Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder

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Running title: CSF IL-6 levels in schizophrenia and depression

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Abstract

Elevated peripheral levels of interleukin-6 (IL-6) are common findings in schizophrenia and depression. However, previous studies that measured cerebrospinal fluid (CSF) IL-6 levels in these disorders reported controversial results. The present study examined whether CSF IL-6 levels are altered in patients with schizophrenia and those with depression. Lumbar punctures were performed in 32 patients with schizophrenia, 30 with major depressive disorder (MDD), and 35 healthy controls. Serum samples were simultaneously collected from all subjects in the patient groups and from 32 of the control group. CSF and serum IL-6 levels were determined by enzyme-linked immunosorbent assay. Both the patients with schizophrenia and MDD had significantly higher CSF IL-6 levels compared to the controls (schizophrenia: $P = 0.0027$; MDD: $P = 0.012$). IL-6 levels were significantly higher in the CSF than in the serum. No significant correlation was observed between CSF and serum IL-6 levels. One limitation of the study was the different smoking prevalence between patient groups and controls, which may have confounded the findings for MDD patients. In all, the present findings suggest that IL-6 of central origin is associated with the pathophysiology of schizophrenia and MDD.

Keywords: schizophrenia; major depressive disorder; interleukin-6; cerebrospinal fluid

Introduction

Elevated serum or plasma levels of interleukin-6 (IL-6) are common findings in schizophrenia (Potvin et al, 2008; Sasayama et al, 2011) and depression (Howren et al, 2009; Liu et al, 2012). Although the source of the elevated blood IL-6 remains to be elucidated, such evidence suggests immune alterations in the peripheral tissues of these disorders.

IL-6 is not only synthesized in immune cells of the peripheral blood but is also produced in the central nervous system (CNS) by astrocytes and microglia. According to the recent microglia hypothesis of schizophrenia (Monji et al, 2009), activated microglia release pro-inflammatory cytokines and free radicals, causing neuronal degeneration, white matter abnormalities, and decreased neurogenesis associated with the pathophysiology of schizophrenia. In previous studies of patients with depression (Hamidi et al, 2004; Ongur et al, 1998), loss of glial elements in mood-relevant brain regions, such as amygdala and subgenual prefrontal cortex, has been observed. Such

findings suggest that the effect of cytokines and central inflammatory processes on glia may play a role in the etiology of depression. These hypothetical models of immune pathophysiology underline the importance of the assessment of CNS levels of IL-6 in schizophrenia and depression. Some previous studies have shown that CSF IL-6 levels may not significantly correlate with peripheral IL-6 levels (Lindqvist et al, 2009; Stenlof et al, 2003). Therefore, measurement in the cerebrospinal fluid (CSF) is necessary for the direct assessment of CNS-derived IL-6.

A few studies have measured IL-6 levels in the CSF in patients with schizophrenia (Barak et al, 1995; Garver et al, 2003) and depression (Carpenter et al, 2004; Levine et al, 1999; Lindqvist et al., 2009; Martinez et al, 2012; Stubner et al, 1999). However, the findings are inconsistent across studies. Barak et al (Barak et al., 1995) reported no significant difference in CSF IL-6 levels between schizophrenic patients and healthy controls, while Garver et al (Garver et al., 2003) found significantly higher CSF IL-6 levels in a subtype of schizophrenia. As for depressed patients, CSF IL-6 levels were found to be decreased (Levine et al., 1999; Stubner et al., 1999), unaltered (Carpenter et al., 2004; Martinez et al., 2012), or elevated (Lindqvist et al.,

2009) compared to healthy controls. However, findings among previous studies measuring CSF IL-6 levels in schizophrenia and depression should be interpreted with caution due to the small numbers of subjects.

Aims of the study

The aims of the present study were to examine whether CSF IL-6 levels were altered in patients with schizophrenia and those with depression. From the inflammatory hypotheses of these disorders (Maes, 2011; Miller et al, 2009; Monji et al., 2009), we hypothesized that the central IL-6 levels would be increased in the patient groups compared to the healthy controls.

Material and methods

Subjects

Lumbar punctures were performed in 32 patients with schizophrenia, 30 patients with major depressive disorder (MDD), and 35 healthy controls. The mean age and sex ratio were matched across the three groups. Most subjects of the patient groups

were on antipsychotic and/or antidepressant treatment. Simultaneously with the lumbar punctures, serum samples were also collected from all subjects in the patient groups and from 32 of the control group. Table 1 shows the demographic and clinical characteristics of the participants. All subjects were biologically unrelated Japanese who were recruited from the outpatient clinic of the National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan or through advertisements in free local information magazines and by our website announcement. Consensus diagnosis by at least two psychiatrists was made for each patient according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria (American Psychiatric Association, 1994), on the basis of unstructured interviews and information from medical records. The controls were healthy volunteers with no current or past history of psychiatric treatment, and were screened using the Japanese version of the Mini International Neuropsychiatric Interview (M.I.N.I.) (Otsubo et al, 2005; Sheehan et al, 1998) by a research psychiatrist to rule out any axis I psychiatric disorders. Participants were excluded if they had prior medical histories of central nervous system disease or severe head injury, if they met the criteria for substance abuse or dependence, or mental

retardation, if they were currently taking anti-inflammatory medication, or if they suffered from any inflammatory, infectious, or systemic immune diseases, based on self-reports, at the time of assessment. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After description of the study, written informed consent was obtained from every subject.

Laboratory Methods

CSF was drawn between 1000 h and 1600 h from the L4-L5 or L3-L4 interspace, with the subject in the left decubitus position. The samples were immediately transferred on ice, centrifuged at 4000 × g, aliquoted and stored at -80°C until they were assayed. Serum samples were collected immediately before the lumbar punctures. All the samples were collected during the period of 2010-2011. CSF and serum levels of IL-6 were determined by a commercially available immunoassay kit (Quantikine, R&D systems, Inc., Minneapolis) according to manufacturer's instructions. The mean minimum detectable dose of the kit was 0.039 pg/ml. The within and between-run coefficients of variance of the assay were less than 10 %.

Clinical measures

Schizophrenic symptoms and depressive symptoms were assessed by an experienced research psychiatrist using the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al, 1987; Yamada et al, 1991) and the Japanese version of the GRID Hamilton Depression Rating Scale, 21-item version (HAMD-21) (Hamilton, 1967), which have both been demonstrated to show good inter-rater reliability (Igarashi et al, 1998; Tabuse et al, 2007). Daily doses of antipsychotics in patients with schizophrenia and antidepressants in patients with MDD were converted to chlorpromazine and imipramine equivalent doses, respectively, using published guidelines (Inagaki et al, 1999).

Statistical analysis

Difference in gender distribution between groups was analyzed by χ^2 analysis. Clinical characteristics between groups were compared using analysis of variance. Because CSF and serum IL-6 levels were not normally distributed, difference between

diagnostic groups was assessed using Kruskal-Wallis test, and thereafter pairwise Mann-Whitney U tests for *post hoc* comparisons. Relationship between IL-6 levels and clinical measures were assessed using Spearman's rank correlation coefficients (ρ). Serum and CSF samples were compared using Spearman's rank correlation and Wilcoxon's signed rank test. All statistical tests were two tailed and statistical significance was considered when $P < 0.05$. Bonferroni correction was applied for the *post hoc* pairwise Mann-Whitney U tests between the three diagnostic groups (significance criteria of $P < 0.017$). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Japan, Tokyo).

Results

As shown in Table 1, no significant difference was found between diagnostic groups in mean age, gender distribution, or body mass index (BMI). The prevalence of smoking was higher in the patients groups compared to controls. Figure 1 shows the CSF and serum IL-6 levels in each diagnostic group. All samples analyzed were well above the lower detection limit of 0.039 pg/ml. The difference in serum IL-6 levels

between the groups was not statistically significant ($\chi^2 = 1.8$, df = 2, $P = 0.40$); however, CSF IL-6 levels differed significantly across the groups ($\chi^2 = 10.7$, df = 2, $P = 0.0049$). *Post hoc* pairwise Mann-Whitney-U test showed that both the patients with schizophrenia and MDD had significantly higher CSF IL-6 levels compared to the controls (schizophrenia: $U = 321$, $P = 0.0027$; MDD: $U = 334$, $P = 0.012$).

No significant correlation between CSF and serum IL-6 levels was observed for each diagnostic group. Spearman's rank correlation coefficients and the 95% confidence intervals (95% CI) were as follows: controls, $\rho = 0.18$ (95% CI: -0.18 to 0.55); schizophrenia, $\rho = 0.23$ (-0.13 to 0.59); MDD, $\rho = 0.19$ (-0.18 to 0.57); and all groups combined, $\rho = 0.20$ (-0.006 to 0.41). IL-6 levels were significantly higher in the CSF than in the serum ($Z = 4.04$, $P < 0.0001$). When analyzed separately in each diagnostic group, the difference between CSF and serum IL-6 levels reached statistical significance in only patients with schizophrenia (schizophrenia: $Z = 3.54$, $P = 0.0004$; MDD: $Z = 1.74$, $P = 0.082$; controls: $Z = 1.82$, $P = 0.068$).

Next, we examined the influence of clinical factors on CSF IL-6 levels (Table 2). CSF IL-6 levels of the schizophrenic patients did not significantly correlate with the

antipsychotic dose ($\rho = 0.12$, $P > 0.1$) or with the PANSS scores (positive symptoms: $\rho = 0.065$, $P > 0.1$; negative symptoms: $\rho = 0.12$, $P > 0.1$). Similarly, CSF IL-6 levels of the patients with MDD did not significantly correlate with the antidepressant dose ($\rho = 0.044$, $P > 0.1$) or with the HAMD-21 score ($\rho = -0.036$, $P > 0.1$). Because smoking prevalence was significantly different between controls and patient groups, we also compared CSF IL-6 levels in only nonsmokers to avoid the confounding effects of smoking. When only nonsmokers were compared, patients with schizophrenia had significantly higher CSF IL-6 levels compared to the controls ($U = 158$, $P = 0.04$), but the difference between MDD patients and controls did not reach statistical significance ($U = 194$, $P = 0.22$). No significant correlation with CSF IL-6 levels was observed for time of day of sampling or number of days between sample collection and IL-6 assay. Furthermore, no significant difference in CSF IL-6 levels of those sampled before and after noon was observed for each diagnostic group.

Discussion

The results showed that CSF IL-6 levels were higher in patients with

schizophrenia and those with MDD than in healthy controls. The present findings further support the evidence for the role of IL-6 in the pathogenesis of these disorders. No significant increase in serum IL-6 levels of patients with schizophrenia or MDD was obtained. However, this does not contradict with previous findings, because the effect size reported in previous meta-analyses (Howren et al., 2009; Potvin et al., 2008) requires a sample more than twice as large as ours to reach 80% power to detect the difference at the 5% significance level (calculated by G*Power 3.1.3 (Faul et al, 2007)). It is of note that significant difference in CSF IL-6 levels was obtained with the present sample, suggesting that the effect size may be larger for CSF than for serum.

No significant correlation was observed between CSF and serum IL-6 levels. Although there is a possibility that a larger sample may yield a significant correlation, the correlation coefficient is likely to be lower than the upper limit of the 95% confidence interval (i.e. $\rho = 0.41$) obtained in the present study. Furthermore, IL-6 levels were higher in the CSF compared to the serum, especially for schizophrenic patients. Thus, the increased CSF IL-6 levels in patients with schizophrenia and MDD are unlikely to be explained by the diffusion from the peripheral circulation. These findings

suggest that IL-6 of central origin is associated with the pathophysiology of these disorders.

Increased CSF IL-6 levels in both patients with schizophrenia and those with MDD suggest that inflammatory mediators may be commonly involved in the pathogenesis of these disorders. Although a plethora of studies examining peripheral cytokine levels also support the hypothesis that inflammation plays a role in these disorders, a unique cytokine profile capable of distinguishing these two disorders has not been described. There is a possibility that common underlying pathogenic mechanisms may be involved in schizophrenia and MDD.

A number of studies indicate involvement of abnormal neurogenesis in the pathophysiology of MDD (Leonard & Maes, 2012) as well as schizophrenia (Balu & Coyle, 2011). Monje et al (2003) have shown that inflammation can inhibit neurogenesis and that IL-6 is implicated as a potential regulator of hippocampal neurogenesis in neuroinflammation. Therefore, increased microglial production of IL-6 may be a common etiological risk factor for schizophrenia and MDD. Another common potential etiological factor of these two disorders may be the changes in kynurenine

metabolism. The increased kynurenine induces increased production of kynurenic acid in schizophrenia and quinolinic acid in depression, which may result in an imbalance in glutamatergic neurotransmission. Raison et al (2010) have shown that the changes in kynurenine metabolism are linked to central cytokine responses. Thus, the increased central IL-6 observed in the present study is in line with the role of kynurenine pathway on the pathophysiology of schizophrenia (Muller et al, 2011) and MDD (Myint et al, 2007; Myint et al, 2011).

Not all individuals with depression or schizophrenia exhibit high levels of CSF IL-6 levels. Therefore, it is likely that inflammation is involved in the pathogenesis of a subgroup of patients. We could not identify any major clinical features specific to those with high CSF IL-6 levels. The positive correlation observed between CSF IL-6 levels and age at onset in patients with schizophrenia suggests that inflammatory mechanism may be more likely to be associated with late-onset schizophrenia; however, the sample size was too small to draw definitive conclusion regarding the association with particular clinical features.

Some previous studies failed to find significant change of CSF IL-6 levels in

patients with schizophrenia (Barak et al., 1995) or those with MDD (Carpenter et al., 2004; Martinez et al., 2012). Because the sample sizes were smaller than that in the present study, insufficient statistical power may have precluded detection of statistically significant differences in these studies. Some other studies have yielded results consistent with the present findings. Garver et al (2003) reported increased CSF IL-6 levels in schizophrenic patients who subsequently responded to antipsychotic treatment. Lindqvist et al (2009) reported that CSF IL-6 levels in patients with MDD after a suicide attempt were higher compared to healthy controls. In contrast to our findings, one previous study of patients with geriatric depression (Stubner et al., 1999) and another of patients with acute severe depression (Levine et al., 1999) have shown that CSF IL-6 levels were lower in depressed subjects compared to controls. Since the majority of the patients in our study were middle-aged and were in the chronic stage of illness, the influence of the patients' age and the illness stage may have resulted in a different outcome. Further studies are necessary to clarify how the clinical characteristics of the disease affect IL-6 levels.

The major limitation of the present study was the uncontrolled medication. The

results showed that neither the chlorpromazine equivalent dose in schizophrenic patients nor the imipramine equivalent dose in MDD patients significantly correlated with CSF IL-6 levels. However, the effects of medication could not be adequately assessed due to the variability in types and doses. Evidence shows that both antipsychotic and antidepressant treatment decrease peripheral IL-6 levels (Hiles et al, 2012; Miller et al, 2011). If similar effects occur in the CSF, the increase in CSF IL-6 levels would be more prominent in untreated patients than observed in the medicated patients in the present study. The present study provides evidence that IL-6 levels of central origin may be increased in patients receiving treatment in the real-world setting. However, the possible confounding effects of medications must be addressed in future studies including medication-free patients. Different smoking prevalence between patients and controls may have also influenced the findings of the present study. The results of comparison in only non-smoking subjects indicate that CSF IL-6 levels are increased in patients with schizophrenia regardless of the smoking status. However, a larger number of non-smoking subjects is needed to confirm the results for MDD patients. Another limitation was that the time of day of sampling was not consistent across subjects.

Although no significant association was found between CSF IL-6 levels and the sampling time of day, larger sample size is necessary to clarify the influence of sampling time on IL-6 levels. However, because the average time of day of sampling was similar between diagnostic groups, it is unlikely that the sampling time of day had a major impact on the overall results of the present study. Finally, the cross-sectional design of the study did not allow determination of whether the increased IL-6 levels preceded or resulted from illness onset. The lack of significant correlation with PANSS or HAMD-21 scores suggests that IL-6 levels are not greatly influenced by the severity of the symptoms. However, further studies with a longitudinal design are required to investigate how CSF IL-6 levels change during the course of the disease.

In conclusion, CSF IL-6 levels were significantly increased in patients with schizophrenia and those with MDD. No significant correlation was observed between CSF and serum IL-6 levels. The present findings suggest that IL-6 of central origin is associated with the pathophysiology of these disorders.

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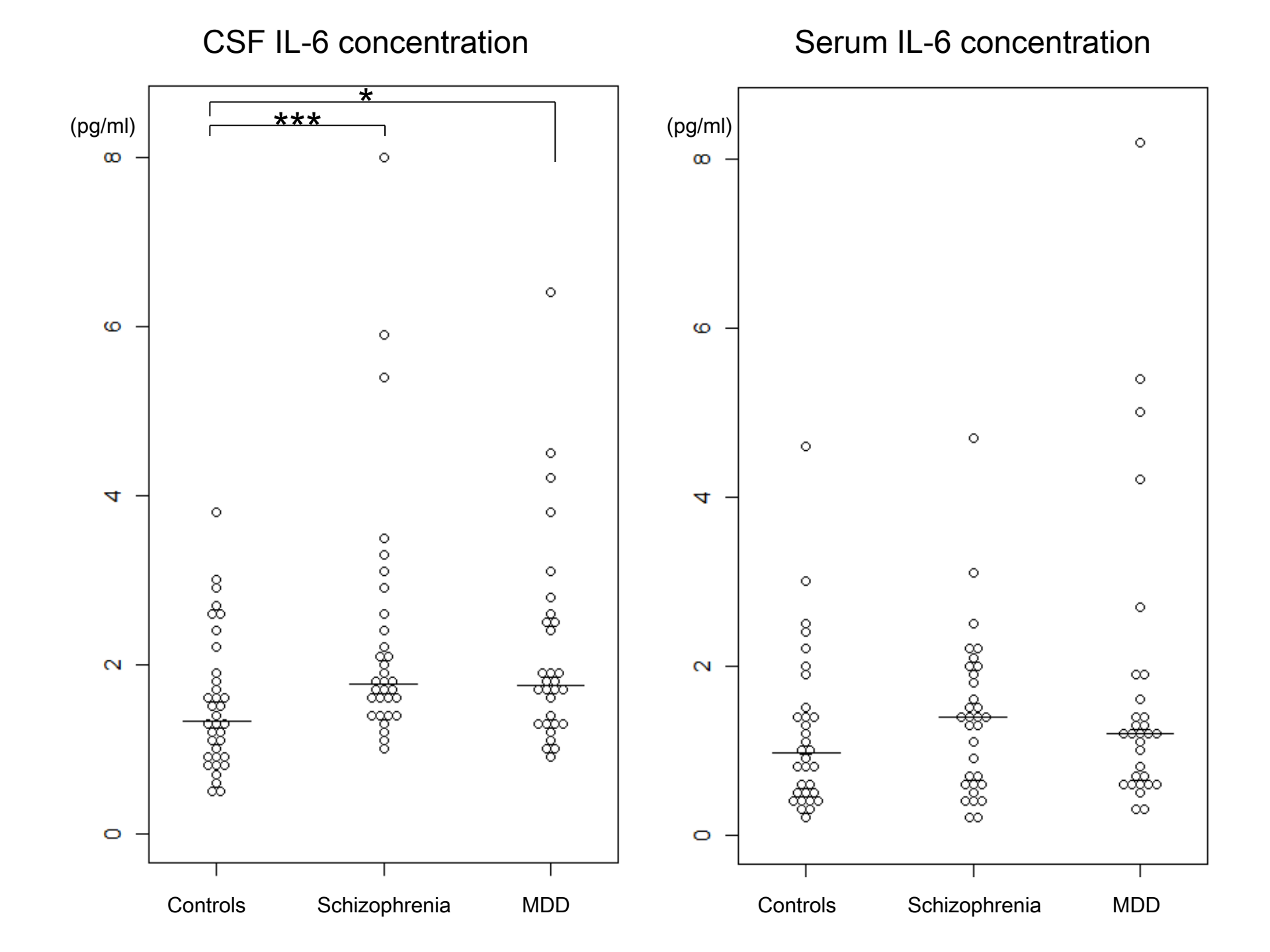
Figure legends

Figure 1: CSF and serum IL-6 levels in patients with schizophrenia, those with major depressive disorder, and healthy controls

CSF IL-6 levels of both the patients with schizophrenia and those with MDD were significantly higher compared to that of the healthy controls. The horizontal lines indicate the median value of each group.

* $P < 0.05$, *** $P < 0.005$ (Mann-Whitney U test)

n.s.: no significant difference; MDD: major depressive disorder; CSF: cerebrospinal fluid; IL-6: interleukin-6


CSF IL-6 concentration
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Serum IL-6 concentration
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Controls
Schizophrenia
MDD

Table 1: Demographic and clinical characteristics

	Controls (N= 35)	Schizophrenia (N= 32)	MDD (N= 30)	Analysis
Age [years]	41.3 (16.4)	40.8 (8.8)	42.7 (8.2)	$F = 0.21$, $P = 0.81$
Gender [M/F]	21/14	20/12	19/11	$\chi^2 = 0.08$, $P = 0.96$
Age at onset [years]		25.0 (8.0)	33.6 (13.3)	
Illness duration [years]		16.2 (7.9)	8.8 (8.9)	
BMI	23.4 (4.0)	24.2 (5.1)	23.1 (4.3)	$F = 0.47$, $P = 0.63$
%smokers	11.4	50.0	46.7	$\chi^2 = 13.5$, $P < 0.01$
CP equivalent dose [mg/day]	0.0 (0.0)	803.5 (583.0)	83.7 (175.2)	$F = 50.2$, $P < 0.01$
IMI equivalent dose [mg/day]	0.0 (0.0)	15.6 (48.7)	164.3 (128.6)	$F = 43.7$, $P < 0.01$
PANSS positive scores		13.2 (5.1)		
PANSS negative scores		14.5 (5.5)		
HAMD-21 scores			13.3 (9.8)	
Time of day of sampling [h]	1340 (0139)	1327 (0129)	1309 (0141)	$F = 0.42$, $P = 0.66$
Number of days between sample collection and IL-6 assay	308 (140)	292 (144)	293 (150)	$F = 0.13$, $P = 0.88$

Values are shown as mean (standard deviation).
MDD: major depressive disorder; BMI: body mass index;
CP: chlorpromazine; IMI: imipramine; PANSS: Positive and Negative Syndrome Scale;
HAMD-21: 21 item Hamilton Rating Scale for Depression

Table 2: Association between cerebrospinal fluid IL-6 levels and clinical factors

		Controls	Schizophrenia	MDD
Spearman's correlation coefficients between CSF IL-6 levels and clinical factors				
Age [years]		$\rho = 0.18$	$\rho = 0.36$ †	$\rho = 0.062$
Age at onset [years]			$\rho = 0.41$ †	$\rho = -0.057$
Illness duration [years]			$\rho = 0.079$	$\rho = 0.067$
BMI		$\rho = 0.36$ †	$\rho = 0.27$	$\rho = 0.11$
CP equivalent dose [mg/day]			$\rho = 0.12$	$\rho = -0.28$
IMI equivalent dose [mg/day]			$\rho = 0.12$	$\rho = 0.044$
PANSS positive scores			$\rho = 0.065$	
PANSS negative scores			$\rho = 0.12$	
HAMD-21 scores				$\rho = -0.036$
Time of day of sampling [h]		$\rho = 0.088$	$\rho = 0.023$	$\rho = -0.11$
Number of days between sample collection and IL-6 assay		$\rho = -0.23$	$\rho = 0.066$	$\rho = -0.17$
Mean (standard deviation) CSF IL-6 levels [pg/ml]				
Gender	Men	1.70 (0.78)	2.57 (1.61)	2.37 (1.37)
	Women	1.30 (0.78)	1.92 (1.29)	1.75 (0.83)
Smoking status	Smokers	1.44 (0.80)	2.06 (0.68)	2.60 (1.48)
	Nonsmokers	1.55 (0.81)	2.60 (2.03)	1.74 (0.80)

† $P < 0.05$

MDD: major depressive disorder; CSF: cerebrospinal fluid; BMI: body mass index; CP: chlorpromazine; IMI: imipramine; PANSS: Positive and Negative Syndrome Scale; HAMD-21: 21 item Hamilton Rating Scale for Depression