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Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia

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ABSTRACT

There may be subtypes in treatment-resistant schizophrenia (TRS), and one of the subtypes may be related to dopamine supersensitivity psychosis (DSP). In developing strategies for prevention and treatment TRS, it is important to clarify the role of DSP in TRS. TRS patients were recruited from 3 hospitals for the present study. Through chart reviews, all patients were judged as either TRS or not, and then possible TRS patients were investigated about their past/present histories of DSP episode(s) by direct interviews. We then compared each factor between the groups with and without DSP episode(s). Out of 611 patients screened, 147 patients met the criteria for TRS and were included in the present analysis. These were divided into groups with and without DSP, comprising 106 (72.1%) and 41 patients (27.9%), respectively. Clinical characteristics in the two groups were similar, except for drug-induced movement disorders (DIMDs), which were significantly more important in DSP patients. Of the DSP patients, 42% and 56% experienced rebound psychosis and tolerance to antipsychotic effects, respectively. The present study revealed that approximately 70% of TRS patients experienced one or more DSP episodes, which may have a strong impact on the long-term prognosis of patients with schizophrenia.

1. Introduction

Although pharmacotherapy with antipsychotics has been a main strategy in treating schizophrenia, only 30–45% of patients experience and adequate response to these drugs (Andreasen et al., 2005; Bertelsen et al., 2009). Patients who respond poorly to treatment with two or more antipsychotic drugs are diagnosed as treatment-resistant schizophrenia (TRS) (Kane et al., 1988; Brenner et al., 1990). Clozapine has been established as the only effective agent for treatment-resistant cases, but some patients poorly respond even to this drug (Chakos et al., 2001; Henna Neto and Elkis, 2007). These data suggest the existence of subtypes in TRS and the importance of clarifying these subtypes in developing strategies for the prevention and treatment of schizophrenia.

One possible type of TRS may be related to antipsychotic-induced dopamine supersensitivity psychosis (DSP), which was first reported by Chouinard et al. (1978) and was recently classified as iatrogenic supersensitivity psychosis (Iyo et al., 2013; Seeman and Seeman, 2013). DSP is considered to develop following increases in antipsychotic dosages accompanying with relapses in patients with schizophrenia, although we should also take account of natural deterioration as a feature of schizophrenia. They progressively may show severer positive symptoms and need higher doses of antipsychotics, reaching TRS. Possible clinical features of this psychosis are co-existence of tardive dyskinesia (TD), relapse episodes immediately following treatment discontinuation (rebound psychosis) and/or developed tolerance to the drugs' antipsychotic effects despite continuous treatment (Chouinard, 1991; Moncrieff, 2006).

We recently proposed possible mechanisms underlying DSP and methods for the prevention and treatment of DSP on the basis of dopamine D2 receptor (DRD2) up-regulation (Iyo et al., 2013). In addition, antipsychotic-induced dopamine supersensitivity can be caused not only by an elevation in DRD2, but also by an increase in dopamine $D2^{High}$ receptors, which are known to represent the functional high-affinity state of the DRD2 (Seeman et al., 2005). Briefly, patients with DSP have an up-regulation and increasing supersensitivity of brain DRD2 induced by long-term over-blockade by antipsychotics and need higher dosages of antipsychotics to suppress the excessive dopamine neurotransmission via the increased DRD2. Higher antipsychotic dosages may yield higher fluctuation in the antipsychotic levels in the body since the

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elimination half-life from the body may be almost same regardless different dosages, leading to unstable psychotic symptoms. We hypothesized that an antipsychotic drug with a longer elimination half-life, which provides a stable plasma level, would produce a stable and optimal DRD2 blockade. Indeed, we reported that risperidone long-acting injectable form (LAI) combined with ongoing oral antipsychotics, which were gradually reduced to achieve maximal clinical effects with minimal side effects, improved refractory psychotic symptoms in the TRS patients with DSP significantly greater than those without DSP (Kimura et al., 2013, 2014). It is suggested that there may be at least two types of TRS from the viewpoint of response to LAI, i.e., DSP and non-DSP. Therefore, it is important to further clarify subtypes in TRS, especially to explore the contributing roles of DSP.

The present study aims to compare the clinical characteristics of TRS between patients with and without DSP by examining the history of their symptoms, and to clarify the roles of DSP in TRS.

2. Methods

2.1. Subjects

The present study was conducted in three psychiatric hospitals. The study protocol was approved by the ethics committees of all relevant facilities and was conducted in accordance with the Helsinki declaration. All 611 patients diagnosed as having schizophrenia or schizoaffective disorder (DSM-IV-TR) in either the outpatient or inpatient divisions of the research facilities were screened as candidate participants, by investigation of medical charts. Among them, a total of 202 patients were selected as meeting the TRS criteria described in the next paragraph (Fig. 1). Both oral and written informed consents were given from the patients or their guardians such as parents or spouse, if the patient was judged by the physician or the researcher to be unable to understand well the content of the present study. On that basis, we conducted a direct interview with each patient and/or his/her guardian(s) to assess whether the patient actually met the TRS criteria and to evaluate symptom severity. Patients with comorbidities like organic brain disease, mental retardation and dependence on alcohol or any illegal drug were diagnosed according to DSM-IV-TR and from available medical records, and were excluded from the present study.

A diagnosis of TRS was defined according to Broadest Eligibility Criteria (Juarez-Reyes et al., 1996) with cases meeting at least one of the two following criteria: (1) In spite of appropriate pharmacotherapy with at least two antipsychotics from different chemical classes, the mean global assessment of functioning (GAF) prior to the most recent year did not exceed 60 points. Appropriate pharmacotherapy for a given agent is defined as 600 mg or greater chlorpromazine-equivalent dosage (CP-dose) for at least 4 weeks. (2) TD with moderate or greater severity was not ameliorated by treatment, resulting in profound distress for the patient. With respect to patients treated with clozapine, all cases were assessed prior to initiation of clozapine, since clozapine was clinically available only 3 years ago in Japan; thus, for almost all patients, the period of the present survey coincides with clinical consideration of clozapine initiation.

2.2. Symptom measurement

2.2.1. Dopamine supersensitivity psychosis

For each patient potentially meeting the study criteria, we reviewed in detail clinical medical records and judged whether the patient had a past history of DSP, according to the criteria shown in Table 1. These criteria were developed by our group, but were slightly modified from the original criteria proposed by Chouinard (1991). Briefly, the criteria focus on three factors as follows; (1) rebound psychosis, (2) developed tolerance to antipsychotic effect, (3) presence of TD. If the patient experienced at least one of these three criteria at any time during the treatment, the patient was judged as the presence of DSP episode.

2.2.2. Other general measurements

Through an interview for each patient, we evaluated the patient's present clinical status with Brief Psychiatric Rating Scale (Kolalowska, 1976), GAF, Clinical Global Impression-Severity (CGI-S) and Drug-Induced Extra-Pyramidal Symptoms Scale (DIEPSS) (Inada, 1996).

In addition, we assessed the structure of negative symptoms for all participants and judged whether each patient was or was not meeting the deficit syndrome (Carpenter, et al., 1988), in order to demonstrate that the lowered GAF (<60) as evidence for "treatment-resistant schizophrenia" was caused by positive symptoms including DSP episode(s), but not simply by negative symptoms. Whereas patients with deficit syndrome present primary negative symptoms and cognitive impairment for a long-term duration, in patients with TRS the effects of secondary negative symptoms and cognitive impairments caused by extrapyramidal symptoms must be evaluated because of their lowered GAF, since these patients generally take high doses of antipsychotic(s) for a long time. In evaluating primary negative symptoms, we used the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984), the Calgary Depression Scale for Schizophrenia-Japanese version (J-CDSS) (Kaneda et al., 2000) and Hospital Anxiety, Depression Scale (HADS) (Zigmond and Snaith, 1983) and DIEPSS.

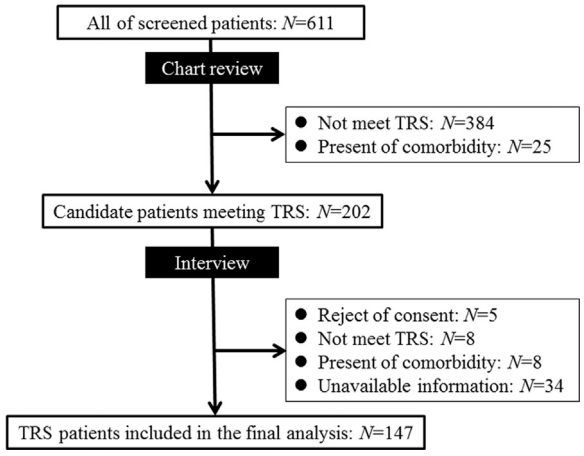

Fig. 1. Overview of participant flow.

Table 1
Criteria for dopamine supersensitivity psychosis in the present study.

(A) The patient must have a 3 month history of receiving antipsychotics
(B) At least one of the following major criteria must be present at any time point during antipsychotic treatment:
(1) Rebound psychosis episode:
- reappearance of psychotic symptoms upon decrease or discontinuation of medication, within 6 weeks for oral medication, 3 months for i.m. depot medication;
- reappearanced psychotic symptoms include new schizophrenia symptom(s) for the patient.

(2) Developed tolerance to antipsychotic effect:
- greater frequency of relapse (acute psychotic exacerbation) during continuous treatment with neuroleptics;
- relapsed psychotic symptoms cannot successfully controlled by overall 20% or more dosage increase of antipsychotic(s).

*The episode(s) of (1) and (2) are required to be observed following clinically "stable" status.

(3) Tardive dyskinesia

These criteria are according to the DSP research criteria proposed by Chouinard (1991) and are modified so as to be possible to apply easily to a retrospective chart review like the present study.