1) Title page:

Neurocognitive functioning in patients with first-episode schizophrenia one year from onset, and comparison with patients 5 years from onset

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Running title: cognitive deficits in first-episode schizophrenia

2) Abstract

Objective: The course of neurocognitive deficits in schizophrenia has not yet been established. Therefore, we followed patients with first-episode schizophrenia to verify the course of these deficits.

Methods: In study 1, tests of neurocognitive functioning were administered to patients with first-episode schizophrenia (FE group) every 6 months. Of the 26 patients who completed the baseline assessment, 19 completed a 6-month follow-up, and 13 completed a 1-year follow-up. In study 2, 19 patients in FE group at 6-months when the neuropsychological measures was less influenced by psychotic symptoms and other patients who experienced schizophrenia 5-years earlier (5-year group) were compared.

Results: In study 1, verbal memory, motor speed and executive functions significantly improved at the 1-year follow up. In study 2, patients in 5-year group performed worse in verbal memory and executive functions than patients in FE at 6-month group, but marginally but significantly better in verbal fluency.

Conclusions: Verbal memory, executive functions and verbal fluency were significantly different between 5-year group and FE at 6-month group, and may indicate progression of schizophrenia. Executive functions may reflect the state of psychosis. Working memory and processing speed which did not change significantly from onset are needed to verify the course in further research.

3) Key words: schizophrenia, first-episode, neurocognitive functioning, prospective study, social functioning

4) Main text

a) Introduction

Early intervention and initial treatment of schizophrenia has been focused on improving long-term prognosis. It has been reported that patients with schizophrenia tend to have a high risk of relapse and social dysfunction during the first 5 years of the onset of the disease, named the "Unstable period" (Utena 1991). Based on these findings, it is reasonable to speculate that the majority of biological, psychological, and social changes occur during this 5-year period (Birchwood et al.1997). A SOHO study that compared the effects of different antipsychotics on outpatients with schizophrenia in Europe concluded that 38.2% of the patients had achieved remission at the first year follow-up, 64.6% had achieved remission 3 years after onset, and that shorter durations of mental disorders increased the rate of remission (Haro et al. 2006). Thus, initial treatment is a clinically important issue.

It is well-known that social dysfunction in schizophrenia is related to neurocognitive impairments (Ikebuchi 2004). Verbal memory and executive functions predict social outcome (Velligan et al. 2000). However, there is a long standing debate regarding the types of neurocognitive impairments seen in schizophrenia. Using advanced brain imaging, it has been shown that the lateral ventricle expands before onset of the disease, and the volume of the left Heschl gyrus and planum temporale gray matter progressively decreases in patients with first-episode schizophrenia (Kasai et al. 2003). As such, progressive neural changes occur in schizophrenia. The previous studies showed that neurocognitive impairments in schizophrenia partially improve (Gold et al. 1999), do not change significantly (Townsend et al. 2002), or partially deteriorate during the course of the disease (Hoff et al. 1999). Meta-analysis of 53 studies concluded that practice effect was likely to account for most of the improvements observed (Szöke et al. 2008). Thus, the longitudinal course of neurocognitive impairments in schizophrenia remains unclear.

The aim of the present study was to investigate the course of changes in neurocognitive deficits in first-episode schizophrenia during the 5-year period after the onset of the disease. This study expands the scope of previous investigations by following patients after their

first-episode schizophrenia and comparing those patients to other patients that first experienced schizophrenia 5 years earlier. The goal was to find whether there is a generalized or specific domain of neurocognitive deficits that endure, improve, or deteriorate.

b) Material and Methods

Subjects

Study 1

Subjects with first-episode schizophrenia (FE group) were recruited from outpatients and inpatients at a hospital attached to the Teikyo University Medical Department and Kawaguchi Hospital in Japan from April 2008 to January 2011. Twenty-six patients of age 16–45 years met the DSM-IV criteria for schizophrenia at registration, based on the Structured Clinical Interview for DSM-IV. Subjects were excluded if they had any of the following: (i) evidence of an organic central nervous system disorder, (ii) a history of drug or alcohol abuse, or (iii) mental retardation (iv) no more than 2 years had passed since psychotic episode started. Of a total of 26 patients of 2 inpatients and 24 outpatients, 19 patients completed a 6-month follow-up, 13 patients completed a 1-year follow-up. Four patients did not complete the follow-up assessment , including two patients whose acute psychotic symptoms were too severe to complete testing, two patients who stopped consultation, two patients who refused to be evaluated, and one patient who committed suicide.

Study 2

Subjects were recruited from outpatients at a hospital attached to the Teikyo University medical department and the Kawaguchi hospital in Japan from December 2009 to January 2011. All subjects met the DSM-IV criteria for schizophrenia. Patients were enrolled if they met the following inclusion criteria: (i) age 16–45 years at registration and (ii) the onset of their symptoms occurred 5 years earlier. Subjects were excluded the similar exclusion

criteria to study 1. Eighteen patients completed clinical and neuropsychological measures.

Psychiatric and demographic assessments

All patients were evaluated with the Positive and Negative Syndrome Scale (PANSS). The duration of untreated psychosis (DUP) was calculated as the time period from the onset of psychotic symptoms to the onset of adequate treatment with antipsychotic drugs. Relapse was operationally defined as exacerbation of psychotic symptoms and rehospitalization, and the time of relapse was recorded. Premorbid intelligence was estimated using The National Adult Reading Test Japanese version (JART) (Nelson 1982) (Matsuoka et al. 2006).

Neurocognitive function assessment

All patients underwent evaluation with the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J) (Keefe et al. 2004) (Kaneda et al. 2007). The BACS-J requires less than 35 minutes to complete in patients with schizophrenia. The BACS-J composite scores were significantly correlated with a standard neurocognitive battery, which includes the following tests: Rey Auditory-Verbal Learning Test, Consonant Trigram Test, General Aptitude Test Battery, Wisconsin Card-Sorting Test and Wechsler Adult Intelligence Scale-Revised subtests (Picture Completion and Information) (Kaneda et al. 2007). The BACS-J is a reliable and practical scale to evaluate neurocognitive functioning (Kaneda et al. 2007). The domains of verbal memory, working memory, motor speed, category instances, letter fluency, processing speed, and executive functions were tested. All test scores were standardized to create the z scores (mean=0, SD=1) based on the means and standard deviations on the assessment of healthy control subjects in Japan, and the composite score was summation of all z scores.

Social functioning assessment

All patients underwent evaluation with Global Assessment of Functioning (GAF) and the Life Skills Profile Japanese version (LSP-J) (Parker et al. 1991) (Hasegawa et al. 1997). LSP-J

is a scale that assesses the capacity of the patient to live independently in a community using five subscales (self-care, non-turbulence, socialization, communication, and responsibility) composed of 39 items rated from 1 to 4 (with higher scores reflecting more independence).

All participants in the FE group gave informed consent to participate in both study 1 and study 2, according to procedures approved by the Ethics Committee of Teikyo University. Eighteen patients in 5-year group gave written informed consent to participate in study 2, which was approved by the local Ethics Committee of Teikyo University.

Study design

The baseline assessments were conducted within 2 weeks of registration. In study 1, the assessments were repeated every 6 months, starting at the first admission of the subject. The doctors of the outpatients continued to treat the patients, including selecting the drug used and the dosage of the drug.

Data analysis

All statistical analyses were performed by using SPSS software (SPSS version 19).

Study 1 (longitudinal study)

The course of psychiatric symptoms, neurocognitive functioning, and social functioning was assessed using one-way ANOVA for PANSS, GAF, LSP-J, and BACS-J among the 13 patients who were followed-up during the 1-year period. We used Pearson's correlation analysis to compare changes in the neurocognitive functioning and social functioning scores with changes in the psychiatric symptom scores during the 1-year period.

Study 2 (cross-sectional study)

T-test was used to determine any differences in the demographic data between the patients in the FE group in study 1 at the time when the neuropsychological measures was less

influenced by psychotic symptoms and patients in the 5-year group were compared. When group differences were identified, the variables for which differences were observed were included as covariates in one-way analysis of covariance (ANCOVA). ANCOVA was used to compare psychiatric symptoms, neurocognitive functioning, and social functioning between both groups.

c) Results and Discussion

Study 1

Demographic data

Of the 13 patients in the FE group who completed a 1-year follow-up, the mean age at registration was 26.0±7.2 years old, the mean DUP was 1.7±1.0 months, the mean JART was 95.2±9.7, and the mean level of education was 13.1±2.5 years.

There were no significant differences in demographic characteristics, psychiatric symptoms, neurocognitive impairment, and social dysfunction at baseline between the patients who completed a 6-month follow-up (n=19) and those who dropped out (n=7).

Changes in the scores of the assessment scales (table1)

All subjects except one patient were taking antipsychotic medication at baseline (Three patients were receiving olanzapine, three were taking aripiprazole, three were taking blonanserin, two were taking risperidone, and one was taking fluphenazine maleate) . One-way ANOVA revealed that, and positive symptoms ($F=9.7$, $p<0.01$), negative symptoms ($F=5.7$, $p<0.05$), and general psychopathology ($F=3.4$, $p<0.1$) significantly improved at the 1-year follow-up. Verbal memory ($F=9.1$, $p<0.01$), motor speed ($F=4.1$, $p<0.05$), executive functions ($F=4.3$, $p<0.05$), and BACS-J composite score ($F=9.8$, $p<0.01$) significantly improved at the 1-year follow-up. In contrast, working memory, verbal fluency, and processing speed did not significantly change. LSP-J socialization ($F=6.5$, $p<0.05$), LSP-J communication ($F=2.8$, $p<0.1$), and GAF ($F=11.7$, $p<0.01$) were significantly improved at the 1-year follow-up.

Relationships among the changes in psychiatric symptoms, social dysfunction, and neurocognitive impairments were significantly different from baseline to the 1-year follow-up (Table2).

There was relationship between LSP-J socialization and BACS-J composite score ($r=0.50$, $p<0.1$). The improvements on negative symptoms was significantly related to the improvements on LSP-J socialization ($r=-0.72$, $p<0.01$), GAF ($r=-0.78$, $p<0.01$), and was marginally but significantly related to BACS-J composite score ($r=-0.55$, $p<0.1$).The improvements on positive symptoms was marginally but significantly related to the improvements on executive functions ($r=0.49$, $p<0.1$) and LSP-J communication ($r=-0.53$, $p<0.1$). The improvements on general psychopathology was significantly related to improvements on LSP-J communication ($r=-0.53$, $p<0.01$) and was marginally but significantly related to GAF ($r=-0.73$, $p<0.1$).

Study 2

Subjects

In study 1, because T-test revealed that positive symptoms ($t=3.57$, $p<0.01$) significantly improved at the 6-month follow-up, we assumed that the baseline assessment was influenced by acute psychotic symptoms. Therefore, 19 patients in the FE at 6-month group and 18 patients in 5-year group were compared.

Demographic data (table3)

Of the 18 patients in the 5-year group, the mean age was 34.4±5.9 years old, the mean DUP was 8.4±14.8 months, the mean haloperidol-equivalent (HP) dose was 9.8±5.8 mg/day, and the mean level of education was 13.2±2.3 years (Table 3). Ten patients were taking a single antipsychotic medication (Six patients were receiving olanzapine; two, risperidone; one, aripiprazole; and one, fluphenazine maleate) and eight patients were taking a combination of antipsychotic medications. Of the 19 patients in the FE at 6-month group, the mean age

was 27.4±7.2 years old, the mean DUP was 2.6±3.6 months, the mean HP dose was 6.2±4.5 mg/day, and the mean level of education was 13.0±2.3 years. The mean age of illness onset ($t=-3.3$, $p<0.01$), the time that had passed since the onset of symptoms ($t=-68.7$, $p<0.01$), and the mean HP dose ($t=-1.7$, $p<0.1$) were all significantly higher in the 5-year group than in the FE at 6-month group. The age of illness was significantly correlated with the time that had passed since the onset of symptoms ($r=0.49$, $p<0.01$).

Group differences

After controlling for age and HP dose, ANCOVA was used to compare psychiatric symptoms, neurocognitive impairments and social dysfunctions between the FE at 6-month group and the 5-year group (Table 4). Patients in the FE at 6-month group performed better in general psychopathology ($F=3.3$, $p<0.1$) than patients in the 5-year group.

Patients in the 5-year group performed significantly worse in verbal memory ($F=6.6$, $p<0.05$) and executive functions ($F=3.5$, $p<0.1$) than patients in the FE at 6-month group. In contrast, patients in the 5-year group performed significantly better in verbal fluency ($F=5.8$, $p<0.05$) than patients in the FE at 6-month group. However, verbal memory may have been influenced by the HP dose, because verbal memory was significantly correlated with the HP dose ($r=-0.40$, $p<0.05$). Both groups did not reach significant levels in working memory, motor speed, processing speed, or BACS-J composite score. Patients in the 5-year group performed better in LSP-J socialization than patients in the FE at 6-month group ($F=3.5$, $p<0.1$).

Discussion

Changes in neurocognitive functioning

Verbal memory, executive functions, and verbal fluency were significantly different between the 5-year group and the FE at 6-month group. The improvement on positive symptoms was significantly correlated with the improvement on executive functions in the FE group. Working memory and processing speed did not change significantly from onset.

Some neurocognitive impairments could be progression markers of schizophrenia that become more apparent as the illness progresses. Stirling et al. reported that 111 first-episode psychosis cases were traced for 10–12 years, and 24 of these patients completed the full battery of tests (Stirling et al. 2003). First-episode cases performed worse in object assembly, picture completion, and design memory than healthy subjects over the follow-up period. Frommann et al. reported that a total of 205 subjects who met the criteria for either an early prodromal state (EPS) or a putatively late prodromal state (LPS) of psychosis were assessed with a comprehensive neuropsychological test battery (Frommann et al. 2001). Verbal memory performance was impaired in the LPS group compared with the EPS group and healthy control group even if the verbal memory deficit was controlled for the performance in the other cognitive domains. In the present study, verbal memory and executive functions were significantly different between the 5-year group and the FE at 6-month group. This supports the use of these measures as progression markers. However, the present study was cross-sectional, and further longitudinal studies are needed.

It is possible that other neurocognitive impairments could be used as markers that reflect the state of psychosis. Bozikas et al. reported that 58 patients with schizophrenia were assessed with a battery of neuropsychological tests. The severity of positive symptoms was related to impairment in semantic verbal fluency ($r=-0.35$, $p<0.01$) and trail making part A ($r=0.43$, $p<0.001$) (Bozikas et al. 2004). In the present study, psychiatric symptoms significantly improved at the 1-year follow-up. Improvement in positive symptoms was significantly correlated with improvement in executive functions from baseline to 1-year follow-up. Executive functions tended to improve at 1-year follow-up in all patients in the FE group. Therefore, executive functions may reflect the state of psychosis. It is necessary to further follow the patients in the FE group to verify these findings.

Other neurocognitive impairments are speculated to be vulnerability markers for schizophrenia, and are believed to have already decreased before the onset of the disease. Keefe et al. reported that 37 patients who met the Criteria of Prodromal States (Miller et al.

2003) for being at risk for psychosis performed more poorly than 47 healthy subjects on measures of vigilance and processing speed during the 1-year period (Keefe et al. 2006). Jahshan et al. reported that a comprehensive neurocognitive battery and clinical assessment were administered to 48 patients who met the criteria on the Structured Interview for Prodromal Syndromes for being at risk for psychosis(Miller et al. 2003), 20 patients with first-episode schizophrenia, and 29 healthy subjects at baseline and at a 6-month follow-up (Jahshan et al. 2010). Six at-risk subjects who progressed to schizophrenia performed worse than 42 at-risk subjects who did not progress to schizophrenia in working memory and processing speed. In the present study, working memory and processing speed did not significantly change for 1 year after the onset of schizophrenia. Prospective studies that evaluate patients both before and after disease onset, and follow them for at least 5 years are needed to verify the course of working memory and processing speed, and if not changed, working memory and processing speed may be the marker of the vulnerability.

Relationships of psychiatric symptoms to neurocognitive impairments and social dysfunctions

In the present study, there was relationship between BACS-J composite score and LSP-J socialization, but no relationship between subgroups of neurocognitive impairments and social dysfunction. Negative symptoms were significantly related to LSP-J socialization, GAF, and marginally but significantly BACS-J composite score.

Green et al. reviewed that neurocognitive functioning is a strong predictor of community functioning, such as social functioning, work performance, and social skills (Green 1996). Negative symptoms were associated with social problem solving. Social functioning is associated with neurocognitive functioning, especially with secondary memory, executive functions, and verbal fluency (Green et al. 2000). A comprehensive neurocognitive battery and community outcome measures were administered to 40 patients with schizophrenia

over 1–3.5 years. Verbal memory predicted all measures of community outcome, vigilance predicted social outcomes, and executive functions predicted work and activities of daily living (Velligan et al. 2000). In this study, there was relationship between BACS-J composite score and LSP-J socialization, but there was no significant relationship with subdomains of neurocognitive function and LSP. One reason may be thought that LSP is used to measure the ability to engage in independent living in a community. Because scoring highly in LSP scores is not difficult for our participants who live independently, the change of LSP was not a sensitive measure in these subjects. It may be necessary to use other social functioning scales that examine occupational abilities or social problem solving to fully capture changes of social functioning of persons living independently. Another reason may be that the sample size is small and the duration of follow-up is short. It may be necessary to increase the number of participants and further follow the patients in the FE group to verify these relationships.

Limitations

The current study involves a number of potential limitations. First, the sample size was small. Second, the time to follow patients with first-episode schizophrenia was short. Third, the improvements observed in the FE group may be interpreted in practice effects because of the lack of a healthy control group. Fourth, we compared FE group with another 5-year group in study 2.

5) Key points:

1. We followed FE group during the 1-year period and compared FE group at 6-months with 5-year group to verify the course of neurocognitive deficits in schizophrenia.
2. Verbal memory, executive functions and verbal fluency were significantly different between 5-year group and FE at 6-month group, and may indicate progression of schizophrenia.
3. Executive functions may reflect the state of psychosis.

4. Working memory and processing speed which did not change significantly from onset are needed to verify the course in further research.

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7) Disclosure of Interest

The authors have no conflicts of interest to declare.

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