Journal for ReAttach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 June; 5 (1): 78-86

Serum immunoglobulin G and M levels in Attention Deficit Hyperactivity Disorder children

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Received: 28-March-2022
Revised: 19-May-2022
Accepted: 30-May-2022

Abstract

Background and Objective: Inflammation and immune response are focused on recently for their possible role in development and pathophysiology of different neuropsychiatric disorders as Attention Deficit Hyperactivity Disorder (ADHD). However, a limited data is present within this research area. Different inflammatory markers could be associated with disease development. The objective of the study is to clarify the role of IgG & IgM in ADHD patients through measuring serum levels of these markers.

Methods: a case-control study that included 90 participants, 45 as patients' group of ADHD with age range 6-12 (35 males and 10 females), in addition to 45 healthy control group. Serum levels of IgM and IgG were measured by using ELISA test.

Results: a significant association between elevated serum level of IgG antibody and ADHD patients was reported. In addition, significant diagnostic utility for IgG. while no significant association with IgM levels were found.

Conclusion: the study concludes higher serum level of IgG which could be used as diagnostic biomarker for differentiating ADHD children from healthy children.

Keywords: ADHD, IgG, IgM, ELISA

1. Introduction

The most common and highly heritable childhood psychiatric disorder is attention deficit hyperactivity disorder (ADHD). The prevalence of this disorder in the children and adolescents are 5.3%. The frequency of this disorder decreased with the age but can continuous in to adulthood and between 2.5 to 4.4% of adults can be affected with this disorder. Some studies found that 25% of adults with a hyperactivity are the parents of children with hyperactivity symptoms (Sharp et al., 2009).
Several evidence in the last years confirming the role of inflammation in the neuropsychiatric disorders others than ADHD. The altered inflammatory mechanisms and neuropsychiatric disorders have a strong relationship with the schizophrenia (Howren et al., 2009), depression (Miller et al., 2011), bipolar disorder (Modabbernia et al., 2013) and posttraumatic stress (Passos et al., 2015). It has been supposed that physiopathology of these disorders is associated with several inflammatory mechanisms such as neuronal damage and degeneration (Réus et al., 2015), increased oxidative stress (Allan & Rothwell, 2001), glial activation (Hassan et al., 2016), altered neurotransmitter metabolism (Sen et al., 2008), reduced neurotrophic support (Kronfol, 2000), and blood-brain

barrier disruption (Pollak et al., 2018). There are three lines of evidence that support the role of inflammatory mechanisms in the ADHD, which includes the autoimmune and inflammatory disorders, genetic studies and biochemical markers. In the children, several studies found a significant relationship between eczema and ADHD disorder (Romanos et al., 2010; Schmitt et al., 2010). Considering that the most common chronic inflammatory condition in the children is the eczema and it is associated with ADHD (Schmitt et al., 2009), this is a powerful indication for the role of inflammation in ADHD development. In addition, there were an important role of immune system in the neuropathological mechanisms of ADHD. The one of the most important research subjects are the interaction between immune system and the central nervous system in the recent years. The immune system has a severe influence on memory, neural plastic and learning (Yirmiya & Goshen, 2011). The disruption of the balance between the inflammatory and anti-inflammatory factors may have a role in the neurobiology of ADHD (Leffa et al., 2018). Several studies reported some results such as increased IL-6, IL-10, anti-purkinje cell antibodies (Donfrancesco et al., 2020), dopamine transporter protein autoantibodies (Giana et al., 2015), increased pro-inflammatory cytokines such as TNF-β and decreased anti-inflammatory cytokines such as INF-y, IL-2 and IL-4 (Verlaet et al., 2014), which indicate the role of inflammation response in ADHD. Further, the increased risk factor for ADHD was associated with children whose mothers have immune system disease like type 1 diabetes, rheumatoid arthritis, hypothyroidism and multiple sclerosis (Instanes et al., 2017). The inflammatory cytokines may lead to ADHD by influencing peripheral inflammation, neurotransmitter composition and prefrontal cortex maturation, as well as, can lead to ADHD by elevating the excitability and activation of microglia through TNF –α (Buske-Kirschbaum et al., 2013; Riazi et al., 2008).

So, present study aimed to explore the possible association between serum IgG & IgM as they are part of inflammatory biomarkers and ADHD pathogenesis.

2. Methods

Study design & settings: This is a case-control study done in Imam AL-Hussain Teaching Medical City in holy Karbala from period of October -2019 to March -2021.

Subjects: patient groups consisted of 45 case with age range 6-12 and composed of 35 males and 10 females, all patients enrolled in this study were collected from psychiatric out patients clinic. Control group included 45 subjects who were matched with patients' group for both age and gender.

Inclusion and Exclusion criteria: ADHD diagnosis was done clinically based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria (*American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders*, 2003), so all patients met these criteria were included. Patients with other psychiatric diseases, autoimmune diseases and any type of infection were excluded. ADHD children were subdivided into 3 classes based on number and kind of symptoms according to DSM-5 criteria (inattention, hyperactivity & ADHD). All control group were healthy with no history of any inflammatory or autoimmune diseases.

Blood sampling and assay: A 5 ml venous blood were drawn from each participant, then separated serum subjected for ELISA analysis using kits for serum human IgG & IgM (Biobase, china) with Catalog No. MBS2511279, MBS2509204 for IgG & IgM respectively. Reference range detection for IgG was 1.56-100ng/ml (1560 -100000 pg/mL) with sensitivity of 940pg/ml. while for IgM was 3.13-200ng/mL with sensitivity of 1.88 ng/ml.

The ethical approval: ethical approval was given by ethical committee of Kerbala College of Medicine in addition to Karbala Health Directorate Committee. Also, verbal and written consent from each child parents were taken before blood sampling and through an interview for data collection.

Statistical analysis: was done by Statistical Package for the Social Science, SPSS, (version 20, IBM, Chicago, Illinois) program & diagnostic utility was determined by MedCalc statistical software. The Shapiro–Wilk test was used for testing normality of the distribution and when data were non normally distributed Mann Whitney U test was used for comparison of means. In addition to chi square and student t test were used to analyze the demographic variables. $P<0.05$ was considered to be statistically significant.

3. Results

Results findings showed that no significant differences in age and gender distribution between study groups as they are matched, but significant number of patients are from urban areas as clarified in demographic data in table-1. Patient's divided into subclasses according to DSM-5 criteria with 46.7 % distributed within ADHD subtype of disease.

Table- 2 revealed that patients group had higher levels of total IgG than control group and the results is statistically significant. Also mean levels of total IgM is higher than control group although result is statistically non-significant.

Table 1

Demographic and clinical characters distribution among study groups

character		**Groups**				**p-value**
		Patient		**Control**		
		N	%	N	%	
Gender	Male	35	77.8%	35	77.8%	P= 1
	Female	10	22.2%	10	22.2%	X^2=0
Age	Mean ± SD	7.9±1.8		8.3±1.9		P= 0.271 t-test=1.1,
Residence	Rural	7	15.6%	0	0%	**0.02 ***
	Urban	38	84.4%	45	100%	

ADHD patients	**Patients with attention deficit**	**Patients with hyperactivity**	**Patients with both (ADHD)**
N (%)	10(22.2%)	14(31.1%)	21(46.7%)

SD: standard deviation, N: number, P: probability, ADHD: attention deficit hyperactivity disease. *: significant. P-value significance at < 0.05.

Table 2

Total IgM & IgG levels in patients and control groups

Parameter	**Group**								**P-value**
	Patient				**Control**				
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	
IgM (ng/mL)	5.99	3.37	6.64	4.23	4.94	2.56	4.6	3.39	0.06
IgG (pg/mL)	1252.02	1886.93	994.48	624.88	816. 10	356.72	737.51	603.602	**0.03***

Mann-Whitney U test. SD: standard deviation, IQR: interquartile range, mg: milligram, dl: deciliter, P: probability. *: significant. P-value significance at < 0.05.

ROC curve analysis was used for assessment of diagnostic utility of both IgG & IgM in differentiating patients from control group. It revealed that IgG had sensitivity & specificity equal to 91.1%, 31.1% respectively at cutoff point of > 491.05. while IgM sensitivity & specificity were equal to53.3%, 75.6% respectively at cutoff point of > 6.19. IgG test had significant p-value (0.031) for area under the ROC curve (Figure1,2 and Table3,4).

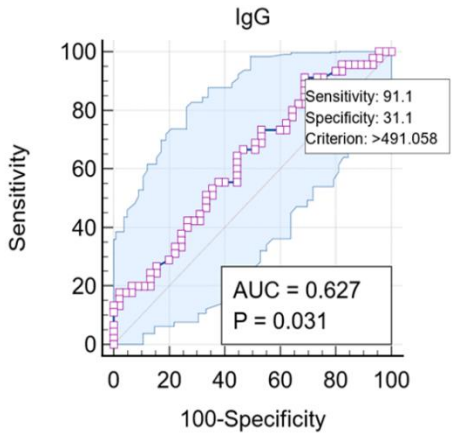

Figure 1. ROC curve analysis for IgG in diagnosis of ADHD

Table 3

Validity and cutoff point of IgG

Cutoff point	**491.05**
Sensitivity	91.1%
Specificity	31.1%
Positive predictive value	6.5%
Negative predictive value	98.5%
Accuracy	76.92%
Area under the ROC curve (AUC)	
Area under the ROC curve (AUC)	0.627
Standard Error	0.0589
95% Confidence interval	0.519 - 0.727
z statistic	2.155
***p*-value**	**0.031***

ROC: Receiver operating characteristic, *: significant p-value.

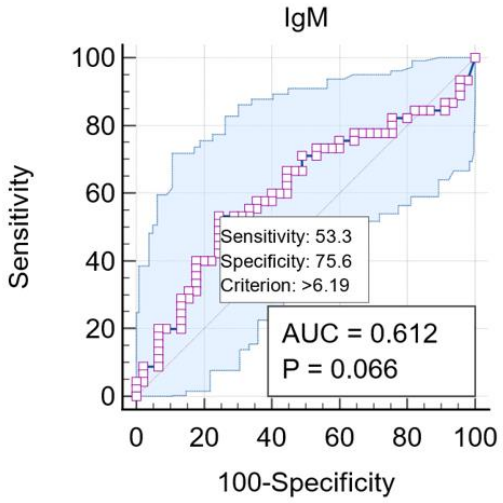

Figure 2. ROC curve analysis for IgM in diagnosis of ADHD

Table 4

Validity and cutoff point of IgM

Cutoff point	**6.19**
Sensitivity	53.3%
Specificity	75.6%
Positive predictive value	10.3%
Negative predictive value	96.9%
Accuracy	73.77%
Area under the ROC curve (AUC)	
Area under the ROC curve (AUC)	0.612
Standard Error	0.0608
95% Confidence interval	0.503 - 0.713
z statistic	1.838
***p*-value**	0.066

ROC: Receiver operating characteristic, *: significant p-value.

lastly table-5 showed no significant differences in mean levels of both IgG and IgM among subclasses of patients group.

Table 5

Total IgM & IgG levels among subclasses of ADH

Parameters	ADHD subtypes									P-value	
	ADHD			Hyperactivity			Attention deficit				
	Mean ±SD	Median	IQR	Mean ±SD	Median	IQR	Mean ±SD	Median	IQR		
IgM (ng/ml)	5.01±3.76	4.86	4.96	6.49±2.30	5.30	3.08				ADHD vs Hyperactivity	0.58
							7.51±3.18	7.79	2.14	ADHD vs attention deficit	0.90
										Hyperactivity vs attention deficit	0.92
IgG (pg/ml)	1499.38±2668.71	976.90	540.56	976.58±400.63	994.48	558.69				ADHD vs Hyperactivity	0.91
							1065.89±526.58	910.27	983.85	ADHD vs attention deficit	0.91
										Hyperactivity vs attention deficit	0.92

Mann-Whitney U test. SD: standard deviation, IQR: interquartile range, mg: milligram, dl: deciliter, P: probability. *: significant. P-value significance at < 0.05.

4. Discussion

Current study concentrate on measuring levels of total serum IgG & IgM among ADHD patients as past knowledge or researches are limited to specific immunoglobulin types mainly against specific infections. Present finding clarified that serum IgG levels were significantly higher in patients group compared to control. This is an indicator of chronic inflammatory process in these patients which could be responsible for part of pathogenesis of disease. Although there is a slight increment in IgM levels but non-significant change between patients and control and this result means that there is no acute process of inflammation (as all causes of acute inflammation were excluded from the study). IgG had significant diagnostic utility with high sensitivity in diagnosing ADHD. Till now a little is known about involvement of inflammation and inflammatory markers in ADHD pathogenesis. No published recorded data for serum total IgG and IgM levels in patients with ADHD ,that discuss the possible role of these markers in diseases development, present.

Past study of Krahel et al. showed a significant increment of saliva IgM & IgG among ADHD patients (Krahel et al., 2021). Other studies searched the association of seropositivity for IgG & IgM in different types of infections (Bekdas et al., 2014; Lam et al., 2020; Noori et al., 2020).

Current study revealed that male distribution in ADHD was 77.8% compared to 22.2% ADHD females. This result is concomitant with Bekdas et al. study which showed 65% of patient group were males(Bekdas et al., 2014). Male higher distribution could be due to paying more attention for male health in our societies. Mean age for patients' group was 7.9±1.8 which is similar to past study that showed mean age = 8.6 ± 1.1 (Krahel et al., 2021). according to DSM-5 updated criteria ADHD presentation is before age of 12 (Kemper et al., 2018). In addition, present study shows that most of cases were from urban area. ADHD is difficult to diagnose and required high level of education in families. School engagement which is important step in diagnosis is more in urban than rural areas.

Regarding symptomatic presentation of present study, most of cases (46.7) were presented as ADHD while attention deficit & hyperactivity constitute 22.2% & 31.1% respectively. This result is near to what was found by previous study were ADHD presentation was 56.6% vs 43.3% with inattention subclass (Bekdas et al., 2014). Also, similar findings were obtained by other past studies (Erşan et al., 2004; Wilens et al., 2009).

5. Conclusion

For conclusion, etiology and pathophysiology of ADHD is difficult to understand with current knowledge. The disease is heterogenous in etiology and inflammatory immune response is seemed to be an important player in development of ADHD. Higher serum levels of both IgG were found in ADHD patients with significant diagnostic utility which encourage more researches in this area with more inflammatory biomarkers.

Acknowledgments

Authors would express grateful thanks for all participants and their families who contributed for this research.

Funding

The authors receive no financial support for this research.

Conflict of Interest:

The authors declare no conflict of interest.

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