

Diagnostic Performance of Erythropoietin and Erythropoietin Receptors Levels in Children with Attention Deficit Hyperactivity Disorder

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Objective: Attention deficit hyperactivity disorder (ADHD) is a heterogeneous, highly heritable, a common childhood neurobehavioural disorder resulting from complex gene-gene and gene-environment interactions. The erythropoietin (Epo)/erythropoietin receptors (EpoR) system turned out to have additional important functions in nonhematopoietic tissue. In this study, we aimed to investigate the levels of Epo and EpoR, and also their diagnostic values in children with ADHD.

Methods: A total of 70 children were included in the study, 35 drug-naive patients with ADHD (age: 6–12 years; male/female: 20/15) and 35 healthy controls (age: 6–12 years; male/female: 22/13). Serum Epo and EpoR levels were determined using a commercial sandwich enzyme-linked immunosorbent assay kit.

Results: The results indicated that the levels of Epo decreased in patients with ADHD compared to control ($p < 0.05$). On the other hand, EpoR levels increased in these patients ($p < 0.05$). Furthermore, the ratio of Epo/EpoR was significantly lower in ADHD patients than controls ($p < 0.05$). Receiver operator characteristic curve analysis showed high diagnostic performance for Epo and EpoR, areas under curve were 0.980 and 1.000, respectively.

Conclusion: This is the first report to investigate the association between serum Epo and EpoR levels in ADHD patients. Our results indicated that Epo may play a role in the etiology of ADHD, and Epo therapy may be beneficial in these disorders if given in addition to the routine treatment of children with ADHD. Furthermore, our results reveal possible diagnostic value of Epo and EpoR.

KEY WORDS: Attention deficit hyperactivity disorder; Erythropoietin; Erythropoietin receptors.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a multifactorial and clinically heterogeneous disorder that is associated with tremendous financial burden, stress to families, and adverse academic and vocational outcomes

[1]. ADHD prevalence has been estimated at 5.0–7.1% in children and adolescents worldwide [2,3]. ADHD is diagnosed more frequently in males than in females [4]. Prospective studies spanning over 30 years have noted the highly impairing consequences of ADHD. Diagnosis in childhood is associated with poor educational, occupational, economic, and social outcomes, as well as higher criminality in adulthood [5,6]. The etiology of ADHD has not been clearly identified, although evidence supports neurobiologic and genetic origins [7]. Structural and functional imaging studies suggest that dysfunction in the fronto-subcortical pathways, as well as imbalances in the dopaminergic and noradrenergic systems, contribute to

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the pathophysiology of ADHD [8].

Erythropoietin (Epo) is an acidic glycoprotein hormone that is produced by the kidney and to a much lesser degree (< 10 percent) the liver. Epo binds to transmembrane erythropoietin receptor (EpoR), which are expressed primarily by hematopoietic progenitor cells but also by non-hematopoietic cells and tissues such as endothelial cells, cardiomyocytes, and neurons, the liver, uterus, and retina [9]. It was showed that Epo has a neuroprotective and neurotrophic effects in animal models. Also, Epo has trophic effects on dopaminergic neurons [10]. *In vitro* evidence established that EpoR promotes the growth, differentiation, and function of cultured dopaminergic cells. Under hypoxic culture conditions, neural progenitors differentiate toward a dopaminergic phenotype, EpoR promotes their survival and differentiation, and these effects are blocked by anti-Epo antibodies [11]. Epo also stimulates striatal dopamine release. Exposure to hypoxia-ischemia alters dopamine receptor and dopamine uptake transporter expression. During development, mesencephalic dopamine neurons exhibit apoptosis that is blocked by Bcl-2 upregulation [12]. As a neuroprotective agent Epo has many functions: antagonizing glutamate cytotoxic action, enhancing antioxidant enzyme expression, reducing free radical production rate, and affecting neurotransmitter release. It exerts its neuroprotective effect indirectly through restoration of blood flow or directly by activating transmitter molecules in neurons that also play a role in erythropoiesis.

Oxidative stress significantly impacts multiple cellular pathways that can lead to the initiation and progression of varied disorders throughout the body [13]. Epo controls a variety of signal transduction pathways during oxidative stress. The role of Epo and EpoR in psychiatric disorders are still poorly understood.

Biomarkers could potentially identify clinically meaningful subgroups within highly heterogeneous populations and thus allow for more precise, individualized medical care by identifying risk, confirming diagnosis or guiding response to treatments. The diagnosis of ADHD is made with subjective criterias according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). The objective markers are yet had not identified for the diagnosis of psychiatric diseases. The diagnostic value of peripheral biomarkers is more important than other biomarkers because their collection and use is easy

and suitable in clinical practice. Previously a growing body of research determined inflammation [14] oxidative parameters [15] and etc. as biomarkers in psychiatric diseases. There is no information on diagnostic values of Epo and EpoR in ADHD.

METHODS

Participants

This prospective study was approved by the Kahramanmaraş Sutcu Imam University ethical committee (Date: 14.12.2018, Decision Number: 2018/312-6), and written informed consent was obtained from all subjects. The study included 35 (20 boys, 15 girls) newly diagnosed drug-naïve children with ADHD aged 6–12 years and a control group of 35 (22 boys, 13 girls) age and sex-matched healthy children. The diagnosis of ADHD was reached based on a clinical interview and using the DSM-5 [7]. To support the diagnosis of ADHD and exclude comorbid psychiatric disorders, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) was applied [16]. The K-SADS-PL is a semi-structured interview, and the version adapted for the Turkish population [17] was used in this study. Patients in ADHD group did not take any medication 6 weeks prior to the study. Patients with comorbid psychiatric disorders, genetic syndromes, metabolic disorders, neurological disease and obesity were excluded from the study. Children without known neurodevelopmental/neurological disorders, without physical and psychiatric disorders, non-obesity and who had not been on any medication were selected for the control group. The children in the patient and control groups were fed a normal diet and their body mass index (BMI) was within normal limits. Medical illnesses in both groups were excluded based on the patient medical history, clinical examinations, and routine laboratory tests (biochemical, hematological, and thyroid function tests). The intelligence quotient (IQ) was determined using Wechsler Intelligence Scale for Children-Revised, and children with an IQ score greater than 80 were included in the study. The parents of the children were given the Conners' Parent Rating Scale-Revised Long Form [18], and the teachers of children from both groups completed the Conners' Teacher Rating Scale [19-21].

Biochemical Analysis

All blood samples were taken from both groups between 7:30 a.m. to 17:00 p.m, because diurnal variation of Epo or EpoR have been reported in literature [14]. Then, the serum was promptly separated, in a refrigerated centrifuge, and stored at -20°C until analysis. Epo and EpoR levels in serum were measured with *in vitro* enzyme-linked immunosorbent assay.

Statistical Analysis

Statistical analysis was performed using the SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA) and MedCalc[®] ver. 11.0.1 (MedCalc Software Ltd, Ostend, Belgium). A p value of less than 0.05 was considered statistically significant. The normality of continuous variables was assessed using Shapiro–Wilk’s W -test. Relationships between the categorical variables were evaluated using the chi-square test. To compare of mean differences for normally distributed continuous variables between the two groups, a Student’s t test was used. The Mann–Whitney U test was used to

Table 1. Sociodemographic characteristics of the study groups

Variable	ADHD group	Control group	p value
Age (yr)	8.83 ± 2.99	8.61 ± 2.93	0.21
Sex			0.43
Male	20 (57.14)	22 (62.85)	
Female	15 (42.85)	13 (37.14)	
BMI (kg/m)	18.34 ± 2.57	17.95 ± 3.89	0.86

Values are presented as mean \pm standard deviation or number (%). ADHD, attention deficit hyperactivity disorder; BMI, body mass index. No significant differences between ADHD and control groups according to age, sex, and BMI ($p > 0.05$).

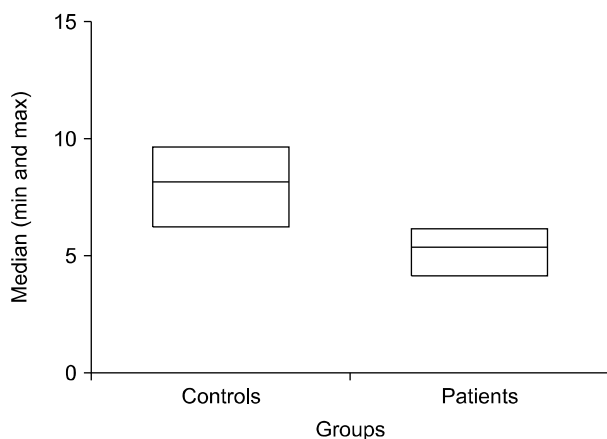


Fig. 1. The levels of erythropoietin in patients and control groups.

compare the two groups when the assumption of normality was not fulfilled. While investigating associations of data, correlation coefficients and their significance were calculated with Spearman’s test (for non-normally distributed variables) and Pearson’s test (for normally distributed variables). A receiver operator characteristics (ROC) curve was plotted in order to find the cut-off point.

RESULTS

Seventy individuals were included in the study. The mean age of the ADHD group ($n = 35$) was 8.83 ± 2.99 years, and 20 (57.14%) were males. The mean age of the control group ($n = 35$) was 8.61 ± 2.93 years, and 22 (62.85%) were males. Sociodemographic characteristics are shown in Table 1. No significant differences were found between the groups in terms of age, sex, weight, height, and BMI ($p > 0.05$ for all).

Epo levels were significantly lower in patients than healthy controls (medians were 5.41 mIU/ml and 8.25 mIU/ml, respectively, $p < 0.001$). The highest and lowest bounds for Epo in ADHD patients were 6.27 mIU/ml and 4.09 mIU/ml, respectively. The highest and lowest bounds for Epo in the control group were 9.76 mIU/ml and 6.15 mIU/ml, respectively (Fig. 1). EpoR levels were significantly higher in patients than in controls (medians were 1.71 ng/ml and 0.57 ng/ml respectively, $p = 0.042$). The highest and lowest bounds for EpoR in ADHD patients were 1.98 ng/ml and 1.54 ng/ml, respectively. The highest and lowest bounds for EpoR in the control group were 0.73 ng/ml and 0.39 ng/ml, respectively (Fig. 2). Further-

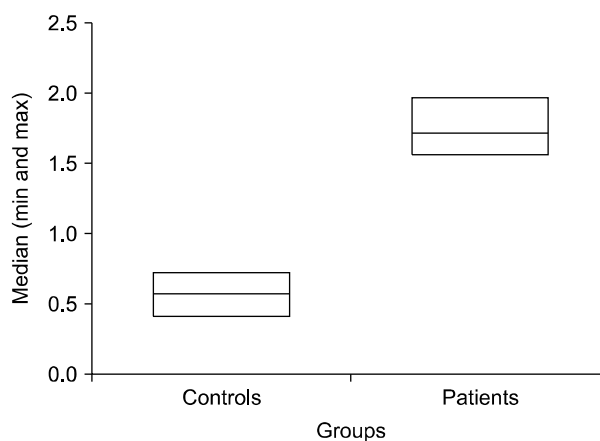


Fig. 2. The levels of erythropoietin receptor in patients and control groups.

more, the ratio of Epo/EpoR was significantly lower in ADHD patients than controls ($p < 0.05$) (Fig. 3).

The lower serum Epo levels corresponded to higher ADHD scores. The Epo levels were negatively correlated with the hyperactivity, Clinical Global Impression-irritability-impulsivity, ADHD index, DSM-IV inattentiveness and hyperactivity, and the total scores of the Conners' Parent Rating Scale-Revised Long Form, as well as with the inattentiveness, hyperactivity and conduct sub-scores of the Conners' Teacher Rating Scale ($p < 0.05$). On the contrary, positive significant correlation was observed between EpoR levels and in all scales ($p < 0.05$) (Table 2).

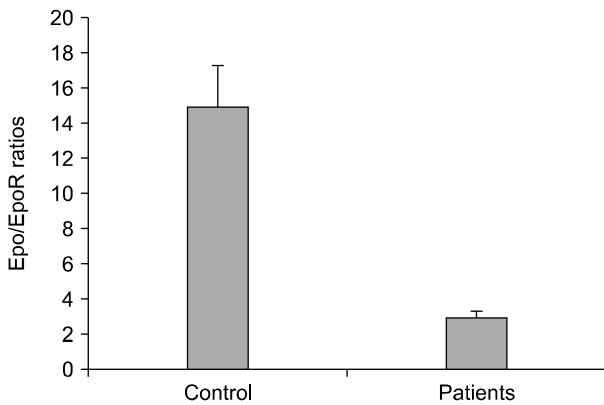


Fig. 3. Erythropoietin (Epo)/erythropoietin receptor (EpoR) ratios in control and patients groups.

A ROC curve was plotted for Epo and EpoR levels. Areas under the curve were 0.980 for Epo ($p < 0.001$), and 1.000 for EpoR ($p < 0.001$). These findings indicate that Epo and EpoR levels are diagnostic. The cut-off point was 6.27 mIU/ml for Epo, and all of the patient group Epo levels were under the cut-off point. The sensitivity and specificity of Epo were 100% and 97.14%, respectively. For EpoR, the cut-off point was 0.73 ng/ml, and all of the patient group EpoR levels were above the cut-off point. The sensitivity and specificity of EpoR were 100% (Fig. 4).

DISCUSSION

To our knowledge, this is the first study examining the levels of Epo and EpoR in children with ADHD. We found that the levels of Epo in patients with ADHD were lower than the controls. However, EpoR levels were increased in these patients. This situation may be due to decreased neuronal function. We thought that EpoR may be a good choice for ADHD treatment. Furthermore, in our study, decreased levels of Epo/EpoR ratio may due to low Epo levels. Until now, Epo/EpoR ratio has not been reported in patients with ADHD. So, we did not compared to our results. We thought that decreased Epo/EpoR ratio may be an important biochemical biomarker for ADHD.

Many studies showed that total oxidant status (TOS)

Table 2. Relationship of Epo and EpoR levels in patients and control groups with the Conners' Parent and Teacher Rating Scale Scores

Scale parameters	Epo		EpoR	
	r	p	r	p
Conners' Parent Rating Scale-Revised				
Oppositional	0.233	0.26	-0.243	0.35
Hyperactivity	0.155	0.01*	-0.107	0.01*
Anxiety-Shy	0.708	0.65	0.564	0.24
Social problems	0.249	0.31	-0.238	0.35
Psychosomatic	0.228	0.48	-0.355	0.42
ADHD index	0.267	0.01*	0.246	0.02*
DSM-IV inattentiveness	0.107	0.04*	-0.467	0.01*
DSM-IV hyperactivity	0.113	0.01*	0.125	0.03*
DSM-IV total	0.176	0.02*	-0.344	0.01*
CGI-irritability-impulsivity	0.208	0.03*	-0.133	0.04*
CGI-emotional lability	0.188	0.53	-0.177	0.42
Conners' Teacher Rating Scale-Revised				
Inattentiveness	0.345	0.04*	-0.423	0.02*
Hyperactivity	0.309	0.02*	-0.338	0.03*
Conduct problems	0.364	0.03*	-0.346	0.02*

Epo, erythropoietin; EpoR, erythropoietin receptor; ADHD, attention deficit hyperactivity disorder; DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders 4th edition; CGI, Clinical Global Impression.

*Significant differences amongs Epo and EpoR levels with the Conners' Parent and Teacher Rating Scale Scores ($p < 0.05$).

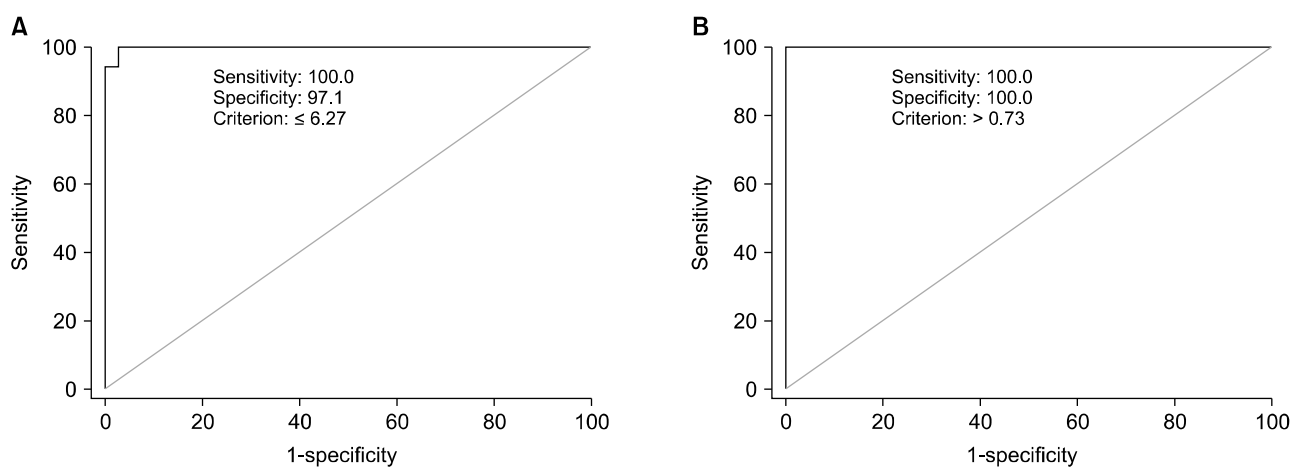


Fig. 4. (A) Receiver operator characteristics (ROC) curve of erythropoietin. (B) ROC curve of erythropoietin receptor.

and oxidative stress index (OSI) values are higher than controls in before treatment individuals with ADHD, thiol is one of the most important components of total antioxidant capacity in plasma that is lower than controls, these were found in a study where before and after medication to oxidative metabolism in adolescents and children with ADHD was evaluated. Levels of antioxidant parameters after treatment are higher than before treatment and OSI values in after treatment are lower than before treatment in the same study [22]. Also, there are studies showing that malondialdehyde (MDA) is an indicator of lipid peroxidation, levels of MDA are high in individuals with ADHD [23], but there are also studies with conflicting results [24].

In our study, we say that these changes of Epo and EpoR levels may relation to oxidative status of patients with ADHD. We thought that elevated oxidative stress and decreased Epo response may be associated with the decreased neuronal function in ADHD. We think that EpoR may act as an Epo "buffer" regulating available circulating Epo concentration. A lower Epo concentration, may increase unbound free plasma EpoR and, therefore, its availability for binding EpoR.

Many studies reported that neural tube defects developed and neuroblasts migration affected suppressed Epo and EpoR genes in mouse embryos [25]. In addition, it has been shown that the reduction of precursor neuronal cells and increased apoptosis with brain development is impaired [26]. Epo, activates to Janus kinase 2 via EpoR and it has function neuronal survival with preservation [27]. Epo and EpoR increase after trauma, lower in intact neu-

rons and glial cells it has been shown in many studies [28]. Studies demonstrate that Epo reduced dorsal root ganglion apoptosis, supports recovery of mechanical allodynia after peripheral nerve injury and Epo may also be effective in treating neuropathic pain [29]. However some studies have been shown, Epo just doesn't have the anti-apoptotic properties of putative neuroprotective agents at the same time it protects against axonal degeneration [30]. Spinal cord injury in study demonstrates that traumatic neutrophil infiltration and decreased at the 24th hour significantly increased myeloperoxidase level, decreased caspase-3 enzyme activity in Epo applied after trauma groups [31]. We said that the biological effects of Epo may not always be beneficial and may be poorly tolerated in a number of clinical scenarios, necessitating further basic and clinical investigations that emphasize the elucidation of the signal transduction pathways controlled by Epo to direct both successful and safe clinical care.

High correlation values constitute an important part of our findings. The correlation coefficient is shown with the 'r' symbol. An r value ≤ 0.35 represents low or weak correlation, between 0.36 and 0.67 shows moderate correlation, 0.68 to 0.90 shows high correlation, and 0.90 to 1.0 shows very high correlation [32]. We found that a significant negative correlation between ADHD scores and Epo levels. However, we found that a positive correlation between ADHD scores and EpoR levels. There are no studies between Epo and ADHD scores, or between EpoR and ADHD scores in patients with ADHD. So, we did not compared to our results. We believe that a high correla-

tion coefficient forms a basis for the detection of biomarkers.

ADHD is associated with a significant deterioration in various areas of functioning, including social and peer functioning, academic achievement, as well as emotional and cognitive functions. In a meta-analysis of 83 studies, Willcutt *et al.* [33] showed that, compared to children without ADHD, children/adolescents with ADHD demonstrate significant deficits in measures of executive functions, such as response inhibition, vigilance, working memory and planning. Low serum Epo levels observed in our ADHD group indicate that the role of Epo in the development of neurocognitive deficits in ADHD should be further investigated.

To the best of our knowledge, our study is the first study investigating the diagnostic value of Epo and EpoR parameters with a ROC curve in ADHD. In ROC curve analysis, diagnostic accuracy is measured according to the area under the curve (AUC). The accuracy of the ROC-AUC test is as follows: 0.9 to 1, excellent; 0.8 to 0.9, good; 0.7 to 0.8, fair; 0.6 to 0.7, poor; and < 0.6, not useful [33]. The AUCs for Epo and EpoR were 0.98 and 1.0, respectively. Epo and EpoR levels represent excellent diagnostic value according to our results. As far as we know, there are no studies evaluating the diagnostic potential of Epo and EpoR. Therefore, we cannot compare these results. Although our results show excellent diagnostic value, we do not interpret these data as a discovery of new biomarkers.

Our results support the concept that a dynamic Epo-EpoR signaling system is present in the ADHD and may offer a new therapeutic modality for ADHD. A number of drugs are used in the treatment of ADHD. These drugs which dysregulated dopaminergic pathways may interfere with normal development in children and deteriorate the functions of neurons in adults with ADHD. It has been demonstrated that methylphenidate treatment increases extracellular dopamine levels in ADHD [10-12]. Therefore, the medications used for the treatment of ADHD as a factor which may be related or alter the results obtained of Epo and EpoR. Thus, further studies are needed in children receiving treatment for ADHD and it will be possible to see the effects of the drugs used on Epo and EpoR. Moreover, increasing understanding of the Epo and EpoR cellular and tissue distribution, as well as its function in ADHD, may contribute to the development of new diagnostic and prognostic approaches and customized treat-

ment modalities.

The limitations of this study include the small sample size and its cross-sectional design. Also, the results obtained with serum Epo and EpoR levels may not completely reflect the brain levels of Epo and EpoR in children with ADHD. Thus, *in vitro* or *in vivo* studies are required to gain more insight into the brain levels of Epo and EpoR and to be considered as a potential biomarker. On the other hand, the major strength of our study is that, as far as we know, this is the first report on serum Epo and EpoR levels in children with ADHD. Additional large-scale studies are needed to clarify the regulatory mechanisms of Epo and EpoR in ADHD.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Meltem Gungor, Ergul Belge Kurutas. Data acquisition: Meltem Gungor, Ergul Belge Kurutas, Hatice Altun, Ozlem Bozkus, Nilfer Sahin. Formal analysis: Erkan Oner, Hatice Altun, Ozlem Bozkus, Nilfer Sahin. Supervision: Meltem Gungor, Ergul Belge Kurutas, Velid Unsal, Hatice Altun, Ali Erdinc Yalin, Serap Yalin. Writing—original draft: Meltem Gungor, Ergul Belge Kurutas. Writing—review & editing: Meltem Gungor, Ergul Belge Kurutas.

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