Because of impulsive violence and severely disorganized behavior, she needed to be kept in isolation for 4 years of her hospitalization. At age 27, she gained slight benefit from ECT, but, her father refused to allow further ECT. She was treated with monotherapy of antipsychotics including risperidone (12 mg/day for 3 months), olanzapine (25 mg/day for 2 months), quetiapine (750 mg/day for 1.5 months), perospirone (48 mg/day for 0.5 months), or various combined treatments of atypical and typical antipsychotics including haloperidol 27+sultopride 1800+levomepromazine 200 mg/day for 2 months, and sultopride 1800+zotepine 450+levomepromazine 200 mg/day for 7 months. However, these pharmacological treatments failed to improve her condition. She was diagnosed as chronic, disorganized, pharmacological treatment-resistant schizophrenia, according to the criteria of Kane et al. (1988). She was transferred to our hospital to receive a clinical trial of clozapine, which had not been marketed in Japan yet. At this time, only 25 cases in Japan had received a clinical trial of clozapine for refractory schizophrenia. Unfortunately, her symptoms did not respond to clozapine, up to 600 mg/day, during 8 months of treatment.

The protocol of the clinical trial of clozapine in Japan did not permit ECT combined with clozapine. After the discontinuation of clozapine, we started olanzapine 40 mg and risperidone 10 mg again. Her speech was disorganized and she talked incoherently to others about members of the Imperial family and famous comedians (word salad). Communication was very difficult because of loosening of associations. For example, she talked about being on the Titanic ship or even Jupiter in a childlike manner. In addition, she exhibited bizarre, childish, and disorganized behavior. She was not able to take care of herself in simple matters such as grooming, eating, hygiene and dressing. She would also squeeze her stool through her fingers, pull out pubic hairs in public, try to drink cleansers, wash her hands in the toilet bowl, undress herself with delusions of pregnancy, pour tea over her head, throw chairs at other people, scratch her wrist with a fork, and knock on the bed post continuously injuring her knuckles. Inappropriate emotional responses also reflected childish attitudes. To improve her disorganized symptoms, modified ECT for her was performed in an operating room. As brief-pulse ECT devices were not approved of in Japan before 2002, we used bilateral sine-wave treatments with constant-voltage, using atropine, propofol, and succinylcholine (or vecronium) as anesthetic medications. The first series of acute ECT, 3 times in the first week and then once weekly for the following three weeks (six times per total 4 weeks) was done, because the schedule of anesthesiologists and the operating room was very tight. This first series of 6 ECT sessions markedly improved her condition: the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; Kolakowska, 1976) score was reduced from 70 to 40. She could exchange greetings with medical staff and act appropriately in some or many situations. However, the effect lasted only for about 2 weeks after the first series of acute ECT, and she relapsed into disorganization. The second series of 12 ECT sessions (twice per week) for 6 weeks produced similar marked effects. This time, we decided to add ECT sessions. The third series of acute ECT (once a week) for the following 3 weeks decreased her BPRS score from 56 to 23. In this time-point, she showed an excellent response and remission for ECT, because of at least 50% of reduction of the initial score of the BPRS. Then, the following continuation ECT (once a week) for 6 weeks (the fourth series) resulted in continued improvement. The patient showed dramatic improvement from 70 to 20 in the BPRS score after acute ECT and continuation ECT. She could politely communicate with other people and behave herself well in a mature manner, not in the childlike manner. In addition, she was able to take care of herself, read books, listen to music, play ping-pong and study English. Her emotional responses were becoming appropriate and stable. Then, risperidone was decreased to 6 mg with reduction of olanzapine to 20 mg, which has been continued until now. Another four-month maintenance ECT enabled her to stay out of the seclusion room in the psychiatric ward. Her Global Assessment of Functioning (GAF; the DSM-IV axis V) score increased from 11 to 45. The interval between ECT sessions was gradually lengthened to six weeks after one year of maintenance treatment. Using outpatient ECT, she was discharged to her home after 7-years hospitalization.

3. Discussion

We observed a patient with treatment-resistant chronic severe disorganized schizophrenia who responded markedly to continuation and maintenance ECT plus olanzapine and risperidone. Combined ECT and neuroleptic therapy is safe and useful for treatment-resistant schizophrenia (Chanpattana et al., 1999; Chanpattana and Chakrabhand, 2001; Braga and Petrides, 2005). Moreover, our current case report may indicate that ECT can be efficacious in clozapine nonresponders suffering from schizophrenia. This is consistent with an open label study about the efficacy of ECT as adjunctive treatment in 11 clozapine nonresponders suffering from schizophrenia (Kho et al., 2004). Unfortunately, our case could not apply the combination of ECT and clozapine, because clozapine is not sold in Japan, and combined ECT and clozapine was not permitted in the protocol of clinical trial of clozapine. The combination of ECT with clozapine in treatment-resistant schizophrenia appears to be safe and effective, and is recommended for the first choice of clozapine nonresponders. However, the beneficial effects of acute ECT with clozapine may be short-lived (Kales et al., 1999). Continuation and maintenance ECT is used to reduce the risk for relapse and recurrence of severe psychiatric disorder in patients who fare poorly with continuation and maintenance medication regimens. Despite the potential value of these ECT schedules, both are relatively neglected in clinical practice (McCall, 2001; Andrade and Kurinji, 2002). On the other hand, several reports (Hoflich et al., 1995; Ucok and Ucok, 1996; Dean, 2000; Stevens et al., 2001; Chanpattana et al., 1999; Chanpattana, 2000; Chanpattana and Chakrabhand, 2000; Chanpattana and Kramer, 2003) showed treatment-resistant schizophrenia was treated successfully with continuation and maintenance ECT. Clinicians should consider applying not only acute ECT, but also continuation and maintenance ECT to patients with refractory schizophrenia. After ECT, this case had

no obvious side effects. Further studies will be required in order to standardize the methods of continuation and maintenance ECT for treatment-resistant patients with schizophrenia.

4. Conclusion

This case report suggests that pharmacological treatment-resistant disorganized schizophrenia can respond to continuation and maintenance ECT.

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Posterior cingulate gyrus metabolic changes in chronic schizophrenia with generalized cognitive deficits

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Abstract

N-Methyl-D-aspartate (NMDA) receptor antagonists are known to induce schizophrenia-like psychotic symptoms and cognitive deficits in humans, and have been shown to cause neuronal damage in the posterior cingulate gyrus (PCG) of rodents. Patients with chronic schizophrenia exhibit generalized cognitive deficits, but it remains unclear whether or not the PCG is related to their cognitive dysfunction. To determine what biochemical changes may occur in the PCG of patients with chronic schizophrenia, and to ascertain whether or not such abnormalities may be related to the incidence of cognitive deficits, we obtained cognitive scores and proton magnetic resonance spectra (MRS) from the PCG and the left and right medial temporal lobes (MTL) of 19 patients with schizophrenia and 18 age- and sex-matched normal healthy controls. Compared to the normal controls, the patients with chronic schizophrenia showed significantly worse cognitive performance on verbal and visual memory tests, verbal fluency tests, and the Trail Making Test. The ratio of *N*-acetylaspartate to creatine and phosphocreatine (NAA/Cr) in the PCG of the patients was significantly lower than that of the controls. Moreover, the NAA/Cr in the PCG of the healthy controls exhibited age-related decline, whereas in the patients with schizophrenia, the corresponding values were consistently low, regardless of age. These findings are thus in accord with current speculation about neuronal dysfunction in the PCG based on the NMDA hypofunction hypothesis regarding the pathophysiology of chronic schizophrenia.

Keywords: Cingulate gyrus; Proton magnetic resonance spectroscopy (^{1}H-MRS); Retrosplenial cortex; Schizophrenia; *N*-Acetylaspartate (NAA); Wechsler Memory Scale-Revised (WMS-R)

1. Introduction

Cognitive deficits are a key feature of schizophrenia (Elvevag and Goldberg, 2000; Gold and Weinberger, 1995; Sharma and Antonova, 2003), not only at the time of the first episode (Bilder et al., 1992; Heydebrand et al., 2004; Mohamed et al., 1999), but also in patients with chronic schizophrenia (Braff et al., 1991; Pantelis et al., 1997). Impairments of cognitive functions such as memory, executive function, and attention are characteristic of most patients with schizophrenia (Egan et al., 2001; Weickert et al., 2000). It remains controversial whether or not the cognitive deficits observed in patients with schizophrenia are better characterized as generalized features, or as reflective of relatively independent

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deficits in different cognitive domains. Dickinson et al. (2004) reported that generalized cognitive deficits might be a core feature of schizophrenia, in contrast to more specific, independent cognitive deficits. Researchers have attempted to determine whether or not there is a relationship between cognitive deficits and localized pathological changes in patients with schizophrenia. However, the biological basis of such generalized cognitive deficits remains unclear.

Proton magnetic resonance spectroscopy (^{1}H-MRS) provides a noninvasive means of examining endogenous brain metabolites, including *N*-acetylaspartate (NAA), choline (Cho), and Creatine (Cr). NAA is one of the most abundant free amino acids in the human brain, and is synthesized and stored primarily in neurons (Baslow, 2003). Since MRS can readily detect endogenous NAA in the human brain, NAA has been used as an intracellular marker of neuronal function (Jenkins et al., 2000); indeed, NAA appears to be an indirect measure of neuronal integrity and synaptic abundance in an expanding number of disorders (Tsai and Coyle, 1995). Cho is a precursor for the neurotransmitter acetylcholine and for the membrane constituent phosphatidylcholine. Levels of Cho have been reported to fluctuate when cellular membranes are degraded or rapidly synthesized (Miller, 1991). Cr reflects the total creatine plus phosphocreatine pool. The working memory function of patients with schizophrenia has been associated with NAA levels in the dorsolateral prefrontal cortex (Bertolino et al., 2000). Low levels of NAA/creatine (NAA/Cr) in the medial prefrontal cortex of schizophrenia patients subclassified as having a deficit syndrome have also been detected (Delamillieure et al., 2000). Although these and related studies have provided evidence of a relationship between prefrontal dysfunction and poor cognitive performance in patients with schizophrenia, it remains unclear whether pathological abnormalities in other brain regions are related to particular cognitive functions.

The *N*-methyl-D-aspartate (NMDA) receptor is a ligand-gated ion channel that participates in a number of neurophysiological processes, including learning and memory (Nakanishi, 1992; Shimizu et al., 2000; Tang et al., 1999). The NMDA receptor antagonists, phencyclidine (PCP) (Javitt and Zukin, 1991), MK-801, and ketamine (Newcomer et al., 1999; Umbricht et al., 2000), are known to induce psychotic behavior and cognitive deficits in both animals and humans. Therefore, hypofunction of the NMDA receptors has been implicated in the pathophysiology of schizophrenia (Hashimoto and Iyo, 2002; Hashimoto et al., 2003; Olney and Farber, 1995; Tsai and Coyle, 2002). Olney et al. (1989) reported that NMDA receptor antagonists induce transient neuropathological changes (neuronal vacuolization) in the posterior cingulate gyrus (PCG)/retrosplenial cortex of the rat brain (Fix et al., 1993). Such findings suggest, based on the putative pathogenetic role of NMDA in schizophrenia, that the effects of NMDA are local rather than generalized, and that MRS could be a candidate technique for the detection of NMDA-induced damage. Furthermore, pathology of the PCG can be suspected to be pathogenetically related to cognitive deficits observed in patients with schizophrenia.

Based on the results of these previous studies, we hypothesized that metabolic abnormalities in the PCG play a pivotal role in the cognitive dysfunctions in patients with schizophrenia. However, to the best of our knowledge, there have been no reports with a focus on the relationship between metabolic changes in the PCG and cognitive dysfunction in patients with schizophrenia. To test our hypothesis regarding the putative role played by PCG in the cognitive deficits observed in patients with schizophrenia, we measured metabolic ratios in three brain regions, namely, in the PCG, and in the left and right medial temporal lobes (MTL) by ^{1}H-MRS; and we also assessed neuropsychological cognitive function in patients with chronic schizophrenia.

2. Methods

2.1. Subjects

The ethics committee of the Chiba University Graduate School of Medicine approved the present study. The procedure was fully explained to all of the subjects, who then provided written informed consent prior to participation in the study. Handedness was determined using the Edinburgh Inventory (Oldfield, 1971), and right-handed subjects underwent the procedure (Table 1). Nineteen patients with schizophrenia (11 men and 8 women) were recruited from Chiba University Hospital and Kimura Hospital, Chiba, Japan. Eighteen age- and gender-matched healthy control subjects (12 men and 6 women) also participated in this study. We selected only healthy control subjects who had neither a medical nor a psychiatric history or diagnosis according to our clinical interview. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 1994). Patients with any other mental or physical illnesses were excluded. At the time of testing, the patients were taking antipsychotic medication. Sixteen patients were receiving treatment with atypical antipsychotic drugs including risperidone and olanzapine, while the remaining patients were being treated with conventional antipsychotic medication. The mean daily chlorpromazine equivalent dose was 650.5 mg (standard deviation = 536.3). Clinical symptoms were assessed using the 18-item Brief Psychiatric Rating Scale (BPRS) (Kolakowska, 1976; Overall and Gorham, 1962). The DSM-IV axis V Global Assess-

Table 1
Characteristics of the patients with chronic schizophrenia and the healthy controls

	Schizophrenia	Healthy controls	*p* value
Age, years	40.4 ± 13.1	34.9 ± 11.4	0.12[a]
Onset, years	24.1 ± 5.0		
Duration, years	16.3 ± 11.9		
Subtype	10 Residual, 9 paranoid		
BPRS	26.5 ± 6.1		
GAF	40.9 ± 5.1		

Normally distributed data are presented as mean ± standard deviation (SD).
Abbreviations: BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning.
[a] Not significant. The comparison between two groups was performed using *t*-test (two-tailed).

ment of Functioning (GAF) scores (American Psychiatric Association, 1994) were also rated as part of the examination.

2.2. Cognitive functioning

The subjects performed a battery of tests designed to assess several domains of cognitive functioning. Verbal memory was evaluated with the Japanese version (Sugishita and Omura, 2001) of the Logical Memory I (immediate) and II (30-min delayed) subtests of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987). Visuospatial memory was evaluated with the Visual Reproduction I (immediate) and II (30-min delayed) tests of the WMS-R.

Verbal fluency was assessed with the letter fluency test and the category fluency test. In the former test, the subjects were instructed to generate as many words as possible beginning with a given letter in Japanese, "Ka", in 60 s. For the latter test, the subjects were instructed to name as many animals as they could, according to the standard protocol (Spreen and Strauss, 1991).

The Trail Making Test (Reitan and Wolfson, 1985) examines psychomotor speed, attention, and set alternation. Part A requires the subjects to draw lines to connect 25 consecutively numbered circles on one worksheet as quickly as possible. In Part B, the subjects are asked to connect 25 consecutively numbered and lettered circles by alternating between the two sequences (e.g. 1–A–2–B–3 etc.). The time taken to complete Parts A and B of the Trail Making Test was recorded in seconds.

2.3. MRS protocol

The subjects and controls were scanned using a 1.5-T Signa MR scanner (General Electric Medical Systems, Waukesha, WI) with a standard quadrature head coil for MR imaging and ^{1}H-MRS. Both the anatomic and spectroscopic data were obtained within approximately 30 min. All MRI scans were reviewed in order to rule out any clinically significant abnormalities. We performed serial axial T1-weighted MR images with a slice thickness of 10 mm to establish a region of interest (ROI) for the proton MR spectroscopic studies. MRS was performed with the automated Proton Brain Examination (PROBE-p) sequence, which consists of a Point Resolved Spectroscopy (PRESS) sequence (TE = 144 ms, TR = 2000 ms) with Chemical-Shift Selective (CHESS) water suppression, to acquire localized spectra in the PCG, and in the left and right MTL (including hippocampal formation) (Fig. 1). The voxel size was 3.375 mL (15 × 15 × 15 mm). Voxel placements were carried out by a trained radiologist. All of the data were

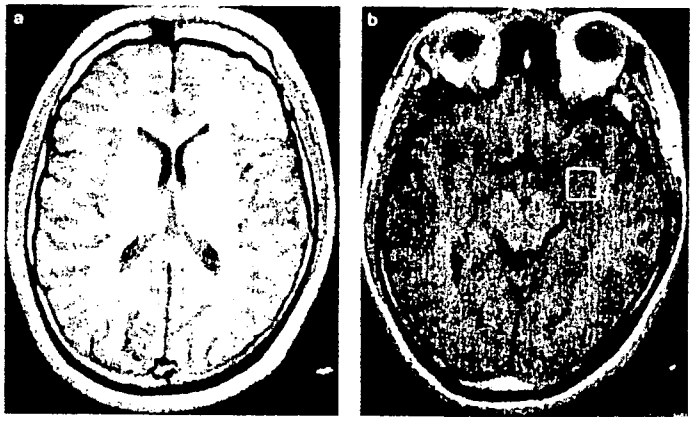

Fig. 1. Voxel size and position in the posterior cingulate gyrus (PCG) (a) and left medial temporal lobe (MTL) (b).

processed using the PROBE/single voxel quantification tool (Webb et al., 1994). Peaks of NAA (2.0 ppm), Cr (3.0 ppm), and Cho (3.2 ppm) were identified. Cr is present throughout various regions of the brain, and levels of Cr do not appear to be affected by neuronal fluctuations (Frahm et al., 1989). Therefore, the Cr peak was used as a reference for comparison with the peaks of the other substrates. The data reflecting the metabolite profiles were described as ratios, i.e., NAA/Cr and Cho/Cr.

2.4. Statistical analyses

Normally distributed data are presented as the mean ± standard deviation (SD); data that were not normally distributed are reported as medians, with interquartile ranges. Calculations were performed using the statistical software package SPSS 12.0 base and advanced systems for Windows (SPSS Inc., Chicago, IL). Fisher's exact test was used for categorical variables, and Student's t-test was employed for the continuous variables. As the scores on the cognitive tests were not found to have normal distributions, the differences between the two groups (patients and controls) were examined using the non-parametric Mann–Whitney U-test with Bonferroni's correction for multiple comparisons (Bland and Altman, 1995). A value of $p < 0.05$ was taken as the standard for statistical significance. Eight cognitive tests were conducted. Because of the multiple comparisons (the number of comparisons was 8), Bonferroni's correction was applied. With this adjustment, the critical level for significance, p, was reduced from the standard value of 0.05 to 0.00625 (i.e., 0.05/8).

Potential differences between patients and controls were tested separately for each metabolite ratio (NAA/Cr and Cho/Cr) by repeated-measures multivariate analysis of variances (MANOVAs), with region (the PCG, or the left or right MTL) as the within-group factor, and diagnosis (patients, controls) as the between-group factor. A post hoc analysis was performed by Tukey's honest significant difference test. Interactions were decomposed with a univariate analysis of variance (ANOVA).

Multiple stepwise regression analyses were used to determine the relative contribution of the metabolite ratios from the three brain regions as predictors of each cognitive score or age. On the other hand, the parameters (clinical and cognitive variables) that predicted the metabolite ratio were determined by multiple stepwise regression analysis. When association between highly significant and normally distributed measured variables was investigated, Pearson's correlation coefficient was obtained.

3. Results

3.1. Cognitive performance measures

Compared to the healthy controls, the patients with schizophrenia showed significant cognitive deficits on all neuropsychological tests, including the episodic memory tests (verbal memory, visuospatial memory) and executive function tests (verbal fluency and the Trail Making Test) (Fig. 2).

3.2. Metabolite ratios by ^{1}H-MRS

Analysis of the within-group effect revealed a significant diagnosis-by-region interaction for NAA/Cr ($F(2,35) = 3.588$, $p = 0.033$). A significant main effect of region was found ($F(2,35) = 42.837$, $p < 0.001$).

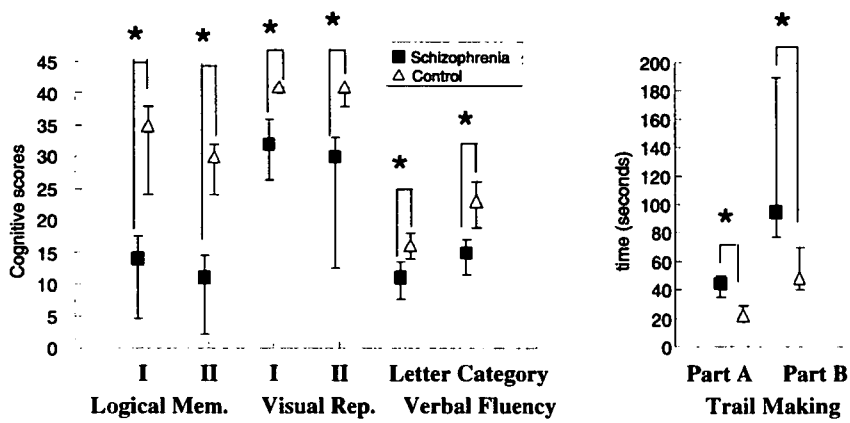

Fig. 2. Scores on cognitive tests of patients with chronic schizophrenia and healthy controls: Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale-Revised (WMS-R) (I, immediate recall; and II, 30-min delayed recall), verbal fluency (the letter fluency test and the category fluency test), and the Trail Making Test (Parts A and B). The data are represented as median ± interquartile range. The p values were determined by Mann–Whitney U-test with Bonferroni's correction on two groups. *Statistically significant difference for $p < 0.00625$ (corrected for multiple comparisons).

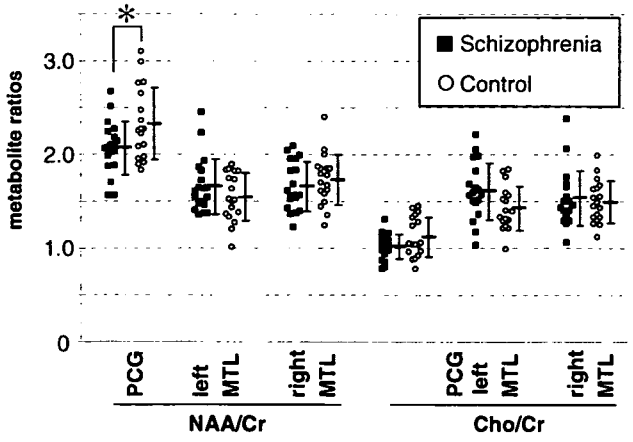

Fig. 3. ^{1}H-MRS metabolite ratios in the posterior cingulate gyrus (PCG) and the left and right medial temporal lobes (MTL) of patients with chronic schizophrenia and healthy controls. The horizontal bars represent mean ± standard deviation. *Statistically significant between-group difference ($F = 5.31$, df = 1,35, $p = 0.027$).

Comparison of the main effect showed that the NAA/Cr ratios of the patients with schizophrenia (2.07 ± 0.28) were significantly ($p = 0.027$, Bonferroni) lower than those (2.30 ± 0.38) of the healthy controls in the PCG (Fig. 3). MANOVA revealed a significantly simple main effect in each group for NAA/Cr, respectively. (patients: Wilks's lambda 0.373, $F(2,34) = 28.62$, $p < 0.001$; controls: Wilks's lambda 0.618, $F(2,34) = 10.509$, $p < 0.001$). Finally, follow-up ANOVA was carried out to analyze the interactions in terms of NAA/Cr; this analysis revealed a significantly simple main effect of diagnosis in the PCG ($F(1,35) = 5.313$, $p = 0.027$).

Comparison of the main effect showed no significant differences of the Cho/Cr ratios between the patients and controls in any of the three regions studied (Fig. 3). Moreover, follow-up ANOVA for the analysis of interactions in terms of Cho/Cr revealed that there was no significantly simple main effect of diagnosis in any of the regions studied.

3.3. Multivariate stepwise linear regression analyses

When the metabolite ratios were considered separately as the PCG and the left and right MTL values in a multivariate stepwise linear regression model, the NAA/Cr ratio in the PCG alone reflected 18.0% of Logical Memory I ($\beta = 0.425$, $p = 0.010$), 20.3% of Logical Memory II ($\beta = 0.451$, $P = 0.006$), and 16.3% of age ($\beta = -0.403$, $p = 0.013$) parameters in all subjects, respectively. A multiple stepwise linear regression model was designed with the NAA/Cr in the PCG as the independent variables with respect to the dependent clinical and cognitive valuables. Only Logical Memory II was accepted by the model, and it significantly accounted for 16.5% of the NAA/Cr ratio in the PCG ($\beta = 0.406$, $P = 0.015$) in all subjects.

Due to the lack of a significant correlation between the NAA/Cr in the PCC and Logical Memory II in the controls ($r = +0.195$, $p = 0.453$) and in the patients ($r = +0.347$, $p = 0.148$), a significant positive correlation ($r = +0.451$, $p = 0.006$) in all subjects was interpreted as a possible indicator of artificially stretched variance. Age-associated memory impairment appeared likely to be a phenomenon of normal aging. Therefore, the Logical Memory scores were excluded from the following selected correlation analysis. A significant negative correlation was found between the NAA/Cr in the PCG and age in all subjects ($r = -0.403$, $p = 0.013$), and also between the NAA/Cr in the PCG in the controls ($r = -0.470$, $p = 0.049$), whereas no correlation was detected among the patients only ($r = -0.217$, $p = 0.371$) (Fig. 4).

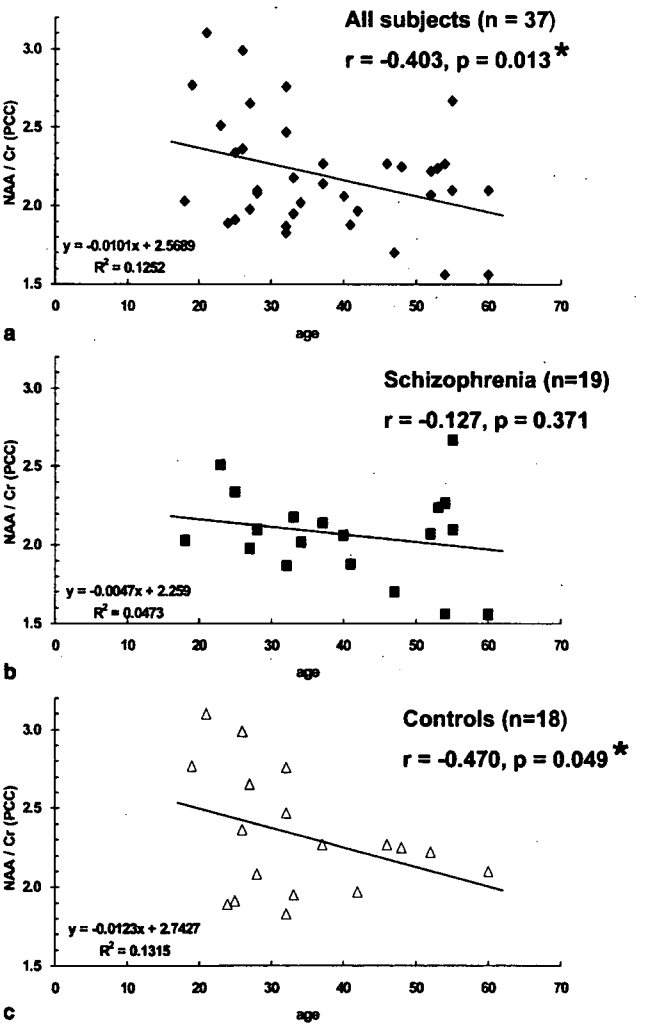

Fig. 4. Scatterplot and least regression line illustrating the relationship between the NAA/Cr ratio in the posterior cingulate gyrus (PCG) and age in all of the subjects (a), in patients with schizophrenia (b), and in healthy controls (c).

4. Discussion

Our results revealed decreased NAA/Cr ratios in the PCG of patients with chronic schizophrenia exhibiting generalized cognitive deficits, as compared to the healthy controls. Moreover, we found that the NAA/Cr of the PCG in healthy controls exhibited age-related decline, whereas corresponding value in patients with schizophrenia were consistently low, regardless of age. The lack of healthy, aging-related decline among the patients with schizophrenia suggested disease-associated neuronal pathology in the PCG. These observations suggested that a reduced NAA/Cr ratio in the PCG might be associated with the pathophysiology of chronic schizophrenia with generalized cognitive deficits.

Valenstein et al. (1987) reported a male case of retrosplenial amnesia following hemorrhage from an arteriovenous malformation. Using positron emission tomography (PET), several researchers reported that the use of the PCG was common to episodic memory (Andreasen et al., 1995; Desgranges et al., 1998; Nyberg et al., 1996; Shallice et al., 1994). Using PET, Minoshima et al. (1994, 1997) also demonstrated the functional importance of the PCG in impairments of learning and memory, which is a feature of very early Alzheimer's disease and mild cognitive impairment. In addition, the NAA/Cr ratios in the PCG have been shown to be decreased in cases of mild cognitive impairment, Alzheimer's disease (Kantarci et al., 2000), and non-demented Parkinson's disease (Camicioli et al., 2004). Taken together, these results suggest that cognitive decline is associated with hypofunction of the PCG. Our regression analysis data, which revealed a relationship between the NAA/Cr in the PCG and the verbal memory of all subjects, suggested that the NAA/Cr in the PCG might be related to episodic memory function.

NMDA receptor antagonists are known to induce neuronal damage in the rodent PCG; these antagonists are thought to be responsible for psychotomimetic activity in humans (Olney and Farber, 1995). Newcomer et al. (1999) reported dose-dependent increases in ketamine in healthy males exhibiting schizophrenia-like symptoms, as well as robust dose-dependent decreases in verbal declarative memory performance. Our data indicating PCG dysfunction in patients with chronic schizophrenia with generalized cognitive deficits provide support for the NMDA receptor hypofunction hypothesis that suggests a link between cognitive impairments and schizophrenia-like symptoms.

Several previous proton MRS studies have demonstrated decreased NAA/Cr ratios in the MTL of chronically medicated patients with schizophrenia (Bertolino et al., 1996, 1998; Deicken et al., 1998; Fukuzako et al., 1995; Maier et al., 1995; Nasrallah et al., 1994; Yurgelun-Todd et al., 1996), while other researchers have reported no such significant alterations (Buckley et al., 1994; Delamillieure et al., 2002; Heimberg et al., 1998). Our results regarding the NAA/Cr in the MTL were consistent with those of the latter group of studies. On the other hand, the results of the present study showing no significant changes in Cho/Cr in the MTL were consistent with those of other studies (Bertolino et al., 1996; Deicken et al., 1998; Delamillieure et al., 2002; Maier et al., 1995; Yurgelun-Todd et al., 1996). One possible explanation for the inconsistency regarding NAA alterations among medicated patients with chronic schizophrenia may be the differential effects associated with atypical vs. typical antipsychotic medications (Bertolino et al., 2001; Fannon et al., 2003; Heimberg et al., 1998). The longitudinal changes in brain chemistry after long-term treatment with antipsychotic agents remain undetermined at the present time.

A number of limitations merit further consideration in this context. As our sample size may be regarded as a weakness of the present study, these results will need to be confirmed using a much larger sample. In addition, because we focused on the relationship between cognitive function and the PCG or the MTL, MRS of the prefrontal cortex and anterior cingulate gyrus was not performed in the current study. Instead of the single-voxel approach used here, further studies using the MRS imaging technique should be conducted to clarify the involvement of other brain regions in schizophrenic patients with generalized cognitive deficits. An additional limitation of the present study was that we derived our conclusions based on metabolite ratios, instead of absolute concentrations. In our study, no significant correlation was found between the NAA/Cr in the PCG and the duration of illness. This finding, when taken together with the finding of a lack of a physiological age-related decline in patients with chronic schizophrenia, suggests the possibility that the NAA/Cr in the PCG might decrease during the initial years of illness, rather than reflect linear neurodegenerative processes. Whether or not the reduced NAA/Cr in the PCG reflects a basic underlying pathophysiological process that is present at the onset of illness, and then progresses during the course of the illness remains unclear. Follow-up MRS examinations for several years, not only in patients with chronic schizophrenia, but also in first-episode patients, will be necessary to clarify the role of the PCG during the disease process in schizophrenia.

In the present study, patients with schizophrenia exhibited not only memory deficits, but also executive dysfunction. Schizophrenia appears to be an amalgamation of many different disorders. For example, Wexler et al. (1998) found a selective deficit in the working memory of a subgroup of patients with schizophrenia who performed as well as healthy controls on a screening test of attention and auditory perception. Moreover, the existence of a subgroup of patients with schizophrenia

having a specific verbal memory deficit was reported (Bruder et al., 2004). Further MRS studies on a subgroup with only specific verbal memory deficits will be necessary in order to confirm the relationship between the NAA/Cr in the PCC and verbal memory in patients with schizophrenia.

In conclusion, a significant disease-specific decrease in the NAA/Cr ratio in the PCG, beyond a physiological age-related decline, was revealed in the present study. These findings are consistent with current speculation focusing on neuronal dysfunction in the PCG based on the NMDA hypofunction hypothesis regarding the pathophysiology of chronic schizophrenia.

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Letter to the Editor (Case report)

Fluvoxamine as a sigma-1 receptor agonist improved cognitive impairments in a patient with schizophrenia

1. Introduction

Patients with schizophrenia exhibit positive and negative symptoms, and these symptoms have been targets for the development of new antipsychotics. In recent years, cognitive impairments in these patients, which may persist across cycles in other aspects of the illness and may be strongly related to the functional outcome, have drawn considerable attention (Hughes et al., 2003; Harvey et al., 2001). It has been reported that the patients themselves are aware of and experience distress due to their cognitive impairments (Ginsberg et al., 2005). Some of the new atypical antipsychotics can improve the impairments, but such amelioration generally remains unsatisfying, and the development of more effective drugs is still necessary (Lehman et al., 1995). Recently, we reported on the efficacy of fluvoxamine, a potent sigma-1 receptor agonist, in improving cognitive impairments in an animal model of schizophrenia (Hashimoto et al., 2007). In the present report, cognitive impairments in a female patient with schizophrenia were dramatically improved by adjunctive treatment of fluvoxamine added to risperidone.

2. Case report

A 19-year-old female college student began to experience auditory hallucinations, including a voice admonishing her to kill herself, and delusions of persecution and reference. She responded by withdrawing socially and engaging in various impulsive behaviors, including wrist-cutting. Her mother took her to a mental clinic, where she was diagnosed with borderline personality disorder. She was prescribed zotepine 50 mg and haloperidol 1.25 mg for approximately 6 months, but her withdrawal and impulsive behaviors did not improve, and she was referred to our hospital at the age of 20. No abnormalities were found in her general laboratory examinations or brain CT. She reported having consistent pathological experiences, such as hallucination and delusions, and was diagnosed with schizophrenia according to the DSM-IV criteria. We discontinued her previous medications and started her on risperidone 4 mg. She quickly stopped hearing voices and cutting her wrists. However, she continued to suffer from impairments of concentration, attention and memory, which she reported having experienced for several years, and felt distress as these impairments often disturbed her motivation to watch TV, read a book or help her mother with housework.

A ten-month treatment with risperidone at a dose ranging from 4 to 8 mg almost completely eliminated her psychotic symptoms, and she was again able to go shopping with her mother several times a week. However, she still reported distressing cognitive impairments. Therefore, we added 20 mg paroxetine in order to reduce her anxiety over the impairments. A five-month treatment with paroxetine did not improve the distress or the cognitive impairments, but rather worsened her anxiety. We therefore stopped the paroxetine and, 3 months later, added 50 mg fluvoxamine. One month after the start of fluvoxamine, she reported that her ability to follow the plots of television dramas had improved, along with her quickness of mind and concentration. Two weeks later, she began to help her mother with housework, including cooking and cleaning rooms, and she stated that these changes were due to her improved concentration. She is now 25 years old and has been treated with the two drugs for 18 months. Her cognitive function remains improved and she continues to help her mother with the housework and to search for a suitable job.

3. Discussion

We have presented the case of a young patient with schizophrenia whose psychotic symptoms were improved by treatment with risperidone, one of the new antipsychotics. Her improvement was complicated by cognitive impairments and resulting stress. Her cognitive impairments were consistent with those often observed in schizophrenia, i.e., impairments in quickness of mind, concentration, memory and executive function, which generally appear early and persist regardless of the phase of the illness.

Paroxetine was administered in the hope of eliminating her anxiety and possibly her cognitive impairments, but it did not improve either even after 5 months of treatment. On the other hand, fluvoxamine prominently and quickly improved her cognitive impairments as measured both subjectively and objectively. It has been reported that the combination therapy of fluvoxamine, but not paroxetine, and antipsychotics improves negative symptoms (Silver, 2004). The improvement of the cognitive impairments in the present patient may have been partly correlated with an improvement in negative symptoms, although the patient felt anxiety rather than loss of affect at the impairments, which disturbed her motivation. Both fluvoxamine and paroxetine are serotonin reuptake inhibitors. However, only fluvoxamine exhibits sigma-1 receptor agonism, i.e., the affinity of fluvoxamine is more than 50 times higher than that of paroxetine (Narita et al., 1996), and we have previously shown that fluvoxamine, but not paroxetine, improved cognitive dysfunction in

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phencyclidine-treated mice via its sigma-1 agonistic activity (Hashimoto et al., 2007). Therefore, one of the possible explanations for the improvement of cognitive impairments in the present case may be the sigma-1 agonism of fluvoxamine, rather than the antidepressant effects of serotonin reuptake inhibition, although there are still many other possibilities as well, including modulation of the GABA system (Chertkow et al., 2006). Nonetheless, our results suggest that sigma-1 receptor agonists, including fluvoxamine, may be one of the candidates for treating cognitive impairments in schizophrenia.

4. Conclusion

We reported here a female case of schizophrenia with cognitive impairments. The cognitive impairments were dramatically improved with adjunctive treatment of fluvoxamine added to risperidone, possibly due to the potent sigma-1 receptor agonism of fluvoxamine.

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臨床精神薬理　10：1147-1152, 2007

統合失調症の認知機能障害

——病態と治療——

伊豫雅臣*

抄録：認知機能障害はKraepelin以来統合失調症の中核的症状であると認識されてきたが，近年さらに認知機能への注目が高まっている。この障害の程度には個人差があるが，全般的に障害されていると報告されている。これらの障害は就労や日常生活に支障をきたすため，その適切な評価と治療法の開発が期待される。認知機能は神経心理学検査により評価されるがそれらは日常臨床にはなじまないことも多く，より臨床的に有用な評価方法の開発が望まれる。統合失調症の認知機能障害の治療では従来型抗精神病薬が認知機能障害に影響している可能性がある一方，新規非定型抗精神病薬は認知機能を悪化させない，または改善する可能性があり，まずは従来型から新規非定型に抗精神病薬を変更することが重要と考えられる。心理社会的アプローチも有用であるが，最近ニコチンα7受容体アゴニストやシグマ1受容体アゴニストなど認知機能改善が期待される薬剤の開発も行われてきている。

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Key words：*schizophrenia, cognitive function, neuropsychological test, atypical antipsychotics*

Ⅰ．はじめに

最近の精神医療福祉では統合失調症患者の地域生活を支えるシステムを構築していくことが重要な課題となってきている。統合失調症では日常生活における自立や就労能力など社会機能の低下をきたすことも多く，その機能障害に応じて支援が必要となってくる。ところで患者が自立した生活を行うのに必要なことは何か。精神医学的には，幻覚妄想などの陽性症状のコントロールと自閉，思考貧困，意欲低下などの陰性症状の改善がまず挙げられる。その一方で注意力や記憶力，実行機能などの認知機能は単に就労だけでなく，日常生活においても重要である。多くの統合失調症患者はこの認知機能に障害があり，QOL（quality of life）や社会復帰を考えると認知機能障害を治療者が十分に認識することとともにその治療は極めて重要である。認知機能障害は陽性症状のような派手さはなく，わずかで神経心理学的検査を行わないとはっきりと捉えられないことも多いが，このような認知機能障害を有する統合失調症患者はばらつきはあるが20数%～70数%と報告されており，多くの患者がこの障害を有している。以上のようなことから，米国の国立精神保健研究所（NIMH）は2004年にUCLAを中心とした5つの学術医療機関に統合失調症の認知機能に関する研究ネットワーク作成のために4年間で900万ドル（約10億800万円）の研究費を支給することとし，統合失調症の認知機能改善を目標として巨大プロジェクトを開始した。

ところで，統合失調症における認知や注意の障

Cognitive dysfunction in schizophrenia—clinical implications and treatment.

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表1　健常者と統合失調症における認知機能の比較（文献2）

Variable	Group Means (SDs)		*F* Score	Significance
	Schizophrenia (n=97)	Healthy Control Subjects (n=87)		
Full-Scale IQ	90.6 (16.2)	105.4 (14.8)	37.91	$p<.001$
Vocabulary	9.1 (3.4)	11.0 (3.5)	8.00	$p=.005$
Similarities	9.2 (2.8)	11.0 (3.1)	12.97	$p<.001$
Information	9.7 (2.8)	11.1 (3.2)	3.10	$p=.08$, ns
Picture Completion	8.5 (3.5)	10.3 (2.9)	10.92	$p=.001$
Block Design	9.2 (3.2)	10.7 (3.0)	5.62	$p=.019$
Matrix Reasoning	9.1 (3.5)	11.6 (3.0)	20.67	$p<.001$
Letter-Number Sequencing	7.6 (2.9)	10.5 (2.8)	40.35	$p<.001$
Spatial Span	8.6 (2.9)	10.3 (2.8)	14.15	$p<.001$
Digit Symbol	7.2 (2.3)	10.4 (2.7)	68.47	$p<.001$
Symbol Search	7.1 (2.6)	10.4 (2.4)	69.84	$p<.001$
Logical Memory I	8.1 (3.5)	11.2 (2.9)	34.80	$p<.001$
Verbal Pairs I	8.0 (2.9)	10.2 (2.7)	22.97	$p<.001$
Logical Memory II	8.6 (3.3)	11.1 (3.1)	25.27	$p<.001$
Verbal Pairs II	8.3 (2.9)	11.0 (3.5)	22.03	$p<.001$
Facial Recogniton I	8.7 (2.8)	10.3 (3.2)	10.33	$p=.002$
Family Pictures I	6.9 (3.0)	10.7 (3.2)	63.10	$p<.001$
Facial Recognition II	8.8 (2.5)	10.2 (2.9)	6.80	$p=.01$
Family Pictures II	6.8 (3.1)	10.5 (2.7)	61.55	$p<.001$

WAIS：Wechsler Adult Intelligence Scale，WMS：Wechsler Memory Scale
コメント：統合失調症患者では健常者に比べてわずかだが全般的な認知機能の障害が認められる。

害はKraepelinが19世紀末に既に記載しており，これら認知機能障害は神経生物学的障害から生じ，統合失調症脆弱性の“基質”とも考えられ，また認知機能障害は統合失調症の予後に大きく影響するものと思われていた[5]。近年の診断基準でもDSM-IVにみられるように幻覚妄想などの陽性症状や感情平板化などの陰性症状のいくつかの症状に加え，認知機能障害の関与も含まれていると考えられる社会的，職業的機能の低下が必須のものとなっている。このようにKraepelinに指摘されて以来，精神科医の関心は認知機能障害に向いていたものの，研究や治療の重点は1970年代は陽性症状に対して置かれ，1980年代には陰性症状が予後不良の要因であると考えられるとともに治療の標的として注目されてきた。しかし1990年代に入ると神経心理学的研究が盛んになり，また発展してきた脳画像診断法と組み合わせることにより，認知の欠損とその脳の責任領域に関する研究が進められるようになってきたと言えよう。そして全般的な認知機能の低下が統合失調症の中核であると考えられてきており[2]（表1），現在では認知機能障害は統合失調症研究のまさにターゲットとなっている。

Ⅱ．認知機能の評価と意義

統合失調症は一般的に思春期から青年早期に発症するが，その発症に先立って，例えば引きこもりであるとか職を転々とするなど，既に社会機能が低下していることも多い。また発病前に既に社会機能が大きく低下していることは予後不良の予測因子であるとされる。社会機能が低いと社会生活においてストレスを受けやすく，それをきっかけに再発し，また社会機能が低いために就業できず，単身生活すらも困難で長期入院となることもあり，社会機能の低下は長期予後に大きく関与し

表2　認知機能障害の有無による予後の違い（文献8）
(CN：cognitively normal，CI：cognitively impaired patients)

	CN patients ($N=20$)	CI patients ($N=83$)	Degrees of freedom	Test	P (two-tailed)
Course of illness					
No relapse	65%	52%			
Relapse after inclusion	30%	41%	2	$\chi^2=1.133$	n. s.
Chronic psychotic	5 %	7 %			
%of time psychotic	27 (36)	33 (33)	102	$F=0.575$	n. s.
%of time full remission	27 (35)	24 (31)	102	$F=0.241$	n. s.
Social disability					
Total GSDS score[a]	0.79 (0.91)	0.83 (0.59)	102	$F=0.062$	n. s.
Self-care[b]	26.3	20.0	1	$\chi^2=0.366$	n. s.
Family role	36.8	56.8	1	$\chi^2=2.458$	n. s.
Kinship role	52.6	48.8	1	$\chi^2=0.933$	n. s.
Partner role	47.4	64.6	1	$\chi^2=1.906$	n. s.
Citizen role	47.4	65.4	1	$\chi^2=2.131$	n. s.
Social role	52.6	58.0	1	$\chi^2=0.183$	n. s.
Work role	42.1	74.1	1	$\chi^2=7.228$	0.007
Need for care					
Number of needs	2.5 (2.1)	3.8 (2.6)	102	$F=3.967$	0.049
Mental health care	0.17 (0.15)	0.28 (0.19)	102	$F=6.453$	0.013
ADL	0.05 (0.10)	0.11 (0.21)	102	$F=1.689$	n. s.
Rehabilitation	0.20 (0.30)	0.26 (0.36)	102	$F=0.481$	n. s.
Services	0.07 (0.12)	0.15 (0.23)	102	$F=1.991$	n. s.
Competitive employment[c]	40	16	1	$\chi^2=5.734$	0.017

[a]Standardized GSDS (Groningen Social Disabilities Schedule) ratings ranging from (0) no disability to (3) extreme disability.
[b]Percentage of subjects showing disability. [c]Percentage of subjects with competitive employment.
コメント：認知機能障害のある患者では仕事上で困難が生じたり，就職において困難が生じやすい

ている。そしてこのような社会機能の低下は認知機能の障害と関係しているのである。すなわち，統合失調症では陽性症状などの明らかな症状が出現する前の前駆期から認知機能障害は存在しており，そして陽性症状が活発な急性期や寛解期，再発などいずれの時期をとってみても存在し，ほぼ一定の障害がみられると考えられている。寛解しても認知機能障害により生じる社会機能障害が残存し，社会適応能力が低下して自立した社会生活が困難となる。そして，十分に仕事ができるほどに回復するものは5分の1程度と考えられている。認知機能障害とストレスへの反応は必ずしも相関していないと報告されているものの[12]，認知欠損は就業能力が不良となる原因の可能性があるとされ[8]（表2），またウィスコンシン・カード・ソーティング・テストにより検出される認知機能障害は再発の予測因子になることが報告されている[1]。このように，認知機能障害は統合失調症の発症，再発，長期予後において極めて重要なのである。

ところで統合失調症で障害されている認知機能はどのようなものか。報告では認知機能全般が障害されているとされ，知覚，注意，短期および長期記憶，実行機能や精神運動機能など様々な側面の認知機能が障害されている。実行機能は情報を取り入れて理解し，その情報をもとに決断していく機能であるが，その欠損は自立して日常生活を送ることを障害する。また，注意機能や学習，記

表3　3ヵ月及び6ヵ月の抗精神病薬治療による臨床症状（文献3改変）

Symptom Domain	Summary of Scores				Change From Baseline (adjusted for baseline values)			
	3 Months		6 Months		3 Months		6 Months	
	Mean	SD	Mean	SD	Mean	SEM	Mean	SEM
Over all								
Olanzapine	3.16	1.09	2.79	1.12	−1.08*$#	0.04	−1.44*$#	0.04
Quetiapine	3.66	1.16	3.20	1.24	−0.58$	0.08	−1.02	0.09
Risperidone	3.28	1.03	2.96	1.07	−0.90*	0.05	−1.24#	0.05
Haloperidol	3.54	0.97	3.39	1.08	−0.68	0.07	−0.87$	0.08
Cognitive								
Olanzapine	2.82	1.22	2.52	1.17	−0.80*$#	0.04	−1.05*$#	0.04
Quetiapine	3.16	1.22	2.91	1.26	−0.43	0.08	−0.61	0.09
Risperidone	2.96	1.18	2.72	1.17	−0.62#	0.05	−0.83#	0.05
Haloperidol	3.24	1.28	3.04	1.26	−0.36$	0.07	−0.54$	0.08

According to the Clinical Global Impressions–Severity of Illness rating scale（1 = normal to 7 = extremely ill）
*p<.001 vs. quetiapine, $p<.001 vs. risperidone, #p<.001 vs. haloperidol
コメント：3ヵ月，6ヵ月いずれの時点においてもolanzapineとrisperidoneは全般的症状でも認知機能においてもhaloperidolよりも有意な改善を認めている。

憶の障害も見られ，これらの機能は社会機能，労働能力，自立生活のいずれにも関係しており，処理速度の低下は就業に大きく影響する。しかし認知機能障害と社会機能障害が関連していると書いたが，研究的に行われている認知機能検査と実際の社会生活機能，日常臨床での評価方法との間にはギャップがあり，臨床医がより適切に統合失調症患者の認知機能を評価し，治療プログラムを立てる方策を考えていくことが必要といわれている[10]。一方，最近の患者調査によると，統合失調症患者自身は認知機能障害に気づいており，回答者の77％は持続している注意・集中困難にストレスを感じていると報告されている[4]。

Ⅲ．認知機能障害の治療

さて，統合失調症の認知機能障害が社会復帰，社会生活に大きな障害となっていることは明らかだが，患者ケアに関わっている臨床医は統合失調症の認知機能障害をあまり認識していないと考えられている。しかし，認知機能障害は統合失調症の主要な症状であり，さらに重要と考えられるのは，薬物療法や心理社会的介入により一部は治療可能であることである。

まずは抗精神病薬による薬物療法の結果，二次的に認知機能を低下させている可能性が高い。特に，従来型の抗精神病薬は認知機能に影響を与えないか，悪化させるとされている[13]。中でも錐体外路系副作用や寡動，過鎮静，抗コリン作用，意識障害は認知機能を悪化させることが知られている。この意識障害はせん妄に近く，多剤による意識障害にもとづく問題行動である。一方，新規抗精神病薬は陽性症状には従来型と同様に効果があり，陰性症状や抑うつ症状に関しては優れている可能性があり，また錐体外路系の副作用は少ない。そしてこれら新規抗精神病薬は認知機能障害に対しては少なくとも悪化させることはなく，むしろ改善させる可能性があるとされている[3]（表3）。したがって，適切に抗精神病薬を使用することが認知機能を回復させる可能性がある。統合

失調症の認知機能障害に関しては作業記憶[16]においても実行機能[14]においても前頭前野の機能低下が示唆されている。新規抗精神病薬が認知機能に関して優れているのは，単に副作用が少ないということだけではなく，前頭前野のドパミン神経活動を活性化させているからかもしれない。また，ドパミンとグルタミン酸神経系との関係も示唆されており，新規抗精神病薬は直接または間接的にNMDA（N-methyl-D-aspartate）受容体やグルタミン酸神経伝達機能を変化させることにより認知機能を改善させているのかもしれない。

このように近年，認知機能障害治療は注目されてきており，また抗精神病薬の認知機能障害に対する効果が検討されているが，現在まで統合失調症の認知機能障害改善を目的として開発された治療薬剤はない。千葉大学の橋本らはphencyclidine（PCP）により引き起こされる認知機能の障害にシグマ1が関連していると仮説し，PCP投与マウスにおきる認知機能障害に対してシグマ1受容体アゴニストであるSSRI，fluvoxamineの効果を調べ，fluvoxamineが認知機能障害を改善させることを示した[7]。また統合失調症では事象関連電位P50の抑制効果に障害があり，これは認知機能の中の感覚ゲートに関係していると考えられており，これはニコチンα7受容体と関係していると考えられている。我々はニコチンα7受容体アゴニスト作用を有する制吐剤，tropisetronのP50抑制に対する効果を調べ，tropisetronが抑制を改善することを示した[6]。これらは抗精神病薬に認知機能改善薬を追加するという方法である。その一方で先に述べたようにグルタミン酸神経機能低下は陽性症状，陰性症状，認知機能障害いずれをも惹起する可能性があり，この機能低下を改善することがいずれの症状をも改善する可能性もある。

さて，統合失調症の症状が陽性症状と陰性症状，認知機能障害に大きく分類され，ここ何十年かはこの順序で研究が行われ，治療ターゲットとして推移してきた。治療薬を開発するにはその疾病モデルが必要となるが，統合失調症の疾病モデル研究では覚せい剤精神病とPCP精神病が有名である。しかし，覚せい剤精神病は陰性症状が目立たないため統合失調症モデルとしてはPCP精神病に主役を譲った感はある。実際，PCP精神病では陽性症状，陰性症状，そして認知機能障害がみられる。すなわち，PCPにより統合失調症の三大症候が引き起こされると考えられ，PCP精神病が統合失調症により近いのかもしれない。またPCPの主たる作用がNMDA受容体遮断であることから，この受容体の機能低下を介してこれら三大症候が引き起こされていると思われる。一方，覚せい剤精神病の示す陽性症状やストレスなどでの再燃は統合失調症の再発パターンに類似している。さらに覚せい剤長期使用者では実行機能障害などの認知機能障害が生じる可能性も報告されている[11]。すなわち，覚せい剤長期投与により陽性症状への脆弱性が獲得されるとともに，認知機能障害が引き起こされたということである。覚せい剤精神病では，側坐核や前頭前野，線条体と脳内ドパミン神経系におけるドパミントランスポーター密度が広範に減少することが示唆されている[15]。そしてそのトランスポーター密度の減少と陽性症状の重症度に関係のあることが報告されているが[15]，ドパミン神経系の障害と認知機能障害の関係については未だ不明である[9]。

表4　統合失調症の認知機能障害のまとめ

- 重症度は異なるが多くの患者にみられる障害である
- 認知機能全般に障害されることが多い
- 前駆期から存在する
- 病期に関わらず一定の障害が持続する
- 予後や社会生活に影響する可能性が高い
- 実地臨床に則した評価方法の開発が望まれる
- 従来型抗精神病薬では認知機能を悪化させる可能性がある
- 認知機能改善を標的とした新しい治療薬の開発が望まれる

Ⅳ．まとめ（表4）

認知機能障害は統合失調症の病態，予後，治療に深く関わっているものである。しかしながら，臨床医にとって研究的に報告される認知機能障害と目の前の患者の社会機能との関係を即座に説明することは困難なことが多く，より臨床に即した

検査法の開発が必要と思われる。また，認知機能障害の修復が予後の改善に深く関係することが考えられ，その治療法の開発も臨床上極めて重要と思われる。新規抗精神病薬は従来型抗精神病薬に比べ認知機能を改善させる可能性があり，それを考慮した薬物療法が重要であろう。またニコチンα7受容体アゴニストやシグマ1受容体アゴニストが認知機能を改善させる可能性があり，これらを含めた，認知機能改善に寄与する新しい薬剤の開発が望まれる。

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講演紹介　CNSフォーラム2006　臨床精神薬理　10：1327-1339, 2007
分科会1：自立生活を支える統合失調症薬物治療

服薬アドヒアランスに関する「千葉県の精神科臨床医による，統合失調症の薬物療法コンセンサス」からの考察

伊豫雅臣*

Ⅰ．アドヒアランスは統合失調症の自立に有用か

2005年秋に，千葉県の精神科臨床医の方々と統合失調症の薬物療法のコンセンサスに関する調査を行った。その結果を用いて，本日の講演テーマ「自立生活を支える統合失調症薬物治療」についてお話しする。合わせて，risperidoneの急性増悪期に関する調査結果についても，その一部を紹介し，自立生活，またはアドヒアランスについて考察したい。

千葉県の精神科臨床医によるコンセンサスについては，県内の病院または診療所の先生55名に依頼し，46人から回答があった。参加施設を表1に挙げた。基本的に，初期研修医または研修医，または学生の教育研修を受け入れている病院，および診療所協会からの推薦のあったところに協力いただいた。

まず，「アドヒアランスは統合失調症の自立に有用か」について，QOLまたは再発という視点から文献的に検討したい。

表1　調査参加施設（略称：50音順）

青葉病院，旭中央病院，浅井病院，あねさき林クリニック，磯ケ谷病院，市川神経科クリニック，市原鶴岡病院，稲毛海岸神経科クリニック，大塚クリニック，柏メンタルクリニック，鎌取メンタルクリニック，木更津病院，木村病院，国府台病院，こころクリニック船橋，さつき台病院，下総精神医療センター，志津クリニック，順天堂大学浦安病院，総武病院，千葉大学，千葉県精神科医療センター，同和会千葉病院，銚子市立総合病院，東邦大学医学部付属佐倉病院，東京慈恵会医科大学附属柏病院，中村古峡記念病院，成田日赤病院，日本医科大学付属千葉北総病院，ポプラクリニック，松戸市立病院，メンタルケア林クリニック，茂原神経科病院，八千代病院，四街道メンタルクリニック，ワコウクリニック
計36施設

Asher-Svanumらは統合失調症の患者を3年間フォローアップし，アドヒアランスの有無で比較した（J. Clin. Psychiatry, 2006）。入院期間は同じでも，アルコール関連問題を起こさない割合はアドヒアランスのある場合が有意に高く（$p<0.001$），精神機能もアドヒアランスのある場合が有意に高い（$p<0.001$）。さらに日常生活の基本的な満足度もアドヒアランスのある場合が高く（$p<0.001$），社会生活の満足度もアドヒアランスのある場合が有意に高い（$p=0.017$）。さらに，人生全般，生活全般に関しての満足度もアドヒアランスのある場合が高い（$p<0.001$）という結果である。

また，アドヒアランスと同じくコンプライアン

2006年7月8，9日，新高輪プリンスホテルにおける講演。参加者は約2,000名。
Drug treatment adherance and concensus for pharmacotherapy of schizophrenia in clinical psychiatrists in Chiba.
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スに関しても報告されている。

Weidenらは，抗精神病薬服用群と中断群の再発率の違いを調べた。服用群では月に3.5%，中断群は11%が再発している。したがって，薬を中断すると10人に1人は再発してしまう。やはりコンプライアンスを保つことは非常に重要である。

さらにMarderは，「統合失調症の再発を考えるときに最も重要な要素はノンコンプライアンスである」と述べている。すなわち，コンプライアンスが不良であることは再発の危険性という点で非常に重要な因子であると考えられる。

Ⅱ．コンプライアンス不良への対処

このことから，アドヒアランスはQOLを向上させ，コンプライアンス不良は再発因子となる。別の言い方をすれば服薬，薬物療法へのアドヒアランスは，統合失調症患者の自立に対して，QOLや再発という視点からみてきわめて重要なことだと考えられる。では，コンプライアンス不良に対してどう対処しているのか，どう対処すべきなのか。

今回の千葉県の研究は，アメリカのエキスパート・コンセンサス・ガイドラインに沿って行った調査で，米国との違い，または類似点を認識することも重要と考え行ったものである。千葉データでは，服薬を遵守しているという患者は大体7割と医師は考えている（表2）。平均値なので，ずれが生じるが，大体7割がきちんと薬を飲んでいると思っているのに対して，文献上は，50%以上が薬を飲まないと報告されている。

つまり，我々は患者のコンプライアンスを過信してしまっているのだろうか。あるいは，コンプライアンスを非常にうまくコントロールして7割に保っているのだろうか。後者であればよいが，忙しい臨床の場では現実と医師側の認識に多少ずれが生じていると思われる。

では，コンプライアンスの悪い場合にどのように対処しているのだろうか。千葉県では，心理社会的介入，患者の教育，または家族への教育，指示，サポートが重要だと考えている。つまり，この部分コンプライアンス，またはノンコンプライアンス，どちらに対しても心理社会的介入が重要だろうということになる。心理社会的介入では，患者への教育，患者の家族の教育またはサポートが重要だとされている。

次に，薬物の視点では，まずこうすべきだろうという一次選択に関するコンセンサスは得られなかった。心理社会的治療を行い，薬は変えずに剤形を変更するという工夫，また完全にノンコンプライアンスの場合にはまず剤形を変更して，それからデポ剤を追加することが試みられるが，一次選択ではなかった。結論としては，さまざまな工夫が必要だろうというものであった（図1，2）。

コンプライアンスの程度に確信が持てない場合やコンプライアンスのない患者で再発した場合，薬を切り替えたり，剤形を変更したり，それから量を増やすという工夫が必要だとしている。しかし最善の選択を提示する結果ではなかった。

コンプライアンスの悪い患者への対処のアンケート調査では，医師が患者のコンプライアンスを過大評価しているという結果が得られた。また部

表2　医師のコンプライアンス評価
文献上，50%以上の患者が病期中ノンコンプライアントを経験（引用文献：「精神科臨床医による統合失調症の薬物療法コンセンサス」じほう，2006）

【服薬コンプライアンス】

本調査では以下のようにコンプライアンスのレベルを定義した。
コンプライアント：ときおり服用を忘れるのみ（処方の20%以下）
部分的コンプライアント：処方の20から80%は服用しない。
ノンコンプライアント：80%以上服用しない。

実際の担当患者さんにおけるコンプライアンスレベルの比率の認識

コンプライアンスのレベル	患者の比率（%）
コンプライアント	69.4
部分的コンプライアント	39.2
ノンコンプライアント	15.9