IJMS
Vol 49, No 4, April 2024

Original Article

Increased Serum Terminal Complements Complex Levels in Attention Deficit Hyperactivity Disorder Children

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Received: 19 December 2022
Revised: 03 March 2023
Accepted: 22 April 2023

Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is a widespread neuropsychiatric disorder in both children and adolescents, which is associated with social isolation and poor academic performance. Complement proteins are regarded as a major player in inflammation and disease development for several neuropsychiatric diseases such as schizophrenia and bipolar diseases. As clarified by previous data, increased levels of complement molecules and other immunological markers as cytokines were demonstrated in these disorders. Limited studies have investigated complement proteins particularly terminal complement complex or membrane attack complex (C5b-9) among ADHD patients. The present research aims to elucidate the association between C5b-9 complex protein and ADHD.

Methods: This is a cross-sectional study. Sera were collected from Al-Hussain Teaching Medical City in Holy Karbala, Iraq, during 2019-2020. Sera were tested for C5-b9 using commercial kits by enzyme-linked immunosorbent assay (ELISA).

Results: In 90 participants included in the study, a significant increment in C5b-9 levels among ADHD patients (P=0.019) was observed. Patients with positive C5b-9 levels had a 2.76 times higher risk of developing ADHD than control subjects. The diagnostic utility for C5b-9 was statistically significant with 71.11% sensitivity, 55.6% specificity, and a high negative predictive value (97.3%).

Conclusion: The study concluded elevation of the C5b-9 terminal complements complex levels in ADHD patients, which could point to the association of complement proteins as inflammatory markers with the ADHD disease process.

Please cite this article as: AL-Hasnawi SMJ, Noori MA, AL-Haidari AF, Hussain MJ. Increased Serum Terminal Complements Complex Levels in Attention Deficit Hyperactivity Disorder Children. Iran J Med Sci. 2024;49(4):229-236.doi: 10.30476/IJMS.2023.97556.2934.

Keywords ● Attention deficit disorder with hyperactivity ● Complement membrane attack complex ● Enzyme-linked immunosorbent assay

What's Known

- Inflammatory and immunological markers, such as cytokines and oxidative stress, have been the focus of studies on neuropsychiatric disorders, as neuropathological causes. Limited data is available about the role of complement proteins as inflammatory biomarkers in attention deficit hyperactivity disorder (ADHD) patients.

What's New

- The current study found elevated serum levels of C5b-9 in ADHD children. Individuals with seropositive C5b-9 had 2.8 times more risk of developing ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral psychiatric disease of childhood and adolescence. ADHD is associated with symptoms such as inattention, hyperactivity, impulsive disruptive behavior, poor concentration, and motor restlessness, which hurt educational achievement and social behavior during the school years.[1, 2]

The underlying etiology of ADHD could be due to genetic

or environmental factors that contribute to disease progression.[3] Environmental factors such as stress, obesity, diet, smoking, and history of maternal infections were proven to be associated with the progression of ADHD in previous research.[4-6]

It was hypothesized that neuropathological mechanisms accompanied by inflammation could underlie the etiology of ADHD. Recently, much evidence suggests the role of inflammation in neuropsychiatric disorders.[7, 8] For example, inflammation was reported in some neuropsychiatric disorders such as depression, schizophrenia (SZ), Autism Spectrum Disorder (ASD), and bipolar disorder (BD).[9-11] Previous reports suggested high levels of persistent oxidative stress markers in children with ADHD, and it was interpreted to probably lead to immune disturbances and abnormalities.[12, 13]

The complement system plays an important role in developing and progressing brain pathologies.[5] The local production of complement proteins in brain tissue explains the role of the classical complement pathway in different brain pathologies.[14, 15] Abnormal complement pathway markers were found in adult patients with psychiatric disorders such as SZ, BD, and ASD.[16, 17]

It was suggested that C5b-9 either directly kills brain cells or indirectly induces the infiltration of inflammatory cells via increasing endothelial leakage. Neutralization of C5a by using a C5a inhibitor reduced ischemic brain injury.[18]

Limited data is available about the role of terminal complement complex protein as an inflammatory biomarker within ADHD patients. Thus, this study aimed to investigate the vital roles of C5b-9 protein in these patients.

Patients and Methods

Subjects

Blood samples were collected from children with ADHD at Al-Hussain Teaching Medical City in Holy Karbala, Iraq, from December 2019 to June 2020. Forty-five patients with ADHD (35 males and 10 females) with an age between 6 to 12 years were enrolled in this cross-sectional study. The diagnosis was based on history and clinical examination, and all patients met DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) diagnostic criteria for ADHD.[1] Patient groups were subdivided according to their presentations into ADHD, hyperactivity, or attention deficit.[1] In addition, 45 healthy control participants (35 males and 10 females) with matching age and sex to the patient groups were included.

Inclusion and Exclusion Criteria

All patients with ADHD, hyperactivity, or attention deficit according to the DSM-5 criteria were included. All the patients should have no history of any autoimmune diseases, or allergies, no history of other psychiatric diseases, and no signs or symptoms of infectious diseases including COVID-19. The control group was healthy with no history of autoimmunological disorders, allergies, infections, COVID-19, or psychiatric diseases. All included participants completed their vaccination program at the age of 4 years.

A sample of 5 mL venous blood from each patient and control child was obtained. Then, the serum was separated and stored in an Eppendorf tube at freezing condition (-20) until the time of analysis.

Human terminal complements complex C5-b9 ELISA kits (Biobase, U.S.A, catalog No. MBS2704384, detective range 1.25-80 ng/mL) were used to analyze the serum levels of C5-b9 among the patients and control groups. 21 control samples and five patient samples were below the detective range for the kit and were regarded as zero for statistical purposes.

Ethical Approval

Ethical approval was given by the Medical Research Bioethical Committee of Karbala College of Medicine with reference number 53 and the Karbala Health Directorate Committee at Holy Karbala. Moreover, verbal and written consent were obtained from all participants' parents.

Statistical Analysis

Data of studied groups were analyzed by using the statistical package for Social Sciences (version 20.0 for Windows, SPSS, Chicago, IL, USA) and MedCalc statistical software. Data normality distribution was examined using the Shapiro–Wilk test, and C5-b9 levels were found to be not normally distributed. Comparison between control and patient groups was done using the Mann-Whitney U test and the Kruskal Wallis test according to normality testing. The relation between qualitative data was studied using the Chi square test. Receiver operating characteristic curve analysis (ROC) was used to assess the validity of C5b-9 in differentiating disease from the control group and determining the cutoff point. A $P<0.05$ was considered statistically significant.

Results

The demographic characteristics of patients and control groups are shown in table 1. In addition, subclasses or subtypes of the ADHD patient group are demonstrated in table 1.

Table 1: Demographic and clinical characteristics and C5b-9 serum levels of study groups

Characteristics		Groups		P value
		ADHD patient	Control	
		N (%)	N (%)	
Sex	Male	35 (77.8%)	35 (77.8%)	≥0.999
	Female	10 (22.2%)	10 (22.2%)	≥0.999
Age (mean±SD)		7.9±1.8	8.3±1.9	0.308
C5b-9 (ng/mL), Median (IQR)		1.367 (2.1285)	0.912 (1.106)	0.019*
Subclasses of ADHD patients	Patients with attention deficiency	10	22.2%	
	Patients with hyperactivity	14	31.1%	
	Patients with both (ADHD)	21	46.7	

Mann-Whitney U test; IQR: Interquartile range; SD: Standard deviation; N: Number. *P<0.05 is significant.

To evaluate C5b-9 serum levels in patients with ADHD and the significant statistical differences between patients and the control group, the Mann-Whitney test was used for probability evaluation. Serum levels of C5b-9 in the patient group were significantly higher than in the control group as clarified in table 1.

To assess the validity of C5-b9 in differentiating ADHD patients from controls, ROC curve analysis was performed. It was revealed that C5-b9 had a good negative predictor value at a cutoff point >0.453. Although accuracy was low, the test still had a significant P value for differentiation of ADHD from control participants (figure 1 and table 2).

A comparison of positive and negative values of C5b-9 levels in both groups of patients and controls was done according to the cutoff point obtained from the ROC curve (0.453). The levels of C5b-9 in positive cases were higher in patients than in controls, while the negative case levels were lower in the control group. The comparison between these groups was significant with an odds ratio=2.76 (table 3).

The levels of C5b-9 among subtypes or subclasses of patients were found without any statistically significant differences when comparing C5b-9 serum levels or seropositivity in the subtypes of ADHD disease (ADHD, attention deficiency, and hyperactivity), table 4 and 5 (P>0.05).

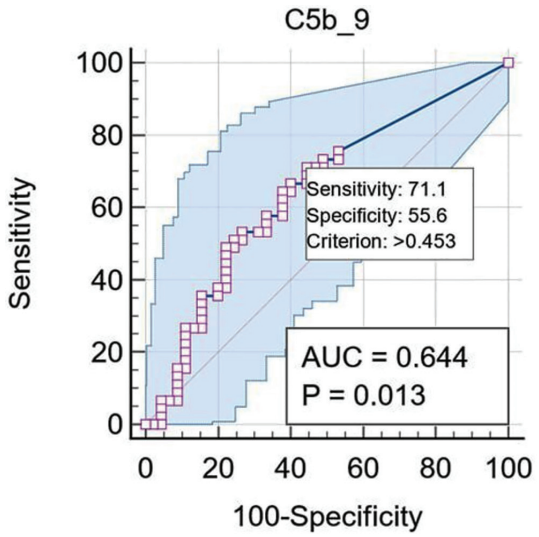

Figure 1: Diagnostic utility of C5b-9 for attention deficit hyperactivity disorder done by receiver operating characteristic curve analysis

Table 2: Validity and cutoff point of C5b-9 in attention deficit hyperactivity disorder (ADHD) and control groups

Cutoff point	0.453
Positive predictive value	7.8%
Negative predictive value	97.3%
Accuracy	56.64%
Area under the ROC curve	
Area under the ROC curve	0.644
Standard Error	0.0578
95% Confidence interval	0.536-0.742
z statistic	2.487
P value	0.013*

ROC: Receiver operating characteristic; *P<0.05 is significant.

Table 3: C5b-9 distribution according to positive and negative values among attention deficit hyperactivity disorder (ADHD) and control groups

C5b-9	Positive	Negative	Odds ratio	95% CI	P value
	N (%)	N (%)			
ADHD group	31 (68.9%)	14 (31.1%)	2.76	1.1682-6.5579	0.033*
Control group	20 (44.4%)	25 (55.6%)			

Chi square test; *P<0.05 is significant.

Table 4: Association of C5-b9 serum levels with attention deficit hyperactivity disorder (ADHD) subtypes and sex in the patient group

C5b-9 (ng/mL) / ADHD subtypes	Median	IQR	P value
Attention deficit	1.50	1.66	0.99
Hyperactivity	1.90	2.74	
ADHD	1.33	1.78	
Sex			
Male	1.44±1.52	2.15	0.925
Female	1.42±1.65	1.91	

Mann-Whitney U test; Kruskal Wallis test; IQR: Interquartile range; P<0.05 is significant.

Table 5: Association of C5b-9 seropositivity with disorder subtypes in attention deficit hyperactivity disorder (ADHD) patient group

Subtypes	C5b-9 (ng/mL)				P value
	Positive		Negative		
	Median	IQR	Median	IQR	
Attention deficiency	1.43	1.66	0.83	2.15	0.563
Hyperactivity	1.90	2.74	0.91	1.83	0.545
ADHD	0.78	1.78	1.43	2.10	0.506

Mann-Whitney U test; IQR: Interquartile range; P<0.05 is significant.

In addition, table 4 shows a non-significant similar result for C5b-9 levels between both sex in the patient group.

Discussion

The most important finding of the present study is the higher serum levels of C5b-9 in the ADHD group than that of the control healthy group. In addition, patients with higher seropositive C5b-9 levels had a 2.76 times higher risk of developing ADHD than healthy control. Roc curve analysis showed that C5b-9 could differentiate and diagnose ADHD patients from healthy controls. Thus, it could be regarded as a good biomarker in diagnosis. The above-mentioned finding could be clear evidence for the important role of the complement system (C5b-9 complex) as part of immune response in the pathophysiology of ADHD. Different studies concentrated on the abnormal physiology of the brain in ADHD with conclusions of incomplete maturation with developmental defects, structural micro- and macrostructural changes, and functional abnormality.[19, 20] It has been suggested in previous studies that complement innate immunity appears to play a fundamental role in brain development with the expression of complement proteins and C5b-9 complex within the brain tissue.[21, 22] A previous study suggested that C5b-9 could bind to nerves and vascular endothelial cells, forming hydrophilic channels that change the intra- and extra-cellular osmotic pressure and then cause cell lysis.[12] These facts suggest the killing of brain cells either directly or indirectly by infiltration of inflammatory cells and increasing endothelial leakage and confirm that increment of C5b-9 in brains of ADHD could kill brain cells.[12]

The relationship between the C5b-9 complex and ADHD is not focused on in previous studies. To our knowledge, limited data are available about possible associations between the complement proteins or the terminal complement complex and ADHD. The only exception is a report for C4b level that showed decreased C4b levels in ADHD patients and concluded a possible etiological role for C4b in the development of the disease, as it could increase the persistence of viral infections to CNS.[23]

Several data from previous studies reported abnormalities in immune response as the role of immune biomarkers other than complement proteins such as anti-Purkinje cell antibodies, serum IL-6, IL-10, and anti-basal ganglia antibodies, which were elevated in ADHD.[24, 25] In contrast, non-significant results were clarified by another study, although increased levels of IL-6 and TNF-alpha were detected in ADHD patients.[26] In past studies about schizophrenia, all the components of the three complement pathways were elevated in patients besides acute phase reactants and inflammatory cytokines.[27, 28] Other psychiatric disorders such as bipolar disorder were investigated for complement proteins and found higher C5b-9 levels in the BD-II subtype patients group than in controls, suggesting immune dysregulation and complement cascade activation in those patients.[29] However, in the study of Akcan and

others, lower concentrations of C4 and sC5b-9 in bipolar disorder patients were found.[30] Lastly, an interesting report linked the high serum levels of C5b-9 complex and "Patients with First Episode Psychosis" compared to the control group, with a significant statistical result.[31]

The present study could not find a significant association between the subclasses of ADHD and mean serum levels of C5b-9. The lack of an observed difference could be due to the sample size of the study. As mentioned above, no recorded or published data have compared levels of C5b-9 complex with ADHD disorder or its subtypes.

The current study showed that ADHD children presented with the disease at an age between 6 to 12 years, which is the age of school entry and engagement in society. This early detection of the disorder may be attributed to antisocial behavior and poor academic progression.[32] This result is in agreement with a previous report by Furukawa and colleagues, which revealed that children presented with ADHD at the age of 7 to 9 years with a mean of 5.3±0.7 years and 8.0±0.8 years for preschool and age, respectively.[33]

Regarding sex distribution in ADHD, the current study revealed that males were more affected by ADHD than females (77.8% males *vs.* 22.2% females). Previous studies showed that ADHD is more prevalent in male children and could reach up to ten times more than females, which supports the current results.[34, 35] In our society, greater attention is given to male patients over females, which could be attributed to a higher presentation rate in males especially in rural areas. In addition, school entry in rural areas is restricted to the male sex, which could contribute to the diagnosis of their disease.[36]

The subgroup distribution of the present study was according to symptoms. Combined ADHD is the higher subgroup with 46.7%, while 22.2% of patients were attention deficit, and 31.1% had hyperactivity. This reflects that ADHD combined presentation is the most common and noticeable type. These findings were consistent with prior reports.[37]

The primary limitation for the generalization of our results is sample size, which could lead to bias. As ADHD is an underdiagnosed disorder, it needs a longer time for sample collection. In addition, the present study was part of a student thesis project with a deadline time limit for submission, which further restricted the sampling process.

Conclusion

Finally, the present study concluded that C5b-9 (terminal complement complex) could be correlated with the development of ADHD. This could point to the role of complement immune system activation in inflammation and disease development. Focus on altered immune response as a possible etiological mechanism for ADHD in specific and other neuropsychiatric disorders, in general, is a growing interest and could highlight and change the future modalities of treatment and give hope to millions of affected patients all over the world. Therefore, we recommend a detailed larger size and long-term study that focuses on complement proteins and ADHD, including the severity of ADHD in children and adult patients. Talking about the limitations of the study, it would be interesting if data of the current study managed to classify patients according to severity score.

Acknowledgment

The authors would express thanks to all participants and their families who contributed to this research.

Authors' Contribution

SMJ.A: Study design, data analysis, data interpretation, drafting, and reviewing the manuscript; MA.N: Study design, data gathering, data analysis, and drafting the manuscript; A.F: Study design, data gathering, data analysis, and drafting the manuscript; MJ.H: data interpretation and analysis, critical reviewing the manuscript; All the authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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