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Research Article

Monocyte/High Density Lipoprotein Ratio in Children and Adolescents with Attention Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğu Olan Olgularda Monosit / Yüksek Yoğunluklu Lipoprotein (HDL) Oranı

Ebru Turan [*1], **Tuğba Menteşe Babayiğit** [*2]

[*1] Aksaray University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Aksaray/TÜRKİYE

[*2] Aksaray Training and Research Hospital, Department of Child and Adolescent Psychiatry, Aksaray/TÜRKİYE

Aim: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity. Recent studies suggest that immune dysregulation and inflammation may play a role in its pathophysiology. The monocyte-to-high-density lipoprotein (HDL) ratio (MHR) has been proposed as a novel inflammatory marker. This study aimed to investigate the relationship between ADHD and MHR

Material and Method: This retrospective, single-center study included 67 children and adolescents diagnosed with ADHD and 75 age- and sex-matched healthy controls. Hemogram and lipid panel parameters were retrieved from medical records, and MHR was calculated for each participant. Monocyte levels, HDL levels, and MHR values were compared between the ADHD and control groups.

Results: Monocyte levels were significantly higher in the ADHD group compared to the controls ($p = 0.028$). However, no significant differences were found between the groups in terms of HDL levels ($p = 0.783$) or MHR ($p = 0.076$).

Conclusion: The findings suggest that systemic inflammation may contribute to the pathophysiology of ADHD, as indicated by elevated monocyte levels. However, the lack of a significant difference in MHR suggests that lipid metabolism alterations may not play a primary role in ADHD-related inflammation. Further studies with larger samples and more inflammatory markers are needed to clarify the role of immune dysregulation in ADHD.

Keywords: ADHD, inflammation, monocyte-to-HDL ratio, immune system, lipid metabolism

Amaç: Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB), dikkatsizlik, hiperaktivite ve dürtüsellik ile karakterize yaygın bir nörogelişimsel bozukluktur. Son çalışmalar, immün disregülasyon ve inflamasyonun DEHB'nin patofizyolojisinde rol oynayabileceğini öne sürmektedir. Monosit-yüksek yoğunluklu lipoprotein (HDL) oranı (MHR), yeni bir enflamatuar belirteç olarak önerilmiştir. Bu çalışmanın amacı, DEHB ve MHR arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmaya, DEHB tanısı almış 67 çocuk ve ergen ile yaş ve cinsiyet açısından eşleştirilmiş 75 sağlıklı kontrol dahil edilmiştir. Tıbbi kayıtlar incelenerek hemogram ve lipid paneli parametreleri değerlendirilmiş ve her katılımcı için MHR hesaplanmıştır. Monosit düzeyleri, HDL seviyeleri ve MHR değerleri DEHB ve kontrol grupları arasında karşılaştırılmıştır.

Bulgular: DEHB grubunda monosit seviyeleri kontrol grubuna kıyasla anlamlı derecede yüksek bulunmuştur ($p = 0,028$). Ancak, gruplar arasında HDL seviyeleri ($p = 0,783$) veya MHR ($p = 0,076$) açısından anlamlı bir fark saptanmamıştır.

Sonuç: Bulgular, sistemik inflamasyonun, yüksek monosit düzeyleriyle gösterildiği gibi, DEHB'nin patofizyolojisine katkıda bulunabileceğini düşündürmektedir. Ancak, MHR'de anlamlı bir farkın olmaması, lipid metabolizması değişikliklerinin DEHB ile ilişkili inflamasyonda birincil bir rol oynamayabileceğini göstermektedir. DEHB'de immün disregülasyonun rolünü açıklığa kavuşturmak için daha büyük örneklem ve daha fazla sayıda inflamatuar belirtecin değerlendirildiği daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: DEHB, inflamasyon, monosit/HDL oranı, bağışıklık sistemi, lipid metabolizması

Corresponding Author: Ebru Turan
Aksaray University, Department of Child and Adolescent Psychiatry, Aksaray/TÜRKİYE
ebrusglm55@gmail.com

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of childhood. The prevalence of ADHD thought to vary depending on factors such as the diagnostic criteria used, the sources from which information is obtained, and differences in measurement tools (1). The worldwide prevalence of ADHD in children and adolescents was reported to be 5.29% and 5.9-7.1% in two meta-analyses conducted in recent years (2, 3). It is characterised by persistent inattention, hyperactivity and impulsivity that are not appropriate for the individual's developmental level. It commonly presents in childhood and may persist into adulthood, impacting academic success, social relationships and work life (4). The pathophysiology of ADHD is complex and involves genetic, neurobiological and environmental factors. Despite considerable research, the precise biological mechanisms underlying ADHD remain poorly understood (5).

Emerging studies have reported associations between neuropsychiatric disorders and inflammation and immune system abnormalities. The role of inflammation in neuropsychiatric disorders such as autism spectrum disorder, depression, schizophrenia, bipolar disorder and post-traumatic stress disorder has also been suggested. However, recent years have seen a growing focus on the potential role of inflammation and oxidative stress in the pathogenesis of ADHD (6-8). The higher prevalence of ADHD in patients with inflammatory and autoimmune diseases, and studies conducted with genes and markers associated with inflammation, support the role of inflammatory mechanisms in the etiology of ADHD (9). In addition, many disorders related to the immune system, such as asthma, atopic dermatitis, ankylosing spondylitis, ulcerative colitis, juvenile arthritis, autoimmune thyroid disease, type 1 diabetes and celiac disease, have been associated with ADHD (10-12).It has been reported that inflammation may contribute to the development of ADHD by causing disruptions in the blood-brain barrier through oxidative stress, neuronal damage, glial activation and neurotrophic factors. Furthermore, studies have demonstrated that inflammatory mediator levels are elevated in patients with ADHD (13). Additionally, research has indicated that ADHD symptom severity is associated with serum levels of inflammatory cytokines and ADHD patients who used psychostimulants in treatment had lower levels of inflammatory markers (14,15). Monocytes are a cell type involved in the release of pro-oxidant and pro-inflammatory cytokines, which have important effects in the control of inflammatory processes. It stimulates proinflammatory and prothrombotic pathways by directly affecting endothelial cells and platelets (16). HDL cholesterol protects endothelial cells from the harmful effects of low-density lipoproteins (LDL) and has antioxidant and anti-inflammatory effects by preventing the oxidation of LDL molecules (17).

The Monocyte/High Density Lipoprotein Ratio (MHR) represents a novel marker of inflammation, involving both the immune system and lipid metabolism. A high MHR is indicative of a pro-inflammatory state and has been linked to a number of cardiovascular and neuropsychiatric conditions (18,19). Given the association between ADHD and both systemic inflammation and altered lipid metabolism, assessment of MHR in patients with ADHD is expected to provide valuable insights into the role of the interaction between the immune system, lipid metabolism andneuroinflammation in the aetiology of ADHD. This study aimed to explore the potential relationship between MHR and ADHD, examining whether an elevated MHR could serve as a biomarker for identifying ADHD. A comprehensive understanding of this association may provide insights into the underlying pathophysiology of ADHD and facilitate the development of novel therapeutic strategies that target inflammation and oxidative stress.

MATERIALS AND METHODS

Study Design

A total of 67 patients, aged 6-18 years, who applied to our child and adolescent mental health and diseases polyclinic between January 2019 and November 2024, were diagnosed with ADHD according to the fifth edition of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by a child and adolescent psychiatrist, were included in the study. Inclusion criteria were a primary diagnosis of ADHD without any additional psychiatric disorders or chronic medical conditions. Due to the retrospective nature of the study, the presence of an active infectious disease at the time of blood sampling could not be determined. We retrospectively analyzed the patients' medical records in the hospital's automated system, recorded their hemogram and lipid panel parameters in the year prior to their presentation, and calculated their MHR. These patients and 75 children and adolescents who applied to our polyclinic during the same period, who applied for consultation between the ages of 6 and 18 years, who had no psychiatric disorders or treatment history, and who were

matched for age and sex, were taken as the healthy control group. The hemogram and lipid panel parameters of the healthy group were similarly recorded and the MHR was calculated. The results of both groups were compared and analyzed.

Ethics Committee Approval

Ethical approval was obtained from the Aksaray University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee dated 26.12.2024 and numbered 2024/172.

Our research was conducted in accordance with the World Medical Association Helsinki Declaration Ethical Principles.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22.0 for Windows, with a significance level set at α=0.05. Descriptive statistics were reported as mean with standard deviation for continuous variables, and as frequency with percentage for categorical variables, based on the distribution of the data. Categorical data were analyzed using Chi-square, while continuous data were assessed using Mann-Whitney U test, depending on group size and normality assumptions.

RESULTS

The average age of the 67 patients included in the study was 11.32, and the average age of the control group was 11.24. The groups were similar in terms of mean age and gender distribution (Table 1). While 40.3% (n=27) of the ADHD group consisted of girls and 59.7% (n=40) of boys, 38.7% (n=29) of the control group were girls and 61.3% (n=46) were boys (p =0.843).

Table 1. Sociodemographic characteristics of the groups

Sociodemographic Variables	ADHD (n = 67) Mean (SD) n (%)	Control (n = 75) Mean (*SD*) n (%)	*p*
Child age (years)[a]	11.32 (3.20)	11.24 (2.71)	0.861
Gender[b]			0.843
Female	27 (40.3)	29 (38.7)	
Male	40 (59.7)	46 (61.3)	

ADHD, attention deficit and hyperactivity disorder; SD, standard deviation [a]: Mann–Whitney U test, [b]: Chi-square test

The analysis of monocyte, HDL and monocyte/HDL ratios of the groups is given in Table 2. While monocyte levels were statistically higher in the ADHD group (p =0.028), there was no significant difference between the groups in terms of HDL levels. The monocyte/HDL ratio, which is described as a marker of inflammation, was found to be higher in the ADHD group, but this difference was not statistically significant (p =0.076).

Table 2: Mean monocytes and HDL levels of children in ADHD and control groups

	ADHD Mean±SD(Median)	Control Mean ±SD(Median)	*p*
Monocytes (10^9/L)	0.49±0.14 (0.47)	0.43±0.13 (0.44)	**0.028[a]**
HDL (mg/dl)	51.90±13.34 (50)	50.83±11.87 (49)	0.783[a]
Monocytes/HDL (10^9/L /mg/dl)	0.010±0.003	0.009±0.003	**0.076[a]**

ADHD, attention deficit and hyperactivity disorder; SD, standard deviation [a]: Mann–Whitney U test

DISCUSSION

In this single-center, retrospective study, we investigated the relationship between ADHD and MHR, which is a marker of inflammation. Our results showed that while monocyte levels were significantly higher in children with ADHD compared to controls, HDL levels did not differ between the groups. The MHR, a potential marker of systemic inflammation, was also higher in the ADHD group, but this difference did not reach statistical significance.

Previous research has highlighted the role of inflammation in the pathophysiology of ADHD. Neuroinflammatory processes and immune dysregulation have been proposed as key mechanisms underlying ADHD symptoms, with inflammatory markers playing a potential role in disease onset and progression (10). The elevated monocyte levels in our study support this hypothesis, as monocytes are critical in inflammatory responses and have been implicated to neuroimmune interactions in psychiatric disorders (6). Recent evidence suggests that ADHD may be associated with neuroimmune changes, including increased activation of microglia and systemic inflammatory markers and monocytes play a pivotal role in this process, as they can cross the blood-brain barrier and contribute to neuroinflammation, potentially affecting the neural circuits involved in attention and impulse control (9).

Consistent with our findings, prior studies have demonstrated increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α in ADHD patients, supporting the notion of low-grade systemic inflammation in

this population (14,15). The elevated monocyte count observed in our study may reflect an ongoing immune activation in children with ADHD, which could contribute to neurodevelopmental alterations. In addition, the presence of GAD65 autoantibodies in children with ADHD suggests a link between immune dysfunction and ADHD pathophysiology (8). The findings of Vázquez-González et al. (2023) further support the idea that immune dysregulation and neuroinflammatory processes may be underlying contributors to ADHD symptoms, highlighting the potential role of immune-targeted interventions in the management of disorder.

The MHR has been explored as an inflammatory marker in several disorders, including cardiovascular disease and schizophrenia (17,20). HDL is known to have anti-inflammatory properties, including the inhibition of monocyte activation and reduction of systemic inflammation (18). Although our study did not find a statistically significant difference in the MHR between ADHD and control groups, this may be due to sample size limitations or individual variability in immune responses. The findings suggest that alterations in lipid metabolism may not play a primary role in ADHD-related inflammation, but further research needs to confirm this hypothesis.

From a clinical perspective, these findings highlight the potential relevance of inflammatory processes in ADHD. While stimulant medications remain the primary treatment for ADHD, emerging evidence suggests that targeting inflammation through dietary interventions, omega-3 fatty acid supplementation, and anti-inflammatory agents may provide additional benefit (21). In addition, maternal immune activation has been associated with an increased risk of ADHD in offspring, suggesting that prenatal and perinatal inflammatory exposures may contribute to the etiology of the disorder (11-13).

In conclusion, our study supports the growing evidence linking ADHD to immune dysregulation and inflammation. While monocyte levels were elevated in children with ADHD, the MHR did not differ significantly between groups. These findings suggest that inflammation may contribute to the pathophysiology of ADHD, but further research is needed to clarify its precise role and clinical implications.

Study Limitations and Strengths

This study has several limitations. First, its retrospective design prevents the establishment of a causal relationship between systemic inflammation and ADHD. Inclusion criteria require a primary diagnosis of ADHD without comorbid psychiatric disorders or chronic medical conditions. However, due to the retrospective nature of the study, it was not possible to determine whether participants had an active infectious disease at the time of blood sampling, which may have influenced inflammatory markers. Second, we did not assess other important markers of inflammation, such as C-reactive protein (CRP) or cytokines, which could have provided a more comprehensive understanding of systemic inflammation. Third, dietary data were not collected for either the ADHD or control groups, despite the known influence of diet on inflammation and lipid metabolism. Finally, our study was conducted in a single centre with a relatively small sample size, which limits the generalisability of the findings. Future studies with larger, multicentre samples and prospective designs are needed to validate and extend our findings. Despite these limitations, this study adds to the growing body of evidence suggesting a possible association between ADHD and systemic inflammation.

CONCLUSION

In conclusion, although autorefractometry yielded significantly higher AA values in myopic and emmetropic participants than in hyperopic participants, the negative lens test did not reveal similar differences. Based on these results, subjective AA assessment by negative lens testing cannot be substituted for objective measurements. Future research with larger sample sizes, diverse refractive groups, and multiple assessment methods is warranted to enhance understanding of the mechanisms and age-related changes in accommodation.

Declarations

Ethics Committee Approval: Ethics committee approval was obtained from the Human Research Ethics Committee of a university (Date: December 26, 2024, Decision No: 2024/172). This study was conducted according to the principles of the Declaration of Helsinki.

Authors' Contributions

ET: Material preparation, data collection, analysis, study conception and design

TMB: study conception, design, review and editing

Both authors have read and approved the final version of the manuscript. Each author meets the ICMJE authorship criteria and accepts responsibility for the integrity and accuracy of the work.

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Corresponding Author: Ebru Turan
ebrusglm55@gmail.com
Orcid: 0000-0002-6030-5549

Author: Tuğba Menteşe Babayiğit
Orcid: 0000-0002-5486-7377