Changes in Serum Interleukin-2, -6, and -8 Levels Before and During Treatment With Risperidone and Haloperidol: Relationship to Outcome in Schizophrenia

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Background: Many studies have indicated that immune cytokines may be involved in the pathophysiology of schizophrenia. Recently, there have been reports that typical and atypical antipsychotic drugs may influence the levels of cytokines or cytokine receptors. The aim of this study was to compare the effect of typical and atypical antipsychotic drugs on serum interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-8 (IL-8) and to investigate the relationship between the changes in cytokines and the therapeutic outcome in schizophrenia.

Method: From April 1996 to August 1997, seventy-eight inpatients with a diagnosis of chronic schizophrenia (DSM-III-R) were randomly assigned to 12 weeks of treatment with 6 mg/day of risperidone or 20 mg/day of haloperidol. Clinical efficacy was determined using the Positive and Negative Syndrome Scale. Serum IL-2 was assayed by radioimmunometric assay, and serum IL-6 and IL-8 concentrations were measured by quantitative enzyme-linked immunosorbent assay in patients and 30 sex- and age-matched normal subjects.

Results: Both risperidone and haloperidol reduced the elevated serum IL-2 concentrations in schizophrenia, and no significant difference was noted in the reduction of serum IL-2 concentrations between risperidone and haloperidol treatment. Neither risperidone nor haloperidol showed significant influence on the higher serum IL-6 or IL-8 concentrations in schizophrenia. Correlations between serum IL-2 or IL-8 concentrations at baseline and the therapeutic outcome were observed, demonstrating that patients presenting with low concentrations of serum IL-2 or IL-8 at baseline showed greater improvement and patients presenting with higher serum IL-2 or IL-8 concentrations at baseline showed less improvement after treatment.

Conclusions: Both typical and atypical antipsychotic drugs may at least partially normalize abnormal immune alterations in schizophrenia. Some immune parameters at baseline may be useful for predicting the neuroleptic response of schizophrenic patients.

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The precise etiology and pathophysiology of schizophrenia remain unknown. Cytokines, known as chemical messengers between immune cells with numerous important functions in immune regulation, have been one of the recent focal points of immunologic research in schizophrenia.[1–3] Some investigators have proposed that interrelationships may exist among cytokines, neurotransmitter abnormalities, and symptomatology in schizophrenia.[1,2,4] Interestingly, it has been shown[4] that the ability of peripherally applied interleukin-2 (IL-2) and interleukin-6 (IL-6) could enhance catecholaminergic neurotransmission in the rat frontal cortex and hippocampus, suggesting that these cytokines play pivotal roles in the pathophysiology of schizophrenia.

Both in vivo and in vitro studies have provided a number of indications that schizophrenia may be accompanied by alterations in cytokines, cytokine receptors, and cytokine activity modifiers, suggesting suppression of some immune functions and activation of others.[5,6] For example, some studies have reported increased serum levels of IL-1, IL-1 receptor antagonist (IL-1RA), IL-6, IL-6 receptors (soluble interleukin- [sIL] 6R), and tumor necrosis factor (TNF)-α,[7–15] as well as increased IL-2 levels in the cerebrospinal fluid (CSF)[16,17] and serum.[18,19] However, the results of the measure of the levels of cytokines and cytokine receptors in schizophrenia are often contradictory. For example, decreased or normal IL-2 levels in serum or CSF,[20,21] unchanged sIL-2R and serum IL-6 concentrations,[22] and decreased sIL-6R concentrations have also been observed.[23]

Until now, in vitro experiments have provided increasingly consistent results, showing decreased mitogen-

induced lymphocyte production of IL-2 and interferon-γ (IFN-γ),[24–28] which are probably the most robust findings of immunologic research in schizophrenia. The reduced production of IL-2 and IFN-γ is possibly due neither to a lower number of T cells nor to an excess production of IL-10, which is the most potent suppressor of IFN-γ, but might rather be caused by intrinsic factors that are still unknown.[29] However, conflicting results were also reported concerning in vitro findings, for example, elevated production of IL-2 and IFN-γ.[30,31] Hence, the available evidence of cytokine dysregulation in schizophrenia is quite inconsistent. Many factors, such as differences in techniques of measuring cytokine levels, differences in tested material, recruitment of illness, and exposure to neuroleptic treatment, may be responsible for the discrepancies.

Immunomodulatory effects of antipsychotic medication were discovered in the 1950s.[32] Recently, there have been reports[5,32] that typical and atypical antipsychotic drugs may influence the levels of cytokines or cytokine receptors. For example, the typical antipsychotic drug haloperidol normalizes the initially increased serum IL-6 and IL-6R,[10,13] whereas repeated administration of atypical antipsychotics, i.e., clozapine and risperidone, significantly increases plasma concentrations of IL-2R, IL-6, and TNF-α.[13,33] However, the effects of antipsychotics on cytokine levels have also been the subject of controversy, since some studies have demonstrated that serum or plasma concentrations of some cytokines or cytokine receptors, such as IL-6, sIL-2R, IL-1RA, or TNF-α, in schizophrenia patients did not vary after treatment with antipsychotic drugs for 6 weeks or 8 weeks.[34,35] The findings of the effects of neuroleptic medications on in vitro cytokine production, however, seem to be consistent. For example, Bessler et al.[36] reported a decreased production of IL-2 in unmedicated patients with schizophrenia, which remained unchanged during neuroleptic treatment. More recently, Rothermundt et al.[37] also found, using a longitudinal design, that neuroleptic treatment did not exert an influence on the production of IL-2 and IFN-γ production in schizophrenic patients who were drug-naive or had not received any drug treatment for at least 6 months, and Arolt et al.[27] replicated this result. On the basis of these results taken together, it is our view that whether neuroleptic drugs influence cytokine levels in schizophrenia remains an important issue deserving further investigation.

Recently, our own study[19] showed that serum levels of IL-2, IL-6, and IL-8 were elevated in patients with a chronic form of schizophrenia who were free of antipsychotic medication for at least 2 weeks. Moreover, there was a relationship between these cytokines and the clinical symptoms of schizophrenia. A recent study[6] also reported significantly increased serum IL-8 levels in schizophrenia and no effects of repeated administration of atypical antipsychotics on serum IL-8. Until recently, however, most studies focused on the pathogenesis of immunologic findings in a cross-sectional design, and few studies have examined the relationships between alteration of serum concentrations of cytokines, psychopathology, and also the responses of patients to neuroleptic treatment in schizophrenia using a longitudinal study design. In addition, it has been reported[5,14] that alterations in the immune system are more pronounced in patients with treatment-resistant schizophrenia.

Therefore, on the basis of these clinical and experimental reports, the present study was undertaken to assess IL-2, IL-6, and IL-8 serum concentrations in a large cohort of chronic, treatment-resistant schizophrenic patients before and after 12-week treatment with risperidone and haloperidol using a randomized double-blind design. The results of this clinical trial have been reported previously.[38] The purposes of the present study were to explore (1) whether there was a significant difference between the influence of typical and atypical antipsychotic drugs on serum IL-2, IL-6, and IL-8 levels; (2) whether there were any relationships between the changes in serum IL-2, IL-6, and IL-8 levels and the changes to psychopathologic symptoms; and (3) whether serum cytokine concentrations could predict the responses of schizophrenic patients to neuroleptics.

METHOD

Subjects

Schizophrenic subjects were the same physically healthy Chinese inpatients who participated in the original study.[19] They were diagnosed as meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition Revised (DSM-III-R) criteria for schizophrenia using the Structured Clinical Interview for DSM-III-R (SCID). All schizophrenic patients were of the chronic type, with an illness course of at least 5 years. The patients and 30 normal volunteers were recruited during the same period from the Beijing, China, area. In view of the possible alteration of cytokine levels in smokers, which is reported to occur at high rates in schizophrenic patients,[39] the controls were intentionally chosen to match the patients in terms of the number of cigarettes smoked per day and the time course of smoking. Characteristics of the patients and normal controls are summarized in Table 1.

All subjects gave informed written consent to participate in the study, which was approved by the Institute Review Board of the Institute of Mental Health at Peking University, Beijing, China. They were screened with a complete physical, neurologic, and psychiatric evaluation conducted by the clinical physicians. Patients with infections, allergies, or a past history of autoimmune disorders were excluded. Neither the schizophrenic patients nor the control subjects suffered from substance abuse/dependence or were receiving immunosuppressive drugs.

Table 1. Demographics of Schizophrenic Patients and Normal Control Subjects

Characteristic[a]	Risperidone (N = 41)	Haloperidol (N = 37)	Control Subjects (N = 30)
Sex, M/F, N	30/11	30/7	22/8
Age, mean ± SD, y	43.8 ± 6.4	43.7 ± 8.1	40.4 ± 10.3
Duration of illness, mean ± SD, y	21.6 ± 10.9	19.2 ± 9.4	NA
Smokers, N (%)	28 (68)	24 (65)	19 (63)
Cigarettes smoked per day, mean ± SD	12.4 ± 8.3	12.1 ± 8.1	11.9 ± 5.0

[a]Risperidone, haloperidol, and control groups did not differ from each other on any characteristic.
Abbreviation: NA = not applicable.

Clinical Treatment and Clinical Ratings

The procedure was described in detail in our earlier report.[38] Briefly, the clinical trials consisted of a 2-week placebo lead-in followed by 12 weeks of double-blind treatment. Seventy-eight patients were randomized into the risperidone group (N = 41) or the haloperidol group (N = 37). The dose of risperidone was increased to 6 mg/day and the dose of haloperidol to 20 mg/day during the first week of blind administration, and doses were maintained at those concentrations until the end of the trial. To assess efficacy, the Positive and Negative Syndrome Scale (PANSS)[40] was administered at baseline and at posttreatment by 4 clinical psychiatrists who were blind to treatment conditions.

Measurement of Serum IL-2, IL-6, and IL-8 Concentrations

Serum samples were taken from the schizophrenic patients between 7:00 and 9:00 a.m. at the end of a 2-week washout period and after the 12-week treatment, and once from the control subjects at the pretreatment point.

Serum IL-6 and IL-8 concentrations were measured by quantitative enzyme-linked immunosorbent assay using a commercially available kit (BanDing Biological Inc.; Chinese Academy of Sciences, Beijing, China). The sensitivities were 0.1 ng/mL and 0.2 ng/mL, with intra-assay coefficients of 7% and 4%, respectively, and inter-assay coefficients of 9% and 8%, respectively. Serum IL-2 was assayed by radioimmunometric assay, which was performed in accordance with the manufacturer's instructions. The sensitivity was 0.4 ng/mL, and intra- and inter-assay variation coefficients were 6% and 8%, respectively. All samples were measured by the same investigator, who was blind to the clinical states and the treatment conditions of patients.

Statistical Analyses

Since the majority of the interleukin variables were not normally distributed in patients (Kolmogorov-Smirnov 1-sample test, IL-2 $Z = 1.75$, $p = .004$; IL-6 $Z = 1.78$, $p = .004$; IL-8 $Z = 2.28$, $p = .000$ at baseline; IL-2 $Z = 1.58$, $p = .01$; IL-6 $Z = 1.67$, $p = .007$; IL-8 $Z = 1.92$, $p = .001$ at posttreatment), although all these variables were normally distributed in normal controls (IL-2 $Z = 0.67$, $p = 0.76$; IL-6 $Z = 1.18$, $p = .34$; IL-8 $Z = 0.78$, $p = .72$), the principal outcome analysis consisted of Friedman 2-way analyses of variance (ANOVAs) for differences in IL-2, IL-6, and IL-8 serum concentrations between the schizophrenic patients and healthy controls at baseline and at posttreatment.

Secondary analyses evaluated change in serum IL-2, IL-6, and IL-8 concentrations during treatment with risperidone and haloperidol using the Wilcoxon test or Mann-Whitney test, and the relationships between changes in IL-2, IL-6, and IL-8 concentrations and the changes in psychopathology, with the Spearman correlation implemented in response to the schizophrenic patients' skewed IL measures. Where there was significance, the Bonferroni correction was used if necessary. Demographic characteristics of the risperidone, haloperidol, and control groups were compared by means of Student 2-sample t test for continuous variables and χ^2 test or Fisher exact test for categorical variables. To compare the differences in serum IL-2, IL-6, and IL-8 concentrations between responders and nonresponders, a patient was considered clinically responsive if there was a 20% decrease in the PANSS total score, using a modification of the criteria of Kane et al.[41] The Mann-Whitney test was used to compare the differences in cytokines between subgroups. All statistical tests were 2-tailed and were considered to be statistically significant when the p values were less than or equal to .05.

RESULTS

Clinical Results

Five subjects dropped out during the course of study: 1 was receiving risperidone, and 4 were receiving haloperidol. The details of the results have been described in a previous study.[38] Briefly, the clinical results suggest that risperidone may be superior to haloperidol for treatment-refractory schizophrenia, especially for negative symptoms, but the differences were not found for positive symptoms.

Changes in Serum IL-2, IL-6. and IL-8 Concentrations Before and After Treatment

Friedman 2-way ANOVA on the serum IL-2 concentration showed a significant difference in the healthy controls (3.3 ± 1.4 ng/mL) and the patients at baseline (9.6 ± 5.2 ng/mL) and at posttreatment (6.7 ± 4.6 ng/mL, $\chi^2 = 11.89$, $df = 2$, $p = .003$). The serum IL-2 concentrations of the schizophrenia patients were significantly lower after treatment than before treatment (Wilcoxon test, $Z = –4.33$, $p = .000$). Compared with the healthy controls, patients' serum IL-2 concentrations were significantly higher both at baseline and at posttreatment ($Z = –3.04$, $p = .002$ and $Z = –2.69$, $p = .007$, respectively).

Table 2. Comparison of Serum IL-2, IL-6, and IL-8 Levels at Baseline and Week 12 in Risperidone (N = 41) and Haloperidol (N = 37) Groups (ng/mL)

Interleukin	Medication	Baseline, mean ± SD	Week 12, mean ± SD	Z	p
IL-2	Risperidone	9.8 ± 4.7	7.2 ± 4.9	–3.46	.0015
	Haloperidol	9.9 ± 5.2	6.1 ± 4.3	–3.64	.0011
IL-6	Risperidone	0.3 ± 0.5	0.23 ± 0.4	–0.24	.6800
	Haloperidol	0.2 ± 0.3	0.17 ± 0.2	–0.11	.9200
IL-8	Risperidone	1.2 ± 2.2	0.72 ± 1.1	–1.15	.2800
	Haloperidol	0.9 ± 1.9	0.73 ± 1.2	–0.85	.4800

Abbreviation: IL = interleukin.

Table 3. Intercorrelations Between IL-2, IL-6, and IL-8 in Patients With Schizophrenia Before and After 12-Week Treatment[a]

Interleukin	IL-2T1	IL-2T2	IL-6T1	IL-6T2	IL-8T1	IL-8T2
IL-2T1	…					
IL-2T2	0.41*	…				
IL-6T1	0.21	0.17	…			
IL-6T2	0.15	0.12	0.38*	…		
IL-8T1	–0.32*	–0.18	0.17	0.23	…	
IL-8T2	–0.05	–0.06	–0.15	–0.12	0.36*	…

[a]T1 and T2 indicate interleukin levels at baseline and at posttreatment.
*p < .01.
Abbreviation: IL = interleukin.

Table 2 shows the serum IL-2, IL-6, and IL-8 concentrations at baseline and week 12 in the risperidone and haloperidol groups. A significant difference in IL-2 concentrations was noted before and after treatment for both groups. There was no significant difference between these 2 groups in IL-2 concentrations at posttreatment. Friedman 2-way ANOVA did not display any significant differences in IL-6 or IL-8 concentrations among the control subjects (mean ± SD = 0.18 ± 0.18 ng/mL for IL-6, mean ± SD = 0.32 ± 0.3 for IL-8) or the schizophrenic patients at baseline and at posttreatment (Friedman 2-way ANOVA, $\chi^2 = 2.13$, df = 2, p = .27; $\chi^2 = 1.86$, df = 2, p = .39). The serum IL-6 and IL-8 concentrations of the schizophrenia patients did not vary before and after treatment (Wilcoxon test, Z = –0.17, p = .86; Z = –0.21, p = .72). When IL-6 or IL-8 concentrations in the risperidone and haloperidol groups at baseline and at posttreatment were tested, they were not found to be significantly different from one another (Friedman 2-way ANOVA, $\chi^2 = 3.7$, df = 3, p = .41; $\chi^2 = 3.1$, df = 3, p = .46). No significant difference in IL-6 or IL-8 concentrations was noted before and after treatment in either the risperidone group or the haloperidol group.

Table 3 shows the correlations among IL-2, IL-6, and IL-8 concentrations in patients with schizophrenia before and after treatment. These correlations remained significant when the results were adjusted by the Bonferroni correction, although with a reduced p value.

Table 4 shows the correlations between the serum concentrations of IL-2, IL-6, and IL-8, and clinical variables. There was a significant correlation between the reduction rate of the PANSS total score and the change in IL-2 concentration before and after treatment (r = 0.38, p = .02), as well as with IL-2 or IL-8 concentrations at baseline (r = –0.34, p = .04; r = –0.35, p = .04). The reduction of the PANSS positive subscore showed a significantly negative correlation with the serum IL-2 levels at baseline (r = –0.36, p = .026), as well as with serum IL-8 levels (r = –0.041, p = . 016) at baseline. In addition, some agitation-related items from the PANSS, such as "excitement," "hostility," "poor impulse control," and "uncooperativeness," were examined to determine whether there was an association with cytokine levels. No significant association was noted when these items were examined individually and in combination (all p > .05).

Based on the criterion of a clinical rating of "responder" or "nonresponder" on the PANSS total score, the responder subgroup showed significantly lower IL-8 concentrations at baseline (Mann-Whitney test, Z = –2.12, p = .036) and a trend for lower IL-2 concentrations at baseline than the nonresponder group (p = .06).

DISCUSSION

The major findings of this study are that both risperidone and haloperidol may reduce elevated serum IL-2 levels in schizophrenia, with no significant difference between these 2 drugs. It appears that neuroleptic treatment might help to normalize serum IL-2 levels. The results of haloperidol treatment are compatible with another study[18] which showed that the plasma concentrations of IL-2 and homovanillic acid (HVA) were significantly lowered after 8 weeks of treatment with haloperidol. However, the results of risperidone treatment are not accordant with a more recent study,[42] which showed that plasma IL-2 concentrations were not significantly different before and after treatment with risperidone for 4 weeks.

There is some evidence that antipsychotic drugs may have immunosuppressive effects. In vitro studies have demonstrated that antipsychotic drugs including chlorpromazine, haloperidol, and clozapine significantly suppress mitogen-induced lymphocyte proliferation and the production of IL-2, IL-4, and IFN-γ. These effects are probably mediated through inhibition of IL-2 production by activated T lymphocytes.[43,44] Recently, haloperidol and clozapine were proved to produce similar suppressive effects on the cytokine secretion, including an IL-2 in vitro experiment with lymphocytes from normal subjects and schizophrenic patients.[44] In combination with the present finding, it is suggested that treatment with typical and atypical antipsychotic drugs might produce a similar suppressive effect on serum IL-2 concentrations in schizophrenia.

It is not clear, however, whether the higher serum IL-2 or CSF IL-2 is related to the pathophysiology or etiology

Table 4. Intercorrelations Between IL-2, IL-6, and IL-8 and Clinical Variables in Patients With Schizophrenia Before and After 12-Week Treatment[a]

Variable	IL-2T1	IL-2T2	IL-6T1	IL-6T2	IL-8T1	IL-8T2
Age	0.04 (.78)	0.06 (.66)	0.02 (.87)	0.02 (.88)	0.08 (.55)	0.06 (.64)
Duration of illness	–0.01 (.95)	0.02 (.91)	0.13 (.34)	0.15 (.31)	0.18 (.27)	0.09 (.50)
PANSS total score, T1	–0.19 (.12)	–0.01 (.93)	–0.11 (.39)	–0.09 (.43)	0.17 (.14)	0.11 (.37)
PANSS positive, T1	–0.31 (.006)*	–0.08 (.51)	–0.01 (.93)	–0.06 (.59)	0.07 (.54)	0.12 (.31)
PANSS negative, T1	0.03 (.84)	0.08 (.51)	0.07 (.56)	0.06 (.62)	0.25 (.036)*	0.12 (.31)
PANSS total score, T2	–0.18 (.15)	–0.08 (.52)	0.08 (.49)	0.07 (.53)	0.24 (.046)*	0.24 (.043)*
PANSS positive, T2	0.11 (.35)	–0.01 (.94)	0.01 (.93)	0.01 (.92)	0.20 (.08)	0.11 (.35)
PANSS negative, T2	–0.12 (.32)	–0.02 (.89)	0.01 (.99)	0.01 (.93)	0.29 (.01)*	0.21 (.07)

[a]T1 and T2 indicate baseline or posttreatment, respectively. Values shown as r (p).
*Significant at $p < .05$.
Abbreviations: IL = interleukin, PANSS = Positive and Negative Syndrome Scale.

of schizophrenia. Moreover, the mechanism of antipsychotic drugs' suppression of the serum IL-2 concentrations in schizophrenia remains unknown. Although decreased IL-2 serum concentrations in schizophrenia might be induced, at least partially, by the direct suppressive effect of antipsychotic drugs as cited previously, there may be another possibility: namely, that the decreased serum IL-2 concentrations were mediated by the improvement of symptoms in schizophrenia. Our finding that there was a significant correlation between the reduction rate of PANSS total score and the change of IL-2 concentrations before and after treatment (Table 4) may provide support for this hypothesis.

Studies have shown that IL-2 stimulates the release of dopamine from rat striatal cells,[45] as well as an increase of dopamine turnover in the prefrontal cortex.[32] More interestingly, a range of psychiatric manifestations including delusions, delirium, paranoia, hallucinations, and lethargy has been observed in patients receiving IL-2 immunotherapeutically.[46] More recently, Kim et al.[18] proved that there were significantly positive correlations between IL-2 and HVA and between IL-2 and the Scale for the Assessment of Positive Symptoms.[47] Furthermore, our own results in the present study showed a significantly negative correlation between the reduction of the PANSS positive subscore and the serum IL-2 concentrations at baseline. All these findings suggest that IL-2 may contribute to the pathophysiology of schizophrenia, especially to the positive symptoms. The results of the present study showed that both risperidone and haloperidol produced a similar effect in the reduction of positive symptoms, which may be associated with the medications' similar effect on serum IL-2 concentrations. However, it is worth mentioning that in the present study, the inverse correlation within the schizophrenic patients between IL-2 concentrations and positive symptoms at baseline is in conflict with Kim and colleagues' report.[18] Possible reasons for this difference may be related to the clinical status of patients. For example, the samples in the Kim et al.[18] study were neuroleptic-free for at least 6 months and included some neuroleptic-naive, first-onset patients, in contrast with our samples, who were neuroleptic-free for only 2 weeks and were treatment-resistant as well. Moreover, there was a marked difference in duration of illness and in age of patients in our study and that of Kim et al. [18] The contradiction between the 2 studies' results seems to be further resolved by Petitto et al.,[48] who demonstrated that IL-2 dose-dependently modulated release of endogenous dopamine in a biphasic pattern, increasing release at lower concentrations and inhibiting release at high concentrations from striatal neurons, thus suggesting that different IL-2 levels may play a different role in the pathophysiologic process of schizophrenia. However, a further understanding of the interactions between the positive symptoms, dopaminergic system, and IL-2 concentration changes is warranted before a final conclusion can be made regarding the relationship between IL-2 and positive symptoms in schizophrenia. In addition, the effects of agitation on serum IL levels in schizophrenia should be considered. It is likely that there exists an epiphenomenon—that is, cytokines may increase in response to agitation rather than in response to psychotic symptoms. This possibility may be ruled out in the present study because there was no significant association between agitation-related items from the PANSS and cytokine levels.

The next major findings of this study are that both risperidone and haloperidol produced no significant influence on the increased serum IL-6 or IL-8 concentrations in schizophrenia. First, the result of no significant effects of antipsychotic agents on serum IL-6 concentrations is in contrast to the results obtained by Maes et al.,[10,13] who found that in vivo, typical antipsychotic drugs suppress plasma IL-6, whereas repeated administration of atypical antipsychotics (i.e., clozapine or risperidone) significantly increases plasma IL-6, TNF-α, and IL-2R concentrations.[13,35] However, some other reports,[18,34] including a study by Maes et al.,[5] have demonstrated that antipsychotic treatment did not have an effect on the serum IL-6 levels. Several factors, such as clinical status of patients (acute vs. chronic, active phase vs. remission), ethnicity, illness course, and the different techniques used to measure IL-6 levels might be responsible for the dis-

crepancy. More recently, Song et al.[44] found that an in vitro experiment with haloperidol and clozapine at concentrations within the therapeutic range produced no effects on IL-6 production, which suggests that antipsychotic drugs may not affect the concentrations of serum IL-6 in schizophrenia.

IL-8 is a chemokine cytokine produced by monocytes, macrophages, endothelial cells, and activated T cells. IL-8 is essential for the directional migration of leukocytes during normal and inflammatory processes. In the present study, the negative findings concerning the effects of haloperidol and risperidone on the elevated serum IL-8 concentrations are in agreement with previous findings that repeated administration of atypical antipsychotics, including clozapine and risperidone, has no significant effects on serum IL-8.[6] These results, together with another finding in the present study of a significantly higher IL-8 concentration at baseline in the nonresponder subgroup than in the responder subgroup, suggest that serum IL-8 concentrations may serve as a trait mark for a subgroup of antipsychotic-resistant patients. At present, however, the role of IL-8 in the immune system and the IL-8 levels in the central nervous system, together with the relationship between peripheral IL-8 and central IL-8 or IL-8 and neurotransmitters in the brain, remain unknown; the mechanism underlying our finding about IL-8 in the response to the neuroleptic drugs in schizophrenia cannot be made clear. A further replication study will be needed to elucidate the clinical importance of this relationship.

The third major finding of this study is that there were correlations between the serum IL-2 or IL-8 concentrations at baseline and the therapeutic outcome, demonstrating that patients presenting low concentrations of serum IL-2 or IL-8 at baseline showed greater improvement and patients presenting higher serum IL-2 or IL-8 concentrations at baseline showed less improvement after treatment, which means that these serum cytokines could be used to predict the responses of patients to neuroleptics. Few immunologic factors have been reported to be markers of the therapeutic outcome of neuroleptic treatment in schizophrenia, except for increases in CD3+ and CD4+ T cells[49] or higher serum IL-6 concentrations.[14] In the present study, further analysis on the basis of a clinical rating of "responder" or "nonresponder" on the PANSS total score demonstrated that the responder subgroup showed a significantly lower IL-8 concentration ($p = .036$) or a trend for the significantly lower IL-2 concentrations ($p = .06$) at baseline than the nonresponder subgroup. These results also suggest that patients who are responders to neuroleptic therapy displayed comparatively "normalized" immune indices at baseline, whereas poor responders presented more abnormal immune parameters. Therefore, it seems that serum IL-8 or IL-2 concentrations may be useful for predicting the neuroleptic response of schizophrenic patients. However, this postulation needs to be substantiated further by other studies before a final conclusion can be made.

Several limitations of the present study should be noted here. First is the measure of IL-6 and IL-8 levels: about 30% of patients and 47% of controls had undetectable serum IL-6 levels, and serum IL-8 levels were not detected in about 24% of patients and 53% of controls. Moreover, the results showed that the mean values for IL-6 and IL-8 levels are smaller than the standard deviations, indicating considerable heterogeneity in the levels of these cytokines in this group of patients. Hence, the results of serum IL-6 and IL-8 levels in the present study may be deviated due to values that were undetectable by our assays. The findings of the relationship of serum IL-6 and IL-8 levels to the outcome of treatment may be of limited value due to the shortcomings in measuring IL-6 and IL-8 levels in the current study.

Second, the possible effects of neuroleptics on patients' cytokine levels in the current study should be considered. The patients in our study had been in long-term, chronic treatment with antipsychotic drugs. Although there was a 2-week washout period before the study, no data are available to determine whether a 2-week washout is adequate to reverse possible drug effects on cytokine levels. The patients might not have returned to a normal physiologic state after withdrawal from the medicine. Hence, it would be helpful to clarify this issue in future research by examining the effects of antipsychotic drugs on cytokine levels in naive, first-episode schizophrenic patients.

Third, it should be noted that interpretation of the association between cytokines and psychotic symptoms to be causal is highly speculative. There is no direct evidence to support the notion that cytokine elevation in schizophrenia might produce psychotic symptoms. Moreover, our interpretation of the reduction of initially elevated serum IL-2 levels in schizophrenia induced by haloperidol and risperidone treatment is also predicated on an assumption and is lacking supportive evidence. Therefore, to date, the exact mechanism underlying the effects of antipsychotic drugs on the cytokine levels in schizophrenic patients is unknown.

A further consideration is the effect of stress on serum IL levels in schizophrenic patients who experienced acute exacerbation of symptoms when withdrawn from neuroleptic treatment, since immunologic aspects of the peripheral blood are more readily influenced by external conditions including stress.[50] Indeed, plasma IL-6 or IL-6 production by peripheral blood mononuclear cells is elevated in rodents following restraint or immobilization stress.[51,52] Moreover, interplay between the immune, nervous, and endocrine systems is most commonly associated with the pronounced effects of stress on immunity.[53,54] The hypothalamic-pituitary-adrenal (HPA) axis is the key player in stress responses, and it is well estab-

lished that both external and internal stressors activate the HPA axis. The HPA system communicates bidirectionally with neuro-immune-endocrine interactions.[54] Therefore, it is possible that differences in serum IL levels may be related to whether subjects feel stressed by their symptoms. Furthermore, hormone levels related to the HPA axis may play a role in producing psychotic symptoms and in the treatment response to neuroleptic drugs. Further studies will need to evaluate the role of stress in these findings through, for example, the measurement of hormone levels related to the HPA axis.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), risperidone (Risperdal).

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