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Impact of dopamine supersensitivity psychosis in treatment-resistant schizophrenia: An analysis of multi-factors predicting long-term prognosis ☆

Hiroshi Yamanaka [a,b], Nobuhisa Kanahara [a,c,*], Tomotaka Suzuki [a,d], Masayuki Takase [a], Toshihiro Moriyama [b], Hiroyuki Watanabe [a,c], Toyoaki Hirata [b], Makoto Asano [b], Masaomi Iyo [a]

[a] Department of Psychiatry, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuou-ku, Chiba 260-8670, Japan
[b] Department of Psychiatry, Chiba Psychiatric Medical Center, 5 Toyosuna, Mihama-ku, Chiba 261-0024, Japan
[c] Division of Medical Treatment and Rehabilitation, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chuou-ku, Chiba 260-8670, Japan
[d] Department of Psychiatry, Koutoku-kai Sato Hospital, 948-1 Kunugizuka, Nanyo City, Yamagata 999-2221, Japan

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ABSTRACT

Background: Although a variety of factors are known to be significantly related to poor prognosis in schizophrenia, their interactions remain unclear. Dopamine supersensitivity psychosis (DSP) is a clinical concept related to long-term pharmacotherapy and could be one of the key factors contributing to the development of treatment-resistant schizophrenia (TRS). The present study aims to explore the effect of DSP on progression to TRS.
Methods: Two-hundreds and sixty-five patients were classified into either a TRS or Non-TRS group based on retrospective survey and direct interview. The key factors related to prognosis, including the presence or absence of DSP episodes, were extracted, and each factor was compared between the two groups.
Results: All parameters except for the duration of untreated psychosis (DUP) were significantly worse in the TRS group compared to the Non-TRS group. In particular, the TRS group presented with a significantly higher rate of DSP episodes than the Non-TRS group. Regression analysis supported the notion that DSP plays a pivotal role in the development of TRS. In addition, deficit syndrome was suggested to be a diagnostic subcategory of TRS.
Conclusions: Our data confirmed that the key predicting factors of poor prognosis which have been established would actually affect somehow the development of TRS. In addition, the occurrence of a DSP episode during pharmacotherapy was shown to promote treatment refractoriness.

1. Introduction

Approximately 20–30% of all patients with schizophrenia show little or no response to appropriate pharmacotherapy and are operationally defined as having treatment-resistant schizophrenia (TRS) (Kane et al., 1988). Over the last three decades, various attempts have been made to clarify factors predictive of poor prognosis or TRS. To date, the factors suggested to predict poor prognosis are male gender (Riecher-Rössler and Häfner, 2000), younger age at onset (Meltzer et al., 1997), lower premorbid social adaptation (Wiersma et al., 2000), and presence of family history of psychiatric disease (Murray and Van Os, 1998). In addition, duration of untreated psychosis (DUP) has been widely studied and longer DUP is now established as a predictive marker for a relatively short disease course (i.e., critical period) (Marshall et al., 2005; Perkins et al., 2005). There have also been numerous researches into the possible relationship between the initial response to antipsychotics and prognosis (i.e., early onset hypothesis; Kapur et al., 2005). Most of these studies demonstrated that the responsiveness at 2 to 6 weeks following treatment introduction for first-episode psychosis (FEP) was significantly predictive of the clinical improvement in the acute stage (Correll et al., 2003; Schennach-Wolff et al., 2011) or chronic disease course (Álvarez-Jiménez et al., 2012; Emsley et al., 2006).

There was, however, no evidence than any specific single factor was a definite predictor for TRS. As regards DUP, its effect on the long-term prognosis is unlikely to be as profound as its effect on the short-term prognosis (Kanahara et al., 2013; White et al., 2009). With respect to initial responsiveness to pharmacotherapy, most studies have been conducted from the viewpoint of prediction for remission, with only limited investigation of the possible role of pharmacotherapy in the development of TRS. Although it appears that these factors affect the

☆ Location of work and address for reprints. The Department of Psychiatry, Graduate School of Medicine, Chiba University Hospital, the Center for Forensic Mental Health Research and Education, Chiba University, Chiba, Japan; the Department of Psychiatry, Chiba Psychiatric Medical Center, Chiba, Japan; the Department of Psychiatry, Koutoku-kai Sato Hospital, Yamagata, Japan.

* Corresponding author at: Division of Medical Treatment and Rehabilitation, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chuou-ku, Chiba-shi, Chiba 260-8670, Japan.
E-mail address: kanahara@faculty.chiba-u.jp (N. Kanahara).

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clinical disease course by interacting with each other, there have been few studies investigating the ability of a combination of factors to predict the development to TRS. Furthermore, the predictive factors in previous studies were mostly limited to parameters related to the stage prior to disease onset or in the very early disease stage, and thus factors related to continuous treatment for the chronic stage were usually omitted.

Dopamine supersensitivity psychosis (DSP) is a clinical concept which is related to antipsychotics treatment (Chouinard, 1991; Iyo et al., 2013) and is characterized by withdrawal psychosis upon the cessation or dose reduction of antipsychotics (Moncrieff, 2006), the development of tolerance to the effects of antipsychotics (Kirkpatrick et al., 1992), tardive dyskinesia (TD; Chouinard and Chouinard, 2008), and acquired vulnerability to minor stress (Fallon et al., 2012). To compensate for these effects, the dosage of antipsychotic(s) is usually increased, and thus the patient in such cases meets the criteria for TRS (Chouinard, 1991; Iyo et al., 2013). As DSP is considered to be induced by dopamine D2-receptor supersensitivity by prolonged antipsychotic treatment, in addition to the dopamine supersensitivity already present in schizophrenia (Kirkpatrick et al., 1992; Iyo et al., 2013; Seeman, 2013; Seeman and Seeman, 2014), this psychosis may be involved in the development of treatment refractoriness. No studies, however, have reported to what extent DSP impacts the long-term prognosis in patients with schizophrenia.

In the present study we attempted to identify factors that are predictive of the prognosis of TRS and are specific to the different clinical stages of TRS. Thus, we considered potential predictive factors prior to the initiation of treatment for psychosis, e.g., DUP and premorbid social functioning, factors related to FEP, e.g., initial response to antipsychotic drugs and their dosages, and factors related to long-term antipsychotic treatment, such as DSP. In this way we sought both to clarify the impact of individual factors on prognosis, and also to examine possible interactions among these predictive factors.

2. Methods

2.1. Subjects

The present study was conducted from April 2012 to September 2014 in three psychiatric hospitals in Japan. Japanese patients being treated for schizophrenia or schizoaffective disorder on an inpatient or outpatient basis were enrolled. All patients were diagnosed according to DSM-IV-TR criteria and patients whose primary diagnosis was any other axis I or II disorder were excluded from the study.

For patients with an acute psychotic episode, the informed consent procedure and subsequent interview were not performed until sufficient recovery from the acute state. In regard to clozapine, this agent was first clinically available in Japan in April 2009, the approximate time of initiation of this study. The assessment was conducted prior to the introduction of clozapine, and thus the data for TRS patients under clozapine treatment were not included in this study.

The present study was approved by the ethics committee of each facility and adhered to the Declaration of Helsinki. All participants provided oral and written informed consent after being provided with a complete description of the study's content. For subjects whose disease may have interfered with comprehension of the study, we instead obtained informed consent from a legally acceptable representative using the same form as used for the participants.

2.2. Study design

The TRS group consisted of TRS patients selected from the three facilities based on a review of their medical records (Fig. 1); all of the TRS participants were also included in our previous study (Suzuki et al., 2015). TRS was defined according to the Broadest Eligibility Criteria (Juarez-Reyes et al., 1995), as shown in Table 1. The Non-TRS group consisted mainly of patients from Chiba Psychiatric Medical Center (CPMC), with a small number of patients from each of the other two hospitals.

Through both retrospective examinations of medical records and direct interview, the required clinical information described in the following sections was collected for each participant. Only subjects with medical records available for their entire treatment period (i.e., from treatment introduction to the present interview) were included in the final analysis.

2.3. Assessments

2.3.1. Factors prior to treatment introduction

Age at onset and DUP were identified at the first hospital admission. Definitions of *onset* and DUP in the present study are based on the generally accepted methodology as described in detail in our previous study (Kanahara et al., 2013). Premorbid adjustment was evaluated by our team using a modified version of the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982); The score is summed from only two ("Education" [#1] and "Employment or school function during a period of 3 years up to 6 months before onset of FEP" [#2]) in the PAS.

2.3.2. Factors related to the treatment of first-episode psychosis

Response of antipsychotic(s) to the FEP was evaluated in the following manner. In the patients introduced as inpatients, Global Assessment of Functioning (GAF) and antipsychotic regimen were identified 1) at the hospital discharge for cases with shorter admission duration under 6 months, and 2) at the 6th month for cases with longer admission duration over 6 months, respectively. In the patients initially introduced as outpatients, GAF and antipsychotics were identified 3) at the time point when the prescription was fixed for at least 4 weeks for cases attaining a clinically stable state within the first 6 months, or 4) at the 6th month for cases that did not attain a stable state within the first 6 months.

2.3.3. Factors related to post first-episode psychosis

2.3.3.1. Dopamine supersensitivity psychosis. We reviewed the clinical medical records in detail and judged whether the patient had a past history of DSP according to the criteria shown in Table 1 and Fig. 1. Briefly, the criteria focus on the following three factors: 1) rebound psychosis, 2) developed tolerance to the therapeutic effects of the antipsychotics, 3) and 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 having experienced a DSP episode.

2.3.3.2. Deficit syndrome. Deficit syndrome was diagnosed according to the Schedule for the Deficit Syndrome (SDS; Kirkpatrick et al., 1992). In addition, we used the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984), Calgary Depression Scale for Schizophrenia Japanese edition (J-CDSS; Kaneda et al., 2000), Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), and Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS; Inada, 1996) to exclude secondary negative symptoms and to assess the possibility of this syndrome comprehensively and individually in each participant.

2.3.3.3. General psychopathology. The patient's general psychopathology was evaluated throughout the interview using the Brief Psychiatric Rating Scale (BPRS; Kolalowska, 1976), GAF and Clinical Global Impressions Scale (CGI-S).

2.4. Statistical analysis

For the comparison between the groups, Student's *t*-test or Mann–Whitney U-test was applied for continuous values and chi-square test or Fisher's exact test was applied for categorical values. The significant threshold level was set at $\alpha = 0.05$. For the multivariate analysis

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