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ORIGINAL ARTICLE

Case Control Study

Association of serum interleukin-6 with negative symptoms in stable early-onset schizophrenia

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Abstract

BACKGROUND

Accumulating evidence suggests that the inflammatory cytokine interleukin-6 (IL-6) contributes to the pathophysiology of psychiatric disorders. However, there was no study concerning the relationship between IL-6 concentrations and clinical features in the chronic phase of early-onset schizophrenia (EOS).

AIM

To investigate the relationship between serum IL-6 concentration and the clinical

features of EOS.

METHODS

We measured serum IL-6 Levels from 74 patients with chronic schizophrenia, including 33 with age at onset < 21 years (EOS group) and 41 with onset ≥ 21 years in [adult-onset schizophrenia (AOS) group], and from 41 healthy controls. Symptom severities were evaluated using the Positive and Negative Syndrome Scale (PANSS).

RESULTS

Serum IL-6 concentrations were higher in both EOS and AOS groups than healthy controls (F = 22.32, P < 0.01), but did not differ significantly between EOS and AOS groups (P > 0.05) after controlling for age, body mass index, and other covariates. Negative symptom scores were higher in the EOS group than the AOS group (F = 6.199, P = 0.015). Serum IL-6 concentrations in the EOS group were negatively correlated with both total PANSS-negative symptom score (r = -0.389, P = 0.032) and avolition/asociality subscore (r = -0.387, P = 0.026).

CONCLUSION

Patients with EOS may have more severe negative symptoms than those with adult-onset schizophrenia during the chronic phase of the illness. IL-6 signaling may regulate negative symptoms and its avolition/asociality subsymptoms among the early-onset chronic schizophrenic patients.

Key Words: Early-onset schizophrenia; Interleukin 6; Negative symptoms; Avolition; Asociality

Core Tip: In this study, we focus on the negative symptoms and inflammatory levels in the chronic stage of early-onset schizophrenia. Patients' clinical symptoms were assessed by the Positive and Negative Syndrome Scale, and the level of inflammation was assessed by serum interleukin-6 (IL-6) Levels. Our study found that patients with early-onset schizophrenia may have more severe negative symptoms than those with adult-onset schizophrenia during the chronic phase of the illness. IL-6 signaling may regulate negative symptoms and its avolition/asociality subsymptoms among the early-onset chronic schizophrenic patients.

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INTRODUCTION

Schizophrenia is a neuropsychiatric disorder of complex etiology with lifetime incidence of about 0.4% and total global prevalence of approximately 1%[1]. Symptoms of the disease are stratified into three domains, positive, negative, and cognitive, with substantial variation in severity among individual patients. Furthermore, these distinct symptom domains can have unique effects on clinical course and outcome. For instance, negative symptoms such as flat affect and asociality impair social functioning[2]. Several schizophrenia subtypes have been defined based on predominant symptom profiles and clinical course, including early-onset schizophrenia (EOS) with age of onset before 21 years[3,4]. According to an der Heiden and Häfner[5], about 41% of patients develop their first symptoms before the age of 20, and numerous studies have found that EOS was associated with more severe negative symptoms, more frequent relapses, poorer social functioning, and worse overall prognosis[6-8]. While the pathological mechanisms contributing to poor outcome among EOS patients are still largely unknown, Fraguas *et al*[9] reported more severe inflammation and oxidative stress in this patient group.

Exploratory factor analyses of Position and Negative Syndrome Scale (PANSS) scores have revealed two negative subsymptom clusters[10-13], expression deficits and avoidance/asociality, with possibly distinct underlying pathological mechanisms. Therefore, uniform treatment strategies for all EOS patients regardless of individual negative symptom profile may produce suboptimal clinical outcomes[11]. The expression cluster includes flat affect, poor rapport, lack of spontaneity, mannerisms and posturing, motor retardation, and avolition, while the asociality factor consists of emotional withdrawal, passive/apathetic social withdrawal, and active social avoidance. The first factor reflects a loss of initiative, and the second factor social amotivation related to community interaction[14]. Based on these findings, we speculated that indices of neuroinflammation will be larger in chronic EOS patients compared to adult-onset schizophrenia (AOS) patients and associated with negative symptom severity. The current study focused primarily on expression deficits and avolition/asociality symptoms.

The inflammatory hypothesis of schizophrenia posits that low grade inflammation contributes to disease course and symptom expression[15-18], and is supported by studies showing higher levels of pro-inflammatory factors such as cytokines in the blood and cerebrospinal fluid of schizophrenia patients. A large epidemiological study also found that severe infections and autoimmune disorders were risk factors for schizophrenia[15,19], while the largest genome-wide association study to date identified 108 Low effect-size risk loci, most of which were associated with inflammatory responses[20].

Interleukin-6 (IL-6) is a highly pleiotropic cytokine involved in multiple aspects of the inflammatory response, including neurotoxicity and neuroprotection[21-23], depending on context. For example, IL-6 overexpression inhibited hippocampal neurogenesis[24], while blockade of IL-6 but not tumor necrosis factor-α (TNF-α) enhanced adult hippocampal neurogenesis by up to 50%[25]. Such findings suggest that IL-6 release from activated microglia is a core regulator of neurogenesis throughout life. Similarly, IL-6 release from microglia is known to maintain chronic inflammation in models of autoimmune encephalitis and various neurological diseases[26]. Recent Mendelian studies have also found that genetically predicted IL-6 signaling strength is likely to influence brain structural changes associated with increased schizophrenia risk[27,28]. Gallego *et al*[29] reported that these changes in serum IL-6 were consistent with cerebrospinal fluid IL-6, suggesting that less invasive blood samples can be used routinely to assess IL-6 activity as a marker for prognosis. A positive correlation was also found between serum IL-6 Levels and negative symptom severity in drug-naïve male schizophrenics[30], while a study of Chinese patients with chronic schizophrenia found that IL-6 concentration was positively correlated with negative symptom scores at both admission and discharge[31]. Golimbet *et al*[32] further reported a correlation between the IL-6 -174 G/C polymorphism and greater avolition and apathy scores among schizophrenia patients. Based on these findings, we speculated that IL-6 Likely contributes to the unique clinical symptoms of chronic phase EOS, but to our best knowledge the associations of serum IL-6 with negative symptom have not been examined in Asian EOS patients.

MATERIALS AND METHODS

Subjects and assessments

Schizophrenia inpatients were recruited from Guangji Hospital, Suzhou, China, from January 2016 to October 2019. Inclusion criteria were as follows: (1) Age 18–75 years; (2) Meeting he Diagnostic and Statistical Manual of Mental Disorders-IV diagnostic criteria for schizophrenia as determined by two psychiatrists using the Structured Clinical Interview for he Diagnostic and Statistical Manual of Mental Disorders (SCID); (3) Disease duration of at least 5 years; (4) Han Chinese ethnicity; (5) Taking stable doses of antipsychotic drugs for at least one year (primarily clozapine, phenazine, risperidone, sulpiride, haloperidol, and chlorpromazine (CPZ); and (6) Agreeing to voluntarily participation with informed written consent. Exclusion criteria were: (1) Comorbid somatic disorders or substance dependence; and (2) Not completing primary education. A demographic assessment questionnaire was used to gather enrollment data, including sex, age, years of education, smoking status/history, body mass index (BMI), age of onset, and duration of illness.

Forty-one healthy controls (HCs) were recruited during the same period from Suzhou local communities through media and pamphlet advertisements. A psychiatrist confirmed health status and family psychiatric history using an unstructured clinical interview. Candidates with relevant physical and mental health problems were excluded. Enrolled candidates provided written informed consent for participation. The study protocol and informed consent form were approved by the Institutional Review Board of a Suzhou City-owned Mental Hospital (No. 2022005).

Definitions of groups

Participants with schizophrenia were asked to identify the age at first acute psychotic symptoms during the SCID, and this information was confirmed by medical records. We divided these patients into an EOS group if age at first psychotic episode occurred before age 21 and an AOS group if first psychotic episode occurred at 21 years or older[3,4,33]. The EOS group included 33 patients (23 males and 10 females) and the AOS group included 41 patients (24 males and 24 females).

Definitions of two subdomains of negative symptom

Exploratory factor analysis yielded a two-factor structure of negative symptoms. The first factor, expressive deficits, consisted of PANSS items N1, N3, N6, G5, G7, and G13, while the second factor, avolition/asociality, consisted of PANSS items N2, N4, and G16[10,34].

Clinical assessment

To ensure the reliability and consistency of assessments across the study period, two psychiatrists with at least 5 years of clinical experience attended a training course on the use of the PANSS. After training, the interobserver correlation coefficient for the PANSS score was maintained above 0.8.

Measurement of serum IL-6 level

Peripheral venous blood samples were drawn from patients and HCs between 7 and 9 AM after an overnight fast, and centrifuged at 3000 rpm for 15 min in procoagulant and anticoagulant tubes to isolate serum and plasma fractions, respectively. The samples were then stored at -80 °C until analysis. Serum IL-6 concentrations were measured using a BDTM FACSCanto Flow Cytometer and BDTM Cytometric Bead Array (CBA) Human Inflammatory Cytokines Kit (BD

Biosciences, San Jose, CA, United States) according to the manufacturers' instructions. A standard curve was also constructed for each sample batch from triplicate measurements of known IL-6 concentrations using the supplied BDTM CBA Human Inflammatory Cytokine Standards. All measurements were performed by the same technician who was blinded to donor identity and clinical information.

Statistical analyses

Statistical analyses were conducted using Statistical Product and Service Solutions 25.00. All datasets were first examined for normality using the Kolmogorov-Smirnov test. Based on results indicating non-normally distributed serum IL-6 concentrations for both EOS and AOS patients and HCs (all $P < 0.05$ by Kolmogorov-Smirnov test), values were converted to natural logarithm values for analysis. Serum log IL-6 concentrations were compared among EOS patients, AOS patients, and HCs by multivariate analysis of covariance (MANCOVA) with diagnosis as a fixed factor, and age, sex, and BMI as covariates. Other continuous variables were compared by Student's *t*-test or one-way analysis of variance, while categorical variables were compared by chi-square test. Results were corrected for multiple comparisons using the Bonferroni method. Associations between variables were evaluated by calculating Pearson's correlation coefficients. Exploratory multiple regression analysis was also performed to examine the relationship between serum log IL-6 and PANSS scores after controlling for age, gender, and BMI as covariates. A corrected $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

RESULTS

Demographic data and clinical characteristics

Chronic schizophrenia inpatients were divided into an early-onset group (EOS group, $n = 33$) with first psychotic episode before 21 years of age and an adult-onset group (AOS group, $n = 41$) with first psychotic episode after 21 years of age. A HC group (HC group, $n = 41$) was also recruited as a control. The demographic and clinical characteristics of all three study groups are summarized in Table 1. There was no significant difference in sex ratio and number of smokers among groups ($P > 0.05$). As expected, there were significant group differences in age, years of education, and BMI ($P < 0.05$), but neither years of education, duration of disease, nor CPZ equivalent dose differed between EOS and AOS groups ($P > 0.05$). According to the criterion for group stratification, age at schizophrenia onset was significantly older in the AOS group. Mean BMI was higher in the EOS group than the AOS group ($P < 0.05$), and so was included as a fixed effect covariate in subsequent analyses.

As shown in Figure 1A, serum log IL-6 concentrations were higher in both EOS and AOS groups compared to the HC group ($P < 0.001$) but did not differ between EOS and AOS groups ($P > 0.05$).

Associations of serum log IL-6 concentrations with clinical symptoms in EOS and AOS patients

In the EOS group, serum log IL-6 concentration was negatively correlated with total PANSS-negative symptom score ($r = -0.389$, $P = 0.032$; Figure 1B) and with avolition/asociality subscore ($r = -0.387$, $P = 0.026$; Figure 1C). Furthermore, the correlation between total PANSS-negative score and serum log IL-6 concentration remained significant after controlling for age, years of education, BMI, smoking status, age of onset, duration of illness, and CPZ equivalence dose ($R^2 = 0.151$, $P = 0.025$). This association was also significant in stepwise multiple regression analysis ($R^2 = 0.150$, $P = 0.026$). In contrast, no such association was found between clinical factors and serum log IL-6 concentration in the AOS group.

DISCUSSION

The main findings of the present study were as follows: (1) Serum IL-6 concentrations were elevated in both EOS and AOS patient groups compared to a control group but did not differ between patient groups; (2) total PANSS-negative score (sum of subscores) was significantly higher in the EOS group than the AOS group, indicating more severe negative symptoms; and (3) total PANSS-negative symptom score and Avolition/Asociality subscore were correlated with serum log IL-6 concentration in the EOS group but not the AOS group. These results suggested that IL-6 inflammatory signaling regulated negative symptom severity in EOS patients. To our knowledge, this is the first study to find an association between serum IL-6 concentration and PANSS-negative symptom severity in EOS patients during chronic stabilization.

BMI in patients with EOS and AOS

Many patients receiving antipsychotic treatments experience unhealthy weight gain, and we found a significant BMI elevation among EOS patients during the first unmedicated phase compared to AOS patients. Lang *et al*[35] found no significant difference in BMI between EOS patients during the first unmedicated phase and AOS patients, but did identify BMI as a risk factor for metabolic syndrome in EOS. A prospective study by Ratzoni *et al*[36] also found that olanzapine and risperidone induced greater weight gain in Israeli adolescent patients than adult patients. Thus, weight gain should be closely monitored in EOS patients. We speculate that elevated BMI in the chronic phase of EOS may contribute to poorer outcome. Obesity is also associated with elevated serum IL-6, although the correlation between IL-6 and total PANSS-negative symptoms among EOS patients remained significant after controlling for BMI as well as other covariates. Nonetheless, further studies are needed to comprehensively assess the influences of confounding factors on BMI in schizophrenia, such as different types of medications, age, ethnicity, duration of illness, and sex.

Table 1 Demographic and clinical characteristics of early-onset schizophrenia patients, adult-onset schizophrenia patients, and healthy controls

	Early-onset schizophrenia	Adult-onset schizophrenia	Healthy control	Statistic (F/χ^2)	*P* value
Sex					
Male	23	24	23	1.57	0.46[1]
Female	10	17	18		
Smoking					
Smoker	7	13	15	2.09	0.35[1]
Nonsmoker	26	28	26		
Age (yr)[a]	38.79 ± 9.21	46.14 ± 7.26	42.61 ± 10.30	5.00	0.008[2]
Educations (yr)[b]	9.64 ± 2.50	9.10 ± 2.96	12.24 ± 2.61	20.78	< 0.001[2]
BMI (kg/m^2)[b]	28.57 ± 4.87	25.56 ± 3.74	23.26 ± 2.72	17.88	< 0.001[2]
Age of onset (yr)[b]	17.00 ± 2.75	28.22 ± 5.69		107.67	< 0.001[2]
Duration of illness (yr)	21.61 ± 9.22	17.88 ± 7.29		3.78	0.056[2]
Dose of CPZ equivalent (mg/d)	653.37 ± 300.04	704.85 ± 311.41		0.52	0.475[2]
PANSS					
Positive subscores	14.54 ± 5.95	14.73 ± 6.71		1.60	0.21[3]
Negative subscores[a]	20.85 ± 5.56	18.15 ± 3.86		6.20	0.015[3]
General subscores	33.21 ± 9.32	31.05 ± 8.24		0.16	0.688[3]
Total scores	68.61 ± 17.90	63.93 ± 14.23		0.004	0.953[3]
Expressive deficits	16.33 ± 4.77	14.17 ± 3.26		3.26	0.075[3]
Avolition/asociality	9.52 ± 3.72	8.44 ± 2.44		2.05	0.157[3]
Log IL-6 level[b]	0.88 ± 0.37	0.81 ± 0.40	0.18 ± 0.03	22.32	< 0.001[3]

[a]$P < 0.05$.
[b]$P < 0.001$.
[1]χ^2 test.
[2]One-way analysis of variance.
[3]The *P* values for Positive and Negative Symptom and log interleukin-6 were adjusted for age, sex, and body mass index.
Mean ± SD are reported for all variables. BMI: Body mass index; CPZ: Chlorpromazine; PANSS: Positive and Negative Symptom; IL-6: Interleukin-6.

Negative symptom in patients with EOS and AOS

Negative symptom scores were higher in the EOS group that the AOS group, consistent with several previous relevant studies[8,37-40] but at odds with several others reporting no difference[41-43]. These disparities may be related to sample heterogeneity (*e.g.*, ethnic background, first-episode or relapse, anti-psychotic drug dose, hospitalized *vs* outpatient, and illness severity). Nonetheless, the current research suggests that intervention for the chronic phase of EOS should place greater emphasis on negative symptoms.

Serum IL-6 Levels in patients with EOS and AOS

Serum IL-6 concentrations were higher in both EOS and AOS patient groups compared to healthy matched controls, suggesting that schizophrenia was associated with a chronic inflammatory response independent of onset age and consistent with the inflammation hypothesis of schizophrenia. Of the few previous studies on serum IL-6 in EOS patients, one found no difference between first-episode EOS and healthy individuals[44], while a clinical two-sample Mendelian randomized study found increased soluble IL-6 receptor levels in patients, which can be explained as a compensatory response to IL-6 elevation[45]. Elevated serum IL-6 suggests microglial cell hyperactivity[26] in the chronic phases of EOS and AOS. While additional studies with larger samples are needed for verification, it appears that elevated serum IL-6 concentration is a ubiquitous feature of stable chronic schizophrenia.

Associations of serum log IL-6 concentrations with clinical symptoms in EOS and AOS patients

Numerous studies have found strong associations between elevated IL-6 and both the development and progression of first-episode psychosis in acute and chronic stages of schizophrenia, suggesting that inflammatory cascade responses contribute to the underlying pathogenesis and symptom expression[18,46]. Indeed, some investigations have found correlations with positive symptoms, negative symptoms, depressive symptoms, and cognitive deficits[47]. A meta-

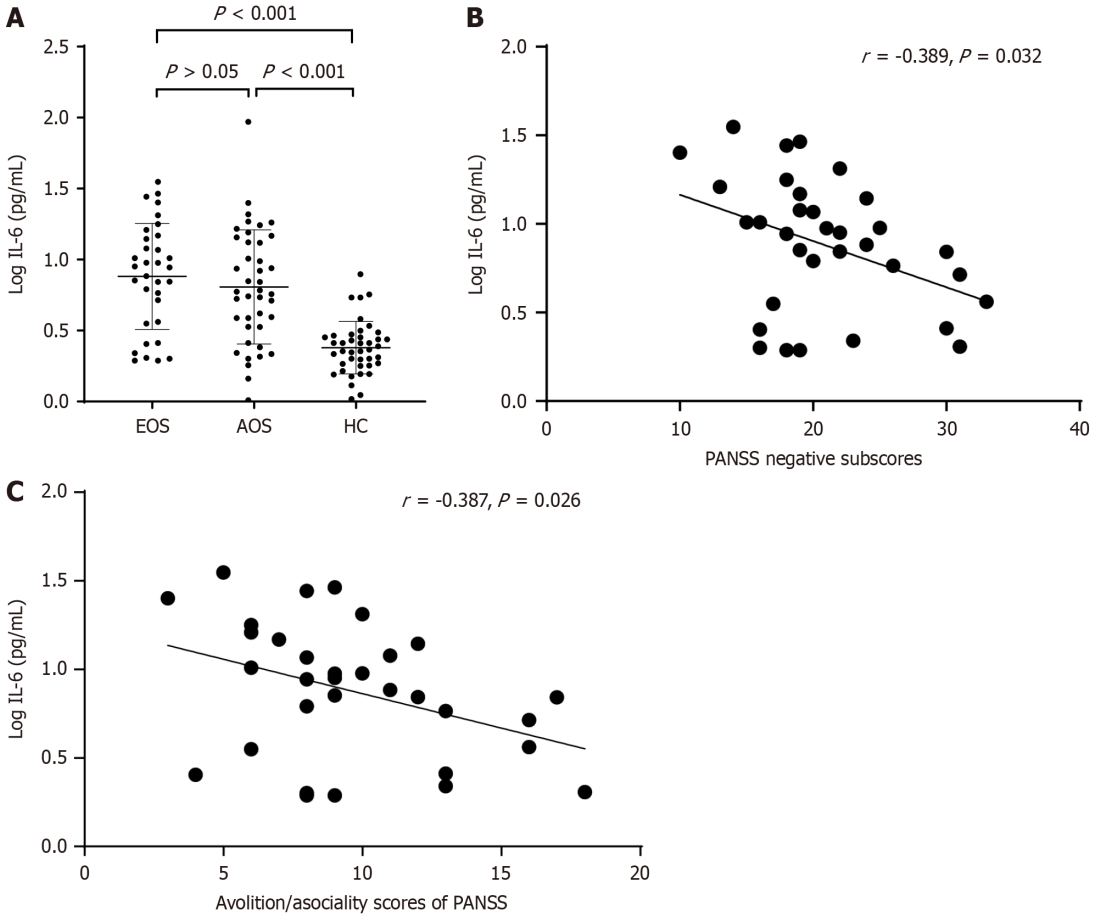

Figure 1 Comparison of serum Log interleukin-6 Levels and the relationship with clinical symptoms in different subject groups. A: Serum log interleukin-6 (IL-6) concentrations in chronic early-onset schizophrenia (EOS) patients, chronic adult-onset schizophrenia patients, and healthy controls (HCs). Concentrations were significantly higher in schizophrenia groups than HCs but did not differ between schizophrenia groups; B: Correlation between serum log IL-6 concentration and total Positive and Negative Syndrome Scale (PANSS)-negative scores in the EOS patient group; C: Correlation between serum log IL-6 concentration and PANSS Avolition/Asociality subscore in the EOS patient group. IL-6: Interleukin-6; EOS: Early-onset schizophrenia; HC: Healthy control; PANSS: Positive and Negative Syndrome Scale; AOS: Adult-onset schizophrenia.

analysis concluded that the IL-6 elevation in patients with first-episode psychosis or acute relapse normalized after antipsychotic treatment[48]. Thus, variations in IL-6 Levels may reflect complex immunoregulatory functions at different stages of the disease. However, we found that higher serum IL-6 concentrations in stably medicated EOS patients were associated with both lower overall PANSS-negative symptom severity and avolition/asociality severity, while most previous investigations have found either a positive correlation or no relationship[48-50]. Stojanovic *et al*[51] did report a negative correlation with PANSS positive subscale scores (but positive correlations with PANSS-negative subscale scores) among outpatients with psychotic disorders, while Gibson *et al*[52] found a negative correlation between serum IL-6 and PANSS total score as well as positive and negative subscales in patients with cannabinoid-positive acute psychiatric disorders. As mentioned, Golimbet *et al*[32] found a link between the IL-6 -174 G/C polymorphism and both dementia and apathy scores that approached significance. To our best knowledge, the current case-control study is the first to find negative correlations between serum IL-6 and both total PANSS-negative symptom score and avolition/asociality subscore among patients with chronic stage EOS.

These discrepancies across studies may reflect the pleiotropic activity of IL-6 signaling in immune regulation[21-23,53,54]. IL-6 can modulate cellular responses in two ways. In the classical signaling pathway, IL-6 binds to its cognate cell membrane receptor (IL-6R) and triggers a heterodimeric association with two membrane-bound gp130 molecules, which in turn initiates downstream pro- and anti-inflammatory responses through activation of three signaling cascades, most prominently the JAK-STAT pathway. Alternatively, in the trans-signaling pathway, IL-6 binds to the soluble form of its receptor (sIL-6R) before forming a complex with membrane-bound gp130. This complex then activates downstream pathways leading to pro-inflammatory responses. However, soluble gp130 (sgp130) inhibits trans-signaling by blocking the association of the IL-6/sIL-6R complex with membrane-bound gp130 molecules[54]. Szabo *et al*[53] reported significantly higher soluble sgp130 concentrations in schizophrenic patients who used cannabis. We propose that IL-6 trans-signaling may regulate negative symptoms and sub-symptoms in the chronic phase of EOS. Negative symptoms are a multidimensional construct with potentially complex interactions between subtypes and with other symptom domains. Serum IL-6 concentrations may also be influenced by genetic differences and psychotropic substance use among other factors not examined in the current study. In addition, differences in study design and methodology may explain these discrepancies with previous studies, including the participant selection process, the time point and method of IL-6

measurement, and the selection of covariates for statistical analyses. This unexpected finding challenges our traditional view of IL-6 signaling function in EOS and suggests that future work must examine the functions of this cytokine in different disorder subtypes, phases, and treatment conditions to identify the context-specific effects on clinical course and symptom expression.

CONCLUSION

We examined serum IL-6 concentrations in patients with EOS and AOS in the chronic phase. Our study demonstrated that serum IL-6 concentrations were elevated in both EOS and AOS patient groups compared to a control group but did not differ between patient groups. Moreover, total PANSS-negative score was significantly higher in the EOS group than the AOS group, indicating more severe negative symptoms. In addition, we found that the mean BMI was higher in the EOS group than the AOS group. And total PANSS-negative symptom score and Avolition/Asociality subscore were correlated with serum log IL-6 concentration in the EOS group but not the AOS group. These results suggested that IL-6 inflammatory signaling regulated negative symptom severity in EOS patients. The present study had several limitations. First, the sample size was relatively small, limiting statistical power. Therefore, more subtle associations and differences may have been missed. Second, although we did not find a relationship between drug treatment (in clozapine equivalents) and IL-6 concentration, such associations may have been influenced by uncontrolled clinical factors, such as drug type, dose, and treatment duration. Third, our findings were essentially cross-sectional, and future longitudinal studies should be conducted to establish causal relationships. Finally, we evaluated only IL-6, while it is known that cytokine signaling factors interact to determine the ultimate inflammatory status. Despite these limitations, the present study suggested that negative symptoms were more severe in EOS compared to AOS and that IL-6 was involved in the underlying pathomechanism.

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FOOTNOTES

Author contributions: Chen P, Yang HD and Wang JJ were responsible for data collection, data curation, and writing original draft; Chen P, Yang HD, Wang JJ, Sun WX and Zhao HM performed the statistical analysis; Zhu ZH, Cai Y and Yin XY were responsible for performing the clinical rating; Zhu HL, Fu JL and Zhang XZ were responsible for recruiting the patients, and collecting the samples; All authors reviewed the manuscript. Hui L and Zhang XB were co-corresponding authors; Zhang XB was responsible for study design, statistical analyses, and editorial revisions; Hui L was responsible for study design, patient recruitment, funding acquisition, supervision, and editing.

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