Article

Cognitive Ability and the Level of Serum Homocysteine Correlations in First-Episode Schizophrenia Subjects

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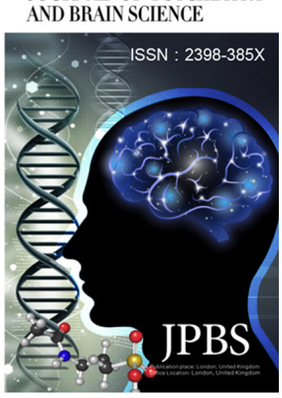

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ABSTRACT

Objective: To explore relationships between cognitive ability and first-episode schizophrenia patient serum homocysteine (Hcy) levels.

Methods: One hundred and twelve (112) first-episode schizophrenia patients (FESP) were selected for the schizophrenia group (SG) and 100 healthy volunteers were selected as the healthy control group (CG or HCG). High homocysteine septicemia (HHcy) and serum Hcy levels were compared between the two. SG Patient psychiatric symptoms were assessed using the Positive and Negative Symptoms Scale (PANSS). Hcy and Non-Hcy subjects cognitive abilities were assessed using the Wisconsin Card Sorting Test (WCST) and MATRICS Consensus Cognitive in Schizophrenia (MCCB).

Results: SG serum Hcy levels were significantly higher than HG Hcy levels with a statistical significance ($p < 0.01$). HG serum Vitamin B12 (VB12) levels were significantly higher the SG with a statistical significance ($p < 0.05$). Folic acid levels of the two groups was different in a statistically significant ($p > 0.05$) way. The difference in the MCCB total score (89.22 ± 3.06) of HHcy SG subjects and non-HHcy SG subjects (96.11 ± 2.74) was a statistically significant ($p < 0.05$). WCST scores, categories completed (Cc) and correct responses (Rc) of HHcy subjects compared to non-HHcy patients were significantly lower and was statistically significant ($p < 0.05$). HHcy subjects error responses (Re), perseverative responses (Rp), and non-perseverative responses (nRp) were significantly higher than non-HHcy subjects and was statistically significant ($p < 0.05$).

Conclusion: Serum Hcy elevation may be used as a laboratory assistant diagnostic index for cognitive dysfunction severity in first-episode schizophrenics.

Keywords: First-episode; Schizophrenia; Homocysteine; Cognitive ability

1 INTRODUCTION

Schizophrenia is a highly recurrent, severely disabling severe chronic mental illness. It brings serious mental and economic burdens to the sufferer's family and negatively impacts society in ways that cannot be overderestimated [1]. Apart from any positive or negative symptoms, schizophrenia patients have significant cognitive disorders and dysfunctions. Currently, the cognitive disorder is recognized clinically as one of the core symptoms of schizophrenics. Schizophrenia pathogenesis and development mechanisms are, as yet, not fully clear. Some studies suggest that schizophrenia pathogenesis may be associated with, among others, DNA methylation changes, mitochondrial dysfunction, glutamate neurotransmitter disorders, and folic acid reduction.

Serum homocysteine (Hcy) is an intermediate which contains quinine amino acid produced after methionine demethylation in the methionine cycle. Clinical trials show that Hcy participates in in-vivo methylation reactions of important substances such as norepinephrine (NE), proteins, and DNA [2-3]. The studies found that schrizophrenic's Hcy levels are significantly increased. Hcy elevates neuronal apoptosis to toxic levels. Abnormal Hcy metabolism may cause DNA methylation abnormalities. It has been speculated that Hcy abnormality is a risk factor for the schizophrenia pathogenesis and morbidity and that schizophrenics' cognitive disorders may be associated with Hcy level increases [4]. Most of schizophrenic subjects in this study had a longer course of disease and their medication history treatment is unclear. Studies on FESP are relatively rare. This paper analyzes the relationships between serum Hcy levels and FESP cognitive functions in order further understand the role of serum Hcy in the schizophrenia pathogenesis.

2 SUBJECT AND METHODS

2.1 Research subject

The medical ethics committee of the Guangxi Zhuang Autonomous Region Brain Hospital authorized a total of 112 first-episode schizophrenia patients (FESP) treated at it between January 2015 and March 2016 to become the schizophrenia group (SG). One hundred 100 healthy volunteers became the healthy control group (CG). All schizophrenia patients (SP) met both the International Classification of Diseases (ICD-10) schizophrenia diagnosis criteria and China Classification of Mental Disorders-Third Edition (CCMD-3) PANSS score > 60 diagnosis criteria. Each subject's psychiatric symptoms were assessed by two attending psychiatric physicians trained in PANSS. Two physicians scored each case and the average of their scores was used to rate the subject. PANSS included: positive symptoms (PS); negative symptoms; general psychopathology (G); and, PANSS score [5-6].

Exclusion criteria: Patients with: severe organ injuries; mental retardation; a history of epilepsy, diabetes or other endocrine and metabolic disorders; a history of tobacco, alcohol, or other psychoactive substance abuse; and, pregnant or lactating women were excluded. There were 71 males and 41 female subjects in the SG. Their PANSS scores ranged from 63 to 98 points, with an average score of 78.6 ± 10.3. Their disease duration ranged from 1 to 15 months, with an average disease duration of 6.9 ± 2.7 months. No patients received antipsychotic medications before testing. Other information appears in Table 1. There was no significant difference in general clinical information between the two groups and an inter-group comparison was made ($p > 0.05$).

Table 1. Basic Information Comparisons

Group	Case		Average age (years)	
	Male	Female	Male	Female
SG	71	41	37.26 ± 8.19	35.38 ± 7.56
CG	64	36	38.44 ± 7.49	35.02 ± 8.07

2.2 Methods

2.2.1 Laboratory determination

In the early morning 4 ml of fasting venous blood was taken and divided into 2 ml for each. A heparin anticoagulant was added and the blood was centrifuged for 10 min at 3000 r/min. The serum was immediately separated and refrigerated at -20 ℃ for later testing. One serum sample was used to determine Hcy level. The Siemens BNII specific protein analyzer and a tHcy detection kit were used to determine Hcy levels using immuno-scatter turbidmetry (ISTM) in accordance with manufacturer operating instructions. The samples were divided into two groups by Hcy levels. A high homocysteine (HHcy) level was defined as a Hcy level higher than 15 μmol/L. A non-HHcy level was defined as a Hcy level lower than 15 μmol/L. The other serum sample was used to measure folic acid and vitamin B12 levels. Folic acid and vitamin B12 levels in the serum were determined with chemiluminescence using a Roche 2010 electrochemiluminescence analyzer and its FA, and VB12, detection kits.

2.2.2 Psychopathological assessment

Cognitive function was assessed using two scales: the MATRICS Consensus Cognitive in Schizophrenia (MCCB); and, the Wisconsin Card Sorting Test (WSCT) [7-9]. MCCB consists of 10 subtests involving seven dimensions: test or assessment of subject processing speed; attention/vigilance; working memory; language learning and memory; visual learning and memory; reasoning and solving abilities; and social cognition. WSCT was used to assess subject cognition, working memory and abstract summary.

2.3 Statistical methods

All data were analyzed and processed using statistical software SPSS 20.0. Measured data were expressed as mean value ± standard deviation ($\bar{x} \pm s$), when, for inter-group comparison, an independent sample t test was used. For intra-group comparison, a paired t test was used. Counting data were expressed as percentage, or rate, (n, %) and an χ^2 test was used for inter-group comparison. $p < 5$ means that the difference was statistically significant.

3 RESULTS

3.1 Comparison of laboratory serum indicator test levels in two groups

SG serum Hcy level and HHcy rates were significantly higher than for the CG. SG VB12 levels were significantly lower than for CG. The difference was statistically significant ($p < 0.01$). There was no significant difference in folic acid levels between the two groups ($p > 0.05$), as shown in Table 2.

Table 2. Comparison of Serum Levels

Group	Case	VB12 (pg /mL)	Folic acid (ng /mL)	Hcy (μmol /L)	HHcy (n, %)
SG	112	450.23 ± 124.88	5.40 ± 1.36	27.56 ± 10.59	34.82 (39)
CG	100	302.49 ± 148.19	5.54 ± 1.09	13.81 ± 6.71	7.00 (7)
t/x^2	-	7.87	0.82	11.14	5.47
p	-	< 0.01	0.41	< 0.01	< 0.05

3.2 SG MCCB score comparison of HHcy and non-HHcy

The SG HHcy MCCB score was 89.22 ± 3.06. The SG non-HHcy MCCB was 96.11 ± 2.74 and showed a statistical significance between two ($p < 0.05$), as shown in Table 3.

Table 3. Comparison of MCCB Scores between HHcy and Non-HHcy in Schizophrenia Group ($\bar{x}$ ± s)

Type	HHcy (39 cases)	Non-HHcy (73 cases)
Connection test	1.18 ± 0.49	1.19 ± 0.28
Symbol coding	19.33 ± 2.54	22.09 ± 3.05
Category fluency	17.21 ± 3.23	16.96 ± 3.54
Continuous performance test	1.16 ± 0.27	1.40 ± 0.18
Digital sequence	8.52 ± 1.03	9.10 ± 0.78
Room size	12.10 ± 1.78	11.69 ± 1.38
Language memory	11.86 ± 1.79	12.33 ± 1.54
Visual memory	11.32 ± 2.23	13.89 ± 2.49
Maze test	1.21 ± 0.36	1.25 ± 0.24
Emotional management	5.33 ± 0.77	6.21 ± 0.36
Total	89.22 ± 3.06	96.11 ± 2.74

3.3 WCST score comparison of SG HHcy and SG non-HHcy

HHcy Cc and Rc was significiantly lower than for non-HHcy patients. The difference was statistically significant ($p < 0.05$). HHcy subject error responses (Re), perseverative responses (Rp), and non-perseverative responses (nRp) were significantly higher than non-HHcy patients and was statistically significant ($p < 0.05$), as shown in Table 4.

Table 4. WCST scores of HHcy and Non-HHcy ($\bar{x}$ ± s) compared

Type	HHcy	Non-HHcy	t	*p*
Cc	1.44 ± 1.03	2.02 ± 1.57	2.08	0.04
Rc	45.94 ± 6.16	49.79 ± 5.72	3.30	< 0.01
Re	76.83 ± 11.85	70.44 ± 9.49	3.11	< 0.01
RP	33.09 ± 7.37	29.42 ± 8.16	2.34	0.02
nRp	69.03 ± 13.75	61.89 ± 10.24	3.11	< 0.01

4 DISCUSSION

Homocysteine (Hcy) is a sulfur-containing amino acid formed after methionine demethylation. It was discovered in the urine in the early 1960s as a methionine cycle intermediate metabolite. Hcy is present, in serum, in a form that binds with serum proteins. A small fraction of it is present in free form [10]. Hcy can oxidize causing damage to the vascular endothelial cells and the brain tissue so as to result in the organic mental disorders. Genetically, the abnormal Hcy metabolism oftens causes DNA methylation disorders and increases the risk of schizophrenia. Along with genetics, diet, metabolism and other conditions, it has been reported that abnormal Hcy increase may result in the high Hcy levels in mothers during fetal development, which may cause a high congenital Hcy level in newborns. Some studies show that the abnormal increases in Hcy level is related to folic acid and VB12 efficiency. The study this paper reports performed a relative comparison. The results showed that only SP had significantly different VB12 and folic acid levels. These levels were not significantly different between the SG and the CG. This result is consistent with the viewpoint of some reports that the supplementing or adding folic acid can improve cognitive disorders [11]. This may be related to sample selections of healthy examinees sample limitations and warrants further investigation.

SG plasma Hcy level and HHcy rates of were significantly higher than the CG. The difference was statistically significant. The results suggest that Hcy level is closely related to schnizophrenia which tends to confirm the view that Hcy metabolism abnormality is an important risk factor for schizophrenia pathogenesis.

Significant cognitive disorders have been clinically recognized in schizophrenics. Prior studies found that serum Hcy can affect 5-hydroxytryptamine, and frontal lobe dopamine, biosynthesis. It may further affect front lobe functions. Prefrontal lobe hypofunction is associated with the cognitive disorder. This allows the speculation that Hcy serum levels in schizophrenics may be correlated with cognitive function. In the FESPs in this study, subjects with serum Hcy levels higher than 15 μmol/L had significantly lower cognitive function than subjects whose serum Hcy level was less than 15 μmol/L. The results showed that, the higher the serum Hcy level is, the more severe the cognitive disorder of the patients may be. The severity of the cognitive function of the patients is positively correlated with Hcy levels. This suggests that serum Hcy levels may provide a basis for clinically diagnosing cognitive disorder severity. The sample size of this study was relatively small and other relevant indicators affecting the Hcy metabolism, such as VB6 and methylenetetrahydrofolate reductase (MTHFR), were not detected. Universality needs to be confirmed by clinical trials of more and larger samples. The specific pathological mechanism of Hcy involvement in the schizophrenia awaits to further study.

This study suggests a lower cognitive score and weaker cognitive ability in schizophrenics with a high Hcy levels. It suggests that the elevated serum Hcy levels may be used as a laboratory-aided diagnostic indicator for cognitive disorder severity in patients with first-episode schizophrenia.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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