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CLINICAL STUDY

Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as inflammation markers for early-onset schizophrenia

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ABSTRACT

OBJECTIVE: The studies on the pathogenesis of schizophrenia reported data indicating that abnormal immune responses might play a role in the development of schizophrenia. One of the markers of systemic inflammation is the neutrophil-to-lymphocyte ratio (NLR). In our study, the relationship between the early-onset schizophrenia, NLR, platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) was investigated.

MATERIALS AND METHODS: The study included 30 patients and 57 healthy controls matched in age and gender. Hematological parameters and Clinical Global Impressions Scale (CGI) scores were obtained from the medical records of the patients. Hematological parameters in the patient group were compared to those in the healthy control groups. The relationship between inflammation markers and CGI scores was investigated in the patient group.

RESULTS: NLR, and neutrophil and platelet counts were found to be higher in the patient group as compared to the control group. A positive correlation was found between NLR and CGI scores.

CONCLUSION: The results of the study support the multisystem inflammatory process model related to schizophrenia, which was revealed in previous studies, also in children and adolescents in the patient group *(Tab. 4, Ref. 36)*. Text in PDF *www.elis.sk*

KEY WORDS: neutrophil-to-lymphocyte ratio, inflammation, early-onset schizophrenia.

Introduction

Schizophrenia is a long-term mental disorder that is characterized by delusions, hallucinations, bizarre behavior, negative symptoms, and social dysfunction (1). Schizophrenia typically develops in late adolescence or early adulthood. When this disorder manifests before the age of 18, it is described as early-onset schizophrenia (EOS), and when it manifests before the age of 13, it is referred to as very early-onset schizophrenia (VEOS) (2). Early-onset schizophrenia is observed 5 times less often than adult-type schizophrenia, the incidence of which is considered to be 0.5–1 % (3,4). EOS is associated with similar epidemiological, clinical, etiological and cognitive characteristics as schizophrenia with an onset in adulthood (5). However, EOS is characterized by a more insidious onset of the disease, more negative symptoms, thought disorders and disorganized behaviors (6, 7).

The etiology and pathophysiology of schizophrenia are not fully known. It is emphasized to be a neurodevelopmental disorder that occurs with a combination of genetic and epigenetic factors (8, 9). The number of data in the studies conducted on the pathogenesis of schizophrenia that indicate abnormal immune response potentially playing a role in the development of schizophrenia, is on the increase recently (8, 10). Current approaches suggest that an exposure to inflammatory modulators during the fetal period leads to disruptions in fetal brain development, and as a result of these disruptions, the risk of developing neurodevelopmental disorders such as schizophrenia increases (11, 12). Neuroinflammation and changes in the immune system in schizophrenia and related disorders have been noted also to lead to changes in the brain over time (9). Many clinical studies have reported an increased peripheral immune response in patients with schizophrenia (13–15). There is significant evidence that impaired cognitive function and negative symptoms in schizophrenia may be associated with increased inflammatory response (13).

Studies examining the link between psychiatric disorders and inflammation in children and adolescents are limited, however there are studies on the inflammatory processes in adult schizophrenia patients. It is possible that prior findings from the adult patient group do not apply to children because of the differences in cytokine production between children and adults (16).

The most practical and accessible markers of systemic inflammation are the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) (17).

The purpose of this study was to investigate how inflammation contributes to the early-onset schizophrenia. For this, early-onset schizophrenia patients were compared to healthy controls using

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NLR, PLR, MLR, and complete blood count measures. The link between NLR, PLR, and MLR and the severity of the condition was also attempted to be measured. In this study, it was assumed that NLR, PLR, and MLR levels in individuals with an early-onset schizophrenia diagnosis would be higher than those in healthy controls.

Methods

Participants and procedure

This study included 30 patients with EOS who visited the pediatric psychiatry unit at Tokat Dr. Cevdet Aykan Mental Health and Diseases Hospital and the Faculty of Medicine at Afyonkarahisar Health Sciences University between 2018 and 2021. During the first admission of patients, the outcomes of routine blood tests taken before the treatment were examined retrospectively. Participants who at the time of admission presented with fever, were taking medications other than antipsychotics (such as steroids, nonsteroidal anti-inflammatory drugs, and antibiotics), or suffered from a medical disease (including autoimmune illnesses, hypertension, diabetes, and infectious diseases) were not included in the study. The presence of psychosis secondary to a known medical condition, mental retardation (IQ below 70), autism spectrum disorder diagnosis, schizophrenia diagnosis made sooner than six months prior to hospitalization, and age over 18 years were all considered exclusion criteria.

The control group for the study consisted of 57 age- and gender-matched healthy children who visited the pediatric polyclinic at the Afyonkarahisar Health Sciences University Hospital for regular checkups and did not have any chronic illnesses or long-term drug use. The Afyonkarahisar University of Health Sciences Ethics Committee granted IRB permission for the study on July 2, 2021 (No: 2021/378). The families of the children who agreed to participate in the study provided written informed consent, and all study methods complied with local laws and regulations as well as with the Declaration of Helsinki.

Information about the sociodemographic, and clinical characteristics and treatments of the patients were obtained from the hospital records. The initial severity of the disease was evaluated using the Clinical Global Impression (CGI) Scale. The CGI scale was completed by the psychiatrist who carried out the treatment and follow-up of the patients.

NLR, PLR, and MLR were calculated from complete blood counts from participants during the first visit. These counts included white blood cells (WBC), neutrophils, lymphocytes, thrombocytes, and monocytes. Hemoglobin and hematocrit values were also obtained.

Measurements

A sociodemographic information form was developed by the researchers and was used to evaluate the sociodemographic and clinical characteristics of the patients (age, gender, status of education continuation, family history of psychotic disorder and other psychiatric illnesses, lifestyle) and treatments carried out.

The *Clinical Global Impression Scale (CGI)* was developed by Guy et al (1976) to assess the clinical course of psychiatric disorders (18). The scale was completed during a semi-structured interview conducted by the interviewer. CGI is a scale composed of three parts. The first part, Clinical Global Impression-Severity of Disease (CGI-S), assesses the severity of the disease at the time the scale was completed between 1 and 7 points: 1 = normal, not ill, 2 =borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = significantly ill, 6 = severely ill, 7 = extremely ill. The second and third parts of the scale assess the improvement in disease severity and side effects of treatment. The second and third parts of the scale were not used in our study.

Statistical analysis

Statistical analysis of the study was performed using the Statistical Package for Social Science (SPSS) 21.0 program. The normal distribution of data was evaluated with the Kolmogorov-Smirnov test, histogram, and skewness-kurtosis coefficients. In order to compare the two groups, the Pearson chi-square test was used for count data, the independent samples t-test was used in measurement data with normal distribution, and the Mann-Whitney U test was used for WBC, NLR, PLR and MLR data without normal distribution. Spearman correlation was used for correlation analysis. The correlation is considered weak, moderate, strong or very strong when the coefficient value is in the range of 0–0.25, 0.26–0.50, 0.51–0.75 or 0.76–1.00, respectively. A value of $p < 0.05$ was accepted as statistically significant.

Results

The sociodemographic data of the participants are given in Table 1. There was no significant difference between the groups in terms of age and gender. The mean age of the mothers and fathers of the participants in the EOS group was statistically significantly higher than in the control group ($p = 0.002$, $p = 0.001$, respectively). The family history of psychotic disorder was significantly higher in the EOS group as compared to the control group ($p = 0.038$).

All of the participants with EOS were found to use at least one psychotropic drug. While eleven of them (36.6 %) used single antipsychotics, the other 19 (63.3 %) used dual antipsychotic

Tab. 1. Comparison of the socio-demographic data of the participants and their parents.

	EOS (n=30)	HC (n=57)	p
Age	16.83±1.23	16.71±1.06	0.654
Gender			
Female	33.4%	38.5%	0.628
Male	66.6%	61.5%	
Status of Continuation to Education			
Yes	46.7%	94.7%	0.000
No	53.3%	5.3%	
Age of mother	44.94±5.66	40.66±5.94	0.002
Age of father	48.46±6.69	43.10±6.54	0.001
Mental disorders in the family			
Psychotic disorder	10.0%	0%	0.038
Other mental disorders	40.0%	5.3%	0.000
Lifestyle			
Urban	43.3%	59.6%	0.147
Rural	56.7%	40.4%	

EOS = early-onset Schizophrenia, HC = healthy control. The values are presented as mean ± standard deviation or percentage. *Indicates statistical significance at $p < 0.05$

Tab. 2. Distribution of antipsychotic treatment and disease severity in patients with early-onset schizophrenia.

	EOS (n=30)	
	n	%
Antipsychotics		
Risperidone	16	53.3
Aripiprazole	8	26.6
Quetiapine	10	33.3
Clozapine	2	6.6
Olanzapine	5	16.6
Ziprasidone	1	3.3
Paliperidone	1	3.3
Haloperidol	6	20.0
CGI-Severity		
Normal, not ill	–	–
Borderline mentally ill	–	–
Mildly ill	6	20.0
Moderately ill	13	43.4
Significantly ill	8	26.6
Severely ill	3	10.0
Extremely ill	–	–

EOS= early-onset Schizophrenia, CGI= clinical global impression

Tab. 3. Comparisons of laboratory parameters between the groups.

	EOS (n=30)	HC (n=57)	Z/t	p
NLR	2.06 (1.25)	1.49 (0.74)	–2.7	0.006[1]
PLR	125.75 (56.68)	126.90 (38.85)	–1.1	0.249[1]
MLR	0.21 (0.15)	0.21 (0.08)	–0.9	0.357[1]
Neutrophil 10^3/uL	4.08±1.02	3.66±1.04	–2.2	0.044[2]
Lymphocytes 10^3/uL	2.08±0.68	2.33±0.46	–1.5	0.125[2]
Platelets 10^3/uL	257.13±52.80	287.68±66.74	–2.1	0.033[2]
WBC 10^3/uL	7.04 (2.92)	6.51 (1.94)	–1.8	0.071[1]
Hemoglobin g/dL	14.39±1.55	14.53±1.17	–0.4	0.634[2]
RBC 10^6/uL	5.05±0.48	5.16±0.43	–1.1	0.271[2]
MPV fL	9.53±1.08	10.03±0.78	–2.4	0.015[2]

EOS: early-onset schizophrenia, HC: healthy controls, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MLR: monocyte/lymphocyte ratio. uL: microliter, Fl: femtoliter, dL: deciliter, [1]Mann-Whitney U test, [2] independent samples t-test

Tab. 4. Correlation between CGI scores and WBC, NLR, PLR and MLR values of the patients.

	p	r
WBC 10^3/uL	0.033	0.391
NLR	0.000	0.669
PLR	0.046	0.367
MLR	0.226	0.228

CGI: clinical global impression, r: Spearman correlation coefficient, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MLR: monocyte/lymphocyte ratio

drugs. Twenty-four subjects (80.0 %) used atypical antipsychotics, whereas typical antipsychotics in addition to atypical antipsychotics had been needed in the treatment of the remaining six patients (20.0 %). Table 2 displays the distribution of medications used by the patients as well as the illness severity at the time of admission.

NLR and neutrophil counts, MPV and platelet counts were found to be statistically different when the laboratory parameters of the two groups were examined, but no other parameters were found to be statistically different (Tab. 3).

In the EOS group, the relationship between blood parameters and disease severity was investigated. When the relationship between blood parameters and disease severity was evaluated, a strong positive significant relationship (r = 0.669; p = 0.000) was found between NLR and disease severity. The WBC and PLR levels and disease severity also showed a positive statistically significant correlation (r = 0.391, p = 0.033 and r = 0.367, p = 0.046, respectively) (Tab. 4).

Discussion

There is an increase in the number of new approaches aiming to clarify the complex pathogenesis of schizophrenia. Among these approaches, recent studies have pointed out that abnormal inflammatory response may be related to the pathophysiology of schizophrenia.

In this study, we researched the relationship between the high NLR value as a surrogate marker for inflammation and schizophrenia in pediatric and adolescent populations. In our study, we found a relationship between EOS and high NLR and neutrophil values. More importantly, we found a positive relationship between the severity of psychotic symptoms and NLR. This, in turn, might suggest that a high NLR value is associated with psychotic episodes. These data suggest that inflammation might contribute to the onset of psychosis.

Previous studies have reported that proinflammatory markers were higher (19) and anti-inflammatory biomarkers were lower (20) in samples with schizophrenia as compared to control samples. Among many inflammatory markers, a high NLR value is noted to be a reliable and sensitive marker. A high NLR value is reported to be an important indicator of adverse outcomes for patients with infection, sepsis, stroke, cardiovascular disease and cancer (21). The relationship between NLR and schizophrenia, on the other hand, has been investigated in many studies conducted with adults. In a study comparing adult schizophrenia patients and control group, the neutrophil and NLR values were found to be high in schizophrenic patients, while lymphocytes were found to be low. The same study reported that there was a positive significant relationship between schizophrenia symptom severity and NLR (22). Another study noted that there was an increase in NLR, and neutrophil, leukocyte, and monocyte counts in adult schizophrenia patients as compared to the control group, while this increase in NLR was independent of metabolic parameters (23). Another study, which compared PLR and MLR (used as inflammation markers in recent studies) in adult schizophrenia patients and in a control group, reported that NLR, MLR and PLR values were higher in adult schizophrenia patients as compared to controls (24).

Although there are several studies examining the relationship between schizophrenia and inflammation in adults, studies conducted on children and adolescents are limited. There was a conclusion in a study investigating the relationship between psychopathology and inflammation in children and adolescents that inflammation markers (interleukin (IL)-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL 10, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein (MCP)-1) might be predictors of the acute psychiatric picture (25). Another study, examining the relationship between the early-onset schizophrenia and inflammation mar-

kers, reported no difference in the levels of inflammatory markers between children and adolescents with schizophrenia and healthy children, whereas a positive correlation was found between IL-4 and IL-10 levels and negative symptoms of schizophrenia (26).

In a study conducted on an adolescent patient population followed up in an inpatient clinic, NLR and leukocyte counts were reported to be higher in psychotic adolescent patients as compared to the non-psychotic patient group, while this increase was observed especially during the acute psychotic attack period (27). In another similar study, the inflammation markers in children with a diagnosis of first-episode psychosis were compared with those in children with diagnoses other than psychosis and healthy controls. In this study, several inflammatory mediators (e.g., IL-1β, IL-6, IL-5, IL-10, TNF-α and IFN-γ) were found to be high in children with psychosis, while an increase in the serum levels of S100B, a peripheral marker of blood-brain barrier damage, was noted (28). In a recent study investigating the relationship between NLR and EOS in adolescents, it was observed that NLR and neutrophil counts were higher in EOS adolescents than in the control group, but the leukocyte, hemoglobin, lymphocyte, and platelet values did not differ between the groups (29).

Similar to these studies, NLR and neutrophil counts were found to be high in the EOS group in our study. Furthermore, the platelet count was found to be significantly higher in the patient group. However, no significant difference was found in WBC, lymphocyte, hemoglobin, PLR and MLR values. We also evaluated the disease severity with CGI scores in our study. We found a positive significant relationship between disease severity and NLR and PLR values. A previous study in which the severity of EOS in adolescents was evaluated with the Positive and Negative Syndrome Scale (PANSS) scores reported that there was no relationship between PANSS scores and NLR (29). In a study in which adolescents with psychosis were compared with non-psychotic adolescents, the disease severity was measured with CGI and no correlation was found between NLR and CGI scores. The same study also reported that the NLR value decreased in the remission period as compared to that assessed during the acute psychosis period in the inpatient psychotic adolescent group (27). There was a positive correlation between PANSS total scores and NLR and leukocyte counts, while in another study with adult patients, there was a negative correlation with the lymphocyte count (22). In a meta-analysis investigating the relationship between schizophrenia and NLR, PANSS-positive scores were noted not to change NLR values (30). In the same meta-analysis, it was stated that subjects taking antipsychotic medication might have a higher NLR value regardless of the diagnosis of schizophrenia. Studies investigating the link between the severity of schizophrenia and inflammatory markers in the literature have not reached a consensus. There is not much information on the association between inflammatory changes and disease onset. The most important reason for this is the fact that conditions such as stress and inflammation that might be encountered in many circumstances would make it difficult to determine a causal relationship between the initial infection and other mediator effects.

We wanted to contribute to the literature by discussing the sociodemographic data of the children and adolescents included in our study. Early-onset schizophrenia has been reported to be seen twice as often in males which is different from the adult-type schizophrenia (31). The presence of a genetic susceptibility that is transmitted through sex chromosomes in males while predisposing to the development of schizophrenia by causing some disruptions in neuronal development has been talked about recently. This has been noted to cause schizophrenia symptoms to appear earlier in life in males than in females (32). In our study, two-thirds of cases diagnosed with the early-onset schizophrenia were males, which is consistent with the literature.

Approximately 10 % of the cases included in our study were found to have a history of schizophrenic disorder in their families. This rate was significantly higher as compared to the healthy control group. Studies conducted to determine the genetic aspect of schizophrenic disorder revealed that the presence of schizophrenic disorder among immediate relatives increases the lifetime risk of developing schizophrenic disorder 5–20 times compared to the general population (33). In a meta-analysis study examining prenatal and perinatal risk factors in the etiopathogenesis of psychotic disorders, one of the important risk factors was noted to be maternal and paternal psychopathology. Also, the same study indicated that maternal age younger than 20 years of age or in the range of 30–34 years was found to be a significant risk factor, while paternal age lower than 20 years or higher than 35 years was reported to be a risk factor (34). In line with the literature, the findings of our study show that genetic factors and advanced parental age are important risk factors in schizophrenic disorder.

Studies show that neurocognitive skills such as attention, problem-solving, information processing speed, verbal memory and learning are adversely affected in cases with EOS(35). While 53.3 % of the cases in our study did not attend school, 10 of the 14 cases who attended had low academic performance. This finding, which is similar to those published in literature, was considered to be a condition that should be taken into account in planning the treatment process of patients.

The results of our study should be considered with some limitations. Firstly, the cross-sectional methodology of this study limited the measurement of inflammatory markers to a single time point. Secondly, the small sample size of the study may not have adequately represented the first episode of EOS patients. Thirdly, the effects of psychiatric drugs used by the patients on blood parameters have not been investigated. On the other hand, the comparison of the patients with the control group, the analysis of the blood samples taken at the first psychotic attack, and the combination of the data collected from two different centers were the strengths of our study. Studies conducted with children may provide better information for understanding the relationship between psychiatric disorders and inflammation. This is because children have a shorter disease duration and lower allostatic load than adults (36). In our study, it was aimed to minimize the confounding factors by examining the blood samples of the patients during the first attack.

According to the study's findings, the multisystem inflammatory process model that was identified in previous studies on schizophrenia may also be relevant to the patient population of children and adolescents. The link between psychiatric disorders and inflam-

matory processes in children and adolescents has not been sufficiently studied in research with large sample sizes. Further research in the many disciplines is needed to investigate the link between inflammation and psychiatric disorders in this age group, including individuals with schizophrenia in all stages, particularly in the prodromal stage. Future studies might help to define the function of inflammatory mechanisms, clarify the pathophysiology of the disease and develop effective therapy strategies. It is possible to evaluate the current study as a contribution to the knowledge on this subject.

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