Psychiatry Research 259 (2018) 364–369

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Prevalence and clinical-demographic correlates of hyperhomocysteinemia in inpatients with bipolar disorder in a Han Chinese population

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ARTICLE INFO

Keywords:
Homocysteine
Bipolar disorder
Prevalence
Body mass index
Valproate
Lithium

ABSTRACT

Recent studies have reported that hyperhomocystinemia (HHcy) is highly prevalent in patients with bipolar disorder (BD), placing them at greater risk of cardiovascular disease and possibly serving as a disease biomarker. However, the correlation of HHcy with demographic or clinical parameters is not well known. In this study, we examined the prevalence of HHcy and its association with these parameters in a sample of Chinese BD patients. Fasting plasma homocysteine (Hcy) levels were determined in 198 BD inpatients and 84 healthy controls. HHcy was defined when Hcy concentration exceeded 15.0 μmol/L. Affective symptomatology was assessed by the Young Mania Rating Scale, Hamilton Depression Rating Scale and the Clinical Global Impressions severity scale. Compared to healthy controls, BD patients had a significantly higher prevalence (34.85% vs. 19.05%) of HHcy and a higher absolute level of homocysteine. Logistic regression analysis demonstrated that BD patients with HHcy were more likely to be male, have elevated BMI, more frequent treatment on lithium but less on valproate. These results suggest that Chinese inpatients with bipolar disorder have a higher rate of HHcy than the general population, and those at greatest risk are male, have an elevated BMI, and take more lithium but less valproate therapy.

1. Introduction

High homocysteine (Hcy) levels have been associated with neuropsychiatric disorders such as schizophrenia or affective disorders (Levine et al., 2005; Vuksan-Cusa et al., 2013; Moustafa et al., 2014). Hyperhomocystinemia (HHcy) has been associated with major depression (Ghanizadeh et al., 2015), and several studies have shown elevated Hcy levels in bipolar disorder (BD) patients (Osher et al., 2004, 2008; Dittmann et al., 2007; Ezzaher et al., 2011; Baek et al., 2013; Chiarani et al., 2013; Permoda-Osip et al., 2013; Awara et al., 2014). Males are more likely to exhibit HHCy than females during a bipolar depressive episode (Permoda-Osip et al., 2013, 2014). This may bear some relationship with medically-induced, diet-induced, or psycopathology-related vitamin B12 and folate vitamin deficiencies, as an inverse relationship between Hcy and these vitamins has been demonstrated in BD patients (Permoda-Osip et al., 2013). Neurocognitive impairment has been found to be a marked feature in BD patients (Demmo et al., 2017; Purper-Ouakil et al., 2017; Träger et al., 2017). Furthermore, elevated Hcy level has been associated with neurocognitive deficits, especially in older BD patients or those with a delayed onset of the disorder (Dias, 2009; Moustafa et al., 2014). In addition, two studies have reported an association of two common polymorphisms in the methylenetetrahydrofolate reductase (*MTHFR)* gene (C677T and A1298C), the product of which processes homocysteine, with BD. These polymorphisms may predict the development of comorbid metabolic syndrome in BD patients (Peerbooms et al., 2011; Ellingrod et al., 2012). Taken together, the findings suggest that Hcy may be considered as a potential biomarker or therapeutic target in BD (Ghanizadeh et al., 2015).

A recent meta-analysis demonstrated that, in China, the lifetime prevalence is 0.11%, much lower than Western estimates and necessitating reexamination of BD pathology in Chinese patients (Zhang et al.,

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http://dx.doi.org/10.1016/j.psychres.2017.08.063
Received 1 July 2016; Received in revised form 29 May 2017; Accepted 23 August 2017
Available online 24 August 2017

2017). BD is associated with a high mortality rate and is associated with a 10–20 year decrease in life expectancy as compared to the general population (Miller and Bauer, 2014). Cardiovascular disease (CVD) —defined as cerebrovascular disease, cardiac arrest, and coronary heart disease including acute myocardial infarction— causes a disproportionately large number of deaths in BD as compared to population rates (Miller and Bauer, 2014; Weiner et al., 2011). Several lines of evidence indicate that Hcy serves as an important atherosclerotic factor; the link between HHcy and cardiovascular diseases including coronary artery disease, myocardial infarction, cerebrovascular disease and peripheral occlusive disease (Trimmer, 2013) is well-established (Moustafa et al., 2014).

Two recent studies reported that HHcy was more frequent in bipolar I patients (Ezzaher et al., 2011) and during a bipolar depressive episode (Permoda-Osip et al., 2013). However, no study has reported the prevalence of HHcy in Chinese BD patients. The aims of the present study were to evaluate the prevalence of HHcy and examine the demographic and clinical correlates of HHcy in a comparatively large sample of Chinese BD patients. We hypothesized the following: (1) the rates of HHcy would be significantly higher in BD patients than the normal population; (2) some demographic characteristics and clinical symptoms would be correlated with HHcy in BD patients.

2. Methods

2.1. Subjects

We conducted a cross-sectional naturalistic study at Beijing Huilongguan Hospital, a city-owned psychiatric hospital. 198 subjects (male/female = 107/91) were randomly and selectively recruited out of all BD patients in the hospital; 104 were manic, 69 were depressed, and 25 patients were in remission. We did not recruit any patients in a hypomanic or mixed-manic episode in order to avoid possible subtype confounding effects and to allow comparison to previous studies (Ezzaher et al., 2011; Permoda-Osip et al., 2013). All patients met the following inclusion criteria: (1) age 18–65 years old, Han Chinese; (2) DSM-IV diagnosis of BD, which two psychiatrists confirmed based on the Structured Clinical Interview for DSM-IV (SCID). (3) ≥ 2 years diagnosed with BD; and (4) receiving stable doses of oral mood stabilizers and/or antipsychotic drugs for ≥ 6 months prior to study entry.

Eighty-eight healthy outpatient controls (males/females = 44/40) matched for age, gender and education were recruited from the local community through the advertisement in media and the pamphlets distributed to local residents. A research psychiatrist assessed, via an unstructured clinical interview, current mental status, personal psychiatric history, and family psychiatric history to identify the presence of mental disorder. If an Axis I disorder was present, they were to be excluded from the study; however, none of the recruited controls had a personal or family history of psychiatric disorders. Unstructured interviews consist of questions posed by the psychiatrist, and both patient responses and behavior were used to ascertain the presence or absence of a diagnosis. This type of interview is considered unstructured because there is no standardization of questioning or recording of patient responses. The research psychiatrist was entirely responsible for deciding what questions to ask and how the resulting information was used in making a diagnosis. The accuracy of diagnoses based on unstructured interviews depends a great deal on the research psychiatrist's ability to recognize DSM-IV diagnostic symptoms.

All subjects were Han Chinese from the Beijing area. Both the patient and normal subjects had a similar socioeconomic status and dietary patterns. Since our patients were comparatively less educated and most of them had a labor job with comparatively less protein diet, we recruited healthy controls from a population demographic which matched these characteristics. We obtained a complete medical history and physical examination and laboratory tests from patients and control subjects. All subjects were in good physical health. Exclusion criteria for the BD patients and healthy controls included: (1) current major medical problems; (2) history of any organic brain diseases; (3) history of substance dependence, or presence of substance abuse within the past 6 months before the study; (4) unable to provide the written informed consent.

All subjects gave written informed consent, which was approved by the Institutional Review Board of Beijing Hui-Long-Guan hospital.

2.2. Data collection

Each subject filled out a detailed questionnaire that recorded general information, sociodemographic characteristics, smoking behavior, medical and psychiatric conditions. The following data were obtained for all the subjects from their medical records: duration of illness, age of onset, number of hospitalizations, mood stabilizers, antipsychotic medicines (type, dose and duration of treatment), and concomitant medications. Additional information was collected from available medical records and collateral data (from family and/or treating clinicians). Additional visits were requested for subjects with missing or ambiguous data.

2.3. Plasma Hcy levels testing

A five milliliter sample of venous blood was taken in the morning from each participant following 12 h of fasting. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and, within 15 min, centrifuged (3000 rpm for 5 min). Serum samples were stored at −80 ℃ until analysis. The Hcy levels were measured by high-performance liquid chromatography (HPLC) with fluorescence detection after derivatization according to a previously described method (Feussner et al., 1997; Frick et al., 2003). As described in previous studies, HHcy was defined when Hcy concentration exceeded 15.0 μmol/L (Ezzaher et al., 2011; Permoda-Osip et al., 2013).

2.4. Body mass index measurement

Body weight and height were assessed to calculate body mass index (BMI; weight for squared height, kilograms per meter squared). Height was measured with the subjects barefooted and standing upright. Body weight was measured with an electronic scale. All measurements were taken in light indoor clothing.

2.5. Clinical assessment

Affective symptoms were assessed with the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAMD, 17-item version), and the Clinical Global Impressions severity scale (CGI-S) by three clinical psychiatrists.

To ensure consistency and reliability of ratings across the study, the psychiatrists, who had worked at least 5 years in clinical practice, attended a training session on the use of the YMRS, HAMD and CGI-S before the start of the study. After training, repeated assessment showed that an inter-observer correlation coefficient greater than 0.8 was maintained for the YMRS, HAMD, and CGI-S total scores.

2.6. Statistical analysis

The prevalence of HHcy was analyzed by X^2 test. Odds ratios (OR) derived from logistic regression analyses compared HHcy and non-HHcy among the BD patients and controls after controlling for the related variables. Since homocysteine level, age of illness onset, and illness duration did not follow a normal distribution, we applied the log transformation to makes the data normal distribution first, and then we used these transformed numbers in the following statistical tests. Demographic and clinical variables were compared between groups using analysis of variance (ANOVA) for continuous variables and X^2 for