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Level of serum thioredoxin and correlation with neurocognitive functions in patients with schizophrenia using clozapine and other atypical antipsychotics

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ABSTRACT

Thioredoxin is a serum antioxidant that has been investigated in the etiology of schizophrenia. The aim of this study is investigating the relationship between serum thioredoxin levels and cognitive functions in acute psychotic episode and remission state patients with schizophrenia; and examining whether there were differences between patients using clozapine and other atypical antipsychotics; including risperidone, olanzapine and amisulpride. This research was performed in schizophrenia patients hospitalized with acute psychotic episode (n=57), reevaluated patients after the initiation of treatment (mean 16 weeks) (n=46), and healthy controls (n=41). Positive and Negative Syndrome Scale, Clinic Global Impressions Scale, Neuropsychologic test battery to assess cognitive performance, and serum thioredoxin levels measured by ELISA were used in this research. Serum thioredoxin levels were highest in acute psychotic episode, lower in the remission state and the lowest in healthy controls. Significant correlation has been established between serum thioredoxin levels and Trail Making Test-A performance in remission state patients. In conclusion, serum thioredoxin levels were increased in acute psychotic episode and decreased in remission state, and its relationship with attention is worth to consider in schizophrenia patients.

1. Introduction

Deterioration in cognitive function is a core feature of schizophrenia, including executive functioning, verbal learning and memory, visual learning and memory, processing speed, attention, problem solving and social cognition. (Andreasen et al., 1999; Green et al., 2004; Keefe et al., 2006; Bozikas et al., 2006). Cognitive impairment related to schizophrenia is widespread, associated with poor clinical and functional outcomes, existing before psychotic symptoms become apparent and persisting without regard to clinical state of schizophrenia. (Green, 1996; Dickerson et al., 2004; Schultze-Lutter et al., 2007; Mesholam-Gately et al., 2009; Lewandowski et al., 2011; Sharma et al., 2003). Although there is no approved medication for the treatment of cognitive impairment in schizophrenia, antipsychotics -especially atypical antipsychotics- have been found to have small but significant positive effect on cognitive function (Lewandowski et al., 2011).

Numerous studies have investigated the relationship between oxidative stress and cognitive function. The imbalance between reactive oxygen species and antioxidant capacity may cause cognitive impairment. (Davies et al., 2000; Liu et al., 2003; Nagai et al., 2003, Ames, 2006) The relationship between cognitive decline and oxidative stress has been studied mostly in neurodegenerative diseases and aging. In literature, there are studies indicating that oxidative stress associated with excessive reactive oxygen species cause cognitive decline and neurodegeneration due to aging (Nicolle et al., 2001; Hu et al., 2006). Recently, developing numbers of schizophrenia researches indicated that evidences of neurodegenerative process have been involved in the etiology of schizophrenia (Meyer-Lindenberg, 2011; Kochunov and Hong, 2014; Rao et al., 2014). At this point of view, cognitive impairment due to neurodegeneration derived from oxidative stress becomes a more interesting topic in schizophrenia.

However, studies examining the relationship between oxidative damage and cognitive functions in patients with schizophrenia remains unclear. Some previous studies had demonstrated exact evidences that

Abbreviations: TRX, thioredoxin; ELISA, enzyme linked immune absorbent assay; DSM-IV, diagnostic and statistical manual of mental disorders, PANSS, positive and negative syndrome scale

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oxidative stress is associated with cognitive impairment in schizophrenia (Bitanihirwe and Woo, 2011; Yao and Keshavan, 2011). In a study examining the relationship between total antioxidant status and cognitive performance in chronic schizophrenia patients; total antioxidant status had been inversely associated with cognitive deficits such as attention and immediate memory (Zhang et al., 2012). Although; in a recent 2 year follow up study in first episode psychosis patients; plasma total antioxidant status was positively associated with global cognitive performance both at baseline and at 2 years of follow up, and this study points to the possibility of using peripheral markers of oxidative and antioxidative balance in patients with first episode psychosis (Martínez-Cengotitabengoa et al., 2014). As mentioned above, studies investigating the relationship between cognition in schizophrenia and oxidative stress has too many contradictions.

Thioredoxin (TRX) is an ubiquitous protein with oxidoreductase activity which plays a role in protection against oxidative stress (Holmgren, 1985). Increased TRX levels has been observed in first episode drug-naive schizophrenia patients and was found greater than chronic schizophrenia patients on antipsychotic medication, but did not differ between chronic schizophrenia patients and healthy controls (Zhang et al., 2009). In another study, increased levels of TRX has been observed in both acute and chronic patients with schizophrenia; and this study has indicated that levels of TRX may not be used as a marker to separate psychotic patients from mentally healthy population. (Owe-Larsson et al., 2011). Finally, serum TRX levels have been negatively associated with attention in schizophrenia patients, but positively associated with attention in healthy controls (Zhang et al., 2013). Hence, TRX is an underinvestigated molecule in cognitive functions of schizophrenia patients, a sensitive antioxidant marker that is easy to measure and reflects the cellular response to oxidative stress (Nakamura, 2005). And also, compatible results of the few studies above; makes TRX a thought-provoking molecule in cognitive functions of schizophrenia patients. Here, we had several hypothesizes as: a) serum TRX level would be increased in patients with schizophrenia than healthy controls, b) serum TRX level would be decreased after antipsychotic treatment, c) the decrement in serum TRX level would be more in patients who treated with clozapine than other antipsychotics (clozapine is well-known as the most effective antipsychotic agent in the treatment of schizophrenia), d) a correlation would be detected between serum TRX level and neurocognitive testing parameters. Thus, we aimed to compare serum TRX levels in patients with schizophrenia and healthy controls and aimed to measure the alteration of serum TRX level between initial and post treatment, according to the use of clozapine or other atypical antipsychotics.

2. Methods

2.1. Settings and sample

Fifty seven schizophrenia patients (To patients) and 41 age and sex-matched healthy controls were included in current study. Twenty eight patients (%49) were started with clozapine treatment, while 29 patients (%51) were started with other atypical antipsychotics; including olanzapine, risperidone and amisulpiride. The mean chlorpromazine equivalent dose of clozapine user To patients is 243 ± 180 mg/day, and 369 ± 89 mg/day for other atypical antipsychotic users. The patients were hospitalized with acute psychotic episode at the time of inclusion in the study, and were in partial or full remission at the time of reevaluation after 16 weeks. Patients who had been changed or discontinued medication or re-hospitalized until the time of reevaluation were excluded from the study, so 46 patients were reevaluated (T_1 patients). Twenty two of T_1 patients were clozapine users (%47), 24 of T_1 patients were other atypical antipsychotic users. The mean chlorpromazine equivalent dose of clozapine user T_1 patients is 550 ± 185 mg/day, and 341 ± 73.4 mg/day for other atypical antipsychotic users.. Exclusion criteria included a history of neurological illness, head trauma, mental retardation, history of substance abuse, electroconvulsive therapy in the previous 6 months, a history of psychosurgery or any other neurosurgical operation and diagnosable or self-reported visual impairment of any other cause. All patients who were diagnosed with schizophrenia attended the inpatient unit of Cerrahpasa Medical Faculty Department of Psychiatry between May 2012 and October 2013. The diagnosis of schizophrenia in these patients was established according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV- TR) criteria (American Psychiatric Association (APA), 2000) after a detailed clinical examination by two consulting psychiatrists.

The study was approved by the Istanbul University Cerrahpasa Medical Faculty Ethical Committee, and all participants and/or legal representatives provided written informed consent.

2.2. Procedures and materials

The principal author (Alper Baş) performed the neuropsychological assessments of each participant in a single session and fixed order, and was not blind to the group allocation. The tests lasted for 1 h, and breaks of 10–15 min were allowed. A battery of neurocognitive functions was designed to assess the following domains: verbal learning and memory, visual memory, and executive functions. The neurocognitive functions were evaluated with the following tests: the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964), the Wechsler Memory Scale- Revised (WMS-R) (Wechsler, 1987) visual reproduction subscale, the Stroop Color–Word Interference Test (SCWIT) (Golden, 1978), forwards and backwards digit span test (Wechsler, 1987) and the Trail Making Test A (TMT-A) and Trail Making Test B (TMT- B) (Reitan, 1958).

The clinical state of the participants was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impression Scale (CGI) (Guy, 1976) by another author (Gözde Gültekin). The pharmacotherapy of patients had been carried out by other psychiatrists, authors were blind to medications until the reevaluation time.

We collected 10 milliliters of venous blood from patients with schizophrenia and healthy controls between 8:00 and 10:00 am. The samples were centrifuged for 15 min at 3000 rpm at room temperature. Then serum was separated and stored at −80C until analysis. Serum TRX levels were measured with sandwich ELISA using a monoclonal anti-TRX antibody. Hangzhou Eastbiopharm Company China Human Thioredoxin ELISA kits had been used.

2.3. Statistical analysis

Prior to data analysis, the data were checked for normality using analytical (Kolmogorov Smirnov/Shapiro-Wilk's tests) and visual methods (histograms and probability plots). With the exception of age, the variables were not normally distributed. The data that failed the tests of normality were subject to analysis with a Mann-Whitney *U* test, which was used to compare the ordinal data between the independent groups. The categorical variables were compared with a chi-square test. The associations between the socio-demographic characteristics, illness variables, cognitive performance and serum TRX levels were explored using the Spearman correlation coefficient r. Normally distributed data were compared with an independent samples *t*-test. For the dependent variables, normally distributed data were compared with paired samples *t*-test, the data that failed the tests of normality were compared with Wilcoxon signed-rank test. Statistical significance was established at $p < 0.05$. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS, Inc., Chicago, IL, USA).

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