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High doses of antipsychotic polypharmacy are related to an increase in serum levels of pentosidine in patients with schizophrenia

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ABSTRACT

Background: Carbonyl stress in patients with schizophrenia has been reported to be reflected by an increase in peripheral pentosidine levels. This cohort study tested whether the accumulation of pentosidine was related to the disease severity or the treatment (routine administration of high antipsychotic doses).
Methods: We followed up our original investigation using a new group of 137 patients with acute schizophrenia and 45 healthy subjects, and then pooled the two cohorts to conduct the following analysis on a total of 274 patients. The associations of serum pentosidine and pyridoxal levels with duration of education, estimated duration of medication, the severity of symptoms, and daily doses of antipsychotics, antiparkinsonian drugs, and anxiolytics were evaluated by multiple linear regression analysis.
Results: The combined cohort of 274 patients exhibited abnormally high serum levels of pentosidine, were associated with a higher daily dose of antipsychotic drugs and a longer estimated duration of medication without statistical significance of diagnosis. This was also observed in the patients treated with antipsychotic polypharmacy, but the serum pentosidine levels of patients treated with first- or second-generation antipsychotic monotherapy showed no relationship with these two variables.
Conclusion: High levels of serum pentosidine were associated with high daily doses of antipsychotic drugs and a longer estimated duration of medication in patients treated with antipsychotic polypharmacy.

1. Introduction

Schizophrenia is a devastating mental disease plagued by limited treatment success due to the high heterogeneity of the disease and a limited understanding of the underlying mechanisms. While positive symptoms are managed by antipsychotics, new drugs are needed to improve cognitive dysfunctions and promote recovery from negative symptoms. Thus, it is crucial to uncover the biochemical anomalies that may be responsible for these aspects of schizophrenia.

Carbonyl stress and associated advanced glycation end-products (AGEs) have recently been the focus of research into neurodegenerative diseases in aging, such as Alzheimer's disease (Takeuchi and Yamagishi, 2008; Yamagishi et al., 2005). Recent studies have also reported high serum levels of toxic AGEs and related molecules in patients suffering from schizophrenia (Arai et al., 2010; Emanuele et al., 2011; Katsuta et al., 2014; Kouidrat et al., 2013; Miyashita et al., 2013, 2014; Steiner et al., 2009; Takeda et al., 2015), compared with those in healthy subjects. In a cross-sectional study of 45 schizophrenic patients and 61 healthy subjects, a detailed investigation of the disease characteristics ranging from psychosocial to genetic factors was conducted (Arai et al., 2010). This showed that a raised level of AGEs was not a disease-specific feature of schizophrenia, but that a subpopulation of schizophrenic patients exhibited significantly higher serum levels of pentosidine, a well-established biomarker for AGEs, as well as significantly lower serum levels of pyridoxal, a form of vitamin B6 that detoxifies reactive carbonyl compounds, compared with the healthy subjects. This study

Abbreviations: AGE, advanced glycation end-product; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; FGA, first-generation antipsychotics; GLO1, glyoxalase I; SD, standard deviation; SGA, second-generation antipsychotic.

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was repeated with another cohort of patients with schizophrenia and healthy subjects, which confirmed the significant increase in pentosidine and decrease in pyridoxal in the peripheral blood of a subpopulation of the patients (Miyashita et al., 2014). A further study by these authors that included 163 patients with schizophrenia revealed that, compared with patients with lower AGE levels, those under higher carbonyl stress were not characterized by any particular clinical variables, but tended to be inpatients, have a low education status, require longer hospitalization, and receive higher doses of antipsychotic medication (Miyashita et al., 2013).

We recently investigated the clinical significance of these potential serum markers in a cross-sectional study of 137 patients with acute schizophrenia, and we were able to confirm the decreased serum levels of pyridoxal (Katsuta et al., 2014). On the other hand, although the overall mean pentosidine level was not significantly altered, some of the patients with schizophrenia had extremely high serum levels of pentosidine. Unfortunately, this study could not identify any of these markers as symptomatic biomarkers (i.e., for the severity of symptoms). Pentosidine and pyridoxal failed to show any correlation with clinical features of schizophrenia (e.g., duration of illness, age at onset, and family history). On the other hand, a significant positive correlation was found between serum pentosidine levels and the daily antipsychotic dose or cumulative antipsychotic exposure (calculated as the daily dose of antipsychotics × the duration of medication) (Katsuta et al., 2014). However, this study did not address the influence of different types and doses of antipsychotics, such as first-generation antipsychotics (FGA; e.g., haloperidol and chlorpromazine), second-generation antipsychotics (SGA; e.g., risperidone, olanzapine, and aripiprazole), and their combinations. In any case, a previous systematic review showed that all of these recent studies, to varying degrees, revealed that carbonyl stress could indeed be involved in the pathophysiology of schizophrenia (Kouidrat et al., 2015).

The aim of the present study was to investigate the relationship between high serum pentosidine levels and schizophrenia using correlation and stepwise multiple linear regression analyses. The largest cohort of patients with schizophrenia ever used in a single analysis was obtained by pooling the data obtained from the patients recruited in the present study with those of our previous study (Katsuta et al., 2014). This approach allowed us to determine whether the accumulation of serum pentosidine is indicative of the patients' clinical characteristics and/or the regimen of antipsychotics. This is an important distinction. Carbonyl stress is associated with the pathogenesis of a number of diseases, including Alzheimer's disease and renal disease; thus, if the kinds and dose of antipsychotic regimen are implicated in producing carbonyl stress (by mechanisms that have yet to be elucidated), this would have implications for patients' long-term health.

2. Materials and methods

2.1. Study population

This study evaluated 137 patients admitted to Juntendo Koshigaya Hospital (Saitama) or Juntendo Hospital (Tokyo) due to worsening symptoms of schizophrenia. They met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), for the diagnosis of schizophrenia. The exclusion criteria were as follows: participation in the previous study (Katsuta et al., 2014), any comorbidity known to influence AGE levels (i.e., diabetes mellitus and chronic renal disease), systemic or neurological diseases, past head trauma with loss of consciousness, and a lifetime history of alcohol or substance abuse. This study also enrolled 45 healthy volunteers who did not meet current or past criteria for any Axis I disorder in DSM-IV and had no present physical disease at the time of enrollment. All participants provided their written informed consent prior to participation, and the Ethics Committee of Juntendo University School of Medicine approved the protocol (2015014).

2.2. Physical examination and laboratory tests

On the day of admission, all patients underwent a physical exam, including the measurement of body mass index (BMI). In addition, a blood sample was collected to measure the baseline levels of glucose, glycated hemoglobin (HbA1C), creatinine, and urea nitrogen. Glomerular filtration rate (normal > 60 ml/min) and urinalysis were also used to measure renal function. The healthy subjects underwent the same physical exam and blood tests as the patients, conducted on the day the serum samples for the biomarkers were collected.

2.3. Evaluation of clinical symptoms

Clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS), with each item rated on a seven-point scale, as previously described (Katsuta et al., 2014; Takeda et al., 2015). The overall total rating and scores related to positive and negative symptom clusters were compared (Bech et al., 1986). The age at onset of the illness was determined as the age at which any schizophrenia symptom described in the diagnostic criteria of DSM-IV first appeared, established from the medical records and/or by detailed questioning of the patients and their family members. A family history of psychiatric disease was defined as having a first- or second-degree relative who met any current or past criteria for any Axis I disorder of DSM-IV; this was ascertained by asking patients or their healthy family members about this. The Juntendo University Schizophrenia Project (JUSP) (Ohnuma et al., 2008) is a retrospective, observational study; the use of drug therapy is not restricted, so that each patient's symptoms can be controlled in the most effective manner.

2.4. Measurement of carbonyl stress markers

All blood samples were taken before breakfast to exclude the influence of food and exercise. Serum pentosidine was measured using a competitive enzyme-linked immunosorbent assay, and serum vitamin B6 (pyridoxal) was measured using high-performance liquid chromatography, as we previously described (Katsuta et al., 2014).

2.5. Statistical analysis

The difference in sex distribution between patients and controls was analyzed using the χ^2 test. The potential differences in clinical characteristics (e.g., healthy subjects vs. schizophrenia patients, or patient groups receiving different antipsychotics) were analyzed using two-tailed Mann–Whitney *U* tests for two-group comparisons and Kruskal–Wallis tests for comparisons of three or more groups. All statistical analyses were performed by employing SPSS Statistics Version 21 (IBM, Chicago, IL, USA). The post hoc analysis of Kruskal–Wallis tests was conducted using two-tailed Mann–Whitney *U* tests. The significance of the *P*-value for these analyses was set based on the Bonferroni correction (the probability level of $p < 0.05$ divided by the number of comparisons in each analysis).

The multiple linear regression analysis included the following factors that potentially contribute to increased pentosidine levels, based on recent studies: 1) duration of education (Miyashita et al., 2013), 2) being an inpatient (number of admissions) (Arai et al., 2010; Miyashita et al., 2013), 3) the duration of the psychiatric illness (Katsuta et al., 2014; Miyashita et al., 2013), 4) the severity of the symptoms of schizophrenia (the total BPRS score) (Miyashita et al., 2013), 5) the estimated duration of medication (in years, calculated as the difference between the total duration of the illness and the duration of untreated psychosis) (Katsuta et al., 2014), 6) the daily dose of antipsychotics (Katsuta et al., 2014; Miyashita et al., 2013), and also frequently accompanied 7) the daily dose of antiparkinsonian drugs, and 8) the daily dose of anxiolytics (including sedatives and hypnotics). As would be expected, three of these variables, 2) the number of