



Can Hematological Parameters Indicate Possible Inflammatory Mechanisms in Children with Intellectual Disability?

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ABSTRACT

Cite this article as:
Soylu Üstkoyuncu P,
Sami Güven A, Dündar MA,
Mutlu FT, Altuner Torun Y.
Can Hematological
Parameters Indicate
Possible Inflammatory
Mechanisms in Children
with Intellectual Disability?
Erciyes Med J 2020;
42(3): 260-3.

Objective: This study aims to interpret the hematological parameters of children with the intellectual disability and to show the relationship between hematological parameters and possible inflammatory mechanisms of intellectual disability.

Materials and Methods: In this study, 50 children with the intellectual disability (32 males, 18 females) and 40 healthy individuals (25 males, 15 females) were retrospectively screened. Lymphocyte and platelet count, white blood cell count, neutrophil, platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), red cell distribution width (RDW) and mean platelet volume (MPV) were recorded for both groups and compared.

Results: Neutrophil to lymphocyte ratio and neutrophil counts in the intellectual disability group were elevated than control. Mean platelet volume in the intellectual disability group was higher than the control and red cell distribution width in children with the intellectual disability was elevated than control. We did not detect any statistical difference in neutrophil to lymphocyte ratio between the groups with or without inborn error of metabolism.

Conclusion: The findings obtained in this study suggest that we can use mean platelet volume, neutrophil to lymphocyte ratio and red cell distribution width as inflammatory markers for the intellectual disability of children.

Keywords: Children, intellectual disability, inflammation

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Submitted
05.09.2019

Accepted
29.02.2019

Available Online Date
10.06.2020

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Available online at
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INTRODUCTION

Intellectual disability (ID) (also called mental retardation) is a descriptive term and is characterized by impairment of cognitive functions, adaptive behavior and life skills with limitations of learning, presenting before 18 years old (1). Although this ratio may differ between populations, there are approximately 2–3% of the patients with ID (2). Inflammation has been accepted as an eventual central mechanism for neurodevelopmental disorders (3, 4). Neutrophils are crucial for cytokine production in inflammatory diseases (5), and lymphocyte depletion is associated with the early apoptosis of lymphocytes during inflammation (6).

Neutrophil to lymphocyte ratio (NLR) is shown to be an important predictor of several rheumatologic, cancer, and/or infectious diseases and is associated with the severity of many diseases and systemic inflammation in many studies in the literature. In addition, platelet to lymphocyte ratio (PLR), mean platelet volume (MPV) and Red Cell Distribution Width (RDW) are associated with inflammation (7–10).

This study aims to interpret the hematological parameters of children with the intellectual disability and to show the relationship between hematological parameters and possible inflammatory mechanisms of intellectual disability.

MATERIALS and METHODS

Sixty-seven patients diagnosed with ID and evaluated for the inborn error of metabolism between April 2014 and June 2017 were reviewed. In this study, 50 children with ID and 40 healthy controls of similar age and sex were included. Children who have any sign of infection, panhypopituitarism, patients in the postictal period, central nervous system (CNS) tumor, and cerebral palsy were not examined.

The patients' age, sex, history of medication, consanguinity, other affected people in family, physical examinations and, peripheral blood cell parameters were recorded. Sex and age matched control group was selected from completely healthy children with no history of neurological impairment and also was chosen from a pediatric outpatient clinic who came for a check-up or preoperative evaluation of minor elective surgery.

Children with a sign of infection or children with systemic illness were not examined in the control group. Physical examination of the patients showed no signs of infection. Complete blood values of their routine controls were used.

Intelligence Quotient (IQ) of 50–70 was accepted as mild mental retardation, and an IQ of less than 50 was accepted as moderate to severe mental retardation.

White blood cell, neutrophil, lymphocyte and platelet count, hemoglobin, MPV and RDW were evaluated for two groups. The ratio of neutrophils to lymphocytes and platelets to lymphocytes was used to calculate NLR and PLR, respectively. The Ethical Committee of Erciyes University, Faculty of Medicine, approved this study (Number: 2018/167).

Statistical Analysis

We used Mann-Whitney U tests to compare the two groups in non-parametric distributions, and the Kruskal Wallis test in the inter-group comparisons for the quantitative variables. Parameters with normal distribution were showed as mean±SD, and parameters with abnormal distribution were shown as median (25th percentile 75th percentile). Pearson, Spearman correlation analysis was used for correlation analysis. P-value under 0.05 was considered statistically significant in all statistical analyses.

RESULTS

Our study included 50 ID (32 males, 18 females) and 40 healthy controls (25 males, 15 females). The mean ages of ID patients and controls were 11.75±2.91 and 11.9±3.07 years, respectively. There was not any difference between the two groups by sex or age ($p>0.05$). Thirty-one (62%) mild and 19 (38%) moderate mental retardation patient was present. We detected specific inherited metabolic disorders (IMD) in six out of 50 patients with ID. Patients had mitochondrial disease, 3-methylcrotonyl CoA carboxylase deficiency, classical phenylketonuria (PKU), hyperphenylalaninemia and tyrosinemia type 2, respectively. Homocysteine significantly elevated in one patient without a specific diagnosis. Five patients (10%) were diagnosed as an autism spectrum disorder (ASD) and 16 patients (32%) were following as epilepsy. Nine patients (18%) had attention deficit hyperactivity disorder (ADHD). The clinical features of the children with ID are shown in Table 1.

NLR of the ID group was higher than the control group ($p<0.001$). We did not detect any statistical difference in PLR between the study and control group. MPV of the children with ID elevated compared to children in the control group ($p<0.03$). Any correlation was not detected between IQ levels and hematological parameters in the study group. A comparison of the patient's complete blood count results with the control group is summarized in Table 2.

DISCUSSION

ID is associated with autism, attention deficit hyperactivity disorder, self-mutilation, systemic organ involvement, such as liver or congenital heart diseases and neurological symptoms, such as epilepsy, emotional and behavioral problems. IMDs rarely cause ID (more than 5%). The diagnosis remains lacking in many cases (1, 11). In this study, 64% of our patients had an associated disorder with ID consistent with the literature. Also, specific IMDs were detected in 12% of our patients.

NLR is an inexpensive parameter that can be obtained from basic blood samples. NLR can be as valuable as some expensive inflam-

Table 1. Clinical and demographic characteristics of the children with ID

	Total number of patients	(%)
Variables	50	100
Sex distribution		
Male	32	64
Female	18	36
Intelligence test score		
Mild mental retardation	31	62
Moderate mental retardation	19	38
Associated disorders		
Attention deficit hyperactivity disorder	8	16
ADHD+epilepsy	1	2
Autism spectrum disorders	4	8
Autism spectrum disorders plus epilepsy	1	2
Epilepsy	12	24
Inherited metabolic disorders	6	12
Mitochondrial disease+ADHD	1	2
Organic acidemia	2	4
Phenylketonuria and epilepsy	1	2
Phenylketonuria	1	2
Tyrosinemia and epilepsy	1	2
Isolated ID with unknown etiology	18	36

ID: Intellectual disability; ADHD: Attention deficit hyperactivity disorder

matory markers, such as interleukins and TNF- α . NLR, PLR and MPV, can be used for predicting the disease activity and prognosis in various systemic and inflammatory diseases.

Yılmaz et al. (12) reported the relationship between prognosis and hematological parameters of children with acute ischemic stroke. The values of white blood cell count and NLR differed significantly in ischemic stroke from those of the control group in their study. They concluded that NLR and white blood cell count might be used for earlier diagnosis in children with acute ischemic stroke.

To our knowledge, there is not any study that has investigated NLR, PLR and MPV values in patients with ID.

Various studies have shown the association between inflammation and ID associated disorders (13–23). Angelidou et al. (13) reported early immune response in autism spectrum disorders that related peripheral and central chronic inflammation. Dysfunction of mast cells and dysregulation of cytokines have been implicated in pathophysiology.

Carmeli et al. (14) found that ID patients with epilepsy presented higher interleukin-6 (IL-6) levels than those without epilepsy in adults. Higher NLR values were attributed to the ID associated disorders (32% of the ID patients had epilepsy, and 10% was accompanied by ASD).

Vezzani et al. (15) reported that an inflammatory mediator's measurements of blood could show the brain inflammation degree.

Table 2. Comparison of the patient's complete blood count results with control group

Variables	Intellectual disability (n=50)	Control (n=40)	p
Gender (Female/Male)	18/ 32	15/ 25	>0.05
Age (year)	11.9±3.07	11.75±2.91	>0.05
WBC (mm ³)	7910 (6295–9350)	7205 (5887–8030)	>0.05
Hemoglobin(g/dl)	13.4±1.26	13.7±0.89	>0.05
Neutrophil (mm ³)	4180 (3285–5387)	3085 (2645–4085)	0.002
Lymphocyte (mm ³)	2610 (2010–3152)	2925 (2422–3297)	0.047
Platelet (mm ³)	274 (227–361)	322 (278–343)	>0.05
NLR	1.50 (1.12–2.22)	1.12 (0.91–1.39)	<0.001
PLR	113.4 (93.2–140.6)	106.4 (97.8–124.1)	>0.05
MPV (fl)	10.05 (9.2–10.55)	9.50 (9.2–10.00)	<0.03
RDW (fl)	39.4 (37.9–41.1)	37.3 (35.7–39.1)	<0.001

Values are presented as median (range) and mean±SD. WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; MPV: Mean platelet volume; RDW: Red cell distribution width

Vascular inflammation can be considered as a potential biomarker, and it may be used for diagnostic and therapeutic purposes in neuroinflammation.

Donfrancesco et al. (16) and Toto et al. (17) reported that patients who have increased levels of interleukin 6 (IL-6) and IL-10 and increased levels of serum antibasal ganglia antibodies support the role of the immune system in attention deficit hyperactivity disorder (18).

Recurrent or persistent elevations of IL-6, IL-8 and TNF levels in premature infants during the first weeks of life were associated with an attention deficit disorder at two years old (19, 20).

Musto and Rana indicated that peripheral inflammation leads to central inflammation because of the blood-brain barrier breakdown and is necessary to conduct further studies to show the relationship between systemic inflammation and epilepsy for prevention and treatment (21). Hamed et al. (22) reported some neuroinflammatory biomarkers for early diagnosis of autism in plasma and also showed the usefulness of TGF- β 2, hematopoietic prostaglandin D2 synthase (H-PGDS) and heat shock protein 70 (HSP70) as diagnostic markers to differentiate between autism spectrum disorder and control.

Ohja et al. (23) reported that patients with autism spectrum disorders present with an increased level of proinflammatory cytokines, such as TNF- α , GM-CSF, IL-6 and IL-8 and a decreased level of inflammatory cytokines, such as IL-10 and TGF- β in the blood. Also, neuro-inflammatory mechanisms may contribute to the pathogenesis of various IMDs. Elevated phenylalanine levels, and its metabolites, may increase the endogenous synthesis of free oxygen radicals and the endogenous synthesis of antioxidants in PKU. Homocysteine is an excitatory amino acid and elevated homocysteine levels are related to oxidative injury, continuous vascular and endothelial impairment. Mitochondrial metabolic cycles are important for inflammatory pathways in immune cells. Mitochondrial dysfunction was shown to trigger innate immune responses and inflammation (24–28). In contrast to these findings, Mozrzymas et al. (29) investigated IL-6 and eight

levels in 20 classical PKU and no significant differences were found in IL-6 and IL-8 concentrations between the study and the control group. Walkowiak et al. (30) reported any correlation between phenylalanine blood levels and fecal calprotectin concentrations in patients with phenylketonuria. We did not recognize any statistical difference in NLR value between the groups with or without inborn error of metabolism ($p>0.05$) similar to these findings.

Limitations of the presented study are its retrospective origin, and patient numbers were small and heterogeneous. There is a need for multicenter prospective studies showing the relationship between inflammation and hematological parameters of children with the intellectual disability in large and homogeneous groups. In conclusion, there is a need for inexpensive and noninvasive practical diagnostic methods for showing inflammation. NLR, PLR, MPV and RDW can be calculated according to the results of basic complete blood counts and can be used as inflammatory markers for intellectual disability.

These parameters are cheap and easy to reach because they are routinely requested. Other parameters showing inflammation like TNF alpha, IL-6, IL-8 and IL-1b are quite expensive and difficult to study and require special methods.

Ethics Committee Approval: The Ethical Committee of Erciyes University, Faculty of Medicine, approved this study (date: 21.03.2018, number: 2018/167).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – PSÜ, ASG; Design – PSÜ, ASG; Supervision – ASG, YAT; Materials – FTM, ASG; Data Collection and/or Processing – MAD, FTM; Analysis and/or Interpretation – MAD, YAT; Literature Search – MAD, FTM; Writing – PSÜ; Critical Reviews – ASG, YAT.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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