively correlated with severity of bipolar represented with clinical global impression scale.

Keywords: bipolar, homocysteine, biomarker, Alexandria.

Introduction

In epidemiological surveys utilising the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, the lifetime prevalence of bipolar disorder is between 0.3 percent and 1.5 percent for bipolar I disorder (BD-I) and between 1.0 percent and 2.0 percent for bipolar II disorder (BD-II).(1-3)

However, accumulating evidence implies that there is a far broader BP spectrum than currently recognised by diagnostic terminology.(4)

Because they do not meet the DSM-IV-TR diagnosis of a 4-day hypomanic episode, a significant minority of community patients (33.5-55%) may not be diagnosed with BP-II.(4)

It's possible that Hcy's connection with glutamatergic transmission is the key relationship between Hcy and psychiatric illnesses.Within N-methyl-D-aspartate (NMDA) receptors, both Hcy and its oxidative metabolite, homocysteic acid, act as agonists.(5)

Hyperhomocysteinaemia-induced long-^{term} NMDA receptor activation causes an increase in calcium ion influx, which causes neurotoxic consequences.(6)

Presynaptic glutamate release increases NMDA receptor currents in postsynaptic neurons, potentially leading to excitotoxicity.(7)

Increasing glutamate levels have been linked to increased mitochondrial reactive oxygen species generation and excitotoxicity in bipolar disorder (BD).

The possible influence of homocysteine or pro-inflammatory mediators, which impair the neurons' resilience capacity in the face of subsequent stressors, can exacerbate the endogenous load of oxidative stress and the resulting neuronal susceptibility.

This is thought to play a role in the pathophysiology of mood disorders.

Inflammatory responses and homocysteine-regulated pathways are also thought to be potential inhibitors of synaptic connections in mood circuits.(8)

Biomarker-related strategies in the treatment of mood disorders have shifted to a more recent investigational approach, as such approaches may modulate plasticity mediators at the cellular level and alter cellular—molecular degenerative processes as well as energy metabolism.(9)

Potential mediators, such as homocysteine levels, inflammatory cytokines, neurotrophins, and oxidative species, contribute to the allostatic load, which influences neural stability or homeostasis.(10)

Materials and methods

Participant and procedures

150 subjects were evaluated for cases group were among bipolar patients in El-Hadara university hospital psychiatric wards. and for control subjects,to be eligible subjects must have the criteria of Age from (18 to 80) years, Patients with previous diagnosis of bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition revised (DSM -IV-TR) criteria,(11) and Controls of matched demographic Data of patients, they were excluded if they Refused to participate in the study, their Age was less than18 years, if the Controls had a

personal or family history of psychiatric disorders, if they have History of any organic brain diseases, or
History of substance dependence, or presence of substance abuse within the past 6 months before the study. (70) subjects were ineligible; (80) subjects met the inclusion criteria and were invited to orientation. Of these, (60) attended the orientation session, provided written informed consent to participate, and were assigned to one of the two groups: one control group composed of (30) subjects were assigned to assessment of homocysteine level and another cases group: composed of (30) students were assigned to also assessment of homocysteine level and assessment of correlation between homocysteine level and severity of bipolar by clinical global impression scale.

Data Collection and assessment

A pre-designed structured interview questionnaire had been used to collect the following data such as socio-demographic data as age, sex, residence, educational level, marital status and occupation and income., Medical and psychiatric history including family history of psychiatric illness for patients and control subjects, Duration of illness, age of onset, number of hospitalizations, psychotropic medications (type, dose and duration of treatment), and concomitant medications for patients. Semi structured interview using diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV-TR) criteria for assessment of bipolar disorders.(11)

Clinical medical examination including neurological examination and Psychometric assessment using Clinical global impressions scale (CGI).(12)

Laboratory assessment

Complete blood count,(13) Homocysteine levels was measured by chemiluminescence technique.(14)
Detailed clinical data had been collected from cases group concerning any change in disease course and severity and their relation to homocysteine level.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages.
Quantitative data were described using mean, standard deviation. Chi-square test for categorical variables, to compare between different groups. Fisher's Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5. Student t-test for normally distributed quantitative variables, to compare between two studied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. The significance of the obtained results was judged at the 5% level.

Ethical considerations

Before conducting this research, ethical approval was obtained from the ethical committee (EC) of Alexandria University Faculty of Medicine. This EC has had a federal-wise assurance (FWA) for more than 20 years now.(15). It operates according to the International Conference of Harmonization Good Clinical Practice (ICH GCP) and applicable local and institutional regulations and guidelines.(16)

Informed consent

Informed consent was obtained from all patients to use their anonymous data for research Purposes.

Results

The present study included 60 subjects; 30 bipolar patients; 30 healthy control subjects.. The mean age of the bipolar patients (37.13 ± 10.44 years old) was lower than that of control (39.27 ± 12.36 years old) but the difference was not statistically significant (p= 0.473).(table I)
According to gender there were more female subjects 53.3% than male 46.7% in case group and also in control group that were 56.7% females and 43.3 % but the difference was not statistically significant (p= 0.795).

Table (I): Comparison between the two studied groups according to demographic data

	Cases (n = 30)		**Control (n = 30)**		**p**
	No.	**%**	**No.**	**%**	
Gender					
Male	14	46.7	13	43.3	0.795
Female	16	53.3	17	56.7	
Age (years)					
Min. – Max.	21.0 – 56.0		20.0 – 58.0		
Mean ± SD.	37.13 ± 10.44		39.27 ± 12.36		0.473
Median (IQR)	35.50(28.0 – 45.0)		38.50(29.0 – 48.0)		

IQR: **Inter quartile range** SD: **Standard deviation** **t: Student t-test**

χ^2: **Chi square test**

p: p value for comparing between the studied groups

(II)- Episode distribution and psychometric assessment

In the present study there was 19 cases were in a manic episode, 11 cases were in depressive episode, Hamilton scale was done to depressive cases with mean scores 18.18 ± 4.24 and young mania scale was done to manic patients with mean scores at 42.05 ± 13.20.

And Clinical global impression scale (CGIS) was done to all cases with mean scores at 4.93 ± 1.86.

Table (II): Descriptive analysis of the studied cases according to different scale at zero in cases group (n = 30)

	No.	Min. – Max.	Mean ± SD.	Median (IQR)
Hamilton scale	**11**	10.0 – 23.0	18.18 ± 4.24	19.0 (16.5 – 21.5)
Young-mania scale	**19**	20.0 – 60.0	42.05 ± 13.20	40.0 (32.5 – 54.5)
Clinical global impression scale (CGIS)	**30**	2.0 – 7.0	4.93 ± 1.86	5.50 (3.0 – 7.0)

IQR: **Inter quartile range** SD: **Standard deviation**

Homocysteine level was higher in cases group by mean (25.25 ± 12.93) than control group by mean (9.88 ± 3.89)

Table (III): Comparison between the two studied groups according to homocystiene level

Homocystiene level at zero (μmol/L)	**Cases (n = 30)**	**Control (n = 30)**	**p**
Min. – Max.	7.89 – 65.0	0.87 – 18.56	<0.001*
Mean ± SD.	25.25 ± 12.93	9.88 ± 3.89	

SD: **Standard deviation**

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

IV- Correlation between Homocysteine level with severity of disease represented by Clinical global impression scale (CGIS) in cases group

In this study the severity of the episode (manic or depressive, mixed) calculated by **Psychometric assessment using (**clinical global impression scale) have a positive relationship with the homocysteine level.

Which mean the more the severity of the episode the more the level of homocysteine, And this relationship is statistically significant as shown in table (IV)

Table (IV): Correlation between Homocystiene level with Clinical global impression scale (CGIS) in cases group

Homocystiene level (μmol/L) vs.	At zero		
	No.	r	p
Clinical global impression scale (CGIS)	**30**	0.761	<0.001*

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

Discussion

Although there is emerging evidence linking elevated Hcy levels to psychiatric diseases, the specifics of this connection are still unknown.

As a participant in numerous processes, Hcy plays a complex role in the Central Nervous System (CNS).

It has been suggested that the key mechanism connecting Hcy and psychiatric diseases, such as BD, together is a change in glutamatergic neurotransmission.(5)

The emerging subject of psychiatric research on the gut-brain-microbiome axis may be relevant.(17)

Given the variable nature of the gut microbiota, more knowledge about the potential molecular links between microorganisms and the brain may become available as this area matures.(18) This may lead to the identification of new targets for therapeutic intervention.

Discussion should be had on the study's strengths and weaknesses.

At first, we only included a small number of studies that used a cross-sectional design, which in addition to having other potential problems such confounding and selection bias, prevents the inference of causality.

Because the scatterplot was symmetric, we were able to rule out publication bias, a problem with biomarkers in mental diseases such major depressive disorder (19) and BD, This is a strength of the meta-analysis.

Additionally, we calculated that 148 missing research with null results would be required in order to invalidate our significant findings.

Additionally, there are so few studies that we were unable to analyse the connection between depressive symptoms and Hcy because we could only find one article that did so.(20)

Similarly, we were unable to conduct meta-regressions to examine any potential relationships between sex, age, and Hcy levels in this subgroup due to the small number of papers that were discovered for mania.

Importantly, drugs such lamotrigine or valproate can affect Hcy levels (19), and all of the patients included in the study were receiving pharmaceutical therapy.

Also, although peripheral Hcy levels were established in all investigations, it is uncertain if these levels are indicative of central Hcy levels given that the CNS and the periphery have different Hcy metabolic routes.(21, 22)

If accessible, information on significant genotype variants would have been helpful as well. Similarly, longitudinal data would be useful to assess whether Hcy is a biomarker of trait or condition from a pathophysiological perspective and whether it may also have clinical utility as a diagnostic of prognosis and/or treatment response.

To be mentioned our results was on line with other studied that showed the homocysteine levels was elevated in the patients with bipolar disorders (23) , In that study(23), Chinese patients with SCZ, BD, and MDD were compared across numerous common biochemical indicators in terms of inflammation, stress hormones, and nutrition.

On other study (24) with the similar demographic data of the patients that 80 patients in remission from BD type 1 were recruited from their outpatient clinic. Patients were adults aged 18–65 years and similar measures of diagnosis as they used for diagnosis of BD was established on the basis of criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision; DSM-IV-TR), According to this study, patients in the HHcy group had noticeably more mixed episodes throughout their illness.

And also our results was similar to previous study (25) that measured oxidative stress biomarkers in drug-free patients with bipolar disorder, and found malondialdehyde (MDA), advanced oxidation protein products (AOPP), protein carbonyls (PC) and homocysteine (Hcys) concentrations and glutathione peroxidase (GSH-Px) activity were significantly increased in patients compared to controls .

Unlike other studies (26) that showed No statistically significant differences were found in Hcy or CRP levels in patients with newly diagnosed BD or their first degree URs (unaffected relatives) compared with healthy controls.

Conclusion

Our study provide evidence that homocysteine level is a potential biomarker for bipolar disorder independently of age and sex, and as its level elevated in bipolar patients rather than control and also its level correlated with the severity of the mood episodes.

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No finds were received for this project.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

None to declare.

Data availability

The data are available upon request.

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