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Original Article

The Profile of Macrophage migration inhibitory factor (MIF) and some Immunoglobulins in patients with Autism

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ABSTRACT

Autism spectrum disorder (ASD) involves a complex interplay of both genetic and environmental risk factors, with immune alterations and synaptic connection deficiency in early life. Immunological imbalance (including autoimmunity) has been proposed as a major etiological component in ASD. The present study was conducted to evaluate the role of Macrophage migration inhibitory factor (MIF), and some immunoglobulin (IgG and, IgM) among patients with autism. We have investigated the serum level of MIF, IgG and IgM in 120 subjects. Sixty were autistic patients while others were apparently healthy individuals used as a controls. Of the 60 patients registered 48(80%) of them are male and 12 (20%) female with male to female sex ratio of 4:1. The statistical results indicated higher mean serum concentration of MIF (mean 13.31 ng/ml) versus (mean 5.61ng/ml), but lower mean serum levels of total IgG (20.66 ug/ml) versus (38.01ug/ml) and total IgM (208.18 mg/dl) versus (245.53 mg/dl) in autistic patients than apparently healthy subjects.

Keywords: Autism spectrum disorder, Immunological markers, MIF, IgG, IgM, ELISA.

INTRODUCTION

Autism spectrum disorder (ASD) involves a complex interplay of both genetic and environmental risk factors, with immune alterations and synaptic connection deficiency in early life. Immunological imbalance (including autoimmunity) has been proposed as a major etiological component in ASD. Also, epidemiological studies have established a correlation of ASD with family history of autoimmune diseases; associations with major histocompatibility complex haplotypes and abnormal levels of immunological markers in the blood [1]. It's a heterogeneous group of behaviorally defined disorders that are widely considered to be genetic in origin on account of the high rates of heritability [2]. It is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and restricted and repetitive behavior [3]. Parents usually notice signs in the first two years of their child's life [4]. it affects boys four times more frequently than girls suggesting involvement of the sex chromosomes [5]. When females are affected, they usually exhibit severe mental retardation [6]. Over the past decades the prevalence of this disorder has dramatically increased. Although the reason for this increase is still up for debate, In 2012, the Autism and Developmental Disabilities Monitoring (ADDM) Network published data from 14 sites for the 2008 surveillance year, reporting a combined ASD prevalence of 11.3 per 1,000 children aged 8 years (or one in 88) children [7]. Comparison of the 2008 findings with those for previous surveillance years showed an increase in ASD prevalence of approximately 23% compared with the 2006 estimates and 78% compared with 2002. While the etiology and pathogenesis of autism are poorly understood, there is evidence that immune system abnormalities are associated with symptoms in a substantial number of affected individuals [8]. Immune dysfunction plays a major role in the pathophysiology of ASD [9]. Inflammatory changes in the central nervous system (CNS) and the peripheral immune system have been repeatedly reported in different biologic samples of individuals with ASD [10], [11]. The aim of present study is to investigate the association of Some Immunological markers such as Macrophage migration inhibitory factor (MIF), and immunoglobulin (IgG and, IgM) among patients with autism**.**

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MATERIALS AND METHODS

The study was carried out on 60 Iraqi children (48 of them are males and 12 females) with age range 3-12 years old with autistic disorder who were registered in Al-Imam AL- Hussein Institute for the care of autistic in AL-Najaf and Ruqayah Center for Hearing and Speech in AL-Diwaniaya. The diagnosis was made by the medical staff responsible at the Institute on the basis of international criteria. All patients were not under drugs and they did not suffer from any other disease. For the purpose of comparison, 60 age and gender matched children were enrolled as a control. From each participating subject, 3-5 ml of blood was obtained by venipuncture. The collected blood was transferred to a plain tube and left to clot at room temperature (20-25°C) for 15 minutes. The clotted blood was centrifuged at 2000 rpm for 15 minutes; and by then, serum was collected and distributed into aliquots of (200µl) in Eppendorf tubes, which were frozen at -20°C until laboratory assessments. Serum samples were collected from all study individuals to determine the seropositivity levels of MIF, IgG and IgM using enzyme linked immunosorbent assay (ELISA) and laboratory kits used by USCN-China Company, during the period from January to March 2016. Furthermore, an informed written consent of participation in the study was signed by the parents or the legal guardians of the all studied subjects.

***Statistical analysis*:** Data were entered and analyzed by using SPSS (Statistical Package for Social Sciences) version 20for Windows. Descriptive statistics (frequencies, percentages, tables, graphs) and inferential statistical were used. Independent T-test used to compare mean between cases and controls. P-value < 0.05 was considered Statistically Significant**.**

RESULTS AND DISCUSSION

Demographic Profile: The demographic profiles of both autistic patient and control groups are shown in Table (2). In which there is a significant difference between the autistic patients and controls at all the male/female ratio but non-significant difference at the age.

***Serum parameters*:** Mean serum concentration of the MIF (13.31 ± 4.00 ng/ml) versus (5.61± 2.26ng/ml) was significantly higher in the patient group in comparison to control group, with a p-value of (P <0.001), Table (3). These results observe a significant association between concentration of MIF and autistic patients, this may be due to its important role in pathophysiology of autism. MIF is a pro-inflammatory immune regulator that is constitutively expressed in brain tissues and has important influences on neural and endocrine systems [12]. The present results are similar to results of Grigorenko *et al.* [12] which revealed that the mean MIF value for cases (13.12 + 9.18 ng/mL) higher than those of control group (6.87 + 2.75 ng/mL) and this difference was statistically significant (P <0.05), but our result disagree with result of Tomoum and Hassan., 2009 [13] which reported that the levels of MIF was lower in the patients (3.73± 3.9); and there was no significant difference from those levels among the control group (4.1± 3.8).

Mean serum concentration of the IgG (20.66 ± 6.13ug/ml) versus (38.01 ± 7.21ug/ml) and IgM (208.18 ± 22.43mg/dl) versus (245.53 ± 15.5mg/dl); was significantly lower in the patient group in comparison to control group, with a p-value of (P<0.001) table (3). These results observe a significant association between concentration of IgG and IgM with autistic patients. These lower serum concentration of IgG in autism suggests an underlying defect in immune function contributing in the development of autism. The present results are similar to results of Heuer *et al.* [14], who revealed that the total IgG was lower in the autistic patients than that of healthy controls (P < 0.001). Chaudhry *et al.* [15] found that the mean IgG value for the cases was (1263 ±490.2) lower than those of control group (1565 ±488.4) and this difference was statistically significant (P <0.05). These results also agree with results of Grether *et al.* [16], who reported that the serum IgG levels were significantly lower in autistic children as compared to controls. The results of our study disagree with results of Spiroski [17] and Trajkovski *et al.* [18] which reported that there was increases in the total IgG level in autistic patients when was compare to healthy controls. The current study conducted a significant association between serum level of IgM and autism (P<0.001), Table (3). These lower serum concentration of IgM also suggests an underlying defect in immune function contributing in the development of autism. The present results are similar to results of Heuer *et al.* [19], who revealed that the total IgM was lower in the autistic patients than that of healthy controls (P < 0.001). Chaudhry *et al.* [15] found the mean IgM value for cases (214.9±95.1) lower than those of control group (221.4±94.1) and this difference was statistically significant (P <0.05). El-Aziz and El-Din., [20] conducted in a study that there was immunoglobulin deficiencies when compare between autistic children and healthy controls. There was significant difference in immunoglobulin levels between two groups. Spiroski [17] and Trajkovski *et al.* [18] disagree with our result when reported that there was an

increased in IgM level in autistic children as compared to control.

CONCLUSIONS

There is significantly higher Concentration of MIF in autistic patients in comparison to control group, and significantly lower Concentration of IgG and IgM in autistic patients in comparison to control group. This provides strong evidence that Immunological parameters play a major role in the pathogenesis of autism spectrum disorders (ASD) in Iraqi population.

Table 1: Immunological Kits with their Remarks.

Immunological Kits	Company	Country
Human MIF ELISA Kit	*USCN*	*China*
Human IgG ELISA Kit		
Human IgM ELISA Kit		

Table 2: demographic characteristics of autistic patients and controls.

Parameters	Patients =60(mean ± SE)	Controls = 60 (mean ± SE)	P value
Age	5.81	6.01	0.194
Male/female	4:1	5:1	0.001

Table 3: The Case-control Difference in Mean Serum Concentrations MIF, IgG and IgM.

	Case-control comparison		
	Healthy controls	Cases (Autism)	P
Serum MIF conc.ng/ml			<0.00
Range	(2.42 - 10.74	(2.55 - 18.73)	
Mean	5.61	13.31	
SD	2.26	4.00	
SE	0.51	0.49	
N	60	60	
Serum IgG conc.ug/ml			<0.00
Range	(26.89 – 50.24)	(10.55 – 34.52)	
Mean	38.01	20.66	
SD	7.21	6.14	
SE	1.61	0.74	
N	60	60	
Serum IgM conc.mg/dl)			<0.00
Range	(200.96- 271.02)	(163.41– 245.75)	
Mean	245.53	208.18	
SD	15.5	22.43	
SE	3.46	2.72	
N	60	60	

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