PERINATAL JOURNAL

Original Article

Perinatal Journal 2026; 34(1):1134-1144

https://doi.org/10.57239/prn.26.034100114

The Pro-Inflammatory cytokines and vital physiological functions exploring among Iraqi ASD children: A comparative and correlation study

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Abstract

Autism is the most prevalent of the pervasive developmental disorders, which are more common in boys than in girls. In recent years, the effects of cytokine interactions as biomarkers for diseases have been studied in more detail. This justifies the present study, which aims to diagnose ASD based on pro-inflammatory cytokines and physiological functions. To determine whether pro-inflammatory cytokines and physiological functions are involved in the pathogenesis of ASD. Samples of ASD cases were recruited from the Children Protection Hospital's ASD Center in Baghdad. They were gathered over the course of four months, spanning from October 2023 to January 2024. The factors covered by the study include IL-4, INF-γ, and ABO/Rh blood systems, as well as some important pathophysiological tests. Our present findings suggest that IL-4 and INF-γ levels may serve as diagnostic biomarkers of ASD. Furthermore, blood group B and Rh+ve had the highest percentage in ASD healthy. These findings detected a significant decrease in ALT and AST levels. Additionally, the blood urea assay was recorded as significantly increased in ASD compared to healthy children. Correlation analysis showed a significant positive relationship between IL-4 and IFN-γ, as well as between IFN-γ and potassium (K) levels, between T3 and T4, and between ALT and AST. A negative correlation was also found between T4 and blood urea levels. Conclusion: This study underlines the significance of pro-inflammatory cytokines and physiological functions in Iraqi children with ASD. In particular, we observed low levels of pro-inflammatory cytokines (IL-4, INF-γ) and conducted a correlation analysis between immunity and hormonal and physiological indexes in children with ASD

Keywords: Cytokines, Physiological functions, Exploring, ASD, Iraq

Introduction

The brain investigation becomes more complicated as a result of the increased number of neurosynaptic connections, which is facilitated by the gathering of more information [1]. Autism spectrum disorder (ASD) is one of the most common neurodevelopmental disorders that occurs in childhood and in adults [2]. The name of the disease comes from the Greek auto, meaning self (alone), and refers to an individual separated from their surroundings [3]. This disease has other names: infantile autism, childhood schizophrenia, childhood psychosis, atypical autism [4]. ASD Children are more prone to congenital abnormalities of the nervous system [5]. It is a complex neurosynaptic disorder and a cause of neuropsychological, cognitive, behavioural, and social dysfunction [6]. In addition, these patients cut off some physical problems such as asthma, labored-breathing condition, and sleeping disorder [7]. In a Swedish study (1987-2009), increased rates of mortality among the ASD patients compared to the general population individuals were observed , 2.60% and 0.91%, respectively [8].

This condition affects approximately 2.3% of children at 8 years old and 2.2% of adults aged 20 to 62 years, based on cited studies [9,10]. The permanent nature of the damage in most—but not all—autistic children as they age is noted in the literature [11,12]. The impact on children and their families is often profound [13]. According to the Centers for Disease Control and Prevention (2023), ASD prevalence has increased to 1 in 36 among children and 1 in 45 among adults [14]. These statistics are leading governments to develop policies and programmes to better understand the syndrome's causes in children [15].

This mystifying disorder (ASD) can be attributed to immunological, environmental, or genetic factors [16,17]. One study revealed an ASD risk of 3.22% among consanguineous parents [18]. Monozygotic

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twin pairs were more often concordant for autism (36%, 4/11) than dizygotic twins (0%, 0/10) [19]. ASD children were more likely to be male and firstborn [20]. Additionally, parental ASD risk is associated with advanced maternal age, preterm birth, diabetes, high body mass index (BMI), immune system diseases, oxygen deprivation to the infant's brain, in utero exposure to endocrine-disrupting drugs, and cesarean section [21]. Brain formation in the uterus starts at 6 weeks of pregnancy. Environmental factors can affect epigenetic programming and interfere with synaptogenesis in the third trimester [22]. The human gut microbiome begins colonizing from the womb and rapidly connects to the brain after birth [21,81]. Viral exposure during critical periods of prenatal neurodevelopment may increase ASD risk, as it can lead to inflammation and affect the developing brain [23].

There is significant evidence for the role of the immune system in autism etiology. This is reflected by changes in immunoglobulins, cytokines, and the presence of autoantibodies to neural antigens [16]. Serum kynurenine pathway (KP), interleukin-6 (IL-6), and indolamine 2–3 dioxygenase (IDO) product levels were significantly different in ASD children compared to controls [24]. Incompatibility in blood group between mother and fetus may induce immunological responses that impact the fetus, potentially increasing the risk of ASD through birth infections [25]. Genetically, immune factors may underlie the involvement of immunologic gene Class I, II, and III 72 AN gene clusters, which are associated with antigen presentation [26]. Altogether, anti-brain neuron antibodies may be critical in the development of disorders such as ASD [14].

The present search was precisely designed to test:

- There is a correlation relationship between levels of pro-inflammatory cytokines (INF- γ, IL-4) and patterns of physiological changes amongst Iraqi ASD patients.
- The detection of a specific ABO/Rh blood antigen among the mentioned patients.

Materials and Methods

Plane subjected: The specimens of 50 ASD and 50 normal children were examined. The ASD children's 5 mL blood samples were obtained from the ASD Center in the Child Protection/Baghdad Hospital/Iraq. In a healthy child, recruited from active and prominent school students with no signs of abnormal behavior by teachers and school administrations. These samples are age and gender-matched. The ages of the children ranged from 6 to 12 years. They were taken during a 4-month period between October / 2023 and January / 2024. Children with ASD were diagnosed by clinical indications using the childhood autism rating scale (CARS). The study investigated the association between the frequency of habitats of the ABO /Rh blood system and ASD, using 156 children with ASD and104 controls to evaluate the accuracy of statistical results.

Peripheral blood samples: They were stored in an EDTA tube, and serum was separated in a gel tube. It is usually turned upside-down several times to mix the blood with the silica particles. The tube is left standing for some time in order to clot the blood. The tube was then centrifuged after clotting and separation of the serum from the clot and other cellular components.

Included tests The serum thus obtained is to be tested:

• Immunological examination: Interferon γ (INF- γ) (interleukin-4 (IL-4), by ELISA using the Sandwich method (Biont Company, Catalog No. YLA1519HU South Coria.
• ABO /Rh blood systems: according to protocol (BIOSCOT Company, Germany, and Lot No. 22AB05).
• However, thyroid hormones were examined by the Architect system (ABBOT Company, Batch No. R3B7K660; Ireland).
•Some physiologically important function tests were detected according to the Human Diagnostic Company HRB 10782, Germany.

Statistical analysis: The results were analyzed statistically by using SPSS (V.20) program. The results were present as Mean±S.E, and the significant differences were considered at $p \leq 0.05$.

Results: Pro-inflammatory cytokines tests: The pro-inflammatory cytokines IFN-γ was significantly

decreased (p<0.027) in studied ASD children as compared to healthy children group (Table1). The means of IFN-γ levels were (116.54±29.27) versus (vs.) (47.61±2.31) ng/L in two groups respectively. Also, the statistical analysis found that IL-4 level significantly decreased (P<0.01) in the patients in comparison to control group . The mean of IL-4 was (80.80±11.93) ng /L in control and (45.67±5.24) ng/L in patients group.

Table 1: The Pro-inflammatory cytokines (IFN-γ, IL-4) levels in the ASD patients than control groups

Parameter	Group	Mean±S.E	P value
IFN-γ (ng/L)	Control	116.54±29.27	0.027 **
	ASD Patients	47.61±2.31	
IL-4 (ng/L)	Control	80.80±11.93	0.01*
	ASD Patients	45.67±5.24	

* significant differences **Highly significant

Blood groups: Our study has helped highlight the relationship between ABO blood groups because the different population and relationship mechanisms understood. The results of this study revealed that no significant differences were found in the number and percentage of blood group A between control and autism patients. Blood group B had highest percentage in ASD 34 (21.79) than the same grouping in healthy children 12 (11.54%). Moreover, no significant was noticed between healthy and ASD patients in blood groups AB. Whereas, a significant high (P<0.03) was showed in the grouping O between healthy control 42 (40.38%) and ASD patients 64 (41. 03%).Therefore, it can be considered B and O blood grouping as reference group in this neurodevelopment disorder (Table 2).

In addition, the ABO blood groups in ASD patients were analyzed to detect if any differences between them. It was revealed to a significant association (P<0.001) between blood groups: blood group O followed by blood group A, blood group B and then blood group AB (Table 2).

Table 2: The ABO blood groups in healthy children (Control) and ASD patients

Blood group / sample	A		B		AB		O		Total
	NO.	%	NO.	%	NO.	%	NO.	%	
Control	40	38.46%	12	11.54%	10	9.62%	42	40.38%	104
ASD Patients	46	29.49%	34	21.79%	12	7.69%	64	41.03%	156
Chi $\varkappa^2$	1.21		10.52		0.18		4.56		-
P value	0.27 NS		0.001**		0.6 NS		0.03*		

** highly sgnificant differences, NS= Non-significant

Table 3: The number and percentage of ABO Blood groups amongst the ASD patients

Blood group / Groups	A		B		AB		O		Chi $\varkappa^2$	P value
	NO.	%	NO.	%	NO.	%	NO.	%		
ASD Patients	46	29.49%	34	21.79%	12	7.69%	64	41.03%	22.80	<0.001**

** highly significant differences

This study included the investigation of Rh factor in ASD patients than control. It was found a significant linked (P<0.002) between ASD patients and control in the Rh+ve NO. While no significant linked was detected between patients and control in the Rh-ve NO. The Rh+ve NO. were 92 (88.46%) in control and 140 (89.74%) in ASD patients. Whereas, the Rh-ve NO. were 12 (11.54%) and 16 (10.26%) in control and patients (Table 3). Furthermore, our result illustrated the Rh+ve and Rh-ve groups in ASD patients only. It analyzed statistically seen a significant increasing Rh+ve group (140, 89.74%) than Rh-ve group (16, 10.26% (Table 4). Therefore, Our study suggested con be dependent on ABO/Rh blood system to predict the morbidity of filial ASDs (Table 5).

Table 4: The Rhesus factor (Rh) in healthy (control) and ASD children

Rh group / Groups	Rh +ve		Rh -ve		Total
	NO.	%	NO.	%	
Control	92	88.46%	12	11.54%	104
ASD Patients	140	89.74%	16	10.26%	156
Chi $\varkappa^2$	9.93		0.57		-
P value	0.002**		0.5 NS		

** highly significant differences, NS= Non-significant

Table 5: The Rhesus factor (Rh) amongst ASD patients.

Rh group / Groups	Rh +ve		Rh -ve		Chi $\varkappa^2$	P value
	NO.	%	NO.	%		
Patients ASD	140	89.74	16	10.26	64	<0.001**

** highly significant differences

Thyroid hormones tests: As shown in table (6), T3 as one of the important thyroid gland hormones, was measured. The results of this study revealed that triiodothyronine (T3) levels were non-significant slightly increased in serum collected from ASD children (3.55±1.02) mg/dL as compared to control group (2.22±0.12 mg/dL) at (P=0.31). In contrast, serum thyroxin (T4) was decreased in patients group in comparison to control group, although this decreasing was non-significant (p=0.16). The serum T4 mean levels was more low-slung in control (93.37±3.78 mg/dL) than ASD patients group (77.15±10.49 mg/dL).

In addition, TSH levels present were similar to above results. There were no discernible variation (P=0.82) detection in its average in the ASD children group as compared to healthy children group (Table 6). The TSH average was (2.24±0.21 mg/dL) vs. (2.31±0.20 mg/dL) in the mentioned samples

Vital functions tests: Our finding indicates the liver dysfunction amongst the ASD children due to the measured common liver enzymes. This findings detected a significant decreasing (P<0.001) in the serum Alanine transaminase (ALT).). ALT means was (44.62±5.37 mg/dL) in intact children and (18.37±1.54 mg/dL) ASD group as summarized in table 7.On the other hand, the recent determined aspartate transaminase (AST) enzyme level in mention groups. It was found that AST significantly declined (P<0.003) in the ASD (35.08±2.91 mg/dL) in contrast to healthy children (53.13±5.59 mg/dL).

The bilirubin statistical analysis resulted non-significant differences (P≥0.27) in ASD compared to healthy children. The data observed that bilirubin levels slightly decreased in patients group (0.80±0.21 mg/dL) compared to control group (1.74±0.81 mg/dL). These changes may be indicated on a red blood cell role in ASD children.

Table 6: Thyroid gland hormones concentration in the ASD patients than control groups

Parameter	Group	Mean±S.E	P value
T3 (mg/dL)	Control	2.22±0.12	0.31 NS
	ASD Patients	3.55±1.02	
T4 (mg/dL)	Control	93.37±3.78	0.16 NS
	ASD Patients	77.15±10.49	
TSH (mg/dL)	Control	2.31±0.20	0.82 NS
	Patients ASD	2.24±0.21	

NS= non-significant differences

Table 7: Liver function concentration in the ASD patients than control groups

Parameter	Group	Mean±S.E	P value
ALT (mg/dL)	Control	44.62±5.37	<0.001**
	Patients ASD	18.37±1.54	
AST (mg/dL)	Control	53.13±5.59	0.003**
	ASD Patients	35.08±2.91	
S. Bilirubin (mg/dL)	Control	1.74±0.81	0.27 NS
	ASD Patients	0.80±0.21	

** Highly significant differences NS= non-significant differences

The sodium electrolyte (Table 8) did not effect in the ASD patients group in comparison to healthy children as (P ≥0.46). The means of serum potassium level were (136.00±1.15 mg/dL) and (137.20±1.03 mg/dL) in control and ASD patients respectively. This reflexes the regulation of blood pressure among ASD patients. The current study addressed the blood urea assay because it's screening to provide crucial details about kidney efficiency (Table 8). The statistical analysis results found that blood urea assay significantly increased (38.65±4.83 mg/dL) in ASD children (16.14±1.84 mg/dL) in comparison to healthy children at (P<0.001).

Table 8: The concentration of Blood urea in the ASD patients than groups

Parameter	Group	Mean±S.E	P value
Blood urea (mg/dL)	Control	16.14±1.84	<0.001**
	ASD Patients	38.65±4.83	

** Highly significant differences

Also, our study determined glucose averages in conjunction to vital functions assessment in ASD children (Table 9). The average analysis glucose do not noticed any significant difference (P ≥0.05) in the ASD patients' group (89.22±5.56 mg/dL) comparative to normal children group (83.03±2.18 mg/dL). Therefore, the current study supported may be not affected this factor in autism disease.

Table 9: The glucose concentration in ASD patients than control groups

Parameter	Group	Mean±S.E	P value
Glucose (mg/dL)	Control	83.03±2.18	0.3 NS
	ASD Patients	89.22±5.56	

NS= non-significant differences

This study(Table 10) do not recorded any significant for serum sodium level in ASD patients (137.20±1.03) than control (136.00±1.15) at(p≥0.46).

In addition, serum potassium level similar to sodium due to did not modulated in the patients (p≥0.94) as compared to control. The serum potassium averages were (4.22±0.34 mg/dL) in control and (4.20±0.12 mg/dL) in ASD patients group.

Table 10: The some serum electrolytes levels in the ASD patients than control groups

Parameter	Group	Mean±S.E	P value
S. Sodium (Na) (mg/dL)	Control	136.00±1.15	0.46 NS
	Patients ASD	137.20±1.03	
S. Potassium (K) (mg/dL)	Control	4.22±0.34	0.94 NS
	Patients ASD	4.20±0.12	

NS= non-significant differences

The correlation analysis found that there is a significant moderate positive between IL-4 and IFN-γ (Pearson Correlation (r) =0.462**, P<0.001). While no significant correlation was seen with other studied parameters. In addition, a significant moderate positive correlation was revealed between IFN-γ and K levels (Pearson Correlation (r) =0.459**, P<0.003). But not with other parameters. T3 levels significantly correlated with T4 moderately (Pearson Correlation (r) =0.556**, P<0.001); a weak colleration also found between T4 and blood urea only (Pearson Correlation (r) =-0.366*, P<0.013), while a strong significant positive correlation was noticed between ALT and AST (Pearson Correlation (r) =0.994**, P<0.001).

Discussion

This discovery highlights the importance of studies aimed at examining immune pro-inflammatory responses and their relationship on several neurological and psychiatric disorders [26]. The findings are presented in contrast to the healthy subjects. The levels of IFN-γ and IL-4 are reduced significantly in ASD children, which is representing a suppression of a normal Th1 and Th2 response as an essential part of cellular immunity in these patients [27,29]. Another study also discovered a pattern of ASD patients were related to immune suppression instead of that hyper responsivness because in the decreasing pro-inflammatory cytokine [30]. Whereas, the former study has found marked higher levels of IFN-γ in ASDs [28]. Another study reported that IFN-γ and IL-4 were elevated in the mothers who later gave a birth to ASD children rather than intact children [20]. Elevated salivary IFN-γ levels were associated with increased prevalence of dental caries in ASDs [29]. A high levels may penetrate the neonatal placental IFN-γ and leads to induction of neuro inflammatory in new born brain that stimulates ASD [31].

Recent findings also demonstrated the advantages of blood groups A,B, Rh+ve compared versus healthy children. The comparisons were made by the same ASD patients Rh+ve, O, A, B and blood group AB in ASD children. Though logistic regression showed the AB +ve blood group to be most significantly new immune protective factor against of the ASD risk [32,33]. Similarly, earlier investigation has indicated that most of the ASD children (85%) were Rh+ve [34]. However, several relevant studies reported no-statistically significant between maternal ABO blood group or Rh status and risk of ASDs [35,36,37]. This relationship is a point of debate by medical professionals because the results conflict, and it's unknown what causes this disorder.

Thyroid hormones are important for neuronal growth, neuronal differentiation and synaptogenesis [38]. Thus the present study corroborating to this concept because of nonsignificant rise in T3, fallT4 and TSH values among autistic. One studies have supported of these by increase T4 to T3 metabolic activity to counteract the deficit in autistic [39]. Furthermore, this is suggestive of a primary central defect in the ASD hypothalamus as result as s fall in T4 would be expected to cause an increase in TSH [40].According to Singh et al., the mean ± SD of healthy children's TSH was higher than that of Indian patients [41]. Study reported that ASD boys and girls were non- significantly than control for T3, T4 and TSH [42]. On the contrary, a study indicated that levels of free T3 and T4 decreased significantly with higher level in TSH in autistic subjects [43]. In addition, in aetiological study OF ASD hypothyroidism were also referred to normal range T4 and elevated TSH [44]. Thus, the present research is recommended routine determination of serum thyroid hormones as a sign diagnosis in ASD.

Mention the current study to a link between the lower liver functions and ASDs compared to healthy individuals [45]. yet another investigation changes in liver functions could affect metabolic and neurodevelopmental pathways [46 Patients are shown normal liver enzymes in the bloodstream, as previously mentioned [47,48]. A study was able to show that early-onset liver disease has a greater probability for development of ASD [49]. A significant elevation in serum AST and ALT were found by comparisons of the liver enzyme profiles between ASD children [50,51,52].The results indicate that TSB concentration may be a more accurate marker of neurotoxicity in preterm infants than total bilirubin [53,54,55,56,67]. Therefore, we performed this study to: i) find out what is the role of bilirubin in child ii) What are happened to brain cell when bilirubin increasing that may be leading to worse condition. ASDs Iraqi children had normal levels in TSB which showed healthy liver along the period of the current study.

In the present study, there was a considerable elevating on urea metabolism. This outcome could be due tothevariationsof protein metabolism andureacycle [58,59,60]. Another study indicated that serum urea of ASD children were not different than those of intacts [61]. The brain primarily uses glucose as an energy source. Even a slight imbalance in this gradient is capable of influencing brain development and maturation [62]. Thus, this study have this factor to it's critical to nutrient of the brain cells. No significant difference between ASD Iraqi children for glucose level compare with control. In opposition, one person reported that certain ASD children experience insulin resistance which could affect central glucose metabolism [63]. However, one study reported blood glucose concentrations in and oral glucose tolerance test were lower in ASD kids [64].

So far, it cannot be concluded that sodium or potassium are the culprit for autism. At the same time, some studies suggest that there may be concentration of may affects brain neurological function in ASDs people [65]. Accordingly, the mineral supplement is a reasonable adjunctive treatment for most children with ASD [66]. The sodium-potassium ion transport mechanism is a key of neuronal transmission regulating of children brain [67,68]. The electrical activity alteration, disturbance of nerve balance, learning impairment then ASD infection [69]. Also, the mutations in this gene affect in nerve and synapse formation and increase the chances of cognitive impairment lead to this disorder [70].

In the correlation aspect, this finding was consistent with the present study (which showed strong positive correlation between IL-4 and IFN-γ), which indicated a probable crosstalk of Th1/Th2 cytokines

activation observed in children with ASD [71]. Also, IL-4 and IFN-γ secretion by ASD children was higher than control subjects, further indicating that the innate immune pathway is simultaneously, rather than exclusively being activated [72,73]. Succeeding calls have been made to connect the influence of cytokine levels with physiological vital disturbances [74].Therefore, the purpose of the present study was to reveal the impact of cytokines on the ASD patient's physiological condition. There is experimental evidence that IFN-γ can influence the expression of K ion transporters. This distribution of intracellular electrolyte and activating neurons is main causes of ASD patients [75]. If someone refer to more investigations are necessary in order to clarify the implication of blood potasium levels and salt consumption in the etiology of ASDs [76].

According to our expectation, current association is a reflection of the close biological interaction that exists between these two hormones involved in metabolism turnover and neurodevelopment. T4 is metabolized into T3 in several tissues and it is the biologically active form of thyroid hormone [77]. In the case of ASD, this correlation reflects the influence of hormonal changes on protein metabolic processes realised in metabolic disorders that can subsequently affect general health status [78].

The correlation strength observed may also illuminate a generalized trend in liver enzymes levels of autisms, perhaps which degrade the liver in these people will similarly affect both of them [79]. These contributors may be oxidative stress, chronic inflammation, or some side effects of particular drugs used to treat symptoms of ASD [80].

Conclusion: The findings demonstrate that there are various patterns of relationships between certain immune, hormonal and physiological parameters among ASD subjects. These suggest a multilayered play among immune, thyroid and liver–kidney functions.

Ethical approval: Peripheral blood samples were drawn from all subjects (ASD and healthy children groups) who's their parents' consent to determine several parameters. All the families accepted to participate in telephone numbers to know the tests results their sons in current study.

Conflict of interest: no conflict of interest personality or financially

Funding: not found

Acknowledgments: Special thanks go to all participations and their parents to willingness to participate in this study. Also, we thank to the ASD Center at the Child Protection Hospital, Baghdad.

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