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Research article

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A retrospective cohort study of the change in inflammatory parameters in childhood schizophrenia and bipolar disorder from childhood to adulthood

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Ethics Committee Approval
Ethics committee approval was received for the study from the Dicle University Faculty of Medicine ethics committee (Number: 393 and Date: 16/07/2020).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The etiologies of childhood schizophrenia and bipolar disorder have not yet been clarified. In cases in which the symptoms of mood are not dominant and psychotic symptoms are more dominant, it may be difficult to distinguish between childhood schizophrenia and bipolar disorder diagnoses. Follow-up studies concerning this subject have indicated that approximately half of the adolescents diagnosed with bipolar disorder were first (and incorrectly) diagnosed with schizophrenia. Therefore, strong markers are still needed to be used in the differential diagnosis at the time of the first application. An increase in the number of studies on the neuroinflammatory process in pediatric schizophrenia and bipolar illness have started to appear in the literature. The neutrophil–lymphocyte, thrombocyte–lymphocyte, and thrombocyte–neutrophil ratio (NLR, TLR, and TNR, respectively) levels in patients with childhood schizophrenia and childhood bipolar disorder at the time of admission and five years later were evaluated to determine whether inflammatory markers changed over time.

Methods: Twelve patients diagnosed with childhood schizophrenia and 14 patients diagnosed with childhood bipolar disorder were included in the study. Active infections, medical, neurological, endocrine, and metabolic illnesses, mental retardation, further concomitant psychiatric diagnoses, and intoxication were all exclusion factors. Hemograms from the same patients who satisfied the inclusion criteria when they originally applied and again at the fifth year follow-up were evaluated. Age, gender, neutrophil, lymphocyte, leukocyte, and thrombocyte values were recorded. NLR was calculated by dividing the neutrophil count by lymphocyte count. TLR value was calculated by dividing the thrombocyte count by lymphocyte count. TNR value was calculated by dividing the thrombocyte count by neutrophil count. Bipolar disorder and schizophrenia status were compared using NLR, TLR, and TNR parameters both at the time of initial diagnosis and at the fifth year of follow-up.

Results: When the initial admission hemograms of patients with childhood schizophrenia or childhood bipolar disorder were examined, no statistically significant differences between the two groups in terms of NLR (P = 0.150) and TLR (P = 0.440) were found. TNR was significantly higher in childhood bipolar disorder patients than in childhood schizophrenia (P = 0.015). At the fifth year follow-up, the hemograms of individuals diagnosed with either childhood schizophrenia or childhood bipolar disorder were compared, and no statistically significant differences between the two groups in NLR, (P = 0.572),TLR (P = 0.758), and TNR (P = 0.328) were found.

Conclusion: It was concluded that NLR and TLR levels did not change significantly over time in either disease and could not be used for the differential diagnosis of either disease. TNR may be considered for differential diagnoses in childhood schizophrenia and bipolar disease, particularly at the time of the first episode after confirmation of this study's findings with future studies.

Keywords: Childhood, Schizophrenia, Bipolar, NLR, TLR, TNR

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Introduction

Although the etiologies of schizophrenia and bipolar disorder are unknown, these conditions are caused by changes and different interactions in or outside the central nervous system due to a variety of factors. These conditions are mental disorders that cause a significant deterioration in functionality and quality of life [1, 2]. While very early-onset schizophrenia seen before the age of 13 is seen in 1 in 40,000 children, the incidence of early-onset schizophrenia before the age of 18 is 50 times higher than very early-onset schizophrenia. The lifetime prevalence of schizophrenia is 1% worldwide [3]. Bipolar disorder, on the other hand, has been found to affect between 0.1% and 2.5% of children and adolescents in studies in the literature [4, 5]. At the same time, bipolar disorder in children and adolescents is a serious illness that causes severe functional decline and can result in repercussions, such as recurrent hospitalizations and suicide attempts [6].

Microglia are thought to be brain macrophages, and these cells can contribute to neurodegeneration by altering the oxidant–antioxidant balance and activating the production of numerous proinflammatory cytokines in response to even minor pathogenic changes in the brain [7]. According to some research, the increase in cytokines linked with this neuroinflammatory process that begins in the central nervous system may influence the blood–brain barrier and have repercussions on the current condition in the peripheral inflammatory system [8]. Neutrophil/lymphocyte and thrombocyte/lymphocyte ratios (NLR and TLR, respectively), which are simple and inexpensive indicators of systemic inflammation, are used as biomarkers in cancer and some systemic diseases [9, 11]. Furthermore, various studies have been conducted to demonstrate the usability of these ratios as biomarkers in both psychotic and mood disorders to shed light on early diagnosis and etiology [12, 13].

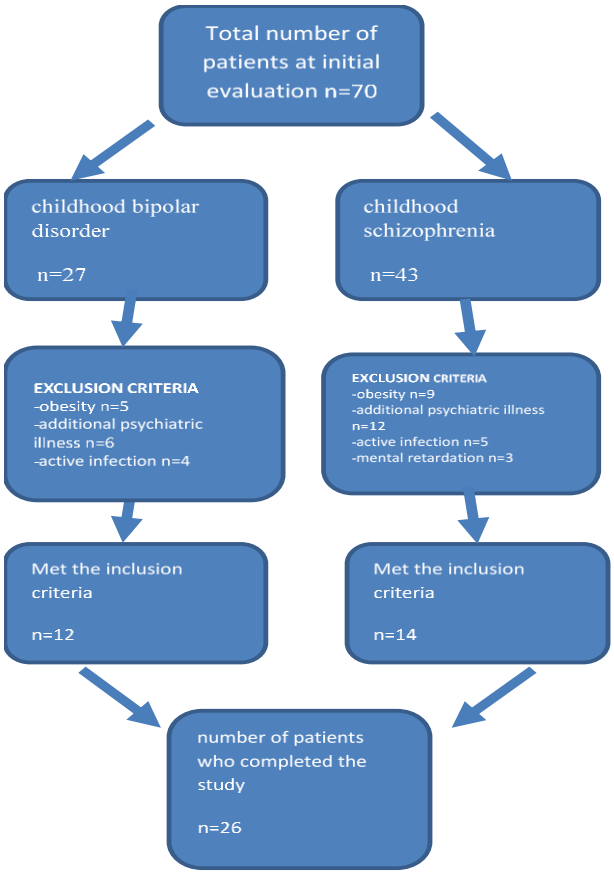
In cases in which the symptoms of mood are not dominant and psychotic symptoms are more dominant, it may be difficult to distinguish between a diagnosis of childhood schizophrenia and one of bipolar disorder. The follow -up studies on this subject show that approximately half of the adolescents diagnosed with bipolar disorder were first diagnosed (incorrectly) with schizophrenia [14, 15]. Therefore, strong markers are still needed to be used in the differential diagnosis at the time of the first application.

However, only a few investigations on how the neuroinflammatory process affects individuals with childhood schizophrenia and bipolar disorder over time have been published. NLR, TLR, and thrombocyte/neutrophil (TNR) levels of patients who were diagnosed with either or both schizophrenia and bipolar disorder as children and who are still being followed up and treated were evaluated. The study aimed to examine how the neuroinflammatory process changes throughout the disease in childhood schizophrenia and bipolar disorder. In addition, the use of NLR, TLR and TNR levels for differential diagnosis of these two diseases were examined.

Materials and methods

Our study was performed by scanning the records of our child and adolescent mental health and illness clinic and adult mental health and diseases clinic between September 1, 2013, and September 1, 2020. The required ethics committee approval (Date:16/07/2020-No:393) was obtained from the Ethics Committee for Non-Interventional Clinical Research, Dicle University Faculty of Medicine, for this study. Patients who presented to our child and adolescent psychiatry outpatient clinic with their first psychotic attack, had not yet been treated, and were diagnosed with schizophrenia in DSM-5 follow-ups, and patients who presented with their first manic attack had not yet begun medical treatment and were diagnosed with bipolar disorder 1 based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) follow-ups were considered for this study. The study was planned with the inclusion of the patients who fulfilled study requirements. Patients diagnosed with schizophrenia without positive symptoms after clinical evaluation using the Positive and Negative Syndrome Scale at their fifth year follow-ups and patients with bipolar disorder in the euthymic phase (Young Mania Rating Scale score ≤ 5 and Hamilton Depression Rating Scale score ≤ 7) were re-evaluated [16-18]. Active infections, medical, neurological, endocrine, and metabolic illnesses, mental retardation, further concomitant psychiatric diagnoses, and intoxication were considered exclusion factors. The study consisted of 12 patients with childhood schizophrenia who satisfied all criteria and 14 individuals with childhood bipolar disorder out of the 70 patients who fulfilled just the diagnostic and follow-up requirements (Figure 1).

Figure 1: Study group follow-up diagram



Hemograms at first admission and five years later were examined for patients who met the inclusion criteria. Complete blood count was calculated by Cell-Dyn 3700 (Abbott Diagnostics, USA). Age, gender, neutrophil, lymphocyte, leukocyte, and thrombocyte values were recorded. NLR was calculated by dividing the neutrophil by lymphocyte value. TLR value was calculated by dividing the thrombocyte by lymphocyte

value. TNR was calculated by dividing the thrombocyte by the neutrophil value.

Statistical analysis

IBM SPSS 21.0 for Windows Statistical Package Program was used for the statistical evaluation of our research data. The mean and standard deviation (SD) of measured variables were reported, whereas categorical variables were presented as numbers and percentages (%). It was determined whether the data conformed to the normal distribution. Does not show normal distribution; Wilcoxon Test was used to compare the previous and next groupings. The Mann Whitney-U test was used to compare two independent groups. A statistically significant result was accepted if *P*-value ≤ 0.05.

Results

In the first phase, the study was started with 70 patients. The study was terminated with 26 patients who met the inclusion criteria (Figure 1). The mean age of 12 patients (five boys, seven girls) diagnosed with childhood schizophrenia was 19. The mean age of 14 patients (eight boys, six girls) diagnosed with childhood bipolar disorder was 19. No significant differences between groups with respect to age and gender were found (P = 0.725, P = 0.630).

When the hemograms of patients who presented with the first childhood psychotic episode and were diagnosed with schizophrenia during follow-ups were compared to the hemogram of the same patients who did not have positive symptoms during the fifth year follow-up, no statistically significant differences in terms of NLR, TLR, and TNR levels during the follow-up period were found (P = 0.730, P = 0.925, P = 0.470, respectively) as shown in Table 1.

Table 1: Comparison of hematological parameters between patients who presented with the first childhood psychotic episode and were diagnosed with schizophrenia during the fifth year follow-up from childhood to adulthood

Hematological Parameter	Period	Median	Mean (SD)	Z	*P*-value
WBC	Childhood	9.09	9.54 (3.38)	0.157	0.875
	Adulthood	8.90	9.46 (1.96)		
TRM	Childhood	238.60	251.07 (79.87)	2.354	0.061
	Adulthood	250.80	285.45 (119.93)		
LYM	Childhood	2.11	2.22 (0.72)	0.565	0.572
	Adulthood	2.38	2.42 (0.75)		
NEU	Childhood	6.04	6.46 (3,12)	0.157	0,875
	Adulthood	5.53	6.17 (1.95)		
NLR	Childhood	2.64	3.41 (3.00)	0.345	0.730
	Adulthood	2.70	2.86 (1.38)		
TLR	Childhood	103.89	124.86 (58.52)	0.094	0.925
	Adulthood	121.00	128.51 (66.56)		
TNR	Childhood	37.34	46.32 (29.70)	0.722	0.470
	Adulthood	43.09	48.89 (22.92)		

n: 14, Median: median value, Mean Rank: Ranks Average, SD: standard deviation, Z: Wilcoxon Signed Rank test value, *P*: Wilcoxon Signed Rank test statistical significance value WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

When the hemograms of patients who had their first manic episode as children and were diagnosed with bipolar disorder during the follow-up period were compared to the hemograms of the same patients who were in the euthymic phase at the fifth year follow-up, no statistically significant differences in terms of NLR, TLR, and TNR levels were found (P = 0.480, P = 0.583, and P = 0.136) as shown in Table 2.

When the first admission hemograms of patients with childhood schizophrenia and childhood bipolar disorder were examined, no statistically significant differences between the two groups in terms of NLR (P = 0.150) and TLR (P = 0.440) were found, but a statistically significant difference in TNR was noted (P = 0.015) as shown in Table 3.

Table 2: Comparison of hematological parameters between patients who had their first manic episode as children and were diagnosed with bipolar disorder during the fifth year follow-up

Hematological Parameter	Period	Median	Mean (SD)	Z	*P*-value
WBC	Childhood	7.70	8.10 (1.79)	1.647	0.099
	Adulthood	8.22	8.72 (2.49)		
TRM	Childhood	295.25	291.90 (74.39)	0.628	0.530
	Adulthood	272.65	275.98 (45.34)		
LYM	Childhood	2.31	2.36 (0.66)	0.078	0.937
	Adulthood	2.25	2.31 (0.68)		
NEU	Childhood	4.49	4.87 (1.85)	1.648	0.099
	Adulthood	4.89	5.56 (2.25)		
NLR	Childhood	1.94	2.33 (1.39)	0.706	0.480
	Adulthood	2.50	2.58 (1.23)		
TLR	Childhood	116.05	129.46 (38.52)	0.549	0.583
	Adulthood	118.49	126.06 (31.30)		
TNR	Childhood	67.90	68.69 (31.11)	1.490	0.136
	Adulthood	47.96	56.90 (22.72)		

n: 12, Median: median value, Mean Rank: Ranks Average, SD: standard deviation, Z: Wilcoxon Signed Rank test value, P: Wilcoxon Signed Rank test statistical significance value, WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

Table 3: Comparison of hematological parameters between patients diagnosed with childhood psychosis and those diagnosed with childhood bipolar disorder

Hematological Parameter	Diagnosis	n	Median	Mean (SD)	U	*P*-value
WBC	Bipolar	12	7.70	8.10 (1.79)	63.00	0.280
	Psychosis	14	9.09	9.54 (3.38)		
TRM	Bipolar	12	295.25	291.90 (74.39)	54.00	0.123
	Psychosis	14	238.60	251.07 (79.87)		
LYM	Bipolar	12	2.31	2.40 (0.66)	72.50	0.554
	Psychosis	14	2.11	2.22 (0.72)		
NEU	Bipolar	12	4.49	4.87 (1.85)	56.00	0.150
	Psychosis	14	6.04	6.46 (3.12)		
NLR	Bipolar	12	1.94	2.33 (1.39)	56.00	0.150
	Psychosis	14	2.64	3.41 (3.00)		
TLR	Bipolar	12	116.05	129.46 (38.52)	69.00	0.440
	Psychosis	14	103.89	124.86 (58.52)		
TNR	Bipolar	12	67.90	68.69 (31.11)	37.00	0.015
	Psychosis	14	37.34	56.64 (31.84)		

n: number, Median: median value, Mean Rank: Ranks Average, SD: standard deviation, U: Mann Whitney U test value, P: Mann Whitney U test statistical significance value, WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

At the fifth year follow-up, the hemogram of patients with childhood schizophrenia and childhood bipolar disorder were compared, and no statistically significant differences between the two groups were found in terms of NLR, (P = 0.572), TLR (P = 0.758), and TNR (P = 0.328) as shown in Table 4.

Table 4: Comparison of hematological parameters at the fifth year follow-up of the group diagnosed with childhood psychosis and the group diagnosed with childhood bipolar disorder

Hematological Parameter	Diagnosis	n	Median	Mean (SD)	U	*P*-value
WBC	Bipolar	12	8.22	8.72 (2.49)	65.50	0.341
	Psychosis	14	8.90	9.46 (1.96)		
TRM	Bipolar	12	272.65	275.98 (45.34)	73.00	0.572
	Psychosis	14	250.80	285.45 (119.93)		
LYM	Bipolar	12	2.25	2.31 (0.68)	77.50	0.738
	Psychosis	14	2.38	2.42 (0.75)		
NEU	Bipolar	12	4.89	5.56 (2.25)	68.00	0.411
	Psychosis	14	5.53	6.17 (1.95)		
NLR	Bipolar	12	2.50	2.58 (1.23)	73.00	0.572
	Psychosis	14	2.70	2.86 (1.38)		
TLR	Bipolar	12	118.49	126.06 (31.30	78.00	0.758
	Psychosis	14	121.99	128.51 (66.56)		
TNR	Bipolar	12	47.96	56.90 (22.72)	65.00	0.328
	Psychosis	14	43.09	48.89 (22.92)		

n: number, Median: median value, Mean Rank: Average of Ranks, SD: standard deviation, U: Mann Whitney U test value, P: Mann Whitney U test statistical significance value, WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

Discussion

Although schizophrenia is an uncommon diagnosis in both children and adolescents, it has substantial consequences for such young patients. Early diagnosis and an effective treatment regimen are expected to minimize losses in quality of life [19]. Again, in pediatric bipolar disorder studies, it has been reported that 70%–100% of patients recovered but recurred to 80% within 2 to 5 years, did not fully recover functionality, attempted suicide, engaged in substance abuse, and/or started having trouble with the

law; thus, early diagnosis is important for minimizing these issues [20–24].

No changes in these parameters were observed in long-term follow-ups in our study, which looked at the long-term consequences of the inflammatory process in individuals diagnosed with schizophrenia and bipolar disorder as children and whose diagnosis and treatment persisted into adulthood. Falcone et al. found a statistically significant increase in monocytes and lymphocytes in the first attack psychosis group compared to the control group in their research comparing blood parameters of 80 pediatric patients with an initial diagnosis of psychosis in 66 healthy children [25]. Ozdin et al. [26] discovered that NLR and TLR were substantially greater in the relapse phase compared to the control group in their research of 105 persons with schizophrenia and 105 healthy controls and that NLR and TLR declined significantly in the remission phase compared to the relapse period. Garcia-Rizo et al. [27] found no differences between the groups in 75 adult patients with the newly diagnosed psychotic conditions and 80 healthy controls in terms of NLR levels. It has been reported that since early-onset psychosis occurs during neurobiological development, it has more permanent effects on an individual in terms of cognitive and psychosocial deterioration, and the prognosis is worse than seen with adult-onset psychosis [28, 29]. In our investigation, the absence of differences in inflammatory markers in long-term follow-ups showed that this process may be connected to the progressive trajectory of this disease.

In our study, no differences were found between NLR, TLR, and TNR measured in the childhood bipolar phase and the euthymic phase at follow-up. In their study of bipolar patients, euthymic patients, and healthy controls, Kalelioğlu et al. [30] discovered that NLR and TLR increased in both bipolar and euthymic phases compared to healthy controls, but no differences in NLR and TLR between bipolar and euthymic phase in the same patients were found. Mazza et al. [12] regarded this scenario as distinct phases of bipolar illness that activated inflammatory processes differently, while a reduced inflammatory response, even though it is euthymic, may continue.

Childhood schizophrenia has a diverse clinical appearance, and other mental diseases, such as bipolar disorder and organic reasons, should be considered before making a diagnosis of schizophrenia [19]. Thrombocytes are hypothesized to be effective in endothelial permeability, neutrophil, and macrophage migration, and neuroinflammatory processes by activating the release of specific cytokines and neurotransmitters. It is predicted that monitoring these parameters may be effective in diagnosing/treating some psychiatric disorders [31]. Özdin et al. [32] compared NLR and TLR levels in patients with adult schizophrenia and bipolar disorder to those in the healthy control group and discovered that NLR, TLR, and thrombocyte counts were greater in the bipolar disorder group, whereas lymphocyte counts were lower. In schizophrenic patients, they found an increase in NLR and TLR values and a decrease in both neutrophil and lymphocyte counts compared to controls. It has also been reported that patients with schizophrenia have higher NLR values than those with bipolar disorder. Our study found that TNR was considerably greater in the bipolar disorder group when compared with children with schizophrenia and bipolar disorder who did use drugs, but this difference did not exist in adulthood. The fact that this difference was observed in the active disease phase and then disappeared in the remission phase for both disease groups led us to believe that TNR could be used in the differential diagnosis of mood disorder and schizophrenia during the first psychotic episode in childhood, which could cause diagnostic confusion. However, it was concluded that studies with a larger number of patients are needed to establish reference values for TNR.

Limitations

The limitations of our study include the limited number of patients and absence of a healthy control group in addition to patients receiving medical treatment during follow-up. Since these diseases are less common in childhood, the number of patients was limited. In addition, the five-year period, which can be considered long for a follow-up period, may have caused the number of patients to be even less. Since this study was carried out with a limited number of patients, the results should be supported by future studies.

Conclusion

Numerous unanswered problems regarding neuroinflammatory processes in pediatric schizophrenia and bipolar illnesses that cause severe functional loss and greatly affect the quality of life exist. It was concluded that NLR and TLR levels did not change significantly over time for both diseases and could not be used for the differential diagnosis of both diseases. TNR may be considered for differential diagnoses in childhood schizophrenia and bipolar disease, particularly at the time of the first episode; however, further confirmation of this study's findings is needed.

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