Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research: Neuroimaging 154 (2007) 85–92
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Proton magnetic resonance spectroscopy reveals an abnormality in the anterior cingulate of a subgroup of obsessive–compulsive disorder patients

Satsuki Sumitani[a,*], Masafumi Harada[b], Hitoshi Kubo[b], Tetsuro Ohmori[a]

[a]*Department of Psychiatry, Institute of Health Biosciences, University of Tokushima Graduate School, 18-15 Kuramoto-cho 3, Tokushima 770-8503, Japan*
[b]*Department of Radiologic Technology, School of Health Sciences, University of Tokushima, Tokushima, Japan*

Received 29 August 2005; received in revised form 30 January 2006; accepted 13 February 2006

Abstract

Numerous neuroimaging studies have suggested that obsessive–compulsive disorder (OCD) patients had a neurobiological abnormality in the frontal-subcortical circuits. On the other hand, there are distinct differences in the responses to pharmacological treatment among OCD patients. In the present study, we measured the concentration of *N*-acetyl aspartate (NAA), a putative marker of neuronal viability, with proton magnetic resonance spectroscopy (MRS) in OCD patients with different pharmacological responses. Participants comprised 20 patients and 26 healthy control subjects. OCD patients were divided into three groups according to the pharmacological response; responders to a selective serotonin reuptake inhibitor (SSRI) (group A: $n=7$), responders to SSRI with an atypical antipsychotic (group B: $n=8$) and non-responders to either SSRI or SSRI with an atypical antipsychotic (group C: $n=5$). Short echo proton MRS was used to measure NAA concentrations in the anterior cingulate, the left basal ganglia and the left prefrontal lobe of subjects. A significantly lower NAA concentration was observed only in group B compared with control subjects in the anterior cingulate. Our results suggest that a subgroup of OCD patients who respond to an SSRI with an atypical antipsychotic have distinct biological abnormalities in the anterior cingulate.
© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Selective serotonin reuptake inhibitor (SSRI); Atypical antipsychotic; Pharmacological response; *N*-acetyl aspartate (NAA); Basal ganglia; Prefrontal lobe

1. Introduction

Although selective serotonin reuptake inhibitors (SSRIs) are the mainstay of pharmacological treatment for obsessive–compulsive disorder (OCD), 40–60% of OCD patients fail to show improvement after an adequate trial with SSRIs (Goodman et al., 1993). When OCD patients experience little improvement with SSRIs, the addition of a low dose of an atypical antipsychotic, such as risperidone or olanzapine, to ongoing SSRI treatment has been shown to be effective (McDougle et al., 2000; Bystritsky et al., 2004). However, there are patients who continue to show little or no improvement after the trial with this augmentation therapy. These differences of pharmacological response suggest the existence of biological differences among

* Corresponding author. Tel.: +81 88 633 7130; fax: +81 88 633 7131.
E-mail address: satsuki@clin.med.tokushima-u.ac.jp (S. Sumitani).

0925-4927/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2006.02.003

OCD patients. Recently, numerous neuroimaging studies in OCD implicate dysfunction within frontal-subcortical circuits (Saxena et al., 2001). Functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT) or positron emission tomography (PET) indicated abnormalities in structures such as the orbitofrontal cortex, anterior cingulate, caudate nucleus, and thalamus (Baxter et al., 1987, 1988; Swedo et al., 1989; Rauch et al., 1994; Hollander et al., 1995; Breiter et al., 1996). Magnetic resonance spectroscopy (MRS) can be used to obtain information about several metabolites that are highly relevant to our understanding of OCD. The aim of this study is to examine *N*-acetyl aspartate (NAA) concentrations in OCD patients who show different responses to pharmacotherapy with proton MRS.

2. Methods

2.1. Subjects

Twenty patients were diagnosed with OCD according to DSM-IV criteria, in addition, 26 healthy comparison subjects participated in this study. The OCD patients were recruited at the Department of Psychiatry, Tokushima University Hospital. The diagnosis of UCD was confirmed by at least two trained psychiatrists. Patients comorbid with other axis I disorders were excluded. OCD patients were subclassified into the following three groups according to pharmacological response: group A, SSRI responders (7 cases in 20 participants); group B, SSRI plus atypical antipsychotic responders (8/20); and group C, non-responders to either SSRI or SSRI plus an atypical antipsychotic (5/20). Severity of OCD symptoms was assessed using the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS). SSRI responders were those who showed a >50% decrease on the Y-BOCS at the end of an 8- to 12-week treatment with a high dose of either fluvoxamine or paroxetine. Then, patients who had no response to SSRI were treated by adding a low dose of either risperidone or olanzapine. When SSRI-refractory OCD patients showed a >50% decrease on the Y-BOCS after institution of augmentation therapy, they were regarded as responders to SSRI plus an atypical antipsychotic. The remaining patients were regarded as non-responders to either SSRI or SSRI plus an atypical antipsychotic. When the MRS scans were performed, 8 patients were initially either drug-naive or drug-free and 12 patients were receiving pharmacological treatment (8 patients took SSRI and 4 patients took both SSRI and antipsychotic medication) and 4 of them already showed

Table 1
Subject characteristics

	OCD			Control	*P*-value
	A	B	C		
No. of subjects	7	8	5	26	
Age	38.4±13.9	25.0±5.6	26.2±7.5	25.2±7.4	0.036
Gender					0.033
Male	6	6	1	10	
Female	1	2	4	16	
Treatment status at MRS					0.978
Before treatment	3	3	2	–	
During treatment[a]	4 (1)	5 (3)	3 (0)	–	
Medication status at MRS					0.095
SSRIs	4	1	3	–	
SSRI+neuroleptics	0	4	0	–	
Drug-naive	3	3	2	–	
Y-BOCS					
Before treatment	21.1±5.6	25.0±4.4	25.6±6.5	–	0.293
At MRS	19.7±5.3	18.1±6.2	24.4±5.4	–	0.183
Percent volume of tissue types in the anterior cingulate					
CSF	19.9±5.4*	18.2±3.5	13.6±2.2*	15.5±3.3	0.011[b]
Gray matter	69.0±8.7	73.6±8.3	77.7±10.4	74.5±7.6	0.150
White matter	11.1±8.5	8.2±6.2	8.7±9.9	8.6±3.9	0.771

A, SSRI responders; B, SSRI with atypical antipsychotics responders; C, non-responders.
Comparisons were made by ANOVA with Bonferroni's post hoc test or Fisher's exact test. The level of statistical significance is $P<0.05$.
[a]Within the parentheses is the number of patients who already showed >50% decrease on the Y-BOCS at the time MRS was performed.
[b]Group C showed a significantly lower CSF percentage than group A ($P=0.03$).

a >50% decrease on the Y-BOCS (Table 1). The mean length of augmentation therapy with atypical antipsychotic was 52.0 ± 36.2 weeks (12–96 weeks). None of the OCD subjects were participating in formal cognitive behavioral therapy at the time of the study. Neither the subjects with OCD nor the healthy control subjects had a history of significant head injury or seizures. No subjects showed anatomical abnormalities on MRI.

2.2. Proton MR spectroscopy

All proton MRS studies were performed at Tokushima University Hospital using a Signa Horizon (1.5T GE, Milwaukee, WI, USA) scanning system. Proton MRS was performed using the STEAM sequence with water suppression by CHESS pulses (TE=18 ms, TR=5000 ms, acquisition=64 times) to minimize the longitudinal and transverse relaxation effect. Neurochemical compounds that can be identified in short-echo proton MRS include *N*-acetyl aspartate (NAA), complex of glutamate and glutamine (Glx), creatine and phosphocreatine (Cr), choline-containing compounds (Cho) and myoinositol (mI). The area under each of the magnetic resonances is proportioned to the concentration of the particular compound. On the basis of previous reports of functional anomalies, the volumes of interest for proton MRS were set at the anterior cingulate, the left basal ganglia and the left frontal lobe as shown in Fig. 1A–C. The anatomical positions of the voxels were chosen from axial localizer images. The voxel of the anterior cingulate was placed to encompass bilateral anterior cingulate (Brodmann area 24/32), left basal ganglia was placed to include the caudate and putamen, and left frontal lobe was placed rostrolaterally from the anterior horn of the lateral ventricle (contained white matter exclusively). (ROI size= 1.7 cm × 1.7 cm × 1.5 cm).

2.3. Processing of spectroscopic data

Metabolite concentrations were estimated using the linear combination model (LCModel) (Provencher, 1993) (Fig. 2). Our basis set for prior knowledge derived from in vitro original data for each metabolite. The accepted shimming criterion was 3–5 Hz of FWHM on the water peak. We excluded data with extremely high spectra (% S.D.>30%). The spectroscopic voxels were volumetrically segmented and quantified by tissue types. The anterior cingulate voxel contained gray matter, white matter and cerebrospinal fluid (CSF) (Fig. 1A). The left basal ganglia voxel was mainly gray matter, including the caudate (Fig. 1B) and putamen,

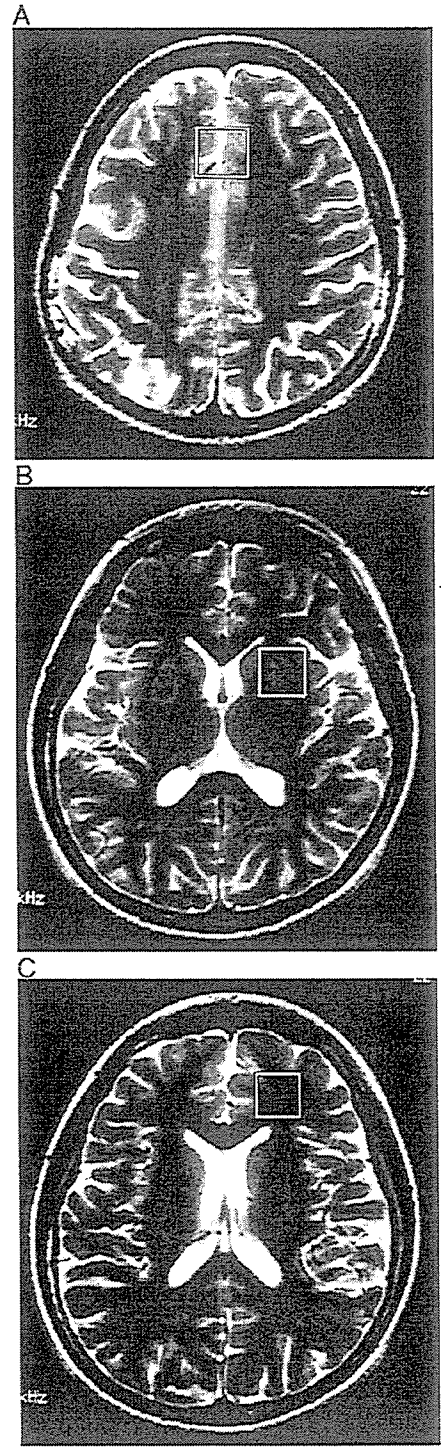

Fig. 1. Location and size of the MRS voxels. (A) anterior cingulate (B) left basal ganglia (deep gray matter) (C) left frontal lobe (white matter).

while the left frontal lobe voxel contained white matter exclusively (Fig. 1C). We adjusted NAA, Cho, and Cr for the anterior cingulate voxel assuming that the

metabolite concentrations in CSF were equal to zero. These corrected NAA, Cho and Cr values were compared among subject groups in the anterior cingulate. Considering that metabolite concentrations varied between white and gray matter tissues (Wiedermann et al., 2001), we compared the percentage of gray matter and white matter in the anterior cingulate among subject groups. However, there were no significant differences in the percentages among subject groups (Table 1).

2.4. Statistics

All statistical tests were performed with SPSS version 11.5 (Tokyo, Japan). All data are expressed as mean± S.D. Means of the metabolite concentrations between all of the OCD patients and healthy subjects were compared with Student's *t*-test. Analyses of variance (ANOVAs) were performed with Bonferroni's post-hoc PLSD to look for significant differences in four groups (three OCD groups and a healthy control group). Pearson's correlation coefficient was used to study the relationship between NAA concentrations and age in the healthy controls, and Student's *t*-test was performed to compare the mean NAA concentrations between male and female healthy subjects.

Table 2
Concentrations of metabolites in three brain regions for OCD patients and healthy controls

	OCD (n=20)	Control (n=26)	P-value
Anterior cingulate cortex (concentrations corrected for CSF)			
NAA	9.14±1.24	9.88±0.99	0.031*
Cho	2.58±0.75	2.36±0.59	0.705
Cr	7.73±1.49	8.07±1.25	0.263
Left basal ganglia			
NAA	8.47±1.29	8.35±0.98	0.739
Cho	2.14±0.33	2.04±0.46	0.470
Cr	7.44±1.19	7.31±0.98	0.692
Left frontal lobe			
NAA	7.86±0.91	8.40±1.16	0.092
Cho	1.97±0.64	1.86±0.53	0.561
Cr	6.13±1.40	5.46±1.27	0.126

Comparisons were made by unpaired *t*-test.
*The level of statistical significance is $P<0.05$.

To confirm pharmacological treatment would not significantly change NAA concentration, ANOVAs were performed among three OCD subgroups (no medication, taking SSRI or taking both SSRI and antipsychotic medication) when proton MRS was

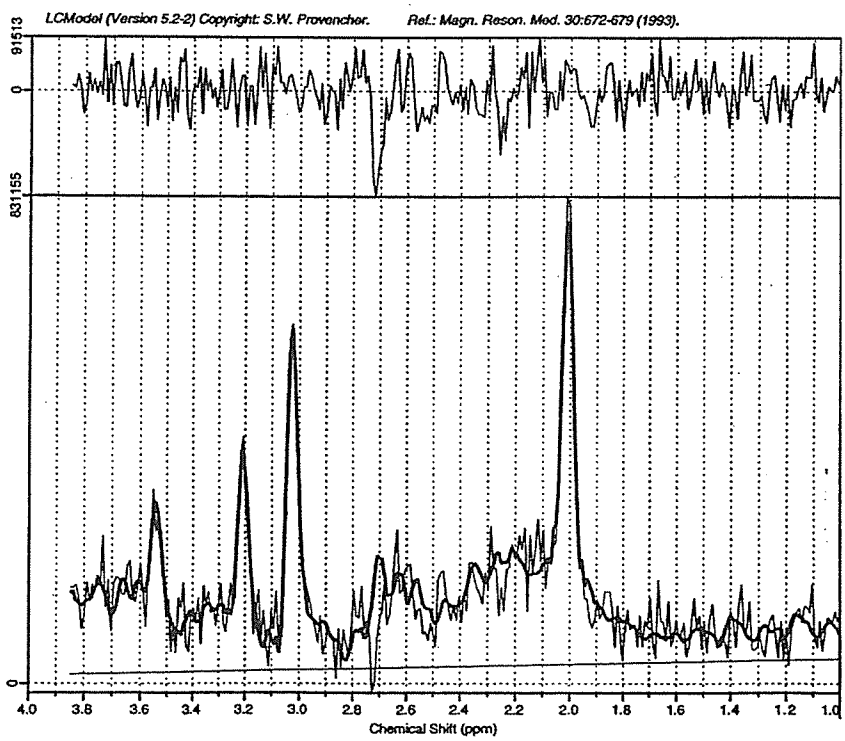

Fig. 2. Representative proton MRS spectrum for the anterior cingulate showing the three largest peaks: NAA, Cre and Cho. The spectrum was collected using a PRESS-CHESS sequence. Chemical shifts are indicated in part per million (ppm).

performed. Pearson's correlation coefficient was used to study the relationship between NAA concentrations and Y-BOCS scores (both before treatment and at MRS scan) to examine the relationship between severity of illness and NAA level. The level of statistical significance was set at $P<0.05$.

3. Results

Metabolite concentrations of three brain regions are given for OCD patients and healthy control in Table 2. OCD patients showed a significantly lower NAA concentration than healthy controls in the anterior cingulate ($t_{44}=-2.2$, $P=0.031$). There were no significant differences in NAA concentrations between OCD patients and healthy controls in either the left basal ganglia or the left frontal lobe.

Metabolite concentrations of the three brain regions are given for three subtypes of OCD patients and healthy control in Table 3. ANOVAs revealed a significant intergroup difference in NAA concentration [$F(3, 42)=4.88$, $P=0.005$] in the anterior cingulate and significant intergroup differences in NAA [$F(3, 42)=3.91$, $P=0.015$] and Cho concentrations [$F(3, 42)=3.84$, $P=0.016$] in the left basal ganglia. In the frontal lobe, no significant intergroup differences were observed in any metabolites.

In the anterior cingulate, group B showed significantly lower NAA concentrations compared with group A (8.51±1.08 vs. 10.06±1.16 mmol/l, $P=0.035$) and to the healthy control group (8.51±1.08 vs. 9.88±0.99 mmol/l, $P=0.013$). In the basal ganglia, group B showed significantly lower NAA and Cho concentrations compared with group A (NAA, 7.74±0.69 vs. 9.50±1.29 mmol/l, $P=0.011$ and Cho, 1.83±0.14 vs. 2.49±0.13 mmol/l, $P=0.013$).

No significant correlation was found between the NAA concentrations and age in healthy controls in the anterior cingulate ($r=-0.025$, $P=0.91$), the left basal ganglia ($r=0.031$, $P=0.88$) or the left frontal lobe ($r=-0.076$, $P=0.71$). There were no significant differences in NAA concentrations between male and female healthy controls in the anterior cingulate ($t_{24}=-1.3$, $P=0.20$), the left basal ganglia ($t_{24}=-0.27$, $P=0.79$) or the left frontal lobe ($t_{24}=0.12$, $P=0.90$). There were no significant differences in NAA concentrations according to medication status (no medication or taking SSRI or taking SSRI with antipsychotic) in the anterior cingulate, in the left basal ganglia or in the left frontal lobe

Table 4
NAA concentrations in different medication status of OCD patients when MRS was performed

	OCD			*P*-value
	No medication ($n=8$)	SSRI ($n=8$)	SSRI and antipsychotics ($n=4$)	
Anterior cingulate	8.94±1.41	9.51±1.13	8.79±1.25	0.570
Left basal ganglia	8.49±1.43	8.66±1.42	8.05±0.87	0.761
Left frontal lobe	7.79±0.96	7.93±1.03	7.88±0.73	0.959

Table 3
Concentrations of metabolites in three subtypes of OCD patients and healthy controls

	OCD			Controls ($n=26$)	*P*-value
	A ($n=7$)	B ($n=8$)	C ($n=5$)		
Anterior cingulate (concentrations corrected for CSF)					
NAA	10.06±1.16*	8.51±1.08*	8.87±0.99	9.88±0.99*	0.005[a]
Cho	2.90±0.97	2.29±0.64	2.60±0.46	2.36±0.59	0.229
Cr	8.41±1.73	7.38±1.44	7.33±1.10	8.07±1.25	0.333
Left basal ganglia					
NAA	9.50±1.29*	7.74±0.69*	8.20±1.26	8.36±0.98	0.015[b]
Cho	2.49±0.13*	1.83±0.14*	2.08±0.18	2.05±0.47	0.016[c]
Cr	7.39±0.87	7.01±1.14	8.10±1.55	7.31±0.98	0.368
Left frontal lobe					
NAA	7.59±1.04	7.96±1.71	8.08±0.27	8.40±2.87	0.319
Cho	1.83±0.83	1.82±0.36	2.50±0.40	1.85±0.53	0.315
Cr	5.58±2.02	6.55±0.95	6.30±0.64	5.46±1.27	0.266

A, SSRI responders; B, SSRI plus atypical antipsychotic responders; C, non-responders.
Comparisons were made by ANOVA and Bonferroni's post hoc test.
*The level of statistical significance is $P<0.05$.
[a] Group B showed significantly lower NAA concentrations than group A ($P=0.035$) and the healthy control group ($P=0.013$), respectively.
[b] Group B showed significantly lower NAA concentrations than group A ($P=0.011$).
[c] Group B showed significantly lower Cho concentrations than group A ($P=0.013$).

(Table 4). There were no significant differences in NAA concentrations between unmedicated and medicated OCD patients in the anterior cingulate ($t_{18}=0.45$, $P=0.661$), in the left basal ganglia ($t_{18}=0.29$, $P=0.778$) or in the left frontal lobe ($t_{18}=-0.83$, $P=0.418$). No significant correlation was found between the NAA concentrations and Y-BOCS scores of the OCD patients before treatment in the anterior cingulate ($r=-0.17$, $P=0.48$), the left basal ganglia ($r=-0.04$ $P=0.84$) or the left frontal lobe ($r=-0.02$, $P=0.94$). There were also no significant correlation between the NAA concentrations and Y-BOCS scores of the OCD patients at the time of MRS scans in the anterior cingulate ($r=-0.004$, $P=0.99$), in the left basal ganglia ($r=-0.02$, $P=0.95$) or in the left frontal lobe ($r=-0.25$, $P=0.28$).

4. Discussion

Proton MRS is an important tool to study in vivo biochemical aspects of brain disorders. By using signals from excitation of the nucleus of hydrogen, proton MRS allows the acquisition of signals from several biochemical compounds such as NAA, Glx, Cr, Cho and mI. Although the roles of these metabolites are not certain, there were several hypotheses about the nature of NAA. NAA was thought to be abundant in neurons and scarce in mature glial cells, and a reduction of NAA was initially considered to reflect a loss of neurons and neural dysfunction. Later, it was reported that NAA might act via glutamatergic NMDA receptors to elevate intracellular calcium (Rubin et al., 1995). More recent evidence suggests a possible role of NAA as a molecular water pump in the brain operating between neurons and oligodendrocytes (Baslow, 2002, 2003). It is thought that NAA levels are sensitive to pathological processes affecting the functioning of neurons, and reduction is often reversible (Baker, 2001).

In agreement with Ebert et al. (1997), who reported a significantly lower NAA/Cr ratio in OCD patients than in normal control subjects in the anterior cingulate, we found significantly lower NAA levels in the same region of OCD patients compared with those in controls. Recently, Rosenberg et al. (2004) reported reduced glutamate concentrations in the anterior cingulate in pediatric OCD patients. Although no other MRS study has focused on the anterior cingulate, other functional imaging studies such as fMRI, SPECT and PET have revealed abnormalities in that region in OCD patients. Our results, together with these, suggest a functional change in the region in OCD patients.

Interestingly, when we divided OCD patients into three groups according to pharmacological response (group A, SSRI responders; group B, SSRI plus atypical antipsychotic responders and group C, non-responders to either SSRI or SSRI plus atypical antipsychotic), we found that only patients who responded to atypical antipsychotics combined with ongoing SSRI (group B) but not other patients showed significantly lower NAA concentration compared with healthy controls in the anterior cingulate. The lower NAA concentration was not accounted for by the effect of antipsychotics or SSRI, since NAA concentration did not differ according to medication status. Besides, antipsychotics have been shown to have no effects on the levels of NAA (Deicken et al., 1997; Bustillo et al., 2004; Bertolino et al., 1998), and SSRI have been reported to have no effects on NAA concentration in OCD patients after paroxetine intervention (Rosenberg et al., 2000).

In the basal ganglia, previous MRS studies have produced different results in the levels of NAA. A significantly lower NAA/Cr ratio in the right striatum (Ebert et al., 1997) or a lower NAA level in the left striatum (Bartha et al., 1998) has been reported in OCD patients compared with controls, while no difference in the NAA/Cr ratio has been observed in either the right or the left lenticular nucleus (Ohara et al., 1999). We found no difference in NAA concentration between the total group of OCD patients and the healthy controls. When the patients were divided into three groups, OCD patients who responded to atypical antipsychotics combined with ongoing SSRI treatment (group B) showed significantly lower NAA concentrations compared with the SSRI responders (group A) in the left basal ganglia. Interpretation of this finding is not easy, since neither group A nor group B showed a significant difference compared with the control group. However, the results suggest that NAA concentrations are different in the left basal ganglia as well as the anterior cingulate among OCD patients with different pharmacological responses. Differences between subtypes of OCD may explain in part the inconsistent results of NAA levels in the basal ganglia in the previous studies.

We divided OCD patients in terms of the response to SSRI and the augmentation with atypical antipsychotics. Recently, a large number of studies have been conducted to find clinical features predictive of treatment response in OCD. It is suggested that positive predictors of response to serotonin reuptake inhibitors (SRIs) and SSRIs are female gender, late onset and lower severity, and that negative predictors are male gender, early onset, poor insight, higher severity, and comorbidity such as tics or schizotypal personality disorder (McDougle et al., 1993; Ravizza et al., 1995; Ackerman et al., 1998, 1999; Steketee et al., 1999; Mundo et al., 1999; Erzegovesi et

al., 2001; Hollander et al., 2002; Ravi Kishore et al., 2004). With respect to augmentation with antipsychotics, McDougle et al. (1990, 1994) found that comorbid occurrence of tic spectrum disorders or schizotypal personality disorder was associated with positive response, although a double-blind, placebo-controlled study did not confirm their findings (McDougle et al., 2000). Our neuroimaging finding, lower NAA concentration in the anterior cingulate, may be useful as a biological marker to predict positive response to combination therapy with SSRI and atypical antipsychotics.

Although functional neuroimaging studies such as MRS, fMRI, SPECT and PET have reported abnormalities in the orbitofrontal cortex, anterior cingulate, caudate nucleus and thalamus in OCD patients, the studies do not always agree with one another (Baxter et al., 1987, 1988, 1992; Swedo et al., 1989; Rauch et al., 1994; Lucey et al., 1995; Schwartz et al., 1996; Saxena et al., 1999; Crespo-Facorro et al., 1999). These discrepancies may be accounted for in part by the heterogeneity of OCD. Actually, experts have suggested that OCD is a highly heterogeneous condition and composed of distinct subtypes. Current knowledge, however, suggests significant limitations to conceptualize subtypes (McKay et al., 2004). The present study showing a specific neuroimaging abnormality in a pharmacologically defined subgroup of OCD may warrant subtyping of OCD by drug response.

In summary, this study found a lower NAA concentration in the anterior cingulate of a subtype of OCD patients who responded to the combination therapy of SSRI plus an atypical antipsychotic. This subtype of OCD patients may have distinct biological abnormalities in the anterior cingulate. This neuroimaging finding may be a useful biological marker to predict drug response. Our results also suggest that it is important to consider subtypes of OCD patients in the biological study of OCD. Further studies with larger numbers of subjects are necessary to confirm and extend the present results.

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (No. 17025029 and No. 15591280), Grants-in-Aid for Scientific Research from the 21st Century COE Program, Human Nutritional Science on Stress Control Tokushima, Japan and The Research Grant (15B-1) for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare.

The authors express their gratitude to the patients and volunteers who completed MRS.

References

Ackerman, D.L., Greenland, S., Bystritsky, A., 1998. Clinical characteristics of response to fluoxetine treatment of obsessive–compulsive disorder. Journal of Clinical Psychopharmacology 18, 185–192.

Ackerman, D.L., Greenland, S., Bystritsky, A., 1999. Side effects as predictor of drug response in obsessive–compulsive disorder. Journal of Clinical Psychopharmacology 19, 459–465.

Baker, P.B., 2001. *N*-acetyl aspartate—a neuronal marker? Annals of Neurology 49, 423–424.

Bartha, R., Stein, M.B., Williamson, P.C., Drost, D.J., Neufeld, R.W., Carr, T.J., Canaran, G., Densmore, M., Anderson, G., Siddiqui, A.R., 1998. A short echo ^{1}H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive–compulsive disorder and comparison subjects. American Journal of Psychiatry 155, 1584–1591.

Baslow, M.H., 2002. Evidence supporting a role for *N*-acetyl-L-aspartate as a molecular water pump in myelinated neurons in the central nervous system: an analytical review. Neurochemistry International 40, 295–300.

Baslow, M.H., 2003. *N*-acetyl aspartate in the vertebrate brain: metabolism and function. Neurochemistry Research 28, 941–953.

Baxter Jr., L.R., Phelps, M.E., Mazziotta, J.C., Guze, B.H., Schwartz, J.M., Selin, C.E., 1987. Local cerebral glucose metabolic rates in obsessive–compulsive disorder—a comparison with rates in unipolar depression and in normal controls. Archives of General Psychiatry 44, 211–218.

Baxter Jr., L.R., Schwartz, J.M., Mazziotta, J.C., Phelps, M.E., Pahl, J.J., Guze, B.H., Fairbanks, L., 1988. Cerebral glucose metabolic rates in non-depressed obsessive–compulsives. American Journal of Psychiatry 145, 1560–1563.

Baxter Jr., L.R., Schwartz, J.M., Bergman, K.S., Szuba, M.P., Guze, B.H., Mazziotta, J.C., Alazraki, A., Selin, C.E., Ferng, H.K., Munford, P., 1992. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive–compulsive disorder. Archives of General Psychiatry 49, 681–689.

Bertolino, A., Callicott, J.H., Elman, I., Mattay, V.S., Tedeschi, G., Frank, J.A., Breier, A., Weinberger, D.R., 1998. Regionally specific neuronal pathology in untreated patients with schizophrenia: a proton magnetic resonance spectroscopic imaging study. Biological Psychiatry 43, 641–648.

Breiter, H.C., Rauch, S.L., Kwong, K.K., Baker, J.R., Weisskoff, R. M., Kennedy, D.N., Kendrick, A.D., Davis, T.L., Jiang, A., Cohen, M.S., Stern, C.E., Belliveau, J.W., Baer, L., O'Sullivan, R.L., Savage, C.R., Jenike, M.A., Rosen, B.R., 1996. Functional magnetic resonance imaging of symptom provocation in obsessive–compulsive disorder. Archives of General Psychiatry 49, 595–601.

Bustillo, J., Wolff, C., Myers-y-Gutierrez, A., Dettmer, T.S., Cooper, T.B., Allan, A., Lauruello, J., Valenzuela, C.F., 2004. Treatment of rats with antipsychotic drugs: lack of an effect on brain *N*-acetyl aspartate levels. Schizophrenia Research 66, 31–39.

Bystritsky, A., Ackerman, D.L., Rosen, R.M., Vapnik, T., Gorbis, E., Maidment, K.M., Saxena, S., 2004. Augmentation of serotonin reuptake inhibitors in refractory obsessive–compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. Journal of Clinical Psychiatry 65, 565–568.

Crespo-Facorro, B., Cabranes, J.A., Lopez-Ibor Alcocer, M.I., Paya, B., Perez, C.F., Encinas, M., Ayoso Mateos, J.L., Lopez-Ibor Jr., J.J., 1999. Regional cerebral blood flow in obsessive–compulsive

patients with and without chronic tic disorder. A SPECT study. European Archives of Psychiatry and Clinical Neuroscience 249, 156–161.

Deicken, R.F., Zhou, L., Schuff, N., Weiner, M.W., 1997. Proton magnetic resonance spectroscopy of the anterior cingulate region in schizophrenia. Schizophrenia Research 27, 65–71.

Ebert, D., Speck, O., Konig, A., Berger, M., Hennig, J., Hohagen, F., 1997. ^{1}H-magnetic resonance spectroscopy in obsessive–compulsive disorder: evidence for neuronal loss in the cingulate gyrus and the right striatum. Psychiatry Research: Neuroimaging 74, 173–176.

Erzegovesi, S., Cavallini, M.C., Cavedini, P., Diaferia, G., Locatelli, M., Bellodi, L., 2001. Clinical predictors of drug response in obsessive–compulsive disorder. Journal of Clinical Psychopharmacology 21, 488–492.

Goodman, W.K., McDougle, C.J., Barr, L.C., Aronson, S.C., Price, L.H., 1993. Biological approaches to treatment-resistant obsessive–compulsive disorder. Journal of Clinical Psychiatry 54, 16–26.

Hollander, E., Prohovnik, I., Stein, D.J., 1995. Increased cerebral blood flow during m-CPP exacerbation of obsessive–compulsive disorder. Journal of Neuropsychiatry and Clinical Neurosciences 7, 485–490.

Hollander, E., Bienstock, C.A., Koran, L.M., Pallanti, S., Marazziti, D., Rasmussen, S.A., Ravizza, L., Benkelfat, C., Saxena, S., Greenberg, B.D., Sasson, Y., Zohar, J., 2002. Refractory obsessive–compulsive disorder: state-of-the-art treatment. Journal of Clinical Psychiatry 63, 20–29.

Lucey, J.V., Costa, D.C., Blanes, T., Busatto, G.F., Pilowsky, L.S., Takei, N., Marks, I.M., Ell, P.J., Kerwin, R.W., 1995. Regional cerebral blood flow in obsessive–compulsive patients at rest: differential correlates with obsessive–compulsive and anxious-avoidant dimensions. British Journal of Psychiatry 167, 629–634.

McDougle, C.J., Goodman, W.K., Price, L.H., Delgado, P.L., Krystal, J.H., Charney, D.S., Heninger, G.R., 1990. Neuroleptic addition in fluvoxamine-refractory obsessive–compulsive disorder. American Journal of Psychiatry 147, 652–654.

McDougle, C.J., Goodman, W.K., Leckman, J.F., Barr, L.C., Heninger, G.R., Price, L.H., 1993. The efficacy of fluvoxamine in obsessive–compulsive disorder: effects of comorbid chronic tic disorder. Journal of Clinical Psychopharmacology 13, 354–358.

McDougle, C.J., Goodman, W.K., Leckman, J.F., Lee, N.C., Heninger, G.R., Price, L.H., 1994. Haloperidol addition in fluvoxamine-refractory obsessive–compulsive disorder. Archives of General Psychiatry 51, 302–308.

McDougle, C.J., Epperson, C.N., Pelton, G.H., Wasylink, S., Price, L.H., 2000. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive–compulsive disorder. Archives of General Psychiatry 57, 794–801.

McKay, D., Abramowitz, J.S., Calamari, J.E., Kyrios, M., Radomsky, A., Sookman, D., Taylor, S., Wilhelm, S., 2004. A critical evaluation of obsessive–compulsive disorder subtypes: symptoms versus mechanisms. Clinical Psychology Review 24, 283–313.

Mundo, E., Bareggi, S.R., Pirola, R., Bellodi, L., 1999. Effect of acute intravenous clomipramine and antiobsessional response to proserotonergic drugs: is gender a predictive variable? Biological Psychiatry 45, 290–294.

Ohara, K., Isoda, H., Suzuki, Y., Takehara, Y., Ochiai, M., Takeda, H., Igarashi, Y., Ohara, K., 1999. Proton magnetic resonance spectroscopy of lenticular nuclei in obsessive–compulsive disorder. Psychiatry Research: Neuroimaging 92, 83–91.

Provencher, S.W., 1993. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magnetic Resonance in Medicine 30, 672.

Rauch, S.L., Jenike, M.A., Alpert, N.M., Baer, L., Breiter, H.C., Savage, C.R., Fischerman, A.J., 1994. Regional cerebral blood flow measured during symptom provocation in obsessive–compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Archives of General Psychiatry 51, 62–70.

Ravi Kishore, V., Samar, R., Janardhan Reddy, Y.C., Chandrasekhar, C.R., Thennarasu, K., 2004. Clinical characteristics and treatment response in poor and good insight obsessive–compulsive disorder. European Psychiatry 19, 202–208.

Ravizza, L., Barzega, G., Bellino, S., Bogetto, F., Maina, G., 1995. Predictors of drug treatment response in obsessive–compulsive disorder. Journal of Clinical Psychiatry 56, 368–373.

Rosenberg, D.R., MacMaster, F.P., Keshavan, M.S., Fitzgerald, K.D., Moore, G.J., 2000. Decrease in caudate glutamatergic concentrations in pediatric obsessive–compulsive disorder patients taking paroxetine. Journal of the American Academy of Child and Adolescent Psychiatry 39, 1096–1103.

Rosenberg, D.R., Mirza, Y., Smith, D.H., Russell, A., Tang, J., Smith, J.M., Banerjee, S.P., Bhandari, R., Rose, M., Ivey, J., Boyd, C., Moore, G.J., 2004. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. Journal of the American Academy of Child and Adolescent Psychiatry 43, 1146–1153.

Rubin, Y., LaPlaca, M.C., Smith, D.H., Thibault, L.E., Lenkinski, R.E., 1995. The effect of *N*-acetyl-aspartate on the intercellular calcium concentration in NTera2-neurons. Neuroscience Letters 198, 209–212.

Saxena, S., Brody, A.L., Maidment, K.M., Dunkin, J.J., Colgan, M., Alborzian, S., Phelps, M.E., Baxter Jr., L.R., 1999. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive–compulsive disorder. Neuropsychopharmacology 21, 683–693.

Saxena, S., Bota, R.G., Brody, A.L., 2001. Brain-behavior relationships in obsessive–compulsive disorder. Seminars in Clinical Neuropsychiatry 6, 82–101.

Schwartz, J.M., Stoessel, P.W., Baxter Jr., L.R., Martin, K.M., Phelps, M.E., 1996. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive–compulsive disorder. Archives of General Psychiatry 53, 109–113.

Steketee, G., Eisen, J., Dyck, I., Warshaw, M., Rasmussen, S., 1999. Predictors of course in obsessive compulsive disorder. Psychiatry Research 89, 229–238.

Swedo, S.E., Schapiro, M.B., Grady, C.L., Cheslow, D.L., Leonard, H. L., Kumar, A., Friedland, R., Rapoport, S.I., Rapoport, J.L., 1989. Cerebral glucose metabolism in childhood onset obsessive–compulsive disorder. Archives of General Psychiatry 46, 518–523.

Wiedermann, D., Schuff, N., Matson, G.B., Soher, B.J., Du, A.T., Maudsley, A.A., Weiner, M.W., 2001. Short echo time multislice proton magnetic resonance spectroscopic imaging in human brain: metabolite distributions and reliability. Magnetic Resonance Imaging 19, 1073–1080.

HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2006; **21**: 439–445.
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.801

Effect of antipsychotic replacement with quetiapine on the symptoms and quality of life of schizophrenic patients with extrapyramidal symptoms

Takahide Taniguchi, Satsuki Sumitani, Michitaka Aono, Junichi Iga, Sawako Kinouchi, Hirosi Aki, Mami Matsushita, Kyoko Taniguchi, Mami Tsuno, Kazunari Yamanishi, Masahito Tomotake, Yasuhiro Kaneda and Tetsuro Ohmori*

Department of Psychiatry, University of Tokushima School of Medicine, Tokushima city, Tokushima, Japan

Replacement of antipsychotic drugs with quetiapine (QTP) was tried in a naturalistic setting in chronic schizophrenic patients who still showed moderate psychiatric symptoms and either showed extrapyramidal symptoms (EPS) or took anti-parkinson drugs for the EPS. QTP was added on and gradually increased while the previous drugs were tapered and discontinued whenever possible. Clinical symptoms, objective and subjective QOL, and EPS were measured before and 6 months after QTP addition, using Brief Psychiatric Rating Scale (BPRS), Quality of Life Scale (QLS), Schizophrenia Quality of Life Scale (SQLS) and Drug-Induced Extrapyramidal Symptom Scale (DIEPSS), respectively. Twenty-one patients completed the trial and received the assessment. It was found that replacement with QTP-improved clinical symptoms, objective and subjective QOL and EPS. This improvement was equally observed in not only patients who switched to QTP monotherapy ($n = 11$) but also patients who took QTP together with reduced small doses (4.4 ± 4.3 mg/day) of previous drugs ($n = 11$). The results suggest that replacement with QTP improves symptoms as well as objective and subjective QOL in a subgroup of schizophrenia. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS—quality of life; quetiapine; replacement; schizophrenia

INTRODUCTION

Improvement of Quality of Life (QOL) is an important aspect of pharmacotherapy of schizophrenia. Meltzer *et al.* (1990) first reported that clozapine, an atypical antipsychotic drug, improved QOL as well as clinical symptoms in the patients who were refractory to typical antipsychotic drugs. Following this study, a large number of studies have compared typical and atypical antipsychotic drugs with respect to their effects on the QOL (Awad and Voruganti, 2004; Lambert and Naber, 2004, for review). While there are many studies suggesting the superior effect of atypical drugs (Rosenheck *et al.*, 1997; Revicki *et al.*, 1999; Ritsner *et al.*, 2004), some contradictory results have also been reported (Breier *et al.*, 1993; Tempier and Pawliuk, 2001; Kilian *et al.*, 2004).

One problem of these previous studies is that levels of QOL were usually accessed by only one rating scale, either by observer-rated objective scale (Meltzer *et al.*, 1990; Breier *et al.*, 1993; Rosenheck *et al.*, 1997) or self-rated subjective scale (Franz *et al.*, 1997; Tempier and Pawliuk, 2001; Kilian *et al.*, 2004). The majority of early studies (Meltzer *et al.*, 1990; Breier *et al.*, 1993; Rosenheck *et al.*, 1997) have relied on Quality of Life Scale (QLS), an observer-rated objective scale that was originally developed to measure the deficit symptoms of schizophrenia (Heinrichs *et al.*, 1984). Some recent studies have measured self-rated subjective QOL (Franz *et al.*, 1997; Tempier and Pawliuk, 2001; Kilian *et al.*, 2004). However, studies including our own (Dickerson *et al.*, 1998; Fitzgerald *et al.*, 2001; Aki *et al.*, 2006) have

* Correspondence to: T. Ohmori, Department of Psychiatry, University of Tokushima School of Medicine, 3-8-15 Kuramoto-cho, Tokushima 770-8503, Japan. Tel: +81-88-633-7130. Fax: +81-88-633-7131. E-mail: tohmori@clin.med.tokushima-u.ac.jp

Copyright © 2006 John Wiley & Sons, Ltd.

Received 10 April 2006
Accepted 3 August 2006

pointed out that objective and subjective QOL scale scores show poor correlation and different symptomatic determinants. A recent cross-sectional study showed that self-rated QOL scores did not reflect observer-rated measures of QOL (Voruganti *et al.*, 2000).

Taking the complex nature of QOL into account, assessment with one type of rating scales may not be accurate enough to detect the real change in QOL. Another problem is that most previous studies preferably focused on clozapine and olanzapine and henceforth a few data are available for the effect on QOL of other atypical antipsychotics.

In the present study, the authors investigated the effect of replacement of previous antipsychotic drugs with quetiapine (QTP), an atypical antipsychotic drug known to induce little EPS, on the QOL as well as symptoms of chronic schizophrenic patient who showed moderate psychiatric symptoms and EPS under the treatment with previous antipsychotic drugs. In order to evaluate QOL change comprehensively, we used QLS as an objective scale and Schizophrenia Quality of Life Scale (SQLS; Wilkinson *et al.*, 2000), a newly developed self-rated scale, as a subjective assessment of QOL.

METHODS

Patients population

Subjects were inpatients or outpatients at the Department of Psychiatry, University Hospital of Tokushima or affiliated medical institutions during the period from October 2001 to September 2003, diagnosed as schizophrenia according to the international classification of diseases (ICD-10, World Health Organization, 1992). Those patients fulfilling all of the following four criteria were enrolled in this study: (1) chronic patients who were not in acute exacerbation; (2) more than 28 points in the BPRS total score; (3) taking antipsychotics at a dose less than 30 mg/day of haloperidol (HPD) equivalent (Inagaki *et al.*, 1999); (4) having drug-induced EPS and/or taking anti-parkinson drugs for the EPS. The investigator fully explained about the treatment trial and only those consented were involved in the study. A total of 34 patients were enrolled.

Study design

The replacement to QTP was started with the add-on administration of QTP over previous drugs at a dose of 50–150 mg/day. Previous drugs then were reduced gradually in a stepwise manner, with four steps or more, by about 25% reduction at each step, and the dose of QTP was adjusted in each patient. QTP monotherapy was recommended to establish in as many patients as possible. The replacement, either total or partial, was completed within the 4th month followed by 2 months observational period until 6th month. The doses of anti-parkinson drugs were reduced gradually after the reduction of previous antipsychotic drugs, and withdrawn wherever possible.

Assessment instruments

Clinical evaluations were performed at study entry (baseline) and after 6 months by the same physician for each patient. The Clinical Global Impression Scale (CGI) for Improvement ratings and Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) Japanese Version (Miyata *et al.*, 1995) were used for evaluation of psychiatric symptoms. The Drug-Induced Extrapyramidal Symptom Scale (DIEPSS; Inada, 1996) was used for evaluating EPS. Schizophrenia Quality of Life Scale (SQLS; Wilkinson *et al.*, 2000) Japanese Version (Kaneda *et al.*, 2002) and Quality of Life Scale (QLS; Heinrichs *et al.*, 1984) Japanese Version (Miyata and Fujii, 1995) were used for evaluating subjective and objective QOLs, respectively. The hospitalization periods of the most of the inpatients were prolonged due to their familial and/or social circumstances, and their symptom levels were considered almost the same as those of outpatients. So evaluations with QOL scales were possible also in inpatients of the present study by making slight modification of question items or evaluation points, although SQLS and QLS were originally developed for outpatients. Item 17 of SQLS 'I tend to stay at home' was modified into 'I tend to stay in my room.' Activities in the occupational and recreational therapies were included for the assessment of items 9–12 of QLS for the instrumental role functioning. The hospitalization status did not change during the study period in any patient.

Data analysis

The scores in the BPRS, QLS, SQLS, and DIEPSS, as well as the doses of anti-parkinson drugs and blood prolactin levels, were analyzed using the Wilcoxon one-sample test, and the data obtained at baseline and 6 months after QTP therapy were compared. The data were represented by a mean value ± standard deviation. The correlation between QOL scales and BPRS

Copyright © 2006 John Wiley & Sons, Ltd.

Table 1. Psychotic symptoms, side effects and QOL

		Baseline	6-month	p
BPRS ($n=21$)	Total score	42.9 ± 7.5	34.4 ± 5.1	<0.001
	Thought disturbance	8.9 ± 2.8	8.0 ± 2.9	0.006
	Anergia	12.8 ± 3.1	9.8 ± 2.5	<0.001
	Anxiety-depression	8.5 ± 3.3	6.9 ± 2.2	<0.001
	Hostile-suspiciousness	6.3 ± 2.7	4.9 ± 1.9	<0.001
	Activation	6.3 ± 1.6	4.9 ± 1.5	<0.001
DIEPSS ($n=21$)		6.0 ± 3.0	2.4 ± 2.5	<0.001
Dose of antiparkinson drugs[a] ($n=21$)		2.7 ± 2.0	0.9 ± 1.6	<0.001
Prolactin levels (ng/mL) ($n=16$)		32.7 ± 26.8	7.1 ± 6.5	<0.001
QLS ($n=21$)	Total score	34.3 ± 15.1	46.5 ± 20.9	<0.001
	Interpersonal relations	11.5 ± 6.6	15.7 ± 10.2	0.007
	Instrumental role functioning	6.8 ± 4.3	9.2 ± 4.7	<0.001
	Intrapsychic foundations	12.0 ± 6.1	16.7 ± 7.0	<0.001
	Common objectives and activities	3.9 ± 1.9	5.0 ± 2.5	0.002
SQLS ($n=17$)	Psychosocial conditions	25.6 ± 11.9	21.2 ± 10.8	0.028
	Motivation/energy	15.5 ± 3.7	14.2 ± 3.2	0.287
	Symptoms/side effects	9.9 ± 4.5	8.6 ± 6.1	<0.148

[a]On a biperiden equivalent dose.

or DIEPSS was analyzed using the Spearman's correlation coefficient.

RESULTS

Thirty four subjects were 14 males and 20 females with the mean age of 45 ± 15 years and the mean morbid period of 21 ± 15 years, receiving various antipsychotic drugs including haloperidol, chlorpromazine, risperidone, olanzapine, etc. at a mean haloperidol (HPD) equivalent dose of 13.9 ± 7.5 mg/day. They included 13 cases of paranoid type, nine cases of residual type and eight cases of hebephrenic type. Nine cases discontinued the QTP treatment during the study period, due to lack of response ($n=4$), patient's will ($n=2$), violation of the inclusion criteria ($n=1$) and adverse events ($n=2$, high blood sugar level, somnolence). Twenty-five cases completed the 6-month study, but four of these were excluded because of incomplete evaluations of the symptoms and QOL, therefore, analyses were performed for 21 cases. Among these 21 cases, 11 were switched to monotherapy with QTP (monotherapy group), while 10 remained on a combination therapy with other drugs including risperidone, olanzapine, etc. (non-monotherapy group). The mean doses of QTP in the monotherapy and non-monotherapy groups were 498 ± 167 and 468 ± 187 mg/day, respectively. Mean dose of previous antipsychotics in these 21 patients at baseline was 13.3 ± 7.7 mg/day, and mean dose of previous antipsychotics left at 6th month in non-monotherapy group was 4.4 ± 4.3 mg/day on HPD equivalence. Fifteen were inpatients and six were outpatients.

BPRS scores of the 21 patients at baseline and after 6 months QTP administration are shown in Table 1. The total score of the BPRS and subscores of the BPRS factors including thought disturbance, anergia, anxiety-depression, hostile-suspiciousness, and activation were significantly improved. There were three cases judged as 'very much improved,' and six cases as 'much improved' by CGI. Significant improvement was equally seen in both the monotherapy group and the non-monotherapy group (Table 2).

In the total group of 21 cases, as well as in both the monotherapy and non-monotherapy groups, the scores of the DIEPSS were significantly improved at 6th month compared to those at baseline (Tables 1 and 3). Likewise, in the total group of 21 cases, as well as in the monotherapy and non-monotherapy groups, the doses of anti-parkinson drugs on biperiden equivalent dose were significantly reduced at 6th month compared to those at baseline (Tables 1 and 3). There was no significant correlation between DIEPSS scores and the QOL measure scores at either the baseline or the 6th month. However, the change of the DIEPSS scores correlated significantly with the change of QLS ($p=0.024$), but not with SQLS scores.

Blood prolactin levels, determined in 16 of 21 patients, showed significant decrease at 6th month compared to those at baseline (Table 1). The significant decrease was observed in both the monotherapy and non-monotherapy groups (Table 2). There was no significant correlation between prolactin levels and the

Copyright © 2006 John Wiley & Sons, Ltd.
Hum Psychopharmacol Clin Exp 2006; **21**: 439–445.
DOI: 10.1002/hup

Table 2. Comparison of BPRS, QLS, SQLS, DIEPSS, dose of anti-parkinson drugs and prolactin levels between monotherapy and non-monotherapy groups

		Baseline	6-month	*p*
BPRS	Monotherapy Group ($n=11$)	39.5 ± 5.4	32.6 ± 3.5	<0.001
	Non-monotherapy Group ($n=10$)	46.7 ± 7.8	36.4 ± 6.1	0.002
QLS	Monotherapy Group ($n=11$)	34.2 ± 13.8	45.6 ± 19.2	0.004
	Non-monotherapy Group ($n=10$)	34.3 ± 17.2	47.6 ± 23.6	0.004
SQLS (Psychosocial conditions)	Monotherapy Group ($n=9$)	21.4 ± 11.5	18.2 ± 10.5	0.266
	Non-monotherapy Group ($n=8$)	30.3 ± 11.3	24.5 ± 10.9	0.078
DIEPSS	Monotherapy Group ($n=11$)	6.6 ± 3.2	2.8 ± 2.6	0.002
	Non-monotherapy Group ($n=10$)	5.3 ± 2.8	1.9 ± 2.4	0.008
Dose of antiparkinson drugs[a]	Monotherapy Group ($n=11$)	2.3 ± 1.8	0.9 ± 1.9	0.016
	Non-monotherapy Group ($n=10$)	3.1 ± 2.3	1.0 ± 1.4	0.016
Prolactin levels (ng/ml)	Monotherapy Group ($n=9$)	37.7 ± 34.7	3.4 ± 3.3	0.004
	Non-monotherapy Group ($n=7$)	26.2 ± 10.0	11.8 ± 6.8	0.031

[a]on a biperiden equivalent dose.

symptoms or QOL measure scores at either the baseline or the 6th month.

The total score of the QLS and the four QLS domains such as interpersonal relations, instrumental role functioning, intrapsychic foundations, and common objects and activities were significantly improved 6 months after QTP treatment (Table 1). Significant improvement of QLS scores was seen in both the monotherapy and non-monotherapy groups (Table 2). The complete data sets of the SQLS were obtained from only 18 cases with three patients failing to fulfill the questionnaire. Psychosocial scale scores were significantly improved (Table 1). This improvement was not observed when patients were divided into monotherapy and non-monotherapy groups (Table 2).

Significant correlations between the QLS total score and the scores of BPRS subscores of anergia and anxiety-depression were observed at both baseline and 6th month (Table 3). With regard to SQLS, the psychosocial and symptoms/side effects scores were significantly correlated with the BPRS total and the subscores of anxiety-depression and hostile-suspiciousness at baseline. The psychosocial score also significantly correlated with activation subscore of BPRS. At 6th month, the psychosocial score was significantly correlated with the BPRS subscores of anxiety-depression and hostile-suspiciousness (Table 3).

DISCUSSION

The present study showed that total or partial replacement of previous antipsychotic drugs with QTP improved not only psychiatric symptoms but also subjective and objective QOL in schizophrenic patients with moderate psychiatric symptoms and

Table 3. Correlations between QOL scores and BPRS

	BPRS total score	Thought disturbance	Anergia	Anxiety-depression	Hostile-suspiciousness	Activation
Baseline						
QLS Total score ($n=21$)	−0.092	−0.16	−0.681[b]	0.481[a]	0.335	−0.196
SQLS ($n=18$)						
Psychosocial conditions	0.530*	0.226	−0.34	0.616[b]	0.650[b]	0.522[a]
Motivation/energy	0.197	−0.24	0.382	0.023	−0.018	0.193
Symptoms/side effects	0.513[a]	0.267	−0.31	0.647[b]	0.663[b]	0.273
6-month						
QLS Total score SQLS	0.035	0.184	−0.659[b]	0.443[a]	0.393	−0.040
Psychosocial conditions	0.400	0.211	−0.408	0.787[b]	0.506[a]	0.197
Motivation/energy	0.294	0.252	0.266	−0.061	0.126	0.324
Symptoms/side effects	0.538[a]	0.410	−0.066	0.467	0.293	0.451

[a]$p < 0.05$.
[b]$p < 0.01$.

Copyright © 2006 John Wiley & Sons, Ltd.
Hum Psychopharmacol Clin Exp 2006; **21**: 439–445.
DOI: 10.1002/hup

EPS under the treatment with other antipsychotic drugs (Tables 1 and 2). The replacement also reduced EPS, the mean dose of the anti-parkinson drugs and the mean levels of prolactin (Tables 1 and 2).

As to QOL change after QTP therapy, Velligan *et al.* (2003) reported that patients switched to QTP for 6 months showed significantly better outcome in QOL measured by QLS, an observer-rated QOL rating scale, compared with those continued on conventional medication, although the two groups did not differ with respect to symptomatic improvement. On the other hand, an independent study of our group showed an improvement in QOL as measured by SQLS, a self-rated QOL scale, after switching to QTP (Kaneda and Ohmori, 2003). The present study is of clinical importance in showing that both an observer-rated (objective) and self-rated (subjective) QOL measures were improved after QTP therapy. It has been shown that objective QOL scale such as QLS and subjective QOL scale such as SQLS show poor correlation and different symptomatic determinant (Aki *et al.*, 2006). QLS, which has been most often used in the previous QOL studies, was originally developed for a measurement of deficit symptoms of schizophrenia (Heinrichs *et al.*, 1984). It is with reason that QLS scores correlate with negative symptom scores (Dickerson *et al.*, 1998; Fitzgerald *et al.*, 2001; Aki *et al.*, 2006). In contrast, subjective QOL scale scores such as SQLS have been reported to correlate not with negative symptoms but with depressive symptoms (Wilkinson *et al.*, 2000; Aki *et al.*, 2006) and positive symptoms (Tomotake *et al.*, unpublished observation). In line with these previous studies, the present study showed significant correlations between the QLS total score and the scores of BPRS subscores of anergia and anxiety-depression, and between the psychosocial and symptoms/side effects scores of SQLS and the BPRS subscores of anxiety-depression and hostile-suspiciousness (Table 3). It is suggested that subjective and objective QOL should be considered as separate and complementary outcome variables, and that total or partial replacement of previous antipsychotic drugs with QTP improved both outcome variables.

Considering the correlations with clinical symptoms, objective and subjective QOL improvement after QTP may be attributable to its therapeutic effects on negative and depressive symptoms, respectively. Although a recent meta-analysis showed no superior effect of QTP to conventional antipsychotic drugs in the treatment of negative symptoms (Schulz *et al.*, 2003), the low rate of EPS may be related to the reduction of secondary negative symptoms. Some studies have shown a greater effect of QTP on depressive symptoms compared with haloperidol (Emsley *et al.*, 2003) or risperidone (Mullen *et al.*, 2001). The present study with a small number of subjects, however, did not show any correlation between the changes in the scores of QLS or SQLS and the changes in the scores of negative or depressive symptoms from baseline to the end of study (data not shown). It is of note, however, the change of the DIEPSS scores correlated significantly with the change of QLS.

It was an unexpected finding that partial replacement was as effective as total replacement. The decision to discontinue the previous antipsychotic drugs or not was left to each clinician's judgment. In some cases, previous drugs were increased again after an observation of exacerbation in clinical symptoms. As a result, previous medication was reduced to a mean dose of 4.4 ± 4.3 mg/day on HPD equivalence but failed to be discontinued in 10 patients (non-monotherapy group). These patients tended to show higher BPRS score at baseline and at 6th month compared with those switched to monotherapy. It is of note, however, that partial replacement resulted in almost the same magnitude of improvement in the symptoms, QOL, EPS, and prolactin levels compared with the group of total replacement (Table 2). The pharmacological basis of this clinical observation is not clear. QTP has a unique pharmacological character to bind to dopamine D2 receptors loosely and transiently, which may explain the clinical characteristics of the drug (Seeman and Tallerico, 1998; Kapur *et al.*, 2000). It is unlikely, however, this character continue to work in the presence of other drugs which bind to D2 receptors rather tightly or continuously. QTP has another pharmacological character to have affinity for various neurotransmitter receptors including serotonin, dopamine, histamine, and adrenergic receptors other than dopamine D2 receptors (Nemeroff *et al.*, 2002). Blocking of these receptors may have relevance to the clinical effects observed in the present study. Alternatively, the reduction of previous antipsychotic doses may have contributed to the improvement of clinical symptoms and subjective and objective QOL. The fact that EPS, the anticholinergic dose and prolactin levels decreased significantly even in the partial replacement group supported this possibility. It has been shown that extremely large dose of antipsychotic drugs paradoxically exasperate psychotic symptoms (Baldessarini *et al.*, 1988; Coryell *et al.*, 1990). Although the dose of previous drugs was not so large in the present patients, the dose reduction together with replacement with QTP may have related to the beneficial effects.

Copyright © 2006 John Wiley & Sons, Ltd.

Hum Psychopharmacol Clin Exp 2006; **21**: 439–445.
DOI: 10.1002/hup

There are a number of limitations in the present study. First, the study is an open study conducted in daily clinical practice. The result of this type of study could be biased by the expectation of patients and doctors concerning the effectiveness of the applied medication. Secondly, both symptoms and QOL ratings were made by a single rater rather than separate raters. Thirdly, long-term inpatients were included in the study. Although a previous QOL study also included inpatients (Franz *et al.*, 1997; Rosenheck *et al.*, 1997), daily life was restricted in inpatients. By making slight modification in the questions of QLS and SQLS, QOL levels were adequately assessed in the present inpatients. Fourthly, the result must be interpreted considering the presence of dropout subjects, since the result is reported in the completers. Lastly, generalization of the present finding to other schizophrenic population should be done with caution, since we set relatively narrow restriction on the inclusion criteria of patients to this study.

CONCLUSIONS

Despite the above limitations, the present study supports the notion that replacement with QTP improves objective and subjective QOL as well as symptoms and EPS in a subgroup of chronic schizophrenic patients having certain degree of symptoms and showing EPS and/or taking anti-parkinson drugs under the treatment with other antipsychotic drugs.

ACKNOWLEDGEMENTS

This work was supported in part by a Grants-in-Aid No 16390325 for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology in Japan and Grants-in-Aid for Scientific Research from the 21st Century COE Program, Human Nutritional Science on Stress Control, Tokushima, Japan.

REFERENCES

Aki H, Tomotake M, Kaneda Y, *et al.* 2006. Subjective and objective quality of life, levels of life skills, and their clinical determinants I outpatients of schizophrenia. *Psychiatry Res* (in press).

Awad AG, Voruganti LN. 2004. Impact of atypical antipsychotics on quality of life in patients with schizophrenia. *CNS Drugs* **18**: 877–893.

Baldessarini RJ, Cohen BM, Teicher MH. 1988. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* **45**: 79–91.

Breier A, Buchanan RW, Irish D, Carpenter WT. 1993. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. *Hosp Community Psychiatry* **44**: 1145–1149.

Coryell W, Kelly M, Perry PJ, Miller DD. 1990. Haloperidol plasma levels and acute clinical change in schizophrenia. *J Clin Psychopharmacol* **10**: 397–402.

Dickerson FB, Ringel NB, Parente F. 1998. Subjective quality of life in out-patients with schizophrenia: clinical and utilization correlates. *Acta Psychiatr Scand* **98**: 124–127.

Emsley RA, Buckley P, Jones AM, Greenwood MR. 2003. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *J Psychopharmacol* **17**: 210–215.

Fitzgerald PB, Williams CL, Corteling N, *et al.* 2001. Subject and observer-rated quality of life in schizophrenia. *Acta Psychiatr Scand* **103**: 387–392.

Franz M, Lis S, Pluddenmann K, Gallhofer B. 1997. Conventional versus atypical antipsychotics: subjective quality of life in schizophrenic patients. *Br J Psychiatry* **170**: 422–425.

Heinrichs DW, Hanlon TE, Carpenter WT. 1984. The Quality of Life Scale: an instrument for rating the schizophrenic deficit symptoms. *Schizophr Bull* **10**: 388–398.

Inada T. 1996. *Evaluation and diagnosis of drug-induced extrapyramidal symptoms: commentary on the DIEPSS and guide to its usage.* Seiwa Shoten: Tokyo.

Inagaki A, Inada T, Fujii Y, Yagi G, Yoshio T, Nakamura H, Yamauchi T. 1999. *Equivalent doses of psychotropic drugs.* Seiwa Shoten: Tokyo.

Kaneda Y, Ohmori T. 2003. Quetiapine impact on quality of life in patients with schizophrenia. *Ann Pharmacother* **37**: 917–918.

Kaneda Y, Imakura A, Fujii A, Ohmori T. 2002. Schizophrenia quality of life scale: validation of the Japanese version. *Psychiatry Res* **113**: 107–113.

Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. 2000. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* **57**: 553–559.

Kilian R, Dietrich S, Toumi M, Angermeyer MC. 2004. Quality of life in persons with schizophrenia in out-patient treatment with first- or second-generation antipsychotics. *Acta Psychiatr Scand* **110**: 108–118.

Lambert M, Naber D. 2004. Current issues in schizophrenia: overview of patient acceptability, functioning capacity and quality of life. *CNS Drugs* **18**(Suppl. 2): 5–17. discussion 41–43.

Meltzer HY, Burnett S, Bastani B, Ramirez LF. 1990. Effects of six months of clozapine treatment on the quality of life of chronic schizophranic patients. *Hosp Community Psychiatry* **41**: 892–897.

Miyata R, Fujii Y. 1995. *Quality of Life Scale Japanese Version.* Seiwa Syoten: Tokyo.

Miyata R, Fujii Y, Inagaki A, Inada T, Yagi G. 1995. Reliability of the Japanese version of Brief Psychiatric Rating Scale (BPRS). *Clin Eval* **23**: 357–367.

Mullen J, Jibson MD, Sweitzer D. 2001. A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the quetiapine experience with safety and tolerability (QUEST) study. *Clin Ther* **23**: 1839–1854.

Nemeroff CB, Kinkead B, Goldstein J. 2002. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry* **63**(Suppl. 13): S5–S11.

Overall JE, Gorham DR. 1962. The brief psychiatric rating scale. *Psychol Rep* **10**: 799–812.

Copyright © 2006 John Wiley & Sons, Ltd.

Revicki DA, Genduso LA, Hamilton SH, Ganoczy D, Beasley CM. 1999. Olanzapine versus haloperidol in the treatment of schizophrenia and other psychotic disorders: quality of life and clinical outcomes of a randomized clinical trial. *Qual Life Res* **8**: 417–426.

Ritsner M, Gibel A, Perelroyzen G, Kurs R, Jabarin M, Ratner Y. 2004. Quality of life outcomes of risperidone, olanzapine, and typical antipsychotics among schizophrenia patients treated in routine clinical practice: a naturalistic comparative study. *J Clin Psychopharmacol* **24**: 582–591.

Rosenheck R, Cramer J, Xu W, *et al.*1997. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. *N Engl J Med* **337**: 809–815.

Schulz SC, Thomson R, Brecher M. 2003. The efficacy of quetiapine vs. haloperidol and placebo: a meta-analytic study of efficacy. *Schizophr Res* **62**: 1–12.

Seeman P, Tallerico T. 1998. Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. *Mol Psychiatry* **3**: 123–134.

Tempier R, Pawliuk N. 2001. Influence of novel and conventional antipsychotic medication on subjective quality of life. *J Psychiatry Neurosci* **26**: 131–136.

Velligan DI, Prihoda TJ, Sui D, Ritch JL, Maples N, Miller AL. 2003. The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. *J Clin Psychiatry* **64**: 524–531.

Voruganti L, Cortese L, Oyewumi L, Cernovsky Z, Zirul S, Awad A. 2000. Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. *Schizophr Res* **43**: 135–145.

Wilkinson G, Hesdon B, Wild D, *et al.* 2000. Self-report quality of life measure for people with schizophrenia: the SQLS. *Br J Psychiatry* **177**: 42–46.

World Health Organization. 1992. The ICD-10 Classification of Mental and Behavioral Disorders: clinical descriptions and diagnostic guidelines.

Copyright © 2006 John Wiley & Sons, Ltd.

Hum Psychopharmacol Clin Exp 2006; **21**: 439–445.
DOI: 10.1002/hup

Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuroscience Letters 401 (2006) 1–5
Neuroscience Letters
www.elsevier.com/locate/neulet

Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in schizophrenia is associated with age at onset and symptoms

Shusuke Numata, Shu-ichi Ueno*, Jun-ichi Iga, Ken Yamauchi, Song Hongwei, Koji Ohta, Sawako Kinouchi, Sumiko Shibuya-Tayoshi, Shin'Ya Tayoshi, Michitaka Aono, Naomi Kameoka, Satsuki Sumitani, Masahito Tomotake, Yasuhiro Kaneda, Takahide Taniguchi, Yasuhito Ishimoto, Tetsuro Ohmori

Department of Psychiatry, Course of Integrated Brain Sciences, Medical Informatics, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-8-15 Kuramoto-cho Tokushima 770-8503, Japan

Received 4 November 2005; received in revised form 25 January 2006; accepted 21 February 2006

Abstract

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that promotes several functions of neurons and modulates neurotransmissions. It has been reported that there are alterations of BDNF levels in schizophrenic brains and that BDNF gene expressional changes would be responsible for the etiology of schizophrenia. Recent studies have shown that a variation of BDNF gene (Val66Met polymorphism) affects the function of neurons, and is associated with several neurological and psychiatrical disorders. We investigated the relationship between BDNF Val66Met polymorphism and the onset age as well as levels of clinical symptoms in 159 of chronic schizophrenia in-patients diagnosed by DSM-IV. The mean onset ages were 27.5 ± 9.5 for BDNF Val/Val, 25.5 ± 7.4 for BDNF Val/Met and 22.9 ± 6.0 for BDNF Met/Met and this polymorphism was significantly associated with age at onset ($P = 0.023$). The mean Brief Psychiatric Rating Scale scores (BPRS) were significantly different among those three groups ($P = 0.003$). No significant differences were demonstrated comparing the BDNF genotype distributions of positive and negative family history ($P = 0.21$). Our investigation indicates that the BDNF gene Val66Met polymorphism is related to the onset age of schizophrenia and the levels of clinical symptoms that remain after long-term antipsychotic treatment.
© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Brain-derived neurotrophic factor; Polymorphism; Schizophrenia; Age at onset

Disturbed neural development has been postulated to be a factor in the pathophysiology of schizophrenia. The neurotrophin hypothesis of schizophrenia proposes that alterations in expression of neurotrophic factors could be responsible for neural maldevelopment and disturbed neural plasticity, thus being an important event in the pathogenesis of schizophrenic psychoses [29]. Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophic factor family that promotes the development, regeneration, survival and maintenance of function of neurons [18]. BDNF has also been demonstrated to modulate neurotransmitter synthesis, metabolism and release, postsynaptic ion channel fluxes, neuronal activity and long-term potentiation [1]. Several groups have reported alterations of BDNF levels in the cortical area and hippocampus of schizophrenic patients [6,28]. A large number of genetic studies have been carried out and demonstrated the possible correlation between BDNF gene polymorphisms and schizophrenia [15,23,27] although some studies have failed to find any correlation [4,26]. It has been reported BDNF controls D3 receptor (DRD3) gene expression [8] and DRD3 genotypes are associated with tardive dyskinesia in schizophrenic patients [24]. Recently, a single-nucleotide polymorphism that results in valine to methionine substituition at codon 66 (Val66Met) in the prodomain of the BDNF gene was reported and 66Met BDNF has been shown to affect intracellular trafficking and activity-dependent secretion of BDNF [5,7]. There were several association studies between this BDNF Val66Met polymorphism and psychiatric disorders [9,10,22,25]. A recent report showed that the Val/Val genotype in schizophrenic patients was significantly associated with clinical response for clozapine [11]. In this study, we investigate the relationship between this BDNF gene Val66Met polymorphism and the age at onset, clinical symp-

* Corresponding author. Tel.: +81 886 33 7130; fax: +81 886 33 7131.
E-mail address: s-ueno@clin.med.tokushima-u.ac.jp (S.-i. Ueno).

0304-3940/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2006.02.054

toms, extra-pyramidal symptoms and family history in chronic schizophrenic patients.

We collected DNA samples from 159 in-patients (115 male and 44 female; mean age: 53.9 ± 12.8 years, mean duration of hospitalization: 12.1 years) with schizophrenia from nine psychiatric hospitals in the neighboring area of Tokushima Prefecture in Japan (population: about 820,000). All the patients were Japanese and biologically unrelated. The diagnosis of schizophrenia was made by at least two experienced psychiatrists according to DSM-IV criteria [2]. Clinical symptoms and antipsychotic-induced adverse effects were evaluated when blood samples were taken by the Brief Psychiatric Rating Scale (BPRS) scores [20] and Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) [13]. The age at first psychotic episode was used as age at onset (mean ± S.D.: 25.9 ± 8.3 years) by referring to the patient's medical records. BPRS and DIEPSS in most patients were rated by three investigators. Inter-rater reliability for BPRS and DIEPSS was tested in a subsample of five patients ($r = 0.81$; $P < 0.01$). Positive family history means that first-degree relatives of patients are diagnosed as schizophrenia. Seventy-two patients received atypical and 44 patients received typical and others received both antipsychotics. All subjects signed informed consent to participate in this study approved by the institutional ethics committees.

Genomic DNA was extracted from EDTA-containing venous blood samples according to standard procedures. Genotyping of BDNF Val66Met polymorphism was performed with taqman probe according to the manufacture's instruction with ABI 7500 (AppliedBiosystems, Tokyo, Japan).

Frequency analysis was performed with Fisher's exact test. To evaluate associations between the genotypes and age at onset, Kaplan–Meier analyses were used for survival curves. Spearman correlation coefficients (two-tailed) were used to evaluate whether clinical symptoms of schizophrenia was correlated with Met allele dose-dependency of BDNF Val66Met gene polymorphism. Group mean comparisons of the BPRS among genotypic BDNF Val66Met polymorphism were performed with the Kruskal–Wallis statistic. Analysis of variance (ANOVA) was used for parametric comparisons after homogeneity of variance was assessed by the Levene test. Two-way ANOVA was performed to compare BPRS scores combined effects of BDNF genotype and age at onset. The criterion for significance was set at $P < 0.05$ for all of the tests. Data are presented as mean ± standard deviation.

Genotype and allele distributions of Val66Met polymorphism in the 159 patients are shown in Table 1. The genotypic distributions did not deviate from the Hardy–Weinberg

Table 1
Genotypes and alleles of the brain-derived neurotrophic factor Val66Met polymorphism in patients with schizophrenia ($N = 159$)

BDNF	Genotypes			Alleles	
	Val/Val	Val/Met	Met/Met	Val	Met
Male	47 (40.9%)	52 (45.2%)	16 (13.9%)	146 (63.5%)	84 (36.5%)
Female	18 (40.9%)	16 (36.4%)	10 (22.7%)	52 (59.1%)	36 (40.9%)
Total	65 (40.9%)	68 (42.8%)	26 (16.3%)	198 (62.3%)	120 (37.7%)

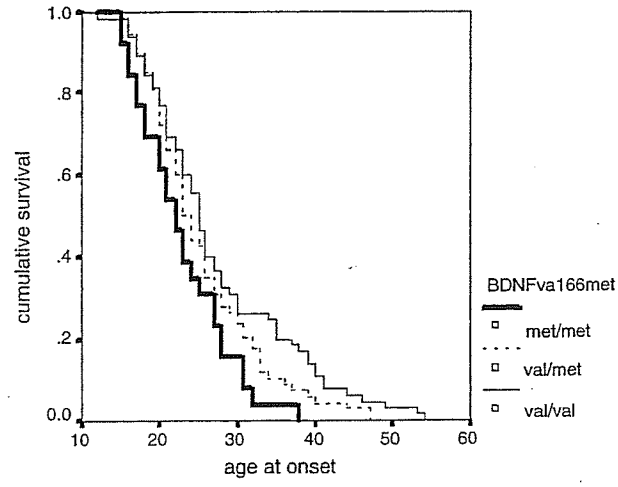

Fig. 1. Age at onset was plotted as a survival function of BDNF Val66Met polymorphism among samples with schizophrenia. The bold solid line is survival curve for individuals with the Met/Met genotype; the thin solid lines is that for individuals with the Val/Val genotype; and the dotted lines is that for heterozygous individuals. Using the Kaplan–Meier method, survival curves for three genotypes were significantly different (log rank statistic: 7.51, $P = 0.023$).

equilibrium at this polymorphism. No association was found between genotype or allele frequency and sex. For our samples of schizophrenic patients, the mean onset ages were 27.5 ± 9.5 for BDNF Val/Val, 25.5 ± 7.4 for BDNF Val/Met and 22.9 ± 6.0 for BDNF Met/Met. Significant differences were observed among genotypes (log rank statistic: 7.51, $P = 0.023$) (Fig. 1). Met/Met homozygotes patients showed significantly earlier age at onset compared to Val/Val group. No significant sex effect was observed in the effect of the BDNF polymorphism on age at onset. The mean BPRS total scores were 42.5 ± 9.5 for BDNF Val/Val and 37.3 ± 9.9 for BDNF Val/Met, 42.4 ± 8.7 for BDNF Met/Met and were significantly different comparing these three genotypic groups ($P = 0.003$). The group of Val/Val showed higher BPRS total scores compared to the group of Val/Met ($P = 0.006$) as well as the group of Met carrier (38.7 ± 9.8; $P = 0.007$). In addition, the mean BPRS positive symptoms (the sum of the scores of conceptual disorganization, hallucinatory behavior, unusual thought content and grandiosity) showed a significant difference among three genotypic groups ($P = 0.032$), while the BPRS negative symptoms (the sum of the scores of emotional withdrawal, motor retardation, blunted affect and disorientation) showed a non-significant tendency ($P = 0.053$). With all schizophrenic patients, no significant differences were demonstrated in the BDNF genotype distributions between patients with positive and negative family history ($P = 0.21$). Neither chlorpromazine-equivalent dose nor the scores of the side effect scale, DIEPSS, showed significant Spearman's rank correlation with Met allele dose-dependency of BDNF Val66Met polymorphism ($P = 0.984$ and 0.702, respectively). No significant effects of sex or duration of illness were observed in the effect of the BDNF polymorphism on BPRS scores, chlorpromazine-equivalent dose and DIEPSS (Table 2).

We investigated the relationship between BDNF Val66Met gene polymorphism and clinical variables of schizophrenia. The

Table 2
Genotypes of the brain-derived neurotrophic factor Val66Met polymorphism and clinical symptoms of patients with chronic schizophrenia

BDNF genotypes	Val/Val		Val/Met		Met/Met	
	Male	Female	Male	Female	Male	Female
Age	53.6 ± 13.0	56.9 ± 11.4	53.3 ± 14.1	53.2 ± 12.2	51.5 ± 9.6	58.5 ± 12.9
	54.6 ± 12.6[a]		53.3 ± 13.6[a]		54.2 ± 11.3[a]	
Age at onset*	26.5 ± 9.5	30.2 ± 9.4	24.2 ± 6.4	29.8 ± 9.0	21.6 ± 4.9	25.0 ± 7.2
	27.5 ± 9.5[a]		25.5 ± 7.4[a]		22.9 ± 6.0[a]	
BPRS-positive* (N = 154)	11.0 ± 3.7	10.6 ± 3.7	9.2 ± 4.5	10.3 ± 2.5	12.7 ± 3.7	8.0 ± 3.1
	10.9 ± 3.7[a]		9.5 ± 4.1[a]		11.1 ± 3.9[a]	
BPRS-negative (N = 154)	12.4 ± 4.1	9.8 ± 3.4	10.5 ± 4.8	10.1 ± 3.7	12.4 ± 3.3	11.6 ± 3.7
	11.7 ± 4.1[a]		10.4 ± 4.5[a]		12.1 ± 3.4[a]	
BPRS-total* (N = 159)	44.2 ± 9.7	38.3 ± 7.8	37.2 ± 10.7	37.6 ± 6.8	44.6 ± 8.0	38.9 ± 9.0
	42.5 ± 9.5[a]		37.5 ± 9.9[a]		42.4 ± 8.7[a]	
DIEPSS	5.4 ± 5.0	3.1 ± 3.2	4.1 ± 3.9	3.8 ± 3.4	5.2 ± 1.8	4.3 ± 5.5
	4.8 ± 4.7[a]		4.0 ± 3.8[a]		4.9 ± 3.6[a]	
Daily neuroleptic dosage (mg/day)	773.3 ± 550.4	611.2 ± 383.5	733.2 ± 546.0	678.6 ± 353.6	951.3 ± 611.5	414.1 ± 344.0
	728.4 ± 512.0[a]		720.3 ± 505.4[a]		744.7 ± 531.4[a]	
Duration of hospitalization (year)	12.2 ± 10.7	13.1 ± 10.9	10.6 ± 12.0	10.2 ± 13.7	12.7 ± 11.8	19.5 ± 18.2
	12.4 ± 10.7[a]		10.5 ± 12.3[a]		15.3 ± 14.6[a]	
Positive first-degree family history (N = 33)	46%	6%	33%	0%	6%	9%
	52%		33%		15%	

BPRS: Brief Psychiatric Rating Scale; DIEPSS: Drug Induced Extra-Pyramidal Symptoms Scale.
[a] Male + female.
* $P < 0.05$.

genotypic frequency of BDNF Val66Met in our sample was almost the same as that of the precedent report of Japanese samples [16]. We report two major findings in this paper.

First, Met/Met homozygotes patients showed significantly earlier age at onset compared to Val/Val group by the Kaplan–Meier analyses (log rank statistic: 7.51, $P = 0.023$). Krebs et al. reported that BDNF gene dinucleotide (GT) repeat polymorphism was associated with the age at onset [15]. Although the definition of age at onset and the type of BDNF polymorphism were different between the two studies, both studies consistently suggest BDNF polymorphisms have an influence on the onset age. BDNF regulates growth and function of DA neurons [12] and interacts with the meso-limbic DA systems [1]. Egan et al. reported that rat hippocampal neurons transfected with the Met allele exhibit abnormal intracellular trafficking and regulated secretion of BDNF in comparison with those transfected with the Val allele [7]. Pezawas et al. found bilateral reductions of hippocampal gray matter volumes in Met carriers compared with Val/Val subjects [21]. BDNF gene with Met allele of BDNF Val66Met polymorphic region might affect the structure and function of the DA neuronal systems.

Secondly, the BPRS total and positive scores showed significant differences among the three BDNF Val66Met polymorphism groups ($P = 0.003$ and 0.032, respectively). Contrary to our prediction, however, the group of Val/Val showed significantly higher BPRS total scores compared to the group of Val/Met ($P = 0.006$) as well as the group of Met carrier ($P = 0.007$). Our subjects are chronic hospitalized patients who have been treated with antipsychotics for long years. Therefore, it is suggested that patients with Val/Val genotype have more positive and other symptoms that are refractory to antipsychotic treatment compared to Met carriers. Patients with Val/Val genotype may be more likely to become treatment-resistant schizophrenia. With this regard, it is interesting that Val/Val genotype has been reported to be over-represented in responders to clozapine [11], a drug that is effective to reduce both positive and negative symptoms in treatment-resistant schizophrenia [3,14]. It would be of value to re-assess BPRS scores after the introduction of clozapine into Japanese market. Indeed, one problem in correlating the genotypes with the level of symptoms is that the latter is a changeable variable but not a lifetime variable. Although most of our patients show little or small fluctuations in their symptoms under long-term antipsychptic treatment, some relatively new patients may still change their symptoms in response to treatment. However, a significant association between the BDNF genotype and the BPRS scores was still observed even when patients who were hospitalized less than 1 year were excluded from the analysis (data not shown). It is necessary to see if the association between the BDNF genotypes and clinical symptoms is confounded by the association between the genotypes and age at onset because age at onset itself is well known to influence severity of schizophrenia [19]. A significant association between BPRS scores and BDNF Val66Met genotypes was found even after the effect of age at onset was adjusted by multiple comparisons ($P = 0.011$). No significant effects of duration of illness were observed in the effect of the BDNF polymorphism on BPRS scores. DIEPSS did not show significant Spearman's rank correlation with Met allele dose-dependency of BDNF Val66Met polymorphism. Liou et al. [17] recently reported that neither the DRD3 nor the BDNF-

Val66Met genotypes and alleles were associated with tardive dyskinesia occurrence in schizophrenic patients [17].

We examined BDNF Val66Met polymorphism because this polymorphism is known to be the only functional polymorphism of BDNF gene. Since other common polymorphisms of BDNF, the dinucleotide repeat polymorphism (GT)n in the promoter region and the –270C/T polymorphism, have already been reported [15,26,27], investigation of the relationship between the other BDNF polymorphisms and clinical variables is needed.

In summary, our finding suggests that the BDNF gene Val66Met polymorphism is related to the onset age of schizophrenia and also influences to the levels of clinical symptoms that are refractory to long-term ordinary antipsychotic treatment. Larger studies will be needed to confirm these results.

Acknowledgements

The authors would like to thank to the doctors who helped us to take clinical data and blood samples in all the mental hospitals (Aizato Hospital, Akita Hospital, Fujii Hospital, Jounan Hospital, Jousei Hospital, Kawauchi Hospital, Kyouritsu Hospital, Nankai hospital and Tokushima University Hospital). The authors would like to thank Mrs. Akemi Okada for her technical assistance. This work was supported by a Health and Labor Science Research Grant from the Japanese Ministry of Health, Labor and welfare, a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology and a Grant-in-Aid for Scientific Research from the 21st Century COE program, Human Nutritional Science on Stress Control, Tokushima, Japan.

References

[1] C.A. Altar, N. Cai, T. Bliven, M. Juhasz, J.M. Conner, A.L. Acheson, R.M. Lindsay, S.J. Wiegand, Anterograde transport of brain-derived neurotrophic factor and its role in the brain, Nature 389 (1997) 856–860.

[2] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, fourth ed., American Psychiatric Press, Washington, DC, 1994.

[3] R.W. Buchanan, Clozapine: efficacy and safety, Schizophr. Bull. 21 (1995) 579–591.

[4] Q.Y. Chen, Q. Chen, G.Y. Feng, C.L. Wan, K. Lindpaintner, L.J. Wang, Z.X. Chen, Z.S. Gao, J.S. Tang, X.W. Li, L. He, Association between the brain-derived neurotrophic factor (BDNF) gene and Schizophrenia in the Chinese population, Neurosci. Lett., in press.

[5] Z.Y. Chen, P.D. Patel, G. Sant, C.X. Meng, K.K. Teng, B.L. Hempstead, F.S. Lee, Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons, J. Neurosci. 24 (2004) 4401–4411.

[6] N. Durany, T. Michel, R. Zochling, K.W. Boissl, F.F. Cruz-Sanchez, P. Riederer, J. Thome, Brain-derived neurotrophic factor and neurotrophin-3 in schizophrenic psychoses, Schizophr. Res. 52 (2001) 79–86.

[7] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell 112 (2003) 257–269.

[8] O. Guillin, N. Griffon, E. Bezard, L. Leriche, J. Diaz, C. Gross, P. Sokoloff, Brain-derived neurotrophic factors controls dapamine D3 receptor expression: therapeutic implications in Parkinson's disease, Eur. J. Pharmacol. 480 (2003) 89–95.

[9] D. Hall, A. Dhilla, A. Charalambous, J.A. Gogos, M. Karayiorgou, Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive-compulsive disorder, Am. J. Hum. Genet. 73 (2003) 370–376.

[10] C.-J. Hong, H.-C. Liu, T.-Y. Liu, C.-H. Lin, C.-Y. Cheng, S.-J. Tsai, Brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in Parkinson's disease and age of onset, Neurosci. Lett. 353 (2003) 75–77.

[11] C.-J. Hong, Y.W.-Y. Yu, C.-H. Lin, S.-J. Tsai, An association study of a brain-derived neurotrophic factor Val66Met polymorphism and clozapine response of schizophrenic patients, Neurosci. Lett. 349 (2003) 206–208.

[12] C. Hyman, M. Hofer, Y.A. Barde, M. Juhasz, G.D. Yancopoulos, S.P. Squinto, R.M. Lindsay, BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra, Nature 350 (1991) 230–232.

[13] T. Inada, G. Yagi, Current topics in neuroleptic-induced extrapyramidal symptoms in Japan, Keio J. Med. (1996) 95–99.

[14] J. Kane, G. Honigfeld, J. Singer, H. Meltzer, the Clozaril Collaborative Study Group, Clozapine for the treatment-resistant schizophrenic, Arch. Gen. Psychiatry 45 (1988) 789–796.

[15] M.O. Krebs, O. Guillin, M.C. Bourdell, J.C. Schwartz, J.P. Olie, M.F. Poirier, P. Sokoloff, Brain-derived neirotrophic factor (BDNF) gene variants association with age at onset and therapeutic response in schizophrenia, Mol. Psychiatry 5 (2000) 558–562.

[16] H. Kunugi, Y. Iijima, M. Tatsumi, M. Yoshida, R. Hashimoto, T. Kato, K. Sakamoto, T. Fukunaga, T. Inada, T. Suzuki, No association between the Val66Met polymorphism of the brain-derived neurotrophic factor gene and bipolar disorder in a Japanese population: a multicenter study, Biol. Psychiatry 56 (2004) 376–378.

[17] Y.J. Liou, D.L. Liao, J.Y. Chen, Y.C. Wang, C.C. Lin, Y.M. Bai, S.C. Yu, M.W. Lin, I.C. Lai, Association analysis of the dopamine D3 receptor gene ser9gly and brain-derived neurotrophic factor gene val66met polymorphisms with antipsychotic-induced persistent tardive dyskinesia and clinical expression in Chinese schizophrenic patients, Neuromol. Med. 5 (2004) 243–251.

[18] P.C. Maisonpierre, M.M. Le Beau, R. Espinosa IIIrd, N.Y. Ip, L. Belluscio, S.M. de la Monte, S. Squinto, M.E. Furth, G.D. Yancopoulos, Human and rat brain-derived neurotrophic factor and neurotrophin-3: Gene structures, distribution and chromosomal localizations, Genomics 10 (1991) 558–568.

[19] A.K. Malla, R.M.G. Norman, R. Manchanda, M.R. Ahmed, D. Scholten, R. Harricharan, L. Cortese, J. Takhar, One year outcome in first episode psychosis: influence of DUP and other predictors, Schizophr. Res. 54 (2002) 231–242.

[20] J.F. Overall, D.R. Gorham, The Brief Psychiatric Rating Scale, Psychol. Rep. 10 (1962) 799–812.

[21] L. Pezawas, B.A. Verchinski, V.S. Mattay, J.H. Callicott, B.S. Kolachana, R.E. Straub, M.F. Egan, A. M-Lindenberg, D.R. Weinberger, The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology, J. Neurosci. 24 (2004) 10099–10102.

[22] M. Ribases, M. Gratacos, L. Armengol, R. De Cid, A. Badia, L. Jimenez, R. Solano, J. Vallejo, F. Fernandez, X. Estivill, Met66 in the brain-derived neurotrophic factor (BDNF) precursor is associated with anorexia nervosa restrictive type, Mol. Psychiatry 8 (2003) 745–751.

[23] A. Rosa, M.J. Cuesta, M. Fatjo-Vilas, V. Peralta, A. Zarzuela, L. Fananas, The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: evidence from a family-based association study, Am. J. Med. Genet. B Neuropsychiatr. Genet. 141 (2006) 135–138.

[24] R. Segman, T. Neeman, U. Heresco-Levy, B. Finkel, L. Karagichev, M. Schlafman, A. Dorevitch, A. Yakir, A. Lerner, A. Shelevoy, B. Lerer, Genotypic association between the dopamine D3receptor and tardive dyskinesia in chronic schizophrenia, Mol. Psychiatry 4 (1999) 247–253.

[25] P. Sklar, S.B. Gabriel, M.G. McInnis, P. Bennett, Y.-M. Lim, G. Tsan, S. Schaffner, G. Kirov, I. Jones, M. Owen, N. Craddock, J.R. DePaulo, E.S. Lander, Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus, Mol. Psychiatry 7 (2002) 579–593.

[26] A. Szczepankiewicz, M. Skibinska, P.M. Czerski, P. Kapelski, A. Leszczynska-Rodziewicz, A. Slopien, M. Dmitrzak-Weglarz, F. Rybakowski, J. Rybakowski, J. Hauser, No associaton of the brain-derived neurotrophic factor (BDNF) gene C-270T polymorphism with schizophrenia, Schizophr. Res. 76 (2005) 187–193.
[27] G. Szekeres, A. Juhasz, A. Rimanoczy, S. Keri, Z. Janka, The C270T polymorphism of the brain-derived neurotrophic factor gene is associated with schizophrenia, Schizophr. Res. 65 (2003) 15–18.
[28] M. Takahashi, O. Shirakawa, K. Toyooka, N. Kitamura, T. Hashimoto, K. Maeda, S. Koizumi, K. Wakabayashi, H. Takahashi, T. Someya, H. Nawa, Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients, Mol. Psychiatry 5 (2000) 293–300.
[29] J. Thome, P. Foley, P. Riederer, Neurotrophic factors and the maldevelopmental hypothesis of schizophrenia psychoses, J. Neural Transm. 105 (1998) 85–100.