RESEARCH ARTICLE

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Examination of Systemic Inflammation Related Hemogram Biomarkers in Children and Adolescents with Generalized Anxiety Disorder

ABSTRACT

Objective: In this study, we aimed to examine the complete blood count parameters and blood-based systemic inflammatory markers in children with generalized anxiety disorder (GAD).

Methods: Retrospectively, complete blood count of 48 GAD diagnosed children and adolescents and age-gender matched 46 healthy controls were compared in terms of hemoglobin (Hb), erythrocyte distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), white blood cell count (WBC), neutrophil, lymphocyte and monocyte counts and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet to lymphocyte ratios (PLR). Chi-square test, independent samples t-test and Mann-Whitney U test were used for statistical evaluation.

Results: MPV levels were found to be significantly higher (p=0.020), while PLT and PDW levels were found to be significantly lower (p=0.018 and p=0.011, respectively) in children and adolescents with GAD. There was no statistically significant difference in terms of Hb, RDW, PCT, WBC neutrophil, lymphocyte and monocyte counts and NLR, MLR, PLR between case and control groups.

Conclusions: Platelet parameters that have been postulated to be associated with inflammation, such as MPV and PDW may be related to possible inflammatory back ground of GAD in children and adolescents and comprehensive prospective studies are required on this subject.

Keywords: Anxiety Disorder, Inflammation, Hemogram, Complete Blood Count, Children and Adolescents

Yaygın Anksiyete Bozukluğu Olan Çocuk Ve Ergenlerde Sistemik İnflamasyon İlişkili Hemogram Biyobelirteçlerinin İncelenmesi

ÖZET

Amaç: Bu çalışmada yaygın anksiyete bozukluğu olan (YAB) çocuk ve ergenlerde tam kan sayımından bakılan sistemik inflamasyon biyo-belirteçlerinin düzeylerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Retrospektif olarak 48 YAB tanılı çocuk ergen ile yaş-cinsiyet açısından eşleştirilmiş 46 sağlıklı kontrol çocuk ve ergenin tam kan sayımı sonuçları; hemoglobin (Hb), eritrosit dağılım genişliği (RDW), trombosit sayısı (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), plateletkrit (PCT), beyaz kan hücre sayımı (WBC), nötrofil, lenfosit ve monosit sayıları ve nötrofil / lenfosit oranı (NLR), monosit / lenfosit oranı (MLR), trombosit / lenfosit oranları (PLR) açısından karşılaştırıldı. İstatistiksel değerlendirmede ki-kare testi, bağımsız örneklemler t-testi ve Mann-Whitney U testi kullanıldı.

Bulgular: YAB olan çocuk ve ergenlerde, MPV düzeyleri anlamlı olarak yüksek (p = 0,020) ve PLT ve PDW düzeyleri anlamlı olarak düşük (sırasıyla p = 0,018 ve p = 0,011) bulundu. Hb, RDW, PCT, WBC, nötrofil, lenfosit ve monosit sayıları, NLR, MLR, PLR açısından olgu ve kontrol grupları arasında istatistiksel olarak anlamlı bir farklılık saptanmadı.

Sonuç: MPV ve PDW gibi inflamasyonla ilişkili olduğu öne sürülen trombosit parametreleri, çocuk ve ergenlerde YAB'nin olası inflamatuar arka planıyla ilişkili olabilir ve bu konuda kapsamlı ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Anksiyete Bozukluğu, İnflamasyon, Hemogram, Tam Kan Sayımı, Çocuk ve Ergenler

INTRODUCTION

Anxiety Disorders are considered among the most common psychiatric conditions in children and adolescents with a prevelance of 18 % worldwide (1) and a prevelance of 16.7% in Turkey (2). Anxiety disorders are related to significant impairments in emotional, social, and academic functioning (3) and predispose to other types of psychopathology, in particular depression (4).

Increasing evidence support that immunological and inflammatory processes play an important role on major psychiatric disorders (5,6,7). Inflammatory processes in anxiety disorder has not been examined widely (5). However, there is evidence of increased inflammatory activity in anxiety related disorders (6) and in particular generalized anxiety disorder (8).

When compared to other biomarkers of inflammation, systemic inflammation biomarkers obtained from hemogram are known to be superior for low price, routine use and high reproducibility across laboratories. Furthermore, inflammatory rates are supposed to combine information on both innate and adaptive parts of immunity and to represent a reliable and practical measure of inflammation (9).

We encountered no study evaluating systemic inflammation biomarkers in children and adolescents with anxiety disorder. We encountered only one study investigating the effect of comorbid anxiety disorder on systemic inflammation biomarkers in adolescents with obsessive compulsive disorder (OCD) (10).

In this study, we aimed to evaluate systemic inflammation biomarkers in children and adolescents with generalized anxiety disorder (GAD).

MATERIAL AND METHODS

Children and adolescents aged between 7–18 years who referred to child and adolescent psychiatry clinic of Düzce University Medical Faculty between July 2017 and February 2019, diagnosed generalized anxiety disorder and whose hemogram results were available, were included in the study. In this retrospective study, we compared blood count of 48 GAD diagnosed children and adolescents with age and gender matched 46 healthy controls. The diagnosis was made according to DSM-5 by an experienced child and adolescent psychiatrist at Düzce University Child and Adolescent Psychiatry Department. Children and adolescents with other psychiatric comorbidities, taking medication, having an infectious or inflammatory disease, chronic medical disease were not included. Patients and controls whose data were missing or incomplete were also not included in the study.

Hemogram parameters, measured from peripheral blood obtained at the initial presentation, were evaluated. Hemoglobin (Hb), erythrocyte distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), white blood cell count (WBC), neutrophil, lymphocyte and monocyte counts and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet to lymphocyte ratios (PLR) were recorded. NLR was calculated by dividing the neutrophil count by the lymphocyte count, MLR was calculated by dividing the monocyte count by the and lymphocyte count, PLR was calculated by dividing PLT by lymphocyte count.

Ethics committee approval was obtained from Düzce University Medical Faculty Research Ethics Committee, with approval date 04.03.2019 and protocol number 2019/47.

Statistical Analyses: SPSS version 21 (SPSS™, IBM Inc., Armonk, NY) was used for the statistical analyses. Relationships between dichotomous variables were assessed with pearson chi-square test. Shapiro-Wilk test was used to determine the conformity of the data to normal distribution. Values conforming to normal distribution were presented as mean ± standard deviation (SD), values not conforming to normal distribution were presented as median and interquartil range. Variables normally distributed were compared using Student's t-test, and Mann-Whitney U test was used when normal distribution was not established. A p value of 0.05 (two-tailed) was considered significant.

RESULTS

The mean age of child and adolescents was (151,00 ± 37,93 month) in the case group and (155,74 ± 22,41 month) in the control group. There were 19 (%39,6) male, 29 (%60,4) female children and adolescents in the case and 17 (%36,96) male, 29 (%63,04) female children and adolescents in the control group. The mean age and gender distribution were not significantly different between two groups (z= -0.434, p=0.664 and x2= 0.069, p=0.793 respectively).

There was no statistically significant difference in terms of Hemoglobin (Hb), erythrocyte distribution width (RDW), plateletcrit (PCT), white blood cell count (WBC), neutrophil, lymphocyte and monocyte counts and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) platelet to lymphocyte ratio (PLR) between case and control groups (Table 1).

MPV levels were found to be significantly higher (z=-2.320, p=0.020), while PLT and PDW levels were found to be significantly lower (t=2.405, p=0.018 and z= -2.531, p=0.011, respectively) in the patient group (Table 2).

Table1. Comparison of hemogram parameters of patient and control groups except platelet parameters

	ANX (n=48)	Control (n=46)	P	z/t
Hb	12.94 ± 1.18	13.31 ± 1.53	0.182	-1.346[a]
RDW	13.70 (13.20-14.98)	13.90 (13.35- 15.13)	0.859	-0.178
WBC	7.64 ± 1.62	7.39 ± 1.46	0.431	0.790[a]
Lymphocyte	2.44 (2.06-2.80)	2.37 (2.08-3.04)	0.961	-0.049
Neutrophil	1.60 (1.17-2.29)	1.50 (1.20-2.38)	0.414	-0.817
Monocyte	0.55 (0.46-0.64)	0.51 (0.44-0.60)	0.552	-0.594
NLR	1.60 (1.17-2.29)	1.50 (1.20-2.38)	0.540	-0.613
PLR	120.13 (96.34-145.79)	117.41 (87.81-140.54)	0.356	-0.923
MLR	0.22 (0.18-0.29)	0.21 (0.17-0.25)	0.452	-0.753

Mann Whitney U test, [a] student t test

Hb: Hemoglobin, **RDW:** Erythrocyte distribution width, **WBC:** White blood cell count, **NLR:** Neutrophil lymphocyte ratio, **PLR:** Platelet lymphocyte ratio

Table 2. Comparison of platelet parameters of patient and control groups

	ANX (n=48)	Control (n= 46)	P	z/t
PLT	315.58 ± 67.34	283.37 ± 62.31	0.018*	2.405[a]
MPV	8.50 (7.90-9.20)	8.00 (7.40-8.95)	0.020*	-2.320
PDW	16.20 (15.93-16.58)	16.50 (16.20-16.80)	0.011*	-2.531
PCT	0.24 (0.21-0.27)	0.22 (0.20-0.25)	0.085	-1.721

Mann Whitney U test, [a] student t test, *p <0.05

PLT: Platelet count, **MPV:** Mean platelet volume, **PDW:** Platelet distribution width, **PCT:** Plateletcrit

DISCUSSION

In this study, we examined systemic inflammation biomarkers obtained from hemogram in children and adolescents with GAD and found increased MPV and decreased PLT and PDW levels in children and adolescents with GAD compared to healthy controls. Furthermore, we found no significant alterations in the other hemogram parameters related to systemic inflammation.

There are limited number of studies indicating alterations of inflammatory biomarkers in children and adolescents with anxiety (10,11). We encountered only one study investigating systemic inflammation biomarkers obtained from hemogram in OCD and anxiety comorbidity in children and adolescents. In that study conducted in adolescents, it was reported that a comorbid anxiety disorder in addition to OCD increased the inflammatory response and that adolescents with comorbid anxiety and OCD had significantly higher WBC, neutrophil counts and log neutrophil-lypmhocyte ratio than adolescents with pure OCD (10). However, we found no significant difference in terms of white blood cell count (WBC), neutrophil, lymphocyte, monocyte counts or neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratios (PLR) between case and control groups.

We encountered studies investigating only platelet parameters as systemic inflammation biomarkers obtained from hemogram in adult panic disorder (PD) (12-18). The results of those studies are conflicting. Consistent with our result, majority of these studies found increased MPV in the PD group (12-15). In one of those studies anxiety symptoms was found to be positively correlated with MPV (15). The other studies found decreased MPV in the PD group (16-18). MPV values were also evaluated in schizophrenia, bipolar disorder and depression in adults (19-24). In adolescents, Ozyurt et al studied MPV, PLT and PLR as platelet indices in depression and found no alterations compared to healthy controls (25).

MPV is known as a marker and determinant of platelet action (16). In addition, PDW is considered among the indicators of platelet activity (26). Platelet parameters are considered to reflect the central serotonergic functions and to present windows of brain serotonergic functions (27). On the other hand, sympathetic system activation and serotonergic system dysfunction are considered to play a crucial role in the neurobiology of GAD (28,29).

Stressful life events and anxiety have been indicated to elevate blood catecholamines. Sympatho-adrenal activation is considered to activate platelets through α-2 receptors, resulting in an increase in platelet volume and activity, and by causing an increase in platelet activity, increased catecholamine levels are considered to activate thrombotic process (12, 30, 31). Increased stress and anxiety have been indicated to cause serotonin to bind 5-HT-2 receptors on platelets and to mediate the release of factors promoting platelet aggregation (32). Supporting this serotonergic hypothesis, treatment with selective serotonin reuptake inhibitors was also shown to cause a decrease in platelet activity (23,33).

The result of increased MPV levels in our study is consistent with the hypothesis of increased platelet activation due to sympathetic system activation and serotonergic imbalance. Also PLT levels were found to be significantly lower in GAD

patients in our study. This finding is consistent with the known inverse relation between MPV and PLT (34). In general, MPV and PDW are also known to be inversely related to each other (35,36). In line with this, decreased PDW levels were found in our study.

Ataoğlu at el (23) and Canan et al. (24) showed that MPV values increased in adult major depression. Ataoğlu et al additionally showed that MPV values decreased after 8 weeks of escitalopram treatment (23). On the other hand, increased MPV levels are indicated to be related to cardiovascular disorders in adults (37). Among multiple mechanisms, changes in platelet reactivity are considered to be one of the major mechanisms linking depression and cardiovascular disease (38). Interestingly, anxiety symptoms in patients with coronary artery disease have been found to be more effective in increased platelet activity than depression (39). This result may point out the inflammatory common aspect of depression, anxiety and cardiovascular disease given that increased platelet activity is known to be related to inflammation (40).

This study has some limitations, including relatively small sample size and retrospective design. However, evaluating almost all of the possible systemic inflammation biomarkers obtained from hemogram is the strength of our study.

In conclusion, we suggest that platelet parameters that have been indicated to be associated with inflammation, such as MPV and PDW, may be related to possible inflammatory background of GAD in children and adolescents and comprehensive prospective studies are required on this subject.

Disclosure

The authors have no conflict of interest.

REFERENCES

1. Bronsard G, Alessandrini M, Fond G, Loundou A, Auquier P, Tordjman S, et al. The Prevalence of Mental Disorders Among Children and Adolescents in the Child Welfare System: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2016;95(7):e2622.
2. Ercan ES, Polanczyk G, Akyol Ardıc U, Yuce D, Karacetın G, Tufan AE, et al. The prevalence of childhood psychopathology in Turkey: a cross-sectional multicenter nationwide study (EPICPAT-T). Nord J Psychiatry. 2019;73(2):132-140.
3. Essau CA, Conradt J, Petermann F. Frequency, comorbidity, and psychosocial impairment of anxiety disorders in German adolescents. J Anxiety Disord 2000;14:263–279.
4. Cole DA, Peeke LG, Martin JM, Truglio R, Seroczynski AD. A longitudinal look at the relation between depression and anxiety in children and adolescents. J Consult Clin Psychol 1998;66:451–460.
5. Renna ME, O'Toole MS, Spaeth PE, Lekander M, Mennin DS. The association between anxiety, traumatic stress, and obsessive–compulsive disorders and chronic inflammation: A systematic review and meta-analysis. Depression and anxiety. 2018;35(11):1081-1094.
6. Felger JC. Imaging the Role of Inflammation in Mood and Anxiety-related Disorders. Curr Neuropharmacol. 2018;16(5):533-558.
7. Miller BJ, Goldsmith DR. Towards an immunophenotype of schizophrenia: progress, potential mechanisms, and future directions. Neuropsychopharmacology. 2017;42(1):299-317.
8. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur Heart J. 2008;29(18):2212-2217.
9. Mazza MG, Rossetti A, Clerici M. A review of neutrophil-lymphocyte, monocyte-lymphocyte, and platelet-lymphocyte ratios use in psychiatric disorders. World J Depress Anxiety 2018: 1(1):1002.
10. Özyurt G, Binici NC. The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescent obsessive-compulsive disorder: Does comorbid anxiety disorder affect inflammatory response?. Psychiatry Res. 2019;272:311-315.
11. Walss-Bass C, Suchting R, Olvera RL, Williamson DE. Inflammatory markers as predictors of depression and anxiety in adolescents: Statistical model building with component-wise gradient boosting. J Affect Disord. 2018;234:276-281.
12. Almis Behice Han, Aksoy Ihsan. Mean platelet volume level in patients with generalized anxiety disorder. Psychiatry and Clinical Psychopharmacology, 2018; 28(1): 43-47.
13. Kokacya MH, Copoglu US, Kivrak Y, Ari M, Sahpolat M, Ulutas KT. Increased mean trombosit volume in patients with panic disorder. Neuropsychiatr Dis Treat. 2015;11:2629–2633.
14. Asoglu M, Aslan M, Imre O, Kivrak Y, Akil O, Savik E, et al. Mean trombosit volume and red cell distribution width levels in initial evaluation of panic disorder. Neuropsychiatr Dis Treat. 2016;12:2435–2438.
15. Bondade Swapna, Manjula Adinarayan, Parineetha P. Bhat. Mean platelet volume in anxiety disorder: a case-control study. Open Journal of Psychiatry & Allied Sciences 2019;10(2): 115-119.
16. Göğçegöz Gül I, Eryılmaz G, Ozten E, Hızlı Sayar G. Decreased mean platelet volume in panic disorder. Neuropsychiatr Dis Treat. 2014;10:1665-1669.

17. Ransing RS, Patil B, Grigo O. Mean platelet volume and platelet distribution width level in patients with panic disorder. J Neurosci Rural Pract. 2017;8 (2):174–178.
18. Gündüz N, Timur Ö, Erzincan E,Tural Ü. Panik bozukluğu hastalarında ortalama trombosit hacmi, nötrofil lenfosit oranı, platelet lenfosit oranı ve eritrosit dağılım genişliği. Anatolian Journal of Psychiatry/Anadolu Psikiyatri Dergisi. 2018;19(1): 5-12.
19. Wysokinski A, SzczepockaE. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. Psychiatry Res. 2016;237:238–245.
20. Inanli I, Aydin M, Çaliskan AM, Eren I. Neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and mean platelet volume as systemic inflammatory markers in different states of bipolar disorder. Nord J Psychiatry. 2019;73(6):372-379.
21. Kirlioglu SS, Balcioglu YH, Kalelioglu T, Erten E, Karamustafalioglu N. Comparison of the complete blood count-derived inflammatory markers in bipolar patients with manic and mixed episodes. Bratisl Lek Listy. 2019;120(3):195-199.
22. Mert DG, Terzi H. Mean platelet volume in bipolar disorder: the search for an ideal biomarker. Neuropsychiatr Dis Treat. 2016;12:2057-2062.
23. Ataoglu A, Canan F. Mean platelet volume in patients with major depression: effect of escitalopram treatment. J Clin Psychopharmacol. 2009;29(4):368-371.
24. Canan F, Dikici S, Kutlucan A, Celbek G, Coskun H, Gungor A, et al. Association of mean trombosit volume with DSM-IV majör depression in a large community-based population: the MELEN study. J Psychiatr Res. 2012;46(3):298–302.
25. Özyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. Psychiatry Res. 2018;268:426-431.
26. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: is there a practical index of platelet activity?. Clin Appl Thromb Hemost. 2003;9(3):177-190.
27. Koudouovoh-Tripp P, Sperner-Unterweger B. Influence of mental stress on platelet bioactivity. World J Psychiatry. 2012;2:134–147.
28. Pohjavaara P, Telaranta T, Väisänen E. The role of the sympathetic nervous system in anxiety: Is it possible to relieve anxiety with endoscopic sympathetic block?. Nord J Psychiatry. 2003;57(1):55-60.
29. Gordon JA, Hen R. The serotonergic system and anxiety. Neuromolecular Med. 2004;5(1):27-40.
30. Durmaz T, Özdemir Ö, Keleş T. Trombosits and sympathetic activity in MI. Turk J Med Sci. 2009;39 (2):259–265.
31. Thompson CB, Eaton KA, Princiotta SM, Rushin CA, Valeri CR. Size dependent trombosit subpopulations: relationship of trombosit volume to ultrastructure, enzymatic activity, and function. Br J Haematol. 1982;50(3):509–519.
32. Garvey MJ, Noyes R Jr, Woodman C, Laukes C. The association of urinary 5-hydroxyindoleacetic acid and vanillylmandelic acid in patients with generalized anxiety. Neuropsychobiology. 1995;31(1):6–9.
33. Galan AM, Lopez-Vilchez I, Diaz-Ricart M, Navalon F, Gomez E, Gasto C, et al. Serotonergic mechanisms enhance trombosit mediated thrombogenicity. Thromb Haemost. 2009;102(3):511–519.
34. Bessman JD, Williams LJ, Gilmer PR Jr. Mean platelet volume. The inverse relation of platelet size and count in normal subjects, and an artifact of other particles. Am J Clin Pathol. 1981;76(3):289–293.
35. Wendland AE, Farias MG, Manfroi WC. Mean platelet volume and cardiovascular disease. J Bras Patol Med Lab. 2009;45:371–378.
36. Shen J, Ran ZH, Zhang Y, Cai Q, Yin HM, Zhou XT, et al. Biomarkers of altered coagulation and fibrinolysis as measures of disease activity in active inflammatory bowel disease: A gender-stratified, cohort analysis. Thromb Res. 2009;123:604–611.
37. Slavka G, Perkmann T, Haslacher H, Greisenegger S, Marsik C, Wagner OF, et al. Mean trombosit volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease. Arterioscler Thromb Vasc Biol. 2011;31(5):1215–1218.
38. Can MM, Guler G, Guler E, Ozveren O, Turan B, DiNicolantinio JJ, et al. Enhanced platelet reactivity in pediatric depression: an observational study. Blood Coagul Fibrinolysis. 2015;26(7):731-735.
39. Zafar MU, Paz-Yepes M, Shimbo D, Vilahur G, Burg MM, Chaplin W, et al. Anxiety is a better predictor of trombosit reactivity in coronary artery disease patients than depression. Eur Heart J. 2010;31(13):1573–1582.
40. Jenne CN, Kubes P. Platelets in inflammation and infection. Platelets. 2015;26(4):286-292.