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Tardive dyskinesia is associated with greater cognitive impairment in schizophrenia

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ABSTRACT

Objective: Schizophrenia is a psychiatric disorder diagnosed by the presence of a number of symptoms with cognitive impairment as a core feature. Long-term antipsychotic treatment is often associated with the emergence of tardive dyskinesia (TD) and the presence of TD is linked to cognitive impairment. This study examined the relationship between TD and cognitive deficits in Chinese patients with schizophrenia.
Methods: We recruited 206 chronic patients with TD ($n = 102$) and without TD ($n = 104$) meeting DSM-IV criteria for schizophrenia and 104 control subjects who were matched on age, gender, and education. All the patients completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Positive and Negative Symptom Scale (PANSS), and the Abnormal Involuntary Movement Scale (AIMS).
Results: The PANSS total score ($p = 0.01$), N subscore ($p = 0.006$), and AIMS total score ($p < 0.001$) were significantly higher in patients with TD compared to patients without TD. Patients with TD scored lower for visuospatial/constructional, attention, and total index scores (all $p < 0.001$) on the RBANS. AIMS orofacial scores were identified as an independent contributor to RBANS total scores and attention index ($p < 0.05$), whereas AIMS limb and truncal scores were an independent determinant to the visuospatial/constructional index of RBANS ($p < 0.05$).
Conclusion: TD was associated with greater cognitive impairment in patients with schizophrenia compared to those without TD. The orofacial and limb-trunk TD specifically appeared to be a risk factor or contributor to the different aspects of cognitive deficits in schizophrenia. The association between schizophrenia and TD may be explained in part by oxidative stress.

1. Introduction

Schizophrenia is a psychiatric disorder characterized by a range of cognitive deficits (Goff et al., 2011; Harvey et al., 2004; Heinrichs and Zakzanis, 1998) that generally persistent during the disease course (Heaton et al., 2001; Irani et al., 2011; Rajji and Mulsant, 2008). Antipsychotic medications are the standard in treating schizophrenia yet chronic use is associated with the emergence of tardive dyskinesia (TD). TD is characterized by involuntary, hyperkinetic, abnormal movements (Correll and Schenk, 2008; de Leon, 2007; Remington, 2007), the presence of which is associated with poor quality of life, non-adherence with medications, and increased medical morbidity and mortality (Ballesteros et al., 2000; Browne et al., 1996; Youssef and Waddington, 1987). The pathophysiology of TD is not well understood and treatments lack efficacy, therefore prevention and early recognition may help improve treatment outcome (Remington, 2007; Soares and McGrath, 1999).

A number of risk factors have been associated with increased risk of developing TD. Some of these risk factors include being older, female gender, length of antipsychotic treatment, prominent negative symptoms and thought disorder, more severe cognitive impairment, early onset extrapyramidal side effects, and diagnosis of diabetes mellitus (Sachdev, 2000). Compared to the western countries, a generally low frequency of TD in Asian schizophrenia patients with inter-ethnic variations was reported in a recent study, which found that the variables including older age, male gender, more severe negative and extrapyramidal symptoms, and less anticholinergic drugs

Abbreviations: TD, tardive dyskinesia; RBANS, Assessment of Neuropsychological Status; PANSS, Positive and Negative Symptom Scale; AIMS, Abnormal Involuntary Movement Scale; CLAT, conceptual analogy test; MMSE, mini-mental state examination; ANOVA, analysis of variance; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; MDA, malondialdehyde.

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were independently associated with TD (Xiang et al., 2011). Among the aforementioned risk factors, a number of studies have consistently implicated chronic antipsychotic treatment and aging as risk factors in the development of TD (Glazer, 2000a, 2000b; Patterson et al., 2005; Zhang et al., 2009b), whereas cognitive impairment has been less frequently studied. Both Wegner et al. and Waddington et al. assessed cognition in approximately 30 individuals with schizophrenia using the conceptual analogy test (CLAT) and an abbreviated ten-question mental test and found those with TD performed worse (Waddington and Youssef, 1986; Wegner et al., 1985a). Further, two studies have linked orofacial dyskinesia and cognitive impairment as assessed by the mini-mental state examination (MMSE) (Byne et al., 1998; Waddington et al., 1987). Earlier studies found cognitive deficits preceded the onset of TD and may be a risk factor (Struve and Willner, 1983; Wegner et al., 1985b), whereas others found that TD was predictive of impaired cognitive function in association with the development of orofacial dyskinesia (Waddington and Youssef, 1996). Overall, although these studies link TD and cognitive impairment in patients with schizophrenia, they were limited by relatively small sample sizes and neuropsychological tests applied, which were either across only a limited number of cognitive domains or relatively insensitive (MMSE) (Randolph et al., 1998).

In the study presented here, we recruited three groups of more than 100 individuals each including patients with schizophrenia with and without TD, as well as age-, gender-, education-matched controls in a Chinese population. Additionally, we assessed subjects using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) across five cognitive domains in addition to the Abnormal Involuntary Movement scale (Randolph et al., 1998). To our knowledge, this was the first study to investigate possible relationships with cognitive function in schizophrenics and TD in a Chinese population.

2. Methods

2.1. Ethics statement

The research protocol was approved by the Institutional Review Board, Beijing Hui-Long-Guan hospital. A psychiatrist explained the research protocol and procedures to the potential subject. The description of the study was tailored to maximize the understanding of the subject using language appropriate to the subject's level of comprehension, and emotional readiness. If the subject was willing to consent to participate in the study the researcher provided an in depth description to the subject and in certain instances, to their parents or guardians. In cases where the parents or guardians were entrusted with assessing the subject's participation, they gave their written consent on behalf of the subject.

2.2. Subjects

Two hundred and six inpatients (Han Chinese) with schizophrenia were recruited from Beijing Hui-Long-Guan hospital, a Beijing-city-owned psychiatric hospital. All patients met the following inclusion criteria: 1) age 40–73 years, Han Chinese; 2) confirmed DSM-IV diagnosis of schizophrenia; 3) with at least 5 years of illness; and 4) had been receiving stable doses of oral antipsychotic drugs for at least 12 months before entry into the study. All patients were of the chronic type and had been ill for an average of 29.9 ± 8.0 years on current antipsychotic treatment for an average of 4.2 ± 4.3 years. Patients were hospitalized for about 9 years (9.1 ± 7.2). Since admission, all patients received dietetically balanced hospital meals, which were occasionally supplemented by gifts (usually fruit). Patients had the opportunity to exercise for about an hour per day. Antipsychotic drug treatment was mainly monotherapy with the most common medications consisting of clozapine, risperidone, perphenazine, sulpiride, chlorpromazine, and haloperidol. A mean daily dose of antipsychotics (Table 1), including both the first- and second-generation antipsychotics, was converted to approximate daily mean chlorpromazine milligram equivalents for each subject using standard guidelines (Lehman et al., 2004; Woods, 2003). In addition, patients received one (n = 67), two or three (n = 10) different antiparkinsonian drugs.

Age-, gender-, and education-matched control subjects (n = 104) were recruited from the local community in Beijing. Current mental status and personal or family history of any mental disorder was assessed by unstructured interviews. None of the healthy control subjects presented a personal or family history of psychiatric disorder. All subjects are Han Chinese recruited at the same period from the Beijing area. Demographic data for patients and normal controls are summarized in Table 1.

A complete medical history, physical examination and laboratory tests were obtained from patients and control subjects. Any subjects with major medical illness were excluded. None of the subjects met criteria for drug or alcohol abuse or dependence.

2.3. Clinical measures

Each subject filled out a detailed questionnaire that recorded general information, sociodemographic characteristics, and medical and

Table 1
Characteristics of controls, schizophrenic patients with and without TD.

Characteristic	Normal controls (n = 104)	Patients without TD (n = 104)	Patients with TD (n = 102)	F or X^2	p value
Male/female	83/21	83/21	81/21	0.007	0.997
Age (yrs)	55.4 ± 5.7	55.2 ± 4.7	55.2 ± 7.6	0.043	0.958
Education (yrs)	9.0 ± 3.3	9.1 ± 2.4	9.4 ± 2.2	0.677	0.509
Age of onset (yrs)		24.9 ± 6.5	25.5 ± 6.4	0.481	0.489
Number of hospitalizations		4.3 ± 4.5	4.0 ± 2.7	0.432	0.512
Antipsychotic types				0.377	0.539
Typical		13	10		
Atypical		91	92		
Daily AP dose (mg/day) (CPZ equivalent)		585.4 ± 801.4	446.3 ± 431.3	2.386	0.124
Duration of treatment (ms)		49.7 ± 54.3	51.7 ± 49.9	0.071	0.790
PANSS total score		59.0 ± 13.8	63.7 ± 12.1	6.609	0.011*
P subscore		12.2 ± 6.1	13.1 ± 5.0	1.417	0.235
N subscore		21.1 ± 7.1	23.8 ± 6.4	7.659	0.006**
G subscore		25.7 ± 5.1	26.9 ± 5.1	2.510	0.115
AIMS total score		1.1 ± 1.3	6.7 ± 2.4	433.513	<0.001**

TD: tardive dyskinesia; AP: antipsychotic; CPZ: chlorpromazine; PANSS: Positive and Negative Symptom Scale; P: PANSS positive symptom subscale; N: PANSS negative symptom subscale; G: PANSS general psychopathology subscale; AIMS: Abnormal Involuntary Movement Scale.
* $p < 0.05$.
** $p < 0.01$.