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Research article

Effect of risperidone on serum homocysteine levels in first-episode, drug-naïve patients with schizophrenia

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HIGHLIGHTS

- Serum Hcy levels were elevated in first-episode drug-naïve schizophrenia patients.
- Serum Hcy levels were significantly decreased in schizophrenia patients after risperidone treatment.
- Severity of negative symptoms was associated with Hcy levels.

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ABSTRACT

Some studies have shown that homocysteine (Hcy) levels are increased in patients with schizophrenia, and may be involved in its pathophysiology. The purpose of this study was to investigate the effect of the atypical antipsychotic drug risperidone on serum Hcy levels and to explore the relationship between the changes in Hcy levels and the therapeutic outcome, which, to our best knowledge have not been investigated.

Fifty-six first-episode and drug-naïve inpatients with schizophrenia were assigned to a 12-week treatment regime with risperidone. Clinical efficacy was determined with the Positive And Negative Syndrome Scale (PANSS). Serum Hcy levels were measured by sandwich enzyme-linked immunosorbent assay in schizophrenia patients before and after the 12-week treatment, and the values were compared with those of fifty-six age- and gender- matched healthy controls.

Serum Hcy levels were significantly higher in first-episode and drug-naïve patients than in control subjects (11.18 ± 4.53 vs. 5.99 ± 3.61 μmol/L, $F = 37.195$, $df = 1$, $p = 1.73 \times 10^{-8}$). Moreover, a significant positive correlation between Hcy levels and PANSS negative sub-score was observed ($r = 0.515$; $p = 4.81 \times 10^{-5}$). Serum Hcy levels were significantly decreased in patients after risperidone treatment (baseline: 11.18 ± 4.53 μmol/L vs. post-treatment: 8.98 ± 4.07 μmol/L, $t = 3.857$, $p = 3.034 \times 10^{-4}$). At post-treatment, there was a significant negative relationship between serum Hcy levels and PANSS negative sub-scores ($r = -0.288$, $p = 0.032$).

High Hcy levels at the onset of psychosis suggests that it may contribute to the pathogenesis of schizophrenia and is related to clinical psychopathology. Serum Hcy levels were significantly decreased in schizophrenia patients after risperidone treatment.

1. Introduction

Schizophrenia is a serious mental illness with unclear etiology. To understand the possible causes of this disorder, studies underlying biological process of the illness have already been ongoing for many years. Evidences from animal experiments, clinical course and neuroimaging studies together with postmortem findings [1–4] suggests that abnormal neurodevelopment plays a role in the pathogenesis of schizophrenia [2]. Interestingly, a recent study suggests that the onset of psychosis is associated with the gray matter reduction in several brain areas [1]. The mechanism of this reduction is undetermined but it could be indicative of maturational changes and/or neurotoxicity occurring during the symptom onset. Some studies indicate that the early neurodevelop-

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Table 1
Age and serum homocysteine levels of patients and controls (Mean ± SD)[a].

		Age(year)	Hcy levels before treatment(μmol/L)	Hcy levels after treatment(μmol/L)
Patients				
Males	21	27.79 ± 7.14	10.49 ± 4.42[b]	8.65 ± 4.01
Females	35	26.80 ± 8.58	11.59 ± 4.61[c]	9.17 ± 4.15
All patients	56	27.17 ± 8.02	11.18 ± 4.53[d,e]	8.98 ± 4.0[e]
Controls				
Males	21	27.43 ± 8.25	7.02 ± 3.84[b]	–
Females	35	27.23 ± 7.12	5.37 ± 3.36[c]	–
All controls	56	27.36 ± 7.78	5.99 ± 3.61[d]	–

[a] All data were reported as mean ± SD. There was no significant difference between schizophrenics and controls in age and gender by *t*-test and chi-square test, respectively.
[b] ANCOVA in males adjusted for age revealed a significant main effect of diagnosis on homocysteine levels [$F(1,42) = 7.626$; $p = 0.009$].
[c] ANCOVA in females adjusted for age revealed a significant main effect of diagnosis on homocysteine levels [$F(1,70) = 40.022$; $p = 2.382 \times 10^{-8}$].
[d] ANCOVA in all subjects adjusted for age revealed a significant main effect of diagnosis on homocysteine levels [$F(1,112) = 37.195$; $p = 1.729 \times 10^{-8}$].
[e] Paired T-test comparing serum homocysteine levels in patients before and after treatment revealed a significant difference ($t = 3.857$, $p = 3.034 \times 10^{-4}$).

ment is affected by neuronal proliferation, migration, apoptosis and synapse formation [2] and its impairment is relate to homocysteine [5].

Hcy is a sulfur-containing amino acid involved in the methionine cycle, which provides methyl for general methylation reactions and generates several physiologically active methyl-containing substances [6]. Hcy metabolism is dependent on the enzyme methylene-tetrahydro-folate reductase (MTHFR) and involves folate, vitamin B6 and vitamin B12 [7,8]. Hcy influences neuronal functions and brain development through multiple cellular pathways, including cytosolic accumulation of calcium, induction of oxidative stress and apoptosis [9], and markedly increased vulnerability of hippocampal neurons to excitotoxicity [10]. The oxidative stress through the induced by Hcy is production of cysteine and glutathione [5].

Some studies have reported increased serum or plasma levels of Hcy in acute and chronic schizophrenia [6,7,11–13]. Increased maternal Hcy level has been found to increase the risk of schizophrenia by influencing the fetal brain structure and/or by inducing subtle damage to the placental vasculature and hence reducing the oxygen supply to the fetus [14]. Hcy has been shown to act as an N-methyl-D-aspartate (NMDA) receptor agonist or a partial antagonist depending on whether the glycine level is in the physiologic or pathological range [15]. Low activity of the NMDA receptor on GABAergic interneurons in the prefrontal cortex may result in neuronal excitotoxicity and lead to schizophrenia [4]. Two other studies have also suggested that increased Hcy may contribute to the neuropsychopathology of schizophrenia [5,16]. Furthermore, Hcy levels were shown to be correlated with the Positive And Negative Syndrome Scale (PANSS) scores, especially with scores of the negative symptoms [17].

As a critical molecule in stabilizing the levels of Hcy, the MTHFR enzyme transfers 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate and maintains the pool of circulating folate and methionine. Several lines of evidence suggest that altered MTHFR polymorphism may cause a reduction of its enzymatic activity and influence Hcy levels and act as a risk factor for neurodevelopmental disorders such as autism spectrum disorder and schizophrenia [6]. Two single nucleotide polymorphisms (C677T and A1298C) in MTHFR gene have been investigated by other studies [8,18,19], but their associations with Hcy concentration and schizophrenia are inconclusive [8,18,19]. Meta-analyses found that the 677TT genotype was associated with schizophrenia, while the significance of the A1298C polymorphism was less convincing [8].

A few studies have examined antipsychotic effects on Hcy levels in schizophrenia, but with inconsistent results. For example, one study reported decreased plasma Hcy levels in antipsychotic-treated schizophrenia patients [17]. Two other studies, however, found that serum Hcy concentrations did not change after antipsychotic treatment in schizophrenia [12,20]. Therefore, the picture emerging is that the effect of antipsychotic agents on Hcy levels merits further examination in cases of schizophrenia.

To our knowledge, there is no published report on the effect of atypical antipsychotic drugs on Hcy levels in first-episode and drug-naïve patients, taking psychopathological symptoms into account. The purposes of the present study were to investigate: (1) whether serum Hcy levels were altered in first-episode and drug-naïve schizophrenia patients, (2) whether treatment with the atypical antipsychotic drug-risperidone-changed the serum Hcy levels in schizophrenia patients, (3) whether there was any relationship between serum Hcy and the therapeutic effectiveness of risperidone.

2. Methods and materials

2.1. Subjects

Fifty-six patients (21 men and 35 women) with schizophrenia, diagnosed by the consensus of two experienced psychiatrists according to the DSM-IV criteria (American Psychiatric Association, 1994), were recruited from Hui-Long-Guan Hospital, a city-run psychiatric hospital in Beijing, China. All patients included in the study were first-episodic and drug-naïve, which was confirmed by collateral histories from family members. Smoking was shown to affect antipsychotics efficacy [21], so, smoking was avoided in our study. Other exclusion criteria included 1) use of vitamin supplementation, such as folic acid, vitamins B6 and B12, which may have influenced serum homocysteine levels; 2) evidence of substance or alcohol abuse; 3) eating disorders; and 4) pregnancy or breastfeeding.

Fifty-six age- and gender-matched control subjects (21 men and 35 women) were selected from the local community. Each of them underwent a standardized diagnostic interview to rule out psychiatric disorders and was required to have a negative family history for any psychiatric disorders. None of the subjects had taken any vitamin supplements at least 3 months before participating in the study.

Complete medical histories, physical examination results, findings for laboratory tests including urine and blood screens, and electrocardiograms were obtained from all participants(both patients and control subjects) to rule out any neurological or other physical diseases (such as organic brain diseases, cardiovascular disease, and gastrointestinal absorption disorders). Dietary protein are the main sources of methionine, and methionine is the sole precursor of Hcy. Protein-rich meals cause high intake of methionine and, hence may raise serum Hcy concentrations. However,