Therefore, the hypothesis predicts that the risk of preeclampsia, eclampsia, or stillbirth may be increased in the birth of patients with schizophrenia as well as in the pregnancies of women with schizophrenia. Indeed, an excess of stillbirths and neonatal deaths among women with schizophrenia has been reported by several investigators (Sobel, 1961; Rieder et al., 1975; Modrzewska, 1980; Webb et al., 2005).

Furthermore, there has been a body of evidence for an increased risk of obstetric complications in the birth of patients with schizophrenia (Dalman et al., 1999; Cannon et al., 2002). A meta-analysis of population-based data (Cannon et al., 2002) found significant estimates for three main categories of obstetric complications: (1) complications of pregnancies, (2) abnormal fetal growth and development, and (3) complications in delivery. Among all, preeclampsia was the strongest individual risk factor detected in the largest single population-based cohort study to date (Dalman et al., 1999).

Although obstetrical events in schizophrenia are often considered as having a direct causative effect, none of the available data can refute the hypothesis that they are merely markers of some other causal process (Rapoport et al., 2005), such as mitochondrial dysfunction which is implicated in this hypothesis.

5.3.7 An apparent signature of positive selection in schizophrenia-associated genes

Since the positive selection of the schizophrenia-associated alleles mentioned above occurs only in the predisposed matrilineal pedigrees, a ubiquitous subpopulation in humans, frequencies of those alleles may not be so high in the general population as if the selection had occurred *recently* in the general population.

Thus, the hypothesis predicts that every schizophrenia-associated nuclear gene shows an apparent signature as if it had been subject to a positive selection in the recent evolutionary history of humans. Recent two reports (Lo et al, 2007; Crespi et al., 2007) seem to be in line with this prediction.

On the other hand, the nuclear genome model predicts that every schizophrenia-associated nuclear gene shows an apparent signature of negative selection due to the strong negative selection pressure.

5.3.8 Genomic instability

It is generally thought that a major cause of DNA damage that leads to mutations is reactive oxygen species, which are generated as a normal part of oxygen metabolism but are also produced by ionising radiation, metabolism of exogenous compounds (Hussain et al., 2003; Finkel, 2003). It has been shown that endogenous mitochondrial oxidative stress can induce many types of DNA damage including double strand breaks, end-to-end fusions, base and sugar modifications, DNA-protein cross-links, and gross chromosomal rearrangements (Ragu et al., 2007; Samper et al., 2003).

Therefore, the hypothesis predicts that the enhanced oxidative stress may cause genomic instability during meiosis and/or early phase of ontogeny, producing increased rates of random point mutations and/or structural variants of the nuclear genome in the

predisposed population. In addition, genomic instability may be more pronounced in males due to lack of antioxidant protection by estrogen.

There have been numerous reports of associations between schizophrenia and chromosomal abnormalities including fragile sites, reciprocal translocations, inversions, insertions, deletions, disomy and trisomy in many autosomes, and sex chromosome aneuploidies (Macintyre et al, 2003). However, with an exception of 22q11 deletion, none of these have been consistently replicated, and with another exception of (1,11) (q42;q14.3) balanced translocation, none provides convincing evidence for the location of a 'susceptibility' gene (Kirov et al., 2005).

A popular explanation in the nuclear genome model may be that most of these structural variants are coincidental findings of no clinical significance. Alternatively, those alterations may indicate genomic instability in schizophrenia. An increased risk of schizophrenia in individuals with 22q11 deletion (Pulver et al., 1994; Murphy et al., 1999) might be due to haplodeficiency of presumptive resistance genes of gain-of-function type and/or presumptive facilitating genes of loss-of-function type aggregated on 22q11.

More recently, it has been reported that rare structural variants such as microdeletions or microduplications of sizes ranging from 100kb to 15MB throughout the genome are more frequent among individuals with schizophrenia than unaffected individuals (Walsh et al., 2008). While many of those structural variants duplicate or delete genes in neurodevelopmental pathways, one third of those do not disrupt genes, leaving their role in causation of the disease unwarranted. Another recent report (Xu et al., 2008) has shown that *de novo* copy number mutations are increased in sporadic schizophrenia. However, the cytobands of those copy number mutations are diverse among the affected individuals and their roles in the pathogenesis still remain unclear. Therefore, no available data can refute the possibility that those structural variants and copy number mutations are not the causes of schizophrenia but the results of the genomic instability in schizophrenia predicted by our hypothesis.

Indeed, direct measure of the de novo mutation rates shows an increased mutation rate in schizophrenia (Awadalla et al., 2010), and genomic and epigenomic instability has been suggested in schizophrenia (Smith et al., 2010). Furthermore, it has been shown that blood cells from patients with schizophrenia present a higher rate of folate-sensitive fragile sites, and that male patients exhibit twice as many fragile sites as females while there are no age effects (Demirhan et al., 2006). This sex difference may indicate that increased fragile sites expression (genomic instability) is the results of enhanced oxidative stress in patients with schizophrenia.

6. Conclusion

Genetic research of schizophrenia based on the nuclear genome model has been one of the most active areas in psychiatry for the past two decades. Although this effort is ongoing, results of association studies have been inconsistent and the situation of molecular genetics of schizophrenia today has become much confused just contrary to our expectation. The consistent major epidemiological findings of schizophrenia, coupled with the results of association studies to date, argue against the nuclear genome model for schizophrenia.

Rather, they seem to argue in favor of the mitochondrial genome model, suggesting a necessity of paradigm shift from the nuclear genome model to the mitochondrial genome model in genetic research of schizophrenia in the coming years.

Note: Cross-generational reduction of females with pathogenic genes in the mitochondrial genome model

At first we define several notations. N_1: the number of normal females in the first generation; N_2: number of female offspring of normal females; S_1: the number of unaffected female siblings of patients in the first generation; S_2: the number of female offspring of unaffected female siblings of patients; P_1: the number of female patients; P_2: the number of female offspring of female patients; r ($0 < r < 1$): the proportion of gene carriers in normal females in the first generation. Then the number of female gene carriers in the first generation is $(rN_1 + S_1 + P_1)$ and the frequency of female gene carriers in the first generation is given by:

$$f_1 = \frac{rN_1 + S_1 + P_1}{N_1 + S_1 + P_1} = r + \frac{S_1 + P_1}{N_1 + S_1 + P_1} \cdot (1 - r) .$$

And the frequency of female gene carriers in the second generation is given by:

$$f_2 = \frac{rN_2 + S_2 + P_2}{N_2 + S_2 + P_2} = r + \frac{S_2 + P_2}{N_2 + S_2 + P_2} \cdot (1 - r) .$$

Thus we have (**Table 3**):

$$-\Delta = f_1 - f_2 = \left(\frac{S_1 + P_1}{N_1 + S_1 + P_1} - \frac{S_2 + P_2}{N_2 + S_2 + P_2} \right) \times (1 - r) < 5.06 \times 10^{-3} .$$

	N	S	P	Total	$(S+P)$/Total
# of females	410,093	11,873	4,784	426,750	0.03903
# of female children	366,460	10,969	1,917	379,346	0.03397
$-\Delta$					$0.00506 \times (1 - r) < 5.06 \times 10^{-3}$

Table 3. Epidemiological data by Haukka et al. (2003)

In this largest-sampled cohort study to date, Haukka et al. comprised all births in Finland during 1950-1959 (N=870,093) and followed up through the National Hospital Discharge Register for Hospitalizations between 1969 and 1992. *N*: normal females; *S*: unaffected female siblings of patients; *P*: female patients with schizophrenia

7. References

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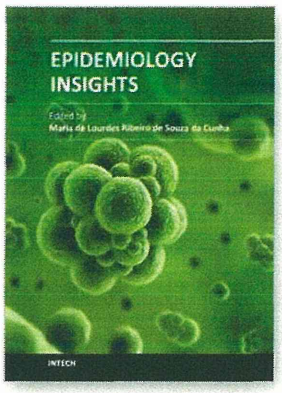

Epidemiology Insights

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This book represents an overview on the diverse threads of epidemiological research, brings together the expertise and enthusiasm of an international panel of leading researchers to provide a state-of-the art overview of the field. Topics include the epidemiology of dermatomycoses and Candida spp. infections, the epidemiology molecular of methicillin-resistant Staphylococcus aureus (MRSA) isolated from humans and animals, the epidemiology of varied manifestations neuro-psychiatric, virology and epidemiology, epidemiology of wildlife tuberculosis, epidemiologic approaches to the study of microbial quality of milk and milk products, Cox proportional hazards model, epidemiology of lymphoid malignancy, epidemiology of primary immunodeficiency diseases and genetic epidemiology family-based. Written by experts from around the globe, this book is reading for clinicians, researchers and students, who intend to address these issues.

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Case Report

Atypical FTLD-FUS associated with ALS-TDP: A case report

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A 30-year-old Japanese woman without relevant family history presented with a behavioral abnormality followed by motor weakness about 14 years later. The patient died at age 45. Post mortem examination revealed degeneration of the frontal and temporal lobes, as well as lower motor neurons in the brainstem and spinal cord. These features were reported previously as being consistent with a diagnosis of frontotemporal lobar degeneration (FTLD) with amyotrophic lateral sclerosis (ALS). In the present study, we show abundant fused in sarcoma (FUS)-positive dystrophic neurites but only a few neuronal cytoplasmic inclusions in the frontal and temporal cortices. TAR DNA-binding protein 43 (TDP-43)-positive inclusions were absent in the cerebrum. However, TDP-43-positive inclusions were present in the lower motor neurons of the brainstem and spinal cord. To our knowledge, this is the first report of a case in which FTLD-FUS pathology is of a dystrophic neurites-predominant type and FTLD-FUS is associated with ALS-TDP.

Key words: amyotrophic lateral sclerosis, dystrophic neurites, frontotemporal lobar degeneration, FUS, neuronal cytoplasmic inclusions, TDP-43.

INTRODUCTION

In frontotemporal lobar degeneration (FTLD) with fused in sarcoma (FUS) accumulation (FTLD-FUS) and FTLD with TAR DNA-binding protein 43 (TDP-43) accumulation (FTLD-TDP), aggregates of pathological proteins occur principally in two forms, neuronal cytoplasmic inclusions (NCI) and dystrophic neurites (DN). There is a pathological subtype of FTLD-TDP in which DNs are the predominant form of TDP-43 accumulation in the cerebral cortex. However, thus far there has been no report of DN-predominant pathology in FTLD-FUS.[1–5] We describe here a case associated with DN-predominant accumulation of FUS in the cerebral cortex.

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CASE

In 2001, one of us (KT) reported an autopsy case of unusual FTLD.[6] The patient developed a behavioral variant of frontotemporal dementia (bvFTD) at age 30. Approximately 14 years later, she showed symptoms and signs of amyotrophic lateral sclerosis (ALS). Post mortem examination revealed atrophy of the frontal and temporal lobes. Atrophy was particularly evident in the convexity of the frontal lobes and in the caudate nucleus (Fig. 1A). Ubiquitin immunohistochemistry demonstrated NCI in the cerebral cortex and amygdala. In the hippocampal dentate gyrus, a small number of DN were seen but no NCI or neuronal intranuclear inclusions (NII) were found.[6]

In the present study, we re-examined this case with immunohistochemistry using the following antibodies: anti-α-internexin (Santa Cruz Biotechnology, Santa Cruz, CA, USA: 2E3), anti-TDP-43 (Proteintech, Chicago, IL, USA, 10782-2-AP), anti-phosphorylated TDP-43 (pS403/404),[7] and anti-FUS (Sigma-Aldrich, St Louis, MO, USA, HPA008784 and Proteintech, 11570-1-AP). Sections were pretreated by autoclaving for 10 min in 10 mmol sodium citrate buffer, pH 6.0, at 120°C.

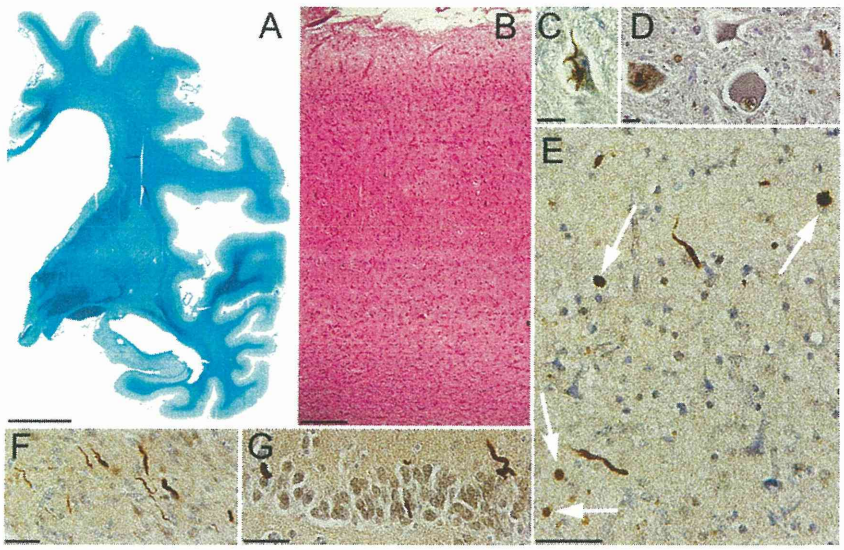

Fig. 1 (A) The left hemisphere showing atrophy of the frontal and temporal cortices and the caudate nucleus. KB staining. (B) HE staining of the entire depth of the frontal cortex. Tissue rarefaction is evident, particularly in the deep layers. (C) A TAR DNA-binding protein 43 (TDP-43)-positive skein-like inclusion in the motor nucleus of the trigeminal nerve. (D) TDP-43-positive inclusions in the spinal cord. (E) Fused in sarcoma (FUS)-positive dystrophic neurites (DN) and dot-like structures (arrows) in the superficial layers of the frontal cortex. (F) FUS-positive DN in the deep layers of the frontal cortex. (G) FUS-positive DN in the hippocampal dentate gyrus. Scale bars = 1 cm (A), 200 μm (B), 20 μm (C, D) and 50 μm (E–G).

In the cerebral cortex, degeneration was more severe in the deep layers than in the superficial layers (Fig. 1B). In subcortical structures, neuronal loss was evident in the caudate nucleus, amygdala, hypoglossal nucleus, dorsal vagal nucleus and spinal cord anterior horn (Table 1). As reported previously, we were not able to confirm the presence of Bunina bodies by HE staining. Apparent NCIs were not visible by HE staining or by α-internexin immunostaining.

A characteristic feature of this case was the accumulation of TDP-43 and FUS in distinct regions of the CNS. TDP-43-positive NCI occurred in the substantia nigra, trochlear nucleus, motor nucleus of the trigeminal nerve (Fig. 1C) and hypoglossal nucleus, as well as in the spinal cord anterior horn (Fig. 1D). TDP-43-positive glial cytoplasmic inclusions (GCI) were also present in all of these regions except for the trochlear nucleus. TDP-43 accumulation was absent in the cerebrum. In contrast, FUS-positive NCI and DN were seen in the cerebral cortex as well as in some subcortical structures. In the cerebral cortex and caudate nucleus, FUS-positive DN predominated over NCI. FUS immunostaining revealed far more numerous DN than did ubiquitin immunostaining. In addition to DN, FUS-positive dot-like structures were seen in the neuropil. The dot-like structures were present mainly in the cortical superficial layers (Fig. 1E), whereas the DNs were frequent in the deep layers (Fig. 1F). In the hippocampal dentate gyrus, a small number of DNs were found but no NCIs or NIIs were seen (Fig. 1G). In the subcortical structures, accumulation of FUS occurred in the caudate nucleus, amygdala, locus coeruleus and periaqueductal gray matter. FUS accumulation was absent in the medulla oblongata and spinal cord. FUS-positive GCIs were not found. The distribution and the degree of TDP-43 and FUS accumulation are summarized in Table 1. Occurrence of abnormal protein aggregates generally paralleled the severity of degenerative changes.

DISCUSSION

In the present case, both TDP-43 and FUS were deposited in a single patient. However, the distribution was entirely different. A recent article described association of FUS with TDP-43 accumulation in sporadic ALS.[8] We were not able to find any overlap between the accumulation of FUS and TDP-43 in this patient. The long interval of more than a decade between the occurrence of bvFTD and ALS suggests that the TDP-43 pathology may not be relevant to the preceding FUS pathology. Therefore, the current neuropathological diagnosis of this case would be FTLD-FUS complicated with ALS-TDP, although such a situation should be extremely rare.

In addition, it has to be noted that this case is atypical of FTLD-FUS. Degenerative changes were relatively mild in the putamen, globus pallidus, hippocampal CA1 and dentate gyrus, subiculum and entorhinal cortex compared with typical FTLD-FUS cases. In such areas, FUS accumulation was also mild. More importantly, FUS accumulation occurred predominantly in the form of DN in the cerebral cortex, hippocampal dentate gyrus and caudate nucleus. To our knowledge, no report has been made so far on FTLD-FUS cases with DN-predominant pathology. Recently, the morphology of abnormal FUS accumulations has been described in detail for each neuropathological subtype of FLTD-FUS.[2] Our case does not seem to match any previously described subtypes. Obviously, there is a need for

Table 1 Distribution and severity of CNS lesions

	FUS+ DN	FUS+ dots	FUS + NCI	TDP-43+ NCI	Degeneration
Superior frontal gyrus (ant./post.)	4/3	3/2	2/2	0/n	+++/+++
Middle frontal gyrus (ant./post.)	3/2	2/2	1/2	0/n	+++/+++
Inferior frontal gyrus (ant.)	4	3	2	0	+++
Orbital gyrus	3	3	2	0	+++
Primary motor cortex	3	3	1	0	++
Superior temporal gyrus (mid/post.)	1/1	1/1	1/2	n/0	+/±
Middle temporal gyrus (mid/post.)	2/2	2/2	1/2	n/0	++/+
Inferior temporal gyrus (mid/post.)	2/2	2/2	1/2	n/0	++/+
Postcentral gyrus	1	1	1	0	+
Supramarginal gyrus	2	2	2	0	+
Insular cortex	3	2	2	0	+++
Cingulate gyrus (ant./post.)	4/2	4/3	2/2	n/0	++/++
Amygdala	1	2	2	n	++
Ambient gyrus	3	2	1	n	++
Hippocampal CA1	1	0	0	0	-
Hippocampal dentate gyrus	2	1	0	0	-
Subiculum	1	0	1	0	+
Entorhinal cortex	2	2	2	0	+
Transentorhinal cortex	2	3	2	0	++
Caudate nucleus	1	3	1	0	+++
Putamen	0	0	0	0	+‡
Globus pallidus	0	0	0	n	+‡
Thalamus†	0	0	0	0	+
Lateral mamillary nucleus	4	3	0	n	+
Nucleus basalis of Meynert	0	1	0	n	+‡
Cerebellar dentate nucleus	n	n	n	n	±
Periaqueductal gray matter	1	1	1	0	±
Oculomotor nucleus	n	n	n	n	±
Trochlear nucleus	0	0	0	3	−
Red nucleus	n	n	n	n	±
Substantia nigra	0	0	0	1	+
CST at the level of midbrain	n	n	n	n	+
FPT at the level of midbrain	n	n	n	n	−
Locus ceruleus	0	0	2	0	−
Pontine nucleus	0	0	0	0	±
Motor nucleus of trigeminal nerve	0	0	0	3	+
CST at the level of pons	n	n	n	n	+
Dorsal vagal nucleus	0	0	0	0	++
Hypoglossal nucleus	0	0	0	3	+++
Inferior olivary nucleus	0	0	0	0	±
Pyramid	n	n	n	n	+
Anterior horn of spinal cord	0	0	0	3	++
CST of spinal cord	n	n	n	n	+

The degree of TDP-43 and FUS accumulation was assessed according to the grading system employed by Neumann *et al.*[5] FUS, fused in sarcoma; TDP-43, TAR DNA-binding protein 43; DN, dystrophic neurite; dots, dot-like structures; NCI, neuronal cytoplasmic inclusion; ant., anterior portion; post., posterior portion; mid, middle portion; CST corticospinal tract; FPT, frontopontine tract; n, not available or not evaluated. The severity of degeneration in the gray matter: −, no degeneration; ±, no neuronal loss but gliosis; +, slight neuronal loss; ++, moderate neuronal loss; +++, severe neuronal loss. Degeneration in the white matter: +, present; -, absent. †The region other than the lateral mamillary nucleus was evaluated. ‡Remaining neurons showed atrophy suggestive of anoxic changes. The cerebrum was evaluated in the left hemisphere.

further, extensive analyses of many cases for abnormal accumulation of FUS and TDP-43.

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

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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. The present findings suggest that IL-6 of central origin is associated with the pathophysiology of schizophrenia and MDD, although confounding effect of smoking status can not be entirely excluded.

1. 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. (1995) reported no significant difference in CSF IL-6 levels between schizophrenic patients and healthy controls, while 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

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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.

1.1. 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.

2. Material and methods

2.1. 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.

2.2. 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%.

2.3. 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).

2.4. 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

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.

(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).

3. 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. Fig. 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: −0.18–0.55); schizophrenia, $\rho = 0.23$ (−0.13–0.59); MDD, $\rho = 0.19$ (−0.18–0.57); and all groups combined, $\rho = 0.20$ (−0.006–0.41). 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.

4. 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

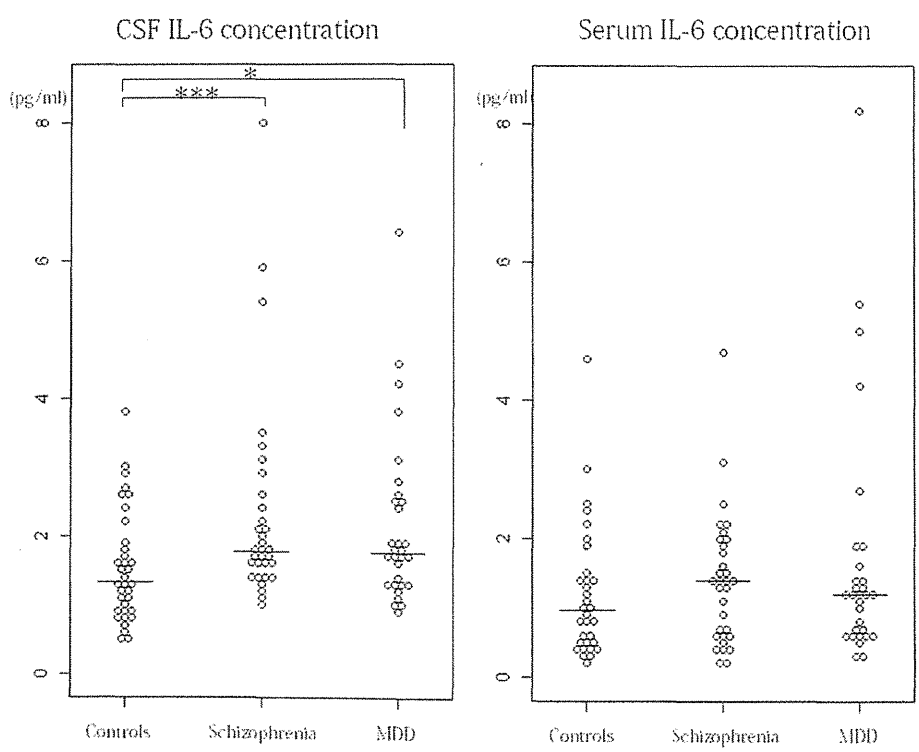

Fig. 1. CSF and serum IL-6 levels in patients with schizophrenia, those with major depressive disorder, and healthy controls CSF IL-6 levels of both the patients with schizophrenia and those with MDD were significantly higher compared to that of the healthy controls. The horizontal lines indicate the 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.

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]		$\rho = 0.18$	$\rho = 0.36^a$	$\rho = 0.062$
Age at onset [years]			$\rho = 0.41^a$	$\rho = -0.057$
Illness duration [years]			$\rho = 0.079$	$\rho = 0.067$
BMI		$\rho = 0.36^a$	$\rho = 0.27$	$\rho = 0.11$
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)

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.
[a] $P < 0.05$.

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 and Maes, 2012) as well as schizophrenia (Balu and 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, 2012).

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