Increased Interleukin-6 Level in Taiwanese Schizophrenic Patients

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Background: Schizophrenia is accompanied by an activation of the immune/inflammatory system. In the present study, the relationships between serum interleukin (IL)-6, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β1 levels and schizophrenia were explored in a group of Taiwanese inpatients. Furthermore, the serum IL-6, TNF-α, and TGF-β1 levels of patients with schizophrenia were compared before and after 1 month of antipsychotic treatment.

Methods: The serum IL-6, TNF-α, and TGF-β1 levels of 34 acute stage schizophrenic patients and 30 healthy control subjects were collected. These levels were again collected in the 34 patients after 1 month of antipsychotic treatment. An analysis of covariance (ANCOVA) adjusted for gender was performed to examine the differences in cytokine levels between the schizophrenic patients and the control group. Repeated measures ANCOVA adjusted for gender was performed to examine the differences in cytokine levels of the schizophrenic patients before and after 1 month of treatment.

Results: Using ANCOVA adjusted for gender, significantly increased IL-6 levels were found in schizophrenic patients compared with the control group (p = 0.02), but there were no significant differences in TNF-α and TGF-β1 levels (p = 0.06 and 0.91, respectively). After 1 month of medical treatment, there were no significant differences in IL-6 (p = 0.64), TNF-α (p = 0.48), and TGF-β1 (p = 0.23) levels in the schizophrenic patients, although IL-6 appeared to be normalizing.

Conclusion: An increase in the IL-6 level may play a role in the pathophysiology of schizophrenia. A larger sample size and a longer period of follow-up are needed to confirm this finding.

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Key words: Interleukin-6 (IL-6), schizophrenia, transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-α (TNF-α)

Although the pathological mechanisms underlying schizophrenia remain unclear, many studies have shown that schizophrenia is accompanied by activation of the immune/inflammatory system.[1,2] A

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recent single nucleotide polymorphism -based genome-wide association study noted significant associations with several markers spanning the major histocompatibility complex region, a finding consistent with the role of the immune system in schizophrenia.[3]

Interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ are produced by T-helper 1 (Th1) cells. IL-4, IL-6, and IL-10 are produced mainly by Th2 cells.[4,5] Transforming growth factor-beta 1 (TGF-β1) is a Th3 cytokine that can inhibit both Th1 and Th2 development and regulate the balance between Th1 and Th2 cytokines.[5-7]

Circulating levels of IL-6 and TNF-α were found to be higher in patients with schizophrenia.[8] The "Th2 hypothesis" suggests that the Th1-Th2 balance is shifted to Th2 in schizophrenia.[4,9] Since IL-6 stimulates B cells to produce antibodies, increased IL-6 activity is considered to be evidence supporting the Th2 hypothesis.[10] Antipsychotics have been reported to influence the production of cytokines.[11] In one study, TGF-β1 levels were significantly higher in patients with schizophrenia than in healthy control subjects, and these levels decreased after antipsychotic treatment.[12]

A gender difference in cytokine profiles has been reported.[13-15] Among urban primary care patients, women had higher circulating levels of IL-6.[16] A gender difference has also been reported in stimulated cytokine secretion.[17,18]

In the present study, the relationships between serum IL-6, TNF-α, and TGF-β1 levels and schizophrenia were explored in Taiwanese inpatients. Furthermore, the serum IL-6, TNF-α, and TGF-β1 levels of patients with schizophrenia were compared before and after 1 month of antipsychotic treatment.

METHODS

Subjects and design

The serum IL-6, TNF-α, and TGF-β1 levels of 34 schizophrenic patients were collected from January 2009 to November 2009 at Chang Gung Memorial Hospital in Kaohsiung, Taiwan. Institutional Review Board approval was obtained from the Ethics Committee of Chang Gung Memorial Hospital. Written informed consents were provided by all participants after the content and context of the study were fully explained. The diagnoses of schizophrenia were established by a psychiatrist according to the criteria of the Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV).[19] All patients were in the acute stage, defined by the exacerbation of psychotic symptoms. All patients were drug free for at least one week prior to admission to our acute ward. Each patient's antipsychotic medication remained the same for 1 month (n = 12, clozapine 100–350 mg/day; n = 19, risperidone 3–5 mg/day; n = 1, olanzapine 20 mg/day; n = 2, risperidone depot 37.5–50 mg/2 weeks). The control group consisted of 30 medical staff members and students with no past or familial history of any psychiatric disorder.

All patients' blood pressure, chest X-ray, electrocardiogram, and hematological and biochemical examination findings were within the normal ranges. The patients were free of acute infections and allergic reactions.

Laboratory data

Venous blood (5 ml) was collected at 7:00 A.M. before breakfast for every subject. Commercial enzyme-linked immunosorbent assay (ELISA) kits were used to measure serum IL-6 (Biosource, Nivelles, Belgium), TNF-α (Biosource), and TGF-β1 (R&D Systems, Inc., Minneapolis, MN, U.S.A.) levels. All samples were assayed by the same technician. The intra-assay and inter-assay variations were less than 10%.

Statistical analysis

All results are presented as mean (standard deviation). Data on age and body mass index (BMI, kg/m^2) were collected. Data analysis was performed using SPSS 10 (Chicago, IL, U.S.A.). ANCOVA adjusted for gender was performed to examine the differences in cytokine levels between the schizophrenic patients and the control group. Repeated measures ANCOVA adjusted for gender was performed to examine the differences in cytokine levels of the schizophrenic patients before and after 1 month of treatment. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 64 participants were recruited, including 34 with schizophrenia (16 male, 18 female) and

30 healthy control subjects. The duration of illness for the schizophrenics was 8.57 (6.15) years. Table 1 shows patient data and the cytokine levels for both the schizophrenic and control groups. Using ANCOVA adjusted for gender, significantly increased IL-6 levels were found in the schizophrenic patients compared with the control subjects ($p = 0.02$), but no significant differences in TNF-α and TGF-β1 levels ($p = 0.06$ and 0.91, respectively) were found.

After 1 month of medical treatment, no significant differences in IL-6 ($p = 0.64$), TNF-α ($p = 0.48$), and TGF-β1 ($p = 0.23$) levels were found in the schizophrenic patients, although IL-6 appeared to be normalizing as shown in Table 2.

DISCUSSION

The first major finding of this study is that schizophrenic patients in the acute stage had significantly higher IL-6 levels than the control group. No significant differences were noted in the levels of TNF-α and TGF-β1 between the schizophrenic and control groups. Many past studies have described increased IL-6 levels[20,21] as well as increased TNF-α levels,[22-24] in schizophrenic patients. Other studies noted no difference or even lower IL-6 levels in schizophrenic patients than in control groups.[25-27] Studies of TNF-α have reported inconsistent results. Many studies reported higher TNF-α levels in schizophrenic patients than in control groups, in terms of both plasma,[22-25] mRNA,[28,29] and soluble tumor necrosis factor receptor 1 (a marker of TNF-α system activation) levels.[30] Other studies found no difference in TNF-α levels between schizophrenic patients and controls.[31,32] Another study found lower TNF-α mRNA levels in schizophrenic patients than in the control group.[33] In one study, TGF-β1 levels were significantly higher in schizophrenic patients than in the control group, and neuroleptic treatment returned TGF-β1 levels to the control values.[12] No significant difference in TGF-β1 levels was found in the cerebrospinal fluid samples of either schizophrenic patients or healthy control subjects, but TGF-β1 may play a role in reducing the activity of Th1 cytokines.[34] Despite the inconsistency of our results with some of the aforementioned studies, the elevated IL-6, static TNF-α, and static TGF-β1 levels could be explained by the "Th2 hypothesis." However, recent findings have suggested otherwise. A recent review found increased levels of com-

Table 1. Patient Data and Cytokine Levels for the Schizophrenic and Control Groups

	Age (years)	BMI (kg/m^2)	IL-6 (pg/ml)	TNF-α (ng/ml)	TGF-β1 (ng/ml)
Schizophrenia (n = 34)	34.65 (10.68)	23.06 (4.51)	4.23 (6.28)	0.40 (0.40)	46.08 (10.90)
Control (n = 30)	27.64 (4.90)	21.88 (2.76)	1.42 (1.72)	2.64 (2.34)	45.94 (9.34)
ANCOVA adjusted for gender			$p = 0.02$*	$p = 0.06$	$p = 0.91$

Abbreviations: BMI: body mass index; IL-6: interleukin-6; TGF-β1: transforming growth factor-β1; TNF-α: tumor necrosis factor-α. *: $p < 0.05$.

Table 2. Patient Data and Cytokine Levels of the Schizophrenic Group before and after 1 Month of Medical Treatment

	Weight (kg)	BMI (kg/m^2)	IL-6 (pg/ml)	TNF-α (ng/ml)	TGF-β1 (ng/ml)
Before (n = 34)	61.06 (13.95)	23.06 (4.51)	4.23 (6.28)	0.40 (0.40)	46.08 (10.90)
After (n = 34)	61.76 (15.05)	23.28 (4.77)	3.17 (2.34)	0.50 (0.58)	45.25 (13.53)
Repeated measures ANCOVA adjusted for gender			$p = 0.64$	$p = 0.48$	$p = 0.23$

Abbreviations: BMI: body mass index; IL-6: interleukin-6; TGF-β1: transforming growth factor-β1; TNF-α: tumor necrosis factor-α. Values are given as mean (SD).

pounds of the IL-6 and TNF system in the serum, suggesting mechanisms for monocyte and T-cell activation, but whether such T-cell activation involves the Th1/Th2/Th17 or Treg systems remained unknown.[1] An earlier meta-analysis, which found an increase in *in vivo* IL-6 but not TNF-α, also found no evidence suggesting the Th2 hypothesis.[2] Our results showed elevated IL-6 in the acute stage of schizophrenia, but more studies are needed to clarify the interplay of cytokines and show how different types of immune/inflammatory cells interact.

Gender also plays a role in cytokine secretion. Higher incidences of a proinflammatory cytokine profile are reported in males.[13-15] A gender difference in proinflammatory cytokines might also contribute to the differences in prevalence of most autoimmune diseases between males and females. However, inconsistent reports have been noted. In urban primary care patients, women had higher circulating levels of IL-6.[16] Women also showed an increase in lipopolysaccharide (LPS)-stimulated monocyte intracellular production of IL-6.[18] Another study showed the opposite result, with males producing significantly more IL-6 and TNF-α in response to either LPS or lipoteichoic acid.[17] Hepatic carcinogen administration caused a greater increase in serum IL-6 in males than it did in females.[35] In yet another study of depression, no significant difference was found in IL-6 between genders.[36] A recent report showed that a TNF-α increase after exposure to swine was gender-dependent, with men showing a significant increase in the wild-type group and women showing a significant increase in the polymorphic group.[37]

Our second major finding is that no significant differences were noted in IL-6, TNF-α, and TGF-β1 levels after 1 month of antipsychotic treatment. Inconsistent results have been observed in past studies, even when specific antipsychotics were investigated separately. Most studies reported cytokine reductions after treatment. IL-6 and TNF-α were significantly reduced after 6 weeks of treatment in one study.[23] Atypical antipsychotics such as clozapine, olanzapine, and risperidone, but not haloperidol, suppressed IL-6 but did not suppress TNF-α in another study.[38] Risperidone significantly lowered the levels of serum IL-6 after 4 weeks and TNF-α after 8 weeks in comparison with pretreatment levels, but clozapine significantly lowered only levels of IL-6 after 6 months.[39] After 8 weeks of antipsychotic treatment, plasma levels of IL-6 but not TNF-α were significantly decreased.[10] *In vitro* studies have often shown some reduction in the levels of inflammatory cytokines. Spiperone attenuated the expression of TNF-α at mRNA levels in BV-2 microglia cells.[40] Atypical antipsychotics such as risperidone, perospirone, ziprasidone, quetiapine, and aripiprazole significantly suppressed TNF-α production in murine 6-3 microglia cells.[41-43] Flupentixol and trifluperidol reduced TNF-α release in LPS-stimulated mixed rat glia and microglia cultures.[44] Other studies reported no obvious changes after treatment. After 12 weeks of double-blind treatment with risperidone 6 mg/day or haloperidol 20 mg/day, IL-6 showed no change.[45] Neither IL-6 nor TNF-α plasma level changed after olanzapine treatment for 8 weeks.[46] The TNF-α level was not different either between the schizophrenic and the control groups or between the before- and after-8-week treatment groups.[32] These discrepancies from previous studies might be explained by factors such as subtype, clinical stage, chronicity, type of antipsychotic, treatment responsiveness, ethnicity, and technique used to measure cytokine levels. In addition, most of these studies had follow-ups of more than 8 weeks, compared with 1 month in our study. Although there was no statistical significance in the cytokine levels after 1 month of antipsychotic treatment, the IL-6 levels appeared to be normalizing.

Conclusions

Our results showed a significantly higher level of IL-6 in patients with acute stage schizophrenia, than in healthy control subjects. After 1 month of antipsychotic treatment, the IL-6 levels appeared to be normalizing, although no statistical significance was achieved. Taken together, our results suggest that disturbance in the IL-6 level may play a role in the pathophysiology of schizophrenia in the acute stage. A larger sample size and a longer period of follow-up will be needed to confirm this finding.

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台灣精神分裂症患者有較高的第六介白素

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背 景： 精神分裂症與免疫發炎系統的活化有相關。本研究探查血中第六介白素 (IL-6)、腫瘤壞死因子 (TNF)-α、以及轉化生長因子 (TGF)-β1 與精神分裂症急性期的關係。此外，在以抗精神病藥治療一個月前後進行這些因子的比較。

方 法： IL-6、TNF-α、及 TGF-β1 的血中濃度取自 34 位急性期的精神分裂症患者與 30 位健康的對照組。在以抗精神病藥治療一個月後，相同因子的血中濃度再由精神分裂症患者身上採取一次。以性別校正之 ANCOVA 來比較急性期患者與對照組，以及患者治療前後之差別。

結 果： 與控制組相比，精神分裂症患者血中的 IL-6 顯著上升 ($p = 0.02$)，但 TNF-α 及 TGF-β1 則沒有差別 (p 分別爲 0.06 及 0.91)。經過一個月的治療後，IL-6、TNF-α、TGF-β1 均無顯著差異 (p 分別爲 0.64，0.48，0.23)，但 IL-6 有恢復正常的趨勢〔4.23 (6.28) 至 3.17 (2.43) pg/ml〕。

結 論： IL-6 的升高可能在精神分裂症的致病機轉中占有一席之地，但需要更大的樣本數及更長的追蹤時間來證實這個發現。

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關鍵詞： 第六介白素，腫瘤壞死因子-α，轉化生長因子-β1，精神分裂症

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