respectively, OPw can be defined by the following equation with reference to equation 9:

$$OPw = ED50 \times (Rt/OAw) \quad (10)$$

Equation 10 indicates that the width of the optimal plasma level is proportional to the D2 density, as OAw is constant. Therefore, the dose range is smaller in cases of lower density; that is, the width becomes half when the density becomes half.

In this simulation, we did not take account of such factors as the dissociation rate constant of the drugs from D2 receptors, the blood-brain permeability of the drugs, or the regional cerebral blood flow. Furthermore, the OOc may be associated with the D2 densities of the nucleus accumbens and striatum. If the regional ratio of the D2 density in the striatum to that in the nucleus accumbens is very low compared with that in normal individuals, no dose of antipsychotics will be able to control psychotic symptoms without induction of EPS.

APPLICATION OF THE PRESENT FINDINGS TO CLINICAL SETTINGS

Late-Onset Psychosis (LOP)

One of the reported clinical features of antipsychotic treatment of LOP is that even a very low dose of antipsychotics easily induces EPS, which disappears for a prolonged time period after discontinuation of antipsychotics.[21,32,33] Here, LOP is considered to be associated with low D2 density. The present study suggests that an increase of antipsychotic dose readily increases the occupancy and decreases the number of available D2 receptors, thereby increasing the risk of EPS in patients with low D2 density. Furthermore, the reduction of the plasma level is slight during a given time period and the number of available D2 receptors increases slowly in these patients, leading to the prolongation of disappearance of EPS. These features of low D2 density are consistent with those of LOP. Therefore, antipsychotics, which can be carefully used in very low doses, should be chosen in patients with LOP. Furthermore, antipsychotics with a short plasma elimination half-life and high dissociation constants may be selected to avoid prolongation of EPS after discontinuation. Antipsychotics whose actions correspond to the "fast-off-D2" theory, that is, antipsychotics that occupy D2 receptors transiently and dissociate rapidly,[34] may also be recommended.

Dopamine Supersensitivity Psychosis (DSP)

Proposed Clinical Features and the Present Findings

The present findings well account for the proposed features of DSP (Table 1).[35,36] If patients with DSP have up-regulated D2 density owing to overblockade of dopamine transmission, they may have a history of EPS and/or presence of TD, suggesting that TD can be used as a predictive factor. They generally receive high doses of antipsychotics to achieve a raised OOc and control their psychotic symptoms and thus are at risk for development of tolerance to antipsychotics. Furthermore, as they receive higher doses of anti psychotics, a reduction or discontinuation of antipsychotics may induce a larger increase in the number of available D2 receptors for dopamine binding during the same period in patients with DSP than in those with standard or low D2 density, when the elimination half-life of the drug is the same, that is, acute relapse or exacerbation of psychosis occurs after dose reduction or discontinuation of antipsychotics. On the other hand, stress increases dopamine levels in the brain[37] and the same level of dopamine may bind to more D2 receptors in competition with preexisting antipsychotics in cases in which D2 density is up-regulated (Fig. 1), leading to vulnerability to minor stress. These facts may increase the risk of appearance of relapse or exacerbation of psychosis.[38,39]

Prevention and Treatment of DSP

One of the predictors for development of TD is the appearance of EPS in the early phase of antipsychotic treatment.[39,40] It has been reported that the incidence of EPS and TD is lower by administration of SGAs than FGAs,[41] although the incidence rate of new-onset TD varies among patients with SGAs.[42] One of the common features of SGAs is high affinity for serotonin 2A (5-HT2A) receptors as antagonists in the brain, which may reduce inducibility of EPS.[43] Therefore, antipsychotics with high affinity for 5-HT2A may have low inducibility of EPS compared with D2 antagonists without high affinity for 5-HT2A. On the other hand, OOc is generally determined by appearance of the EPS for the upper limit and treatment response to psychotic symptoms for the lower limit.[9,27] Ideally, one of the characteristic adverse effects of an excessive blockade of D2 receptors in the nucleus accumbens is reported to be dysphoria.[44,45] Antipsychotics-induced dysphoria may be one of the clinical indicators of the upper limit of the OOc for prevention of developing DSP. Furthermore, SGAs are reported to be less likely to elicit dysphoric responses.[46] Taken together, these facts indicate that SGAs may be better for prevention of development of DSP than FGAs.

The present study indicates that the length of the plasma elimination half-life of an antipsychotic drug affects the risks of appearance and exacerbation of psychotic symptoms in DSP. Antipsychotics with a long plasma elimination half-lives, or dosage forms with extended release, that is, those using osmotic drug release technology,[47] and long-acting injectable antipsychotics[48] may be recommended to treat patients with DSP, if used at the appropriate dosage. Furthermore, to prevent stress-induced dopamine from replacing antipsychotics for binding to D2 receptors, antipsychotics with relatively high affinity for D2 receptors may be useful to prevent the exacerbation of psychosis in patients with DSP. In fact, we found that long-acting injection of risperidone and/or extended-release paliperidone showed dramatic efficacy in patients with treatment-resistant DSP (in preparation).[49]

Our previous preclinical study[19] suggested that chronic treatment with dopamine partial agonists might reverse dopamine super sensitivity and then ameliorate the conditions that readily induce DSP. However, under a dopamine supersensitive state, dopamine agonistic effects may easily induce DSP during the treatment, as aripiprazole may bind more D2 receptors and elicit larger agonistic effects. In fact, it has been reported that aripiprazole carries risks for the induction of transient DSP.[50] From this point of view, aripiprazole may be added to the existing antipsychotics and titrated gradually from a very small dose to avoid exacerbation of psychosis in patients with DSP.

CONCLUSION

We estimated an OOc under the assumption that the optimal range of the number of D2 receptors available for dopamine binding is constant whereas D2 density changes. We found that either the optimal plasma level or the OOc changed in correspondence with changes in the D2 density. These results

suggest that a higher antipsychotic dose is needed in cases of higher D2 density and that the reduction of the plasma level will be larger within the same time period, which may have greater effects on the exacerbation of psychosis, in cases of higher D2 density. On the other hand, a lower dose of an antipsychotic drug could be used for optimal treatment in cases of lower D2 density, and a reduction of the plasma level of antipsychotics is smaller during a certain time period, which may prolong disappearance of EPS after discontinuation of the drug, in cases of lower D2 density. The results well account for the proposed clinical features of DSP or LOP. It is suggested that SGAs with a long plasma elimination half-life or in a long-acting injectable form may be recommended if used within the proper dosage in treatment of DSP. On the other hand, low doses of antipsychotics with low affinity for D2 receptors and a short plasma elimination half-life are recommended for the treatment of LOP. Preclinical studies suggest that dopamine partial agonists may decrease up-regulated D2 density and thereby ameliorate dopamine supersensitivity.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Orbitofrontal cortex abnormality and deficit schizophrenia

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ABSTRACT

Deficit syndrome, which is characterized by primary and enduring negative symptoms, is a homogeneous subtype within schizophrenia. Negative symptoms in schizophrenia are currently considered to be closely linked with frontal lobe impairment. However, the etiology in the frontal lobe of people with deficit syndrome is not fully understood. We measured regional cerebral blood flow (rCBF) with single photon emission computed tomography (SPECT) in 33 patients with deficit syndrome, 40 patients with nondeficit syndrome, and 45 healthy controls, and we compared groups using the voxel-wise method. Schizophrenia combined group, the deficit syndrome and the nondeficit syndrome presented hypoperfusion in mainly the medial and lateral prefrontal cortices. The deficit syndrome group showed a significant decrease in rCBF in the right orbitofrontal cortex (OFC) compared to the nondeficit group. These results demonstrated that at-rest hypofrontality was a common feature within the disease group and suggested that the OFC might play an important role in the development of severe negative symptoms in people with deficit syndrome.

1. Introduction

Schizophrenia is a syndrome or disorder comprising several subtypes of disease with high heterogeneity (Carpenter and Kirkpatrick, 1988; Tandon et al., 2009). Deficit syndrome (Carpenter et al., 1988) is characterized by primary and enduring negative symptoms which have been present for the preceding 12 months, always with clinical stability. The syndrome is generally considered to be a clinically homogeneous subtype of schizophrenia based on empirical and symptomatological findings. As compared to nondeficit schizophrenia, deficit syndrome is associated with earlier disease onset (Kopelowicz et al., 2000), poorer social prognosis (Strauss et al., 2010), and broader cognitive deficits (Cohen et al., 2007), as well as more evident negative symptoms. Furthermore, several symptomatological studies have revealed that the degree of positive symptoms in patients with deficit syndrome was equal to or slightly weaker than that in those with nondeficit syndrome (Kirkpatrick et al., 1993; Cohen et al., 2010), and the state of illness in those with deficit syndrome remains very stable from 5 years (Fenton et al., 1994) to 20 years (Strauss et al., 2010) after the initial diagnosis.

Several neuroimaging studies have examined frontal impairment in the brains of patients with schizophrenia and found that negative symptoms were closely related with frontal lobe dysfunction (Semkovska et al., 2001; Roth et al., 2004). Interestingly, however, most MRI studies on deficit syndrome failed to demonstrate a significant prefrontal volume reduction in people with deficit syndrome relative to those with nondeficit syndrome, while significantly smaller volume in the prefrontal cortex of patients with deficit syndrome was observed compared with the volume in normal controls (Buchanan et al., 1993; Quarantelli et al., 2002; Galderisi et al., 2008). Only two reports have described findings of greater CSF space in the temporal lobe (Turetsky et al., 1995) and of several smaller brain regions including the frontal lobe (Cascella et al., 2010), in patients with deficit syndrome than in those with nondeficit syndrome. This sequence of findings suggests that the neuronal substrates of deficit syndrome are not sufficiently understood, while the clinical manifestations of deficit syndrome assume distinctive characteristics.

In functional neuroimaging studies with PET and SPECT, at-rest rCBF or regional glucose metabolism ratio (rGMR) in the prefrontal cortex of the patients with schizophrenia have repeatedly been reported to be reduced (Davidson and Heinrichs, 2003; Hill et al., 2004). In addition, negative symptoms were found to have a negative relationship with rCBF or rGMR in the prefrontal cortex (Liddle et al., 1992; Wolkin et al., 1992; Schröder et al., 1996; Erkwoh et al., 1997), although some studies failed to confirm the relationship (Vita et al., 1995; Min et al., 1999). Three previous studies (Tamminga et al., 1992; Vaiva et al., 2002; Gonul et al., 2003) measured rCBF in deficit syndrome, and used the region of interest (ROI) method with SPECT. One of these studies revealed

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significantly hypoperfused regions in the bilateral dorsolateral prefrontal cortex (DLPFC) in people with deficit syndrome compared to those with nondeficit syndrome (Vaiva et al., 2002). Another showed a significant decrease in rCBF in the right superior and inferior frontal gyri in patients with deficit syndrome relative to those with nondeficit syndrome and normal controls (Gonul et al., 2003). However, the report by Vaiva et al. did not include a normal healthy control group, and the report by Gonul et al. revealed no differences in any regions between a nondeficit syndrome group and normal controls. The other study by Tamminga et al. (1992) had a small sample size ($N=4$ patients with deficit syndrome). Therefore, neither of these studies indicated that the observed hypoperfused regions reflected findings of schizophrenia itself, nor did either study provide conclusive findings specific to deficit syndrome. In order to address these inconsistent findings among the three groups (i.e., the deficit syndrome, nondeficit schizophrenia and normal groups), researches with larger sample size and analysis covering the whole brain are needed.

In this study, we first compared rCBF by voxel-based analysis and examined the relationship between deficit syndrome and each prefrontal region within patients' brains. Our hypothesis is that both deficit and nondeficit schizophrenia exhibit significant hypoperfusion in the prefrontal region relative to normal controls. In addition, we suggest that a more profound hypoperfusion is observed in the prefrontal lobe in patients with deficit syndrome than in those without it.

2. Materials and methods

2.1. Subjects

The study protocol was approved by the ethics committee of Chiba University. Written informed consent was obtained from all participants after they had been provided with a detailed explanation of the study procedures. All participants were Japanese speakers. All patients were recruited from the outpatient or inpatient settings of Chiba University Hospital and were determined to meet the criteria for schizophrenia according to the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). From April 2005 to December 2009, we included patients in this study, provided they approved of the enrollment. Deficit schizophrenia was defined according to the Schedule for Deficit Syndrome (Kirkpatrick et al., 1989). Each patient was diagnosed with either the deficit or nondeficit type of schizophrenia by a trained psychiatrist (N.K.), based on a direct interview and medical records. In particular, secondary negative symptoms due to depression/anxiety, parkinsonism and mental retardation were excluded through careful examination and assessment. As a result, 33 cases were assigned to the deficit schizophrenia group, and 40 cases to the nondeficit schizophrenia group (Table 1).

As regards pharmacotherapy, the dose of neuroleptics was fixed for at least 4 weeks prior to SPECT scanning. In both groups, most patients were taking atypical antipsychotics, and the two disease groups exhibited similar distributions across classes of antipsychotics. The chlorpromazine-equivalent dose (CP-dose) in the deficit group was significantly higher than that in the nondeficit group (Table 1).

Forty-five normal healthy controls from our own SPECT normal database were also enrolled, and these subjects were statistically matched in terms of age and sex with the participants in the two illness groups. All control subjects were free from any Axis I or II psychiatric disorder, based on the Structured Clinical Interview for DSM-IV Non-patient Edition (SCID-NP; Table 1).

Exclusion criteria for all three groups were a history of loss of consciousness, organic brain disorder, past alcohol/drug abuse, present pregnancy, or a history of any physical disease on the basis of medical interviews, physical examinations, brain MRI, and laboratory data. Patients' clinical symptoms were assessed using the 18-item Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1964). BPRS item scores ranged from 1 to 7, where the positive symptom level was defined by the sum of four items (#4 conceptual disorganization, #11 suspiciousness, #12 hallucinations, and #15 unusual thought content), and the negative symptom level was defined by the sum of three items (#3 emotional withdrawal, #13 motor retardation, and #16 blunted affect). Further, we defined the sum of four items (#2 anxiety, #5 guilty, #9 depression, and #10 hostility) as the emotional score. These four items are generally used as a proxy for deficit syndrome (Kirkpatrick et al., 1993) in order to exclude the possibility of secondary negative symptoms. In addition, Calgary Depression Scale for Schizophrenia (CDSS; Japanese version; Kaneda et al., 2000) was also evaluated. Drug-induced extrapyramidal symptoms (EPS) were assessed according to Drug-Induced Extra-Pyramidal Symptoms Scale (DIEPSS; Inada, 2009) by a qualified author (N.K.). There were no patients with moderate or high levels of EPS. Concurrently, the shortened version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), which included knowledge, picture completion, and digit span forward/backward, was performed to estimate IQ. Handedness was defined according to the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2. SPECT scanning procedure

The procedure used for SPECT scanning was described in detail in our previous report (Kanahara et al., 2009). Briefly, after measurement of their vital signs, the subjects were examined in a supine resting position with their eyes closed in a silent room. The subjects were injected with 111 MBq of ^{123}I-IMP in the antecubital vein, and scanning was initiated 30 min after the bolus injection.

2.3. Image analysis and statistical analysis

All of the image analysis processes were performed using the Statistical Parametric Mapping 5 software (SPM5) included with Matlab version 7.5 (Mathworks, Natick, MA). We performed two comparisons, i.e., one between the deficit group and normal controls, and the other between the nondeficit group and normal controls. Furthermore, in order to examine the characteristic rCBF pattern in deficit syndrome, we conducted a comparison between the deficit and the nondeficit group. Age, CP-dose, and duration of illness were included as the covariates, because age and CP-dose potentially exert effects on rCBF in the brain and also because CP-dose and the duration of illness differed significantly between our deficit and nondeficit groups.

Using the Z-statistic on a voxel-by-voxel basis, we identified voxels in which the corresponding effect was significant. Only those clusters are reported that passed a family-wise error (FWE)-corrected significance threshold of $p<0.05$ at the voxel level and a corrected threshold of $p<0.05$ at the cluster level. The anatomical location of each cluster was identified based on the voxel of peak significance.

3. Results

The two illness groups have similar backgrounds with respect to age, sex distribution, age at disease onset, years of education, and estimate IQ (Table 1). However, the duration of illness in the deficit group was statistically longer than that in the nondeficit group ($p<0.01$). Furthermore, although the positive symptom scores did not differ between the two groups, the negative symptom and total scores were significantly different ($p<0.001$ and $p<0.05$, respectively). The emotional scores, CDSS and DIEPSS did not differ between the two groups (Table 1).

3.1. Schizophrenia (combined group) vs. normal controls

The cluster-level analysis ($p_{corrected}<0.05$) showed that hypoperfused regions in patients with schizophrenia (i.e., patients in both the deficit and nondeficit groups) were observed in two clusters as compared to normal controls; one cluster was in the right lateral prefrontal cortex

Table 1
Demographic characteristics of the groups.

Clinical valuables	Deficit schizophrenia	Nondeficit schizophrenia	Normal control	Statistical values
Male/female	26/7	23/17	27/18	N.S.[a] ($p=0.09$; chi-square)
Age	35.0 (8.5)	31.2 (9.1)	34.8 (12.0)	N.S.[a] (ANOVA)
(range)	19–56	16–64	18–57	
Handedness (L/R)	0/33	2/38	1/44	N.S.[a] (chi-square)
Duration of illness (year)	13.0 (7.7)	7.4 (7.8)		<0.01
Age at onset	22.1 (5.8)	23.7 (5.6)		N.S.
Years of education	12.9 (2.4)	14.0 (2.4)	15.0 (2.4)	<0.01[b] (ANOVA), DefSZ<NC
Dose of antipsychotics[c]	766.4 (481.4)	351.6 (358.2)		<0.001
(range)[c]	0–1500	0–1200		
Free	4	11		N.S.[d] (chi-square)
Risperidone (range)	12 (4–12 mg)	17 (2–12 mg)		
Olanzapine (range)	8 (5–20 mg)	8 (5–20 mg)		
Aripiprazole (range)	1 (30 mg)	1 (30 mg)		
Quetiapine (range)	5 (200–1000 mg)	1 (600 mg)		
Perospirone (range)	2 (24 mg)	1 (4 mg)		
Haloperidol (range)	1 (9 mg)	1 (4.5 mg)		
BPRS total	41.1 (9.7)	35.5 (11.5)		<0.05
Positive symptoms[e]	10.0 (4.0)	9.8 (5.0)		N.S.
Negative symptoms[f]	10.0 (2.2)	5.3 (2.9)		<0.001
Emotional score[g]	7.0 (2.3)	7.2 (2.7)		N.S.
CDSS	1.9 (3.2)	1.3 (1.9)		N.S.
DIEPSS	3.3 (1.4)	3.1 (1.6)		N.S.
Estimate IQ	82.8 (22.5)	88.9 (25.5)		N.S.

All values show the mean and the standard deviation of the mean (parenthesis) in individual item.
[a] Not significant in comparisons between the three groups.
[b] Significant in comparison between deficit and normal groups by Bonferroni correction following ANOVA.
[c] Corresponding to daily chlorpromazine dose (mg).
[d] Not significant in rate of antipsychotics free patients between deficit and nondeficit groups.
[e] BPRS positive scores consist of those of conceptual disorganization, suspiciousness, hallucinations and unusual thought content.
[f] BPRS negative scores consist of those of emotional withdrawal, motor retardation and blunted affect.
[g] BPRS emotional scores consist of anxiety, guilty, depression and hostility.

(LPFC) and the other was in the bilateral medial prefrontal cortex (MPFC)/LPFC extending to the left temporal lobe (Fig. 1, Table 2). The peak Talairach coordinates were $x=8$, $y=43$ and $z=6$ (Z score = 6.44) in the right anterior cingulate cortex (ACC).

On the other hand, there was no hypoperfused region in the normal controls as compared to the schizophrenia combined group.

3.2. Deficit/nondeficit schizophrenia vs. normal controls

Hypoperfused regions in each the deficit schizophrenia group and the nondeficit schizophrenia group compared with normal controls are shown in Fig. 2 and Table 2. Both cluster-level analysis ($p_{corrected}<0.05$) revealed only one significant cluster, including the bilateral ACC, the right OFC (orbital cortex and inferior frontal cortex), the right LPFC (middle/inferior frontal gyrus and insula). The deficit schizophrenia presented also significantly decreased region in the right superior temporal gyrus (STG).

On the other hand, there was no hypoperfused region in the normal controls as compared to the deficit schizophrenia and the nondeficit schizophrenia group.

3.3. Deficit schizophrenia vs. nondeficit schizophrenia

3.3.1. Comparison between the two groups with age/illness duration/CP-dose as covariates

The significant hypoperfused regions in deficit schizophrenia compared to nondeficit schizophrenia are shown in Fig. 3 and Table 2. The cluster-level analysis ($p_{corrected}<0.05$) revealed a significantly decreased rCBF in the right OFC and the right (anterior part of) insula in the deficit group compared to the nondeficit group. The peak coordinates in the cluster were $x=45$, $y=30$, $z=-20$ (Z score = 4.62) and were located in the right OFC. On the other hand, our SPM analysis revealed no significantly decreased region in rCBF in the nondeficit group compared to the deficit group.

Additionally, when we conducted an exploratory analysis for drug-free patients (deficit group, $N=4$: nondeficit group, $N=11$) despite of small sample, no significant aberrant region ($p_{uncorrected}<0.001$ in cluster-level) was observed between the two groups.

3.3.2. Comparison between the two groups with negative symptoms and factors in Section 3.3.1 as covariates

In order to exclude the possibility that a high score on negative symptoms, rather than actual deficit syndrome, contributed to the decreased rCBF in the OFC in deficit syndrome, we again performed a comparison including negative symptoms as well as the original three factors (i.e., age, CP-dose and illness duration) within covariates. The results showed that, in the cluster-level analysis ($p_{uncorrected}<0.05$), two clusters in the right OFC remained as significantly hypoperfused regions in our deficit group as compared to our nondeficit group (data not shown).

3.4. Negative symptoms and rCBF in schizophrenia (combined group)

There were bilateral frontal and temporal regions with a significant negative relationship between negative symptoms and rCBF in the combined group in multiple regression with age and CP-dose and illness duration as nuisance covariates ($p_{uncorrected}<0.05$; peak coordinates: $x=-34$, $y=5$, and $z=-46$ with a Z score = 3.97, located in the left STG).

On the other hand, there were no regions with a positive relationship between negative symptoms and rCBF.

4. Discussion

There were two main findings of the present study. First, both the deficit and nondeficit groups exhibited significant hypoperfusion in the bilateral ACC, the right LPFC, the OFC, and the insula, and similar patterns were observed between the groups in terms of the distribution and extent of rCBF reduction, as compared with normal controls.

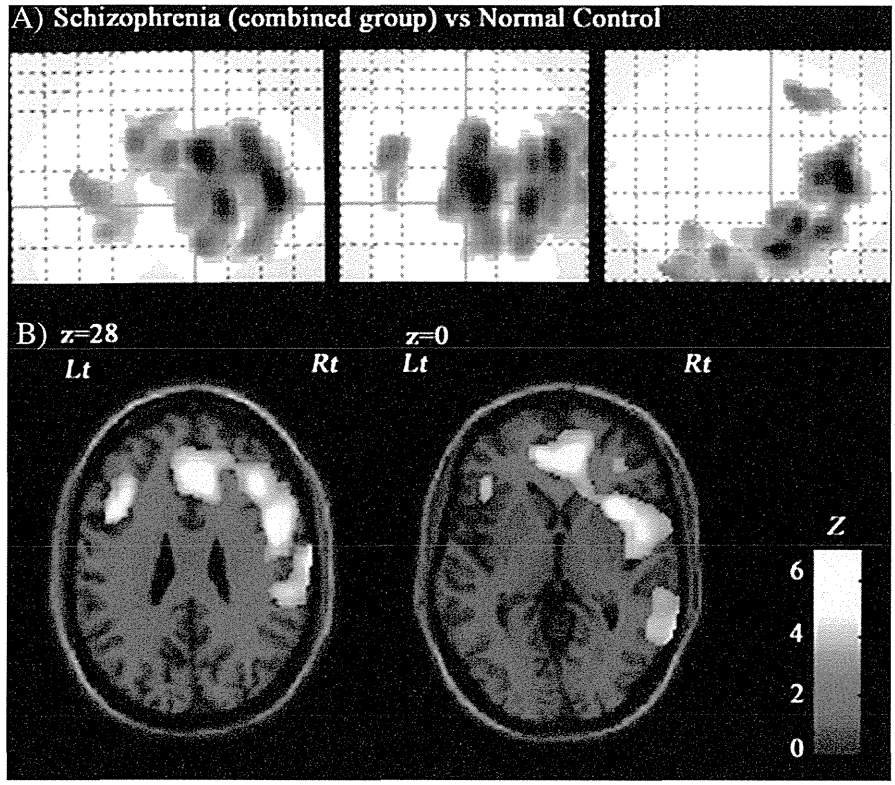

Fig. 1. The regions with significantly decreased rCBF ($p<0.05$, corrected) in the combined schizophrenia group ($N=73$) compared with the normal controls ($N=45$). A) The glass brain, and B) the MRI templates show the main hypoperfused regions, which were the bilateral MPFC, LPFC and the left temporal regions.

The other major finding was that compared to the nondeficit group, the deficit group showed significant rCBF reduction only in the right OFC and anterior part of the insula. One might assume that the latter finding do not necessarily reflect homogeneity of deficit syndrome; this result could be related to just high negative symptoms. Thus an additional comparison, in which negative symptoms were included as covariates in addition to other factors, was conducted. The result showed significant hypoperfusion in the frontal cortex including OFC in the deficit group. As far as we know, the present study is the first to identify abnormality in the OFC in people with deficit syndrome, whereas three previous studies found no rCBF/rGMR reduction in the OFC of patients with the deficit syndrome (Tamminga et al., 1992; Vaiva et al., 2002; Gonul et al., 2003). Although these previous reports did not find abnormality in the OFC in the deficit

Table 2
Significant decreased regions in each comparison.

Cluster-level		Voxel-level						Corresponding cortex
$p_{corrected}$	k_E	$p_{FWE\text{-}corr}$	T	(Z)	x	y	z	
1. Schizophrenia (combined group) vs. normal controls								
Schizophrenia (combined group)<normal controls								
0.000	17,999	0.000	7.09	6.44	8	43	6	Rt anterior cingulate cortex
		0.000	6.80	6.22	50	5	23	Rt inferior frontal cortex
		0.000	6.29	5.82	36	16	−1	Insular
0.002	1136	0.009	5.09	4.82	−42	15	21	Lt middle frontal cortex
2. Deficit schizophrenia vs. normal controls								
Deficit schizophrenia<normal controls								
0.000	7281	0.000	6.52	5.78	6	43	5	Rt anterior cingulate cortex
		0.007	5.38	4.93	48	2	−2	Rt superior temporal cortex
		0.007	5.37	4.92	16	30	−20	Rt orbitofrontal cortex
3. Nondeficit schizophrenia vs. normal controls								
Nondeficit schizophrenia<normal controls								
0.000	7641	0.000	6.23	5.61	−12	46	−6	Lt anterior cingulate cortex
		0.001	5.87	5.34	12	43	5	Rt anterior cingulate cortex
		0.003	5.54	5.08	26	9	−13	Rt inferior frontal cortex
4. Deficit schizophrenia vs. nondeficit schizophrenia								
Deficit schizophrenia<nondeficit schizophrenia								
0.002	1259	0.020	5.03	4.62	45	30	−20	Rt orbitofrontal cortex

Coordinates were converted from MNI to Talairach space with Ginger ALE. Anatomic labels were based on Talairach client using a nearest gray-matter search.

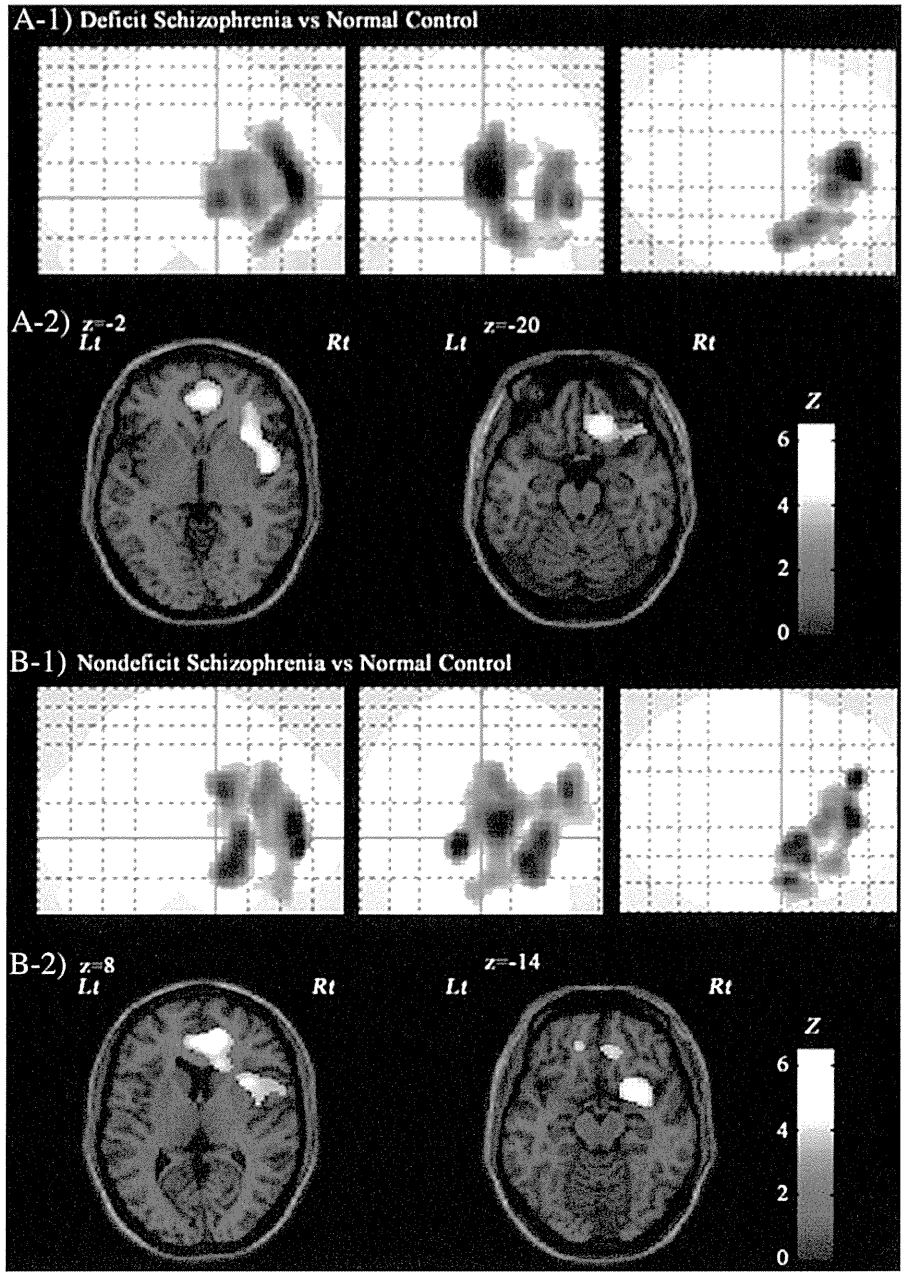

Fig. 2. A) The regions with significantly decreased rCBF ($p<0.05$, corrected) in the deficit schizophrenia ($N=33$) compared with the normal controls ($N=45$). A-1) The glass brain, and A-2) the MRI templates show the main hypoperfused regions, which were the MPFC, OFC, and LPFC. B) The regions with significantly decreased rCBF ($p<0.05$, corrected) in the nondeficit schizophrenia ($N=40$) compared with the normal controls ($N=45$). B-1) The glass brain, and B-2) the MRI templates show the main hypoperfused regions, which were the MPFC, OFC, and LPFC.

syndrome, focal damage of the region has been demonstrated to cause major changes in lack of affect (Rolls and Baylis, 1994; Hornak et al., 2003). Thus the abnormality in this region might contribute to the pathophysiology of deficit syndrome.

In this study, rCBF values in the bilateral ACC, LPFC and left temporal lobe were lower in the combined schizophrenia and the bilateral ACC and right LPFC in both types of schizophrenia showed significantly lower rCBF than controls; these findings are quite consistent with those of previous SPECT and PET studies showing at-rest hypofrontality. It has been reported that patients with schizophrenia exhibit significantly lower rCBF or rGMR in the MPFC and/or LPFC than do normal controls (Ashton et al., 2000; Kim et al., 2000; Molina et al., 2005). Numerous structural MRI studies have also shown volume reductions in the LPFC and MPFC in schizophrenia. Our combined group presented hypoperfusion in these broad areas including the frontal and temporal lobe, in spite of a strict significant threshold ($p_{corrected}<0.05$). This result might be related to the large sample size in this study. Furthermore, the three comparisons (combined, deficit, or nondeficit schizophrenia vs. normal controls) showed right-sided distribution of hypoperfusion in the schizophrenia group. Previous MRI studies have reported brain structural asymmetry in patients with schizophrenia, particularly in the LPFC and temporal regions. Therefore, hypoperfusion and asymmetric distribution in rCBF in these regions may be a common feature in schizophrenia, regardless of disease subtype. On the other hand, it has been reported that patients with deficit syndrome showed a

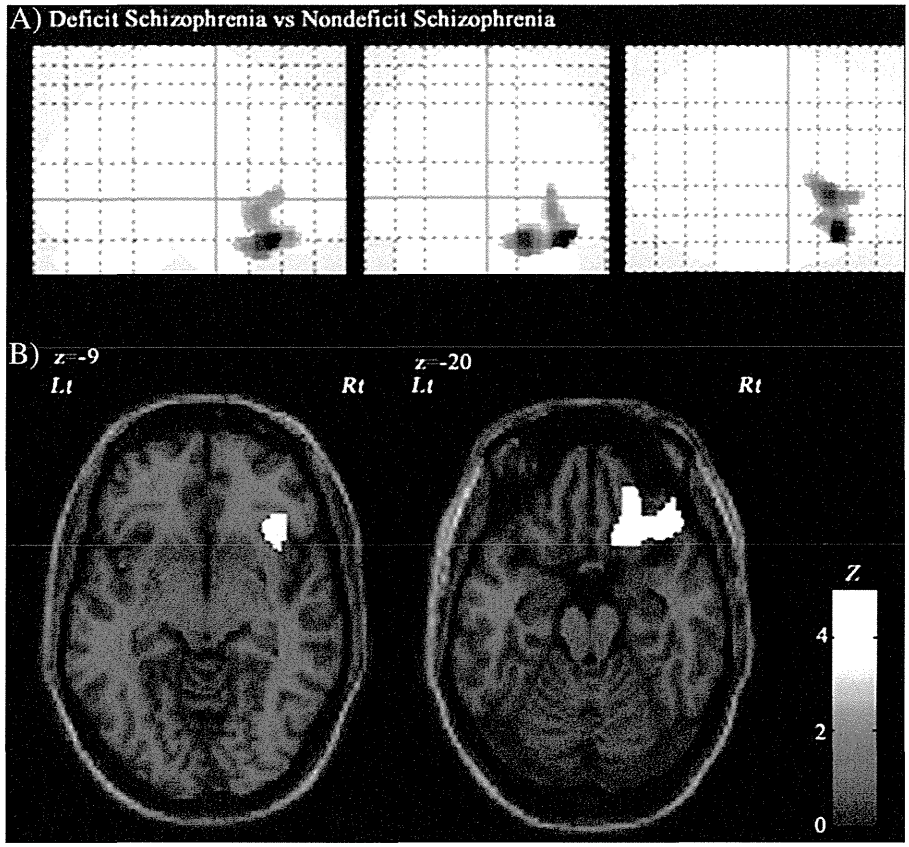

Fig. 3. The regions with significantly decreased rCBF ($p<0.05$, corrected) in the deficit schizophrenia ($N=33$) compared with the nondeficit schizophrenia ($N=40$). A) The glass brain, and B) the MRI templates show the hypoperfused regions in the OFC and insula.

significant reduction in rCBF in the LPFC compared to patients with nondeficit syndrome (Vaiva et al., 2002; Gonul et al., 2003); no significant differences in this region were observed in the present study. These inconsistencies between previous studies and the present study with regard to the extent of hypofrontality, particularly in the LPFC, might have been caused by several factors, including the heterogeneous degree of the nondeficit group, medication status (drug-free, typical antipsychotics, or atypical antipsychotics), and the analytic methodology, including the ROI or voxel-based method and statistical threshold used.

Significant differences between the deficit and nondeficit groups were observed only in the OFC and anterior insula. The OFC is known to be closely related to evaluation, response, and learning with respect to a variety of stimuli (Kringelbach and Rolls, 2004). Furthermore, the OFC is involved in emotional expression and plays a central role in hedonic experiences in humans and primates (Kringelbach, 2005). These impairments in the OFC in schizophrenia appear to be associated with the core disease pathophysiology. The present study showed a decrease of rCBF in the OFC in individuals with nondeficit schizophrenia as well as in those with deficit syndrome (Fig. 2). Furthermore, the present results suggested that the evident abnormality in the OFC could be characteristic of the deficit group, since the aberrant region remained significant in another comparison in which the authors controlled for negative symptoms (Section 3.3.2). Given the potential differences in emotional state among patients and the diverse potential roles of the OFC in humans, impairment in the OFC would be related not only with the profound negative symptoms, but also with other factors relevant to deficit syndrome, including diminished emotional state or cognitive deficits (Cohen et al., 2007).

This study has several limitations. The first limitation is related to the differences in clinical characteristics between disease groups, i.e., years of education, duration of illness and CP-dose (Table 1). In measurements of rCBF, the two latter items are of particular importance. In this study, duration of illness in the deficit group was longer than in the nondeficit group. One feature of patients with deficit syndrome is earlier onset of disease (Kopelowicz et al., 2000) with profound negative symptoms, which may lead to prolongation of the duration of illness (Marshall et al., 2005). In the present study, the older mean age and younger mean age of onset in the deficit group, although there was no statistically significant difference in either of these parameters between the groups, may have affected the longer illness duration. Second limitation was that the patients in the deficit group received larger doses of antipsychotics than did those in the nondeficit group. This difference was also partly due to the higher number of drug-free patients in the nondeficit group than in the deficit group. Most of our patients took atypical antipsychotics such as risperidone and olanzapine, which were demonstrated to have less effect on rCBF and rGMR than typical antipsychotics (Miller et al., 2001; Buchsbaum et al., 2007). Concerns regarding the potential impacts of these parameters (duration of illness and antipsychotic dosage) on rCBF led us to minimize the effects of both parameters by dealing them as covariates. Third limitation of this study is related to the use of an at-rest condition for the scanning methodology. During at-rest imaging, there are no cognitive tasks to control the mental states of the participants, and thus a variety of brain activities may be involved; this increase in variability might potentially have affected the results. In order to more precisely examine this issue, studies using H_2O-PET or fMRI on patients given specific cognitive tasks are needed. Fourthly, the fact that we hardly take partial volume effect

into consideration is a limitation of this study. Previous volumetric studies on deficit syndrome have not reported a significant reduction in the OFC region. However, since numerous MRI studies demonstrated volume reductions in multiple prefrontal regions, further study involving the combination of rCBF and volume is needed. Finally, in the analytic method, we applied voxel-based analysis in this study, and so the interpretation of regions with reduced rCBF in the present study in comparison to previous studies done using the ROI method requires caution.

Taken together, our findings show that the distribution of resting rCBF are similar distributions in the LPFC and MPFC between the deficit and nondeficit forms of schizophrenia, and that the OFC was the only region with significant hypoperfusion in our subjects with deficit schizophrenia. To the best of our knowledge, this is the first report to suggest that OFC hypoperfusion may play an important role in the pathogenesis of deficit schizophrenia.

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Contributors

N. Kanahara designed the study, wrote the protocol and the manuscript, and performed imaging analysis. T. Haraguchi recruited patients and normal subjects to the study and performed imaging analysis. Y. Uchida performed graphic processing of SPECT imaging. E. Shimizu designed the study. Y. Sekine, K. Hashimoto and M. Iyo supervised throughout the study. All authors contributed to and have approved the final manuscript.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgments

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Letter to the Editor

Potential treatment strategy of risperidone in long-acting injectable form for schizophrenia with dopamine supersensitivity psychosis

Dear Editors,

Development of tolerance to antipsychotics in the treatment of schizophrenia sometimes leads to increases in their doses and in the risk of dopamine supersensitivity, i.e., neurologically tardive dyskinesia and psychiatrically dopamine supersensitivity psychosis (DSP) (Chouinard, 1990). DSP may occur at a high rate among patients with schizophrenia (Kane et al., 1988), and the features are described as acute exacerbation after discontinuing antipsychotics and after only minor stress (Fallon and Dursun, 2011). DSP may be closely related to the up-regulation of dopamine D2 receptor (D2R) density in the brain which is induced by chronic treatment with antipsychotics (Chouinard, 1990). Severe cases with DSP meet the criteria for treatment-resistant schizophrenia and the effective pharmacological treatment for DSP has not been established except the use of clozapine (Kane et al., 1988). We recently hypothesized that the continuous optimal percentage in D2R occupancy, which is increased with up-regulated D2R, by antipsychotics is effective for the treatment of DSP (Tadokoro et al., 2012; Iyo et al., 2012). We report here two cases with severe DSP who were successfully treated using long-acting injectable forms (LAI) of antipsychotics under this hypothesis.

Mr. A, a 43-year-old Japanese-male with schizophrenia, had worked full-time under a recovery state for 11 years under treatment with risperidone (RIS) 5 mg/day after his first episode. At age 43, following self-discontinuation of the medication, auditory hallucination and persecutory delusions acutely developed again with psychomotor agitation. Under admission, the administration of either RIS 12 mg, aripiprazole 30 mg or olanzapine (OLZ) 20 mg for several weeks did not improve his symptoms sufficiently to allow him to be discharged from a protection room. Therefore, we initiated RLAI 25 mg/2 weeks and increased it to 50 mg/2 weeks as OLZ tapered off. His symptoms were gradually but clearly improved over the next 8 weeks. He was discharged from our hospital with an ongoing treatment of RLAI 50 mg/2 weeks and RIS 2 mg.

Mr. B, a 42-year-old Japanese male with schizophrenia has been in clinical remission for 15 years under treatment with haloperidol (HPD) 12 mg and clocapramine 75 mg, following admission for his first psychotic episode at age 22. At age 40, triggered by minor troubles with his family, he discontinued medication and four weeks later, his persecutory delusion intensely relapsed, and he required admission. OLZ 20 mg and HPD 9 mg, and further RIS 11 mg induced only slight improvement in his symptoms, but could not prevent his symptoms from fluctuating due to subtle stresses over the next 6 months. Then we initiated RLAI 25 mg/2 weeks up to 50 mg/2 weeks along with a reduction of oral antipsychotics. His symptoms gradually improved over the next year. Eventually, his daily functioning level returned to that before this episode.

The present two cases showed good responses to antipsychotics in the early stages of their diseases and maintained remission states for long periods of time (Table 1). In the case of Mr. A, however, oral administration of antipsychotics in sufficient doses could not reduce his acute exacerbated psychotic symptoms following the discontinuation of antipsychotics. Mr. B's psychosis was extremely exacerbated one month later following medication discontinuation, and it was not controlled by quite high dosages of neuroleptics. According to the original criteria proposed by Chouinard (1990), the episodes of both

Table 1
Clinical change during one year with RLAI treatment in two cases with DSP.

	Mr. A					Mr. B				
DSP symptom	Rebound psychosis					Rebound psychosis, developed tolerance				
Phase (Months)	Before relapse	Before RLAI introduction	RLAI treatment			Before relapse	Before RLAI introduction	RLAI treatment		
			0	6	12			0	6	12
BPRS	27	60	60	32	30	30	61	61	28	22
GAF	60	20	20	50	55	60	31	31	61	81
ESRS	18	16	16	9	13	5	5	0	0	0
Main oral AP (mg)	RIS 5 (11 years)	RIS 12 (4 weeks) ⇒APZ 30 (3 weeks) ⇒OLZ 20 (8 weeks)	OLZ 20	RIS 2	RIS 2	HPD 12 CLP 75 (15 years)	OLZ 20 HPD 9 (21 weeks) ⇒RIS11,OLZ5, HPD 3, LVM 25 (14 months)	RIS 11, OLZ 5, HPD 3, LVM 25	RIS 3, LVM 25	LVM10
CP-dose (mg)	500		800	200	200	787.5		1475	325	10
RLAI (mg/2 weeks)			25	50	50			25	50	50

Abbreviations: AP: antipsychotics, APZ: aripiprazole, BPRS: brief psychiatric rating scale (Overall and Gorham, 1962), CLP: clocapramine, CP: chlorpromazine, ESRS: extrapyramidal symptom rating scale (Chouinard and Margolese, 2005), GAF: global assessment of functioning, HPD: haloperidol, LVM: levomepromazine, OLZ: olanzapine, RIS: risperidone, RLAI: risperidone long-acting injectable form.

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Mr. A and Mr. B corresponded to rebound psychosis, and further Mr. B's episode indicates the development of tolerance to neuroleptics.

We consider that oral high dose administration may induce a high elimination dose from the body over a certain period of time, increasing the risk of fluctuation of the psychotic symptoms (Iyo et al., 2012), whereas LAI form may yield a stable plasma level of the drugs and an optimal percentage of D2R occupancy over time of period, which prevent the fluctuation and then improve treatment-resistant DSP (Kane et al., 2003; Eerdenkens et al., 2004). The use of clozapine may improve their symptoms (Kane et al., 1988), but clozapine has risks of profound side effects such as agranulocytosis and cardiomyopathy and needs intensive monitoring of these side effects. Therefore, the present cases suggest alternative approaches for treatment-resistant DSP to clozapine. However, the frequency of DSP was estimated to be approx. 50% among patients with schizophrenia, indicating high heterogeneity (Chouinard and Chouinard, 2008), and patients with typical DSP such as our two cases might be a part of treatment-resistant schizophrenia in actual clinical practice. Therefore, further studies are needed to confirm our strategy for the treatment of DSP.

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Contributors
N. Kanahara was an attending physician and provided guidance about this report. H. Kimura was an attending physician and wrote this report. H. Watanabe and M. Iyo supervised throughout all process from treatment for patients to writing this report. All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors declare no conflict of interest.

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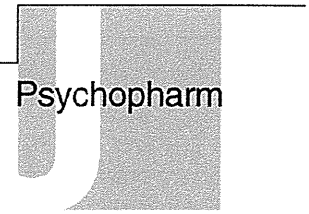

Dopamine supersensitivity psychosis and dopamine partial agonist: A retrospective survey of failure of switching to aripiprazole in schizophrenia

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Abstract

The administration of aripiprazole (ARI), a dopamine partial agonist, could provoke abrupt psychotic worsening in patients with schizophrenia. We explored the relationship between this psychotic worsening and dopamine supersensitivity psychosis (DSP), which is a clinically vulnerable state. We conducted a retrospective investigation for 264 patients whose treatment medication was switched to ARI from other antipsychotics. We divided the patients into the DSP(+) group with a history of DSP episode(s) (N = 70) and the DSP(−) group without such a history (N = 194), and then compared the clinical factors relevant to the success or failure of the switch to ARI between them. The results revealed that patients in the DSP(+) group experienced psychotic worsening following the switch to ARI with a significant higher rate compared to the DSP(−) group (23% vs. 8%, $P < 0.01$). Moreover, the dosages of the drugs before the ARI introduction in the patients experiencing the psychotic worsening in the DSP (-) group were higher than those in other patients of the group. Our findings suggest that patients who receive high dosages of antipsychotic drugs form overt or covert DSP and such state is highly associated with psychotic worsening following ARI treatment.

Keywords

Antipsychotic, dopamine partial agonist, dopamine supersensitivity, schizophrenia, tardive dyskinesia

Introduction

Antipsychotics have been a mainstay in treating patients with schizophrenia for the past decades, but approximately 50% of patients are unable to attain symptomatic remission regardless of appropriate pharmacotherapy; this is known as treatment-resistant schizophrenia (TRS). Dopamine supersensitivity psychosis (DSP) (Chouinard, 1991; Chouinard et al., 1978) is characterized by the need for high antipsychotic dosages for the treatment of patients with schizophrenia (Kirkpatrick et al., 1992), tardive dyskinesia (TD) (Chouinard and Chouinard, 2008), and/or an abrupt relapse triggered by the reduction or discontinuation of antipsychotics (Moncrieff, 2006). Vulnerability to minor stress has been raised as an important element of DSP (Fallon et al., 2012). DSP develops with multiple relapses, and some patients with these episodes develop TRS. It has been speculated that approximately 50% of the cases of TRS are due to DSP (Chouinard and Chouinard, 2008). An up-regulation of dopamine D2 receptor (DRD2) caused by long-term treatment with antipsychotic(s) may contribute considerably to DSP (Iyo et al., 2013). It has been suggested that dopamine supersensitivity is potentially formed through an interaction between the etiology of schizophrenia and its long-term treatment with antipsychotic(s). Thus, DSP has an iatrogenic aspect, and the prevention and treatment of DSP could have a great impact on patients' long-term prognosis.

It was reported that patients with schizophrenia treated with aripiprazole (ARI), a DRD2 partial agonist (DPA), have lower rates of relapse of psychosis and treatment discontinuation compared to those treated with other antipsychotics, including several new atypical antipsychotics (Azekawa et al., 2011; Gorwood, 2006). We demonstrated in an animal model that a chronic administration of ARI did not induce a DRD2 up-regulation or behavioral supersensitivity, whereas equivalent doses of haloperidol, a full DRD2 antagonist, induced a prominent DRD2 up-regulation and behavioral supersensitivity (Tadokoro et al., 2012). ARI may induce little dopamine supersensitivity due to its unique DPA profile, which is different from those of other antipsychotics (Iyo et al., 2013). Taken together, the existing data suggest that treatment with ARI could provide a more stable clinical course and better prognosis for patients with schizophrenia compared to other antipsychotics.

However, it has been reported that ARI can provoke acute psychotic worsening, i.e. relapse or exacerbation, particularly when a patient's treatment is switched from another antipsychotic to ARI

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(Adan-Manes and Garcia-Parajua, 2009; DeQuardo, 2004). These switching failures were speculated to be attributable to its unique receptor profile of DPA (Takeuchi et al., 2009). Indeed several ARI trials suggested that a switching method of concomitant ARI initiation and tapering off of the current medication could cause a relapse of psychosis (Lin et al., 2009; Pae et al., 2009), although this result was not always confirmed in other trials (Casey et al., 2003; Kim et al., 2009). In addition, Pae and colleagues noticed a possible association between psychotic relapse following switching to ARI and DSP (Pae, 2009; Pae et al., 2010). We consider that ARI's agonistic effects may yield excessive dopaminergic effects via the high DRD2 density in patients with DSP, leading to psychotic worsening and switching failure. To date, however, there have been no clinical studies that investigated the relationship between switching to ARI and DSP.

Here we conducted a retrospective survey of patients with schizophrenia who experienced the switch from treatment with another antipsychotic to ARI, in order to explore the relationship between failure of switching to ARI and DSP. We hypothesized that patients with a DSP history would show clinical worsening of psychosis following the ARI introduction more frequently than those without such a history. The results may provide evidence that dopamine supersensitivity is closely related to switching failure with ARI. In addition, the clinical features of such failure cases may provide predictors of psychotic worsening evoked by switching to ARI.

Methods

Subjects and study design

We collected the medical records of all in-/out-patients who met the diagnostic criteria for schizophrenia according to the DSM-IV-TR who were treated at Chiba University Hospital in the period from 1 September 2006 to 31 December 2012. Among them, we selected all of the patients who received the switching process to ARI from any other antipsychotic(s). In the present study we did not select candidate subjects based on any a priori hypothesis. We then identified the clinical information of each patient, including the presence or absence of DSP history before ARI introduction and his/her clinical outcome following the introduction. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine in Chiba University and was conducted in accord with the Helsinki Declaration.

Measurements

Dopamine supersensitivity psychosis. We evaluated the presence of DSP episode(s) within the five years prior to each patient's ARI adjunction. The DSP criteria in the present study were based on the original version by Chouinard (1991), but were slightly modified by our team as follows: (a) *withdrawal psychosis*: an acute relapse or exacerbation of psychosis appeared after a dose reduction or discontinuation of antipsychotics, within six weeks for oral medication or three months for long-acting intramuscular injection; or (b) *the development of tolerance to antipsychotic effects*: an acute relapse or exacerbation of psychosis that occurred independently of a dose reduction or discontinuation of antipsychotic therapy and could not be successfully controlled by a 20% increased titration of drug; or (c) *a mixed episode* meeting the criteria of both (a) and (b): psychotic symptoms which were new to the patient, or of greater severity, that occurred immediately after a decrease in drug dosage.

Based on available information from the medical records, if at least one of the three items above was met, the patient was classified as a member of the DSP(+) group, whereas the other patients were classified as the DSP(–) group. Since DSP was generally considered to be a secondary state which could be relevant to pharmacotherapy for some duration, we excluded the patients who received ARI for their first acute episode of psychosis. We also excluded the patients with comorbidities such as substance abuse/dependence, and the patients who were clearly judged to refuse treatment and take medication. Involuntary movement disorder including TD and exacerbation caused by minor stress, both of which are related to DSP (Fallon and Durson, 2011; Fallon et al., 2012), are not necessarily covered by the DSP criteria of the present study.

Clinical outcome following the switch to aripiprazole. Regarding the outcome after the switch to ARI, we categorized each case to one of the following three subgroups based on the patient's clinical course subsequent to the ARI introduction: continuation of ARI (CON), discontinuation of ARI due to worsening positive symptoms (D-POS), or discontinuation of ARI due to any other reason(s) (D-OTH).

CON was defined as the continuation of ARI treatment from its introduction to the present survey (December 2013) regardless of any clinical prognosis, i.e. improvement or not. D-POS was defined as the discontinuation of ARI due to the worsening of psychosis after the start of ARI treatment. The worsening of psychosis was defined as the exacerbation of positive symptoms, based on a 5 point or greater reduction in the patient's Global Assessment of Functioning (GAF) score and an increase of $\geqslant 1$ point on the Clinical Global Impression-Severity scale (CGI-S). D-OTH was defined as the discontinuation of ARI treatment due to any other reason(s) except for the worsening by ARI initiation, including lack of sufficient antipsychotic effects, discontinuation by the patient him/herself, any adverse effect such as extrapyramidal symptom, insomnia and nausea, and other reasons. If clinical information necessary for the above judgment was not available due to transference to another hospital or discontinuation of visits to our hospital, the patient's outcomes were judged by the state at the final visits.

We also examined the outcomes of the patients with the D-POS pattern in detail, to investigate whether the relevant worsening of psychosis met the criteria of a DSP episode: that is, whether the worsening episode was related to the introduction of ARI, particularly in the patients with a history of DSP episode(s).

Statistical analysis

We used SPSS ver. 19.0 (IBM, Armonk, NY) for the statistical analysis in this study. We applied Student's t-test and an analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. The statistical threshold level was set at $\alpha = 0.05$.

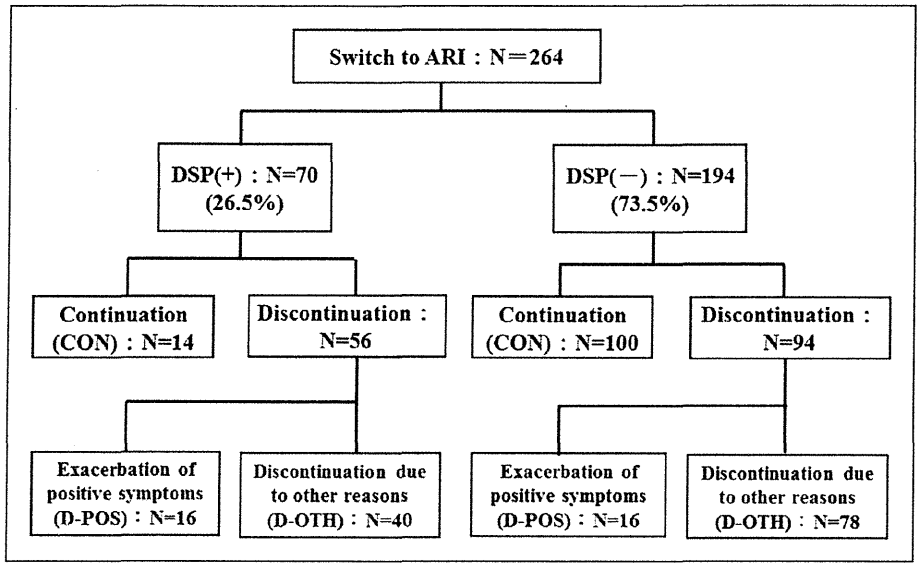

Figure 1. Overview of subject flow.

Results

We found that the treatment medication of 264 patients with schizophrenia (mean age, 40.5 yr; male/female ratio, 104/160) was switched to ARI from other antipsychotics during the surveyed period. None of these patients received ARI for the first-episode psychosis. Seventy patients (26.5%) were categorized in the DSP(+) group and 194 patients (73.5%) comprised the DSP(–) group (Figure 1). There was no significant between-group difference in any of the demographic factors, including the treatment indexes such as treatment duration and the distribution of antipsychotic class prior to the switch to ARI (Table 1).

Clinical course subsequent to aripiprazole switch and dopamine supersensitivity psychosis

In the DSP(+) group, the rates of CON, D-OTH and D-POS were 20%, 57% and 23%, respectively, whereas these values were 52%, 40% and 8% in the DSP(–) group (Figure 2), with a significant difference in the distribution between the two groups ($P < 0.01$). This result indicated that the discontinuation ratio of ARI and the worsening ratio in the DSP(+) group were significantly higher than those in the DSP(–) group.

The distributions of the primary reasons for D-OTH in the DSP(+) and DSP(–) groups were as follows: insufficient antipsychotic effects in 28.6% ($N = 20$) and 12.4% ($N = 24$), self-interruption in 8.6% ($N = 6$) and 5.7% ($N = 11$), insomnia in 0% ($N = 0$) and 6.2% ($N = 12$), nausea in 5.7% ($N = 4$) and 4.1% ($N = 8$), and extrapyramidal symptoms in 4.3% ($N = 3$) and 5.2% ($N = 10$), respectively.

Dosage of antipsychotics prior to aripiprazole introduction

The chlorpromazine-equivalent dose (CPZeq-dose) just prior to the start of ARI adjunction in the DSP(+) group (762.4 ± 376.0 mg) was significantly higher than that in the DSP(–) group (473.5 ± 373.3 mg) ($P < 0.01$, Table 1). There were no significant differences in the dosages among the CON (734.3 ± 344.9 mg), D-OTH (807.6 ± 413.9 mg) and D-POS (673.9 ± 269.2 mg) patterns within the DSP(+) group (Figure 3). However, there was a significant difference among the CON (425.2 ± 340.1 mg), D-OTH (496.6 ± 411.8 mg) and D-POS (662.7 ± 294.9 mg) patterns within the DSP(–) group ($P = 0.048$), and a post hoc Tukey test revealed that the dose in the D-POS subgroup was significantly higher than that of the CON subgroup within the DSP(–) group ($P = 0.048$) (Figure 3).

Effects of aripiprazole exposure and reduction of preceding antipsychotics on the worsening of psychosis

Among the D-POS patients, there were no significant differences between the DSP(+) group ($N = 16$) and the DSP(–) group ($N = 16$) in the CPZeq-dose just prior to ARI initiation, or in the duration from the initiation of ARI treatment to the exacerbation of psychosis (21.8 ± 53.5 wk and 16.3 ± 18.1 wk), or in the reduction rate of the preceding antipsychotic dosages (56.1 ± 39.1% and 33.9 ± 37.3%) or ARI dosage (21.8 ± 6.7 mg and 19.5 ± 9.1 mg) at the worsening (Table 2). The mean values for these patients (combined group of DSP(+) and DSP(–) groups) indicated that the worsening occurred at 19 weeks following the ARI initiation, and at the worsening, 20.6 mg ARI was being administered per day and there was a 45% reduction of the preceding antipsychotic dosage.

Lastly, we investigate whether or not the switching methodology influenced the worsening of psychosis. No patients with immediate ARI initiation and a simultaneous immediate discontinuation of previous antipsychotics (i.e. immediate suspension) experienced the D-POS pattern. The switching methods of all 32 patients with the D-POS pattern were up-titrating ARI and simultaneously tapering off previous antipsychotics over several weeks, or tapering off previous antipsychotics after several weeks following ARI adjunction (i.e. gradual suspension).

Table 1. Clinical characteristics and treatment state of the DSP(+) and (-) groups.

	DSP(+) ($N = 70$)	DSP(-) ($N = 194$)	P-value
Sex (male/female)	29/41	75/119	NS
Age (yr)	37.9 (12.6)	41.5 (14.7)	NS
(range)	(15–80)	(15–78)	
Duration of medication (yr)	13.0 (9.25)	11.6 (10.0)	NS
Follow-up duration following ARI initiation (yr)	1.26 (1.51)	1.71 (1.85)	NS
Antipsychotic before ARI initiation:			$P < 0.01$
Dosage (CPZeq: mg)	762.4 (376.0)	473.5 (373.3)	
Class of antipsychotic drug, *N* (%)			
Risperidone	32 (45.1%)	91 (47.2%)	
Olanzapine	18 (25.4%)	45 (23.3%)	
Quetiapine	8 (11.3%)	22 (11.4%)	
Perospirone	5 (7.0%)	15 (7.8%)	
Haloperidol	1 (1.4%)	9 (4.7%)	
Others	6 (8.5%)	12 (6.2%)	

Data are means (SD).
DSP: dopamine supersensitivity psychosis; ARI: aripiprazole; CPZeq: chlorpromazine-equivalent dose; NS: not significant.

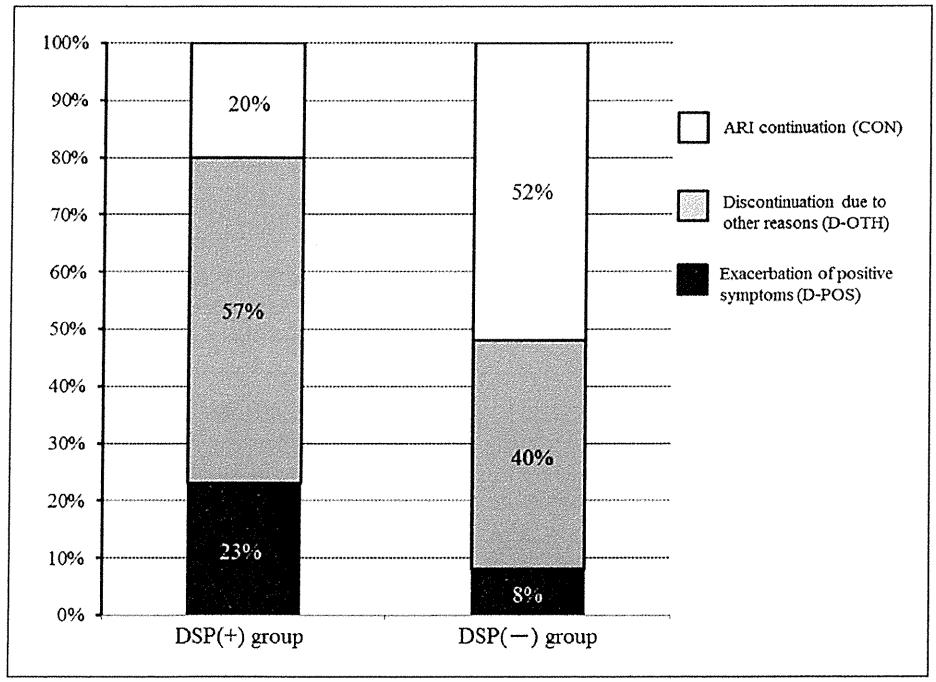

Figure 2. Distribution of clinical outcome following aripiprazole treatment in the DSP(+) and DSP(-) groups.

Discussion

The main finding in the present study is that the patients in the DSP(+) group showed a significantly higher rate of ARI discontinuation due to psychotic worsening compared to the DSP(–) group during the ARI switching process. In addition, even in the DSP(–) group, 8% of the patients experienced psychotic worsening during the switching process. We also found that the DSP(+) patients had significantly higher antipsychotic doses prior to ARI introduction, compared to the DSP(–) patients. The patients in the DSP(–) group who exhibited worsening during the switching process also had significantly higher prior antipsychotic doses, comparable to those in the DSP(+) group, compared to the other patients in the DSP(–) group. These results support our hypothesis that patients with a DSP history tend to suffer psychotic worsening during the process of switching to ARI. Our present findings also suggested that even the patients without a DSP history but treated with high antipsychotic doses also tended to suffer the worsening of symptoms, which may be a revelation of covert DSP. Overall, the present findings strongly suggest that a failure of switching to ARI in patients with schizophrenia treated with high antipsychotic doses could be closely associated with DSP.

We categorized the patients who had experienced the switching of antipsychotic medication to ARI into DSP(+) and DSP(–)

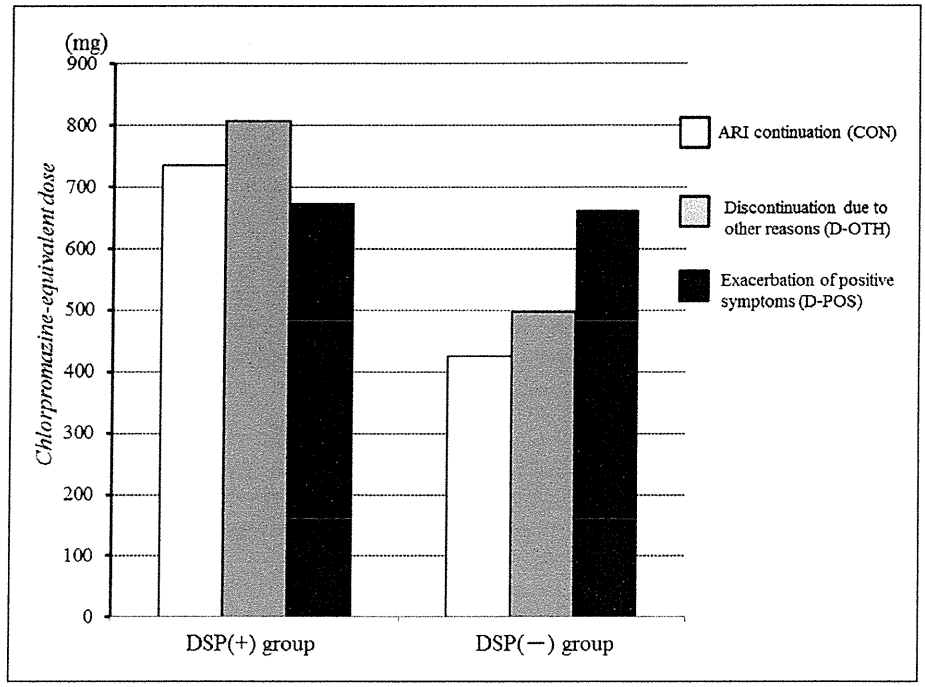

Figure 3. Chlorpromazine-equivalent dose of antipsychotic(s) just prior to the aripiprazole initiation in each subgroup.

Table 2. Worsened psychotic episodes relevant to the switch to ARI between the DSP(+) and DSP(-) groups.

	DSP(+) (N = 16)	DSP(-) (N = 16)	P-value
Index of clinical status prior to ARI switching:			
Dosage of antipsychotics (CPZeq: mg)	673.9 (269.2)	662.7 (294.9)	NS
GAF	41.6 (10.3)	41.3 (9.9)	NS
CGI-S	4.44 (0.70)	4.25 (0.90)	NS
Index of worsened psychosis following ARI switching:			
Duration from ARI switch to worsening (wk)	21.8 (53.5)	16.3 (18.1)	NS
Dosage of ARI (mg)	21.8 (6.7)	19.5 (9.1)	NS
Reduction rate of preceding antipsychotics (%)	56.1 (39.1)	33.9 (37.3)	NS
GAF	25.9 (9.6)	31.3 (10.7)	NS
CGI-S	6.00 (0.61)	5.44 (0.86)	NS

Data are means (SD).
DSP: dopamine supersensitivity psychosis; ARI: aripiprazole; CPZeq: chlorpromazine-equivalent dose; GAF: Global Assessment of Functioning; CGI-S: Clinical Global Impression-Severity scale; NS: not significant.

groups based on the retrospective clinical information of the presence or absence of a history of DSP, such as withdrawal psychosis and tolerance to antipsychotic effects within the five years before their ARI initiation. These episode(s) and/or clinical course are the core concept of DSP, as proposed by Chouinard (1991) and Kirkpatrick et al. (1992). On the other hand, the presence of TD and vulnerability to minor stress, which are important elements of DSP as well (Fallon and Durson, 2011; Fallon et al., 2012), were not required factors upon the diagnosis of DSP in the present study, since it is difficult to accurately identify these episodes from the viewpoint of study design. In the present study based on the former classification, the DSP(+) patients had a significantly higher rate, about 23%, of marked worsening of psychosis after the ARI initiation than the DSP(–) patients. The antipsychotic dosages prior to ARI initiation in the DSP(+) group were also significantly higher than those in the DSP(–) group, in agreement with our previous report that patients with DSP need high antipsychotic doses (Iyo et al., 2013). This finding suggests that a switch to ARI may greatly worsen the psychosis in patients with a history of DSP induced by previous treatment with high doses of antipsychotic drugs.

In the present DSP(–) group, 8% of the patients exhibited the D-POS pattern, i.e. worsening during the switching process and subsequent ARI discontinuation. Their preceding antipsychotic dosages were significantly higher compared to other patients within the DSP(–) group and comparable to those in the DSP(+) group. We speculate that the DSP had insidiously developed in these patients and was revealed by the switch to ARI, and we suspect that patients with high doses of preceding antipsychotic(s), regardless of the presence or absence of previous DSP episode(s),

may suffer psychotic worsening during the process of switching to ARI. It was reported that patients with abrupt psychotic relapses related to ARI switching had received high doses of antipsychotics, i.e. amisulpride 800mg/day (Adan-Manes and Garcia-Parajua, 2009) and olanzapine 60mg/day (DeQuardo, 2004). These patients might also experience a DSP episode with the introduction of ARI, in agreement with the present study's results.

In our DSP(+) group, 20% of the patients were able to continue ARI for a long period of time and 57% of the patients discontinued ARI due to reasons other than psychotic worsening (such as insufficient antipsychotic effects, 28%), although they had received high antipsychotic doses comparable to those of the patients showing psychotic worsening. We suspect that as the ARI dosage increases or the dosage of other antipsychotics is reduced following ARI initiation, the extent of ARI's binding to DRD2 increases, accompanied by an increase of ARI-induced dopaminergic effects due to a fixed ratio of intrinsic activity, approximately 17% (Tadori et al., 2009). In such a scenario, ARI-induced dopaminergic effects can exceed levels high enough to exacerbate psychosis in individuals with DSP, who have sufficiently high numbers of DRD2 for ARI binding, leading to psychotic worsening. When the increased ARI-induced dopaminergic effects are equivalent to pre-existing dopaminergic effects before the initiation of ARI, the severity of psychosis may not change between pre- and post-ARI initiation. This speculation may explain the reason of discontinuation due to insufficient antipsychotic effects of ARI in the D-OTH patients within the DSP(+) group.

In the D-POS patients, it is strongly suggested that the switch to ARI was a trigger for relapse, although several clinical factors such as a lack of insight into the disease and poor adherence are well-known predictors of a higher relapse rate in schizophrenia (Llorca, 2008; Masand et al., 2009; Valenstein et al., 2002) (Table 2). In the present study, the worsening occurred at 19 weeks on average following ARI initiation at the mean ARI dosage of 20.6mg and mean 45% reduction of preceding antipsychotic dosage, whereas Chouinard (1991) defined that psychotic worsening appears within six weeks after a dose reduction or discontinuation of oral antipsychotics in patients with DSP. These clinical index values upon relapse were relatively consistent with previous switching trials with ARI: one study showed immediate relapses following adjunction of ARI (Casey et al., 2003) and another study showed a higher drop-out rate in patients who received higher dosages of prior agents (Lin et al., 2009). In addition, all of the D-POS patients experienced the switching process of the gradual tapering-off regimen, whereas there was no patient with the immediate suspension of previous agents in the D-POS patients. This result supports the concept that the action of ARI contributes more to the worsening of psychosis than the discontinuation or the tapering off of previous antipsychotics. The extent of developed dopamine supersensitivity (i.e. the extent of an increase in the number of DRD2) in addition to the rates of ARI increase and the reduction of other drugs might differ among the patients. We thus suspect that the timing of the appearance of worsening psychosis following ARI initiation might have a wide range, and this might have occurred slightly later than the cases with a dose reduction or discontinuation of oral antipsychotics that showed worsening only two weeks after the initiation of ARI, which meets Chouinard's rebound psychosis criteria (i.e. within six weeks after the discontinuation of current agents) as reported by Pae et al. (2009).

The present study has several limitations, and thus caution is warranted when interpreting our findings. First, our sample size, particularly that of the patients with the D-POS pattern, was relatively small. If there were slight but significant differences in the distribution rate of the D-POS pattern among the switching cases, such differences would not be detected with only a small sample size presenting with the D-POS pattern. Second, a relapse episode of DSP might include relapse under treatment (i.e. not withdrawal psychosis), which leads to an overestimation of the number of DSP cases. Finally, with respect to the diagnosis of DSP, our study is in accord with both the criteria proposed by Chouinard (1991) and the concept described by Kirkpatrick et al. (1992), but it did not include the presence of involuntary movement disorder or vulnerability to minor stress as proposed by Fallon et al. (2012). This difference in the criteria used upon the diagnosis of DSP might have had some influence on the study results. However, DSP can present covertly with the dopamine supersensitivity state formed but without occurrence as DSP, and such a case was judged to belong in the DSP(–) group in this study. This may imply a limitation of the dichotomy of DSP.

In conclusion, this is the first study focusing on the possible relationship between the failure of a switch to ARI treatment and DSP. Our results strongly suggest that the abrupt worsening of psychosis following the initiation of ARI after treatment with other antipsychotics in patients with schizophrenia is associated with DSP.

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A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis

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ABSTRACT

Objective: Dopamine supersensitivity psychosis (DSP) is considered to be one cause of treatment-resistant schizophrenia (TRS). The authors investigated the efficacy of risperidone long-acting injections (RLAI) in patients with TRS and DSP.
Method: This is a multicenter, prospective, 12-month follow-up, observational study that included unstable and severe TRS patients with and without DSP. 115 patients with TRS were recruited and divided into two groups according to the presence or absence of DSP which was judged on the basis of the clinical courses and neurological examinations. RLAI was administered adjunctively once every 2 weeks along with oral antipsychotics. We observed changes in scores for the Brief Psychiatric Rating Scales (BPRS), Clinical Global Impression—Severity of Illness (CGI-S), Global Assessment of Functioning Scale (GAF), and Extrapyramidal Symptom Rating Scale (ESRS) during the study. Of the assessed 94 patients, 61 and 33 were categorized into the DSP and NonDSP groups, respectively.
Results: While baseline BPRS total scores, CGI-S scores and GAF scores did not differ, the ESRS score was significantly higher in the DSP group compared with the NonDSP group. Treatment significantly reduced BPRS total scores and CGI-S scores, and increased GAF scores in both groups, but the magnitudes of change were significantly greater in the DSP group relative to the NonDSP group. ESRS scores were also reduced in the DSP group. Responder rates (≥20% reduction in BPRS total score) were 62.3% in the DSP group and 21.2% in the NonDSP group.
Conclusions: It is suggested that DSP contributes to the etiology of TRS. Atypical antipsychotic drugs in long-acting forms, such as RLAI, can provide beneficial effects for patients with DSP.
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1. Introduction

Antipsychotics are usually effective against the acute symptoms of schizophrenia (Freedman, 2003), especially for the first episode of the

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