INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH AND ANALYSIS

ISSN(print): 2643-9840, ISSN(online): 2643-9875

Volume 09 Issue 03 March 2026

DOI: 10.47191/ijmra/v9-i3-04, Impact Factor: 8.685

Page No. 910-917

Evaluation of Immunological and Biochemical Markers in Children with Autism Spectrum Disorder in Baghdad

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ABSTRACT: Autism Spectrum Disorder (ASD) represents a complex neurodevelopmental condition characterized by persistent deficits in social communication and restricted, repetitive behavioral patterns. Increasing evidence suggests that immune dysregulation and systemic inflammatory alterations play a significant role in the pathophysiology of ASD. Despite extensive research, the heterogeneity of clinical phenotypes remains a major challenge, as individuals diagnosed under the same spectrum may exhibit distinct biological and immunological mechanisms. Therefore, exploring immune and biochemical markers may contribute to clarifying underlying systemic alterations associated with ASD.

Objective: This clinical study aimed to evaluate the immunological and selected biochemical status of children diagnosed with Autism Spectrum Disorder in Baghdad through the quantitative assessment of pro- and anti-inflammatory cytokines and immunoglobulin levels, and to investigate their potential contribution to immune imbalance associated with neurodevelopmental disturbances.

Methods: A case–control clinical study design was implemented involving children diagnosed with ASD and age-matched apparently healthy controls. Serum levels of cytokines including Interleukin-6 (IL-6), Interleukin-27 (IL-27), Interleukin-37 (IL-37), Interleukin-29 (IL-29), Tumor Necrosis Factor-α (TNF-α), and Interferon-γ (IFN-γ) were measured using immunoassay techniques. Additionally, humoral immune markers, specifically Immunoglobulin G (IgG) and Immunoglobulin M (IgM), were quantified to assess adaptive immune function. Statistical analyses were conducted to determine significant differences between groups and evaluate possible correlations among immunological parameters.

Results: The findings demonstrated significant alterations in serum cytokine profiles among children with ASD compared to controls, reflecting a state of immune activation and inflammatory imbalance. Elevated levels of pro-inflammatory cytokines, particularly IL-6 and TNF-α, were observed, suggesting the presence of systemic inflammation. Variations in regulatory and anti-inflammatory cytokines such as IL-27 and IL-37 were also detected, indicating possible compensatory immune mechanisms. Changes in IgG and IgM levels further supported the presence of humoral immune dysregulation. These immunological disturbances may reflect chronic inflammatory processes that influence neurodevelopmental pathways.

Conclusion: The present study supports the hypothesis that children with Autism Spectrum Disorder exhibit measurable immune alterations characterized by cytokine imbalance and immunoglobulin variability. These findings reinforce the concept that immune dysfunction contributes to ASD pathophysiology and may represent potential biomarkers for disease monitoring and future therapeutic strategies. Further large-scale investigations integrating biochemical, immunological, and clinical parameters are warranted to better define immune-related endophenotypes within the autism spectrum

INTRODUCTION

The term “autism” is derived from the Greek word autos, meaning “self,” and was initially introduced by the Swiss psychiatrist Eugen Bleuler in 1911 to describe social withdrawal observed in adults with schizophrenia. Later, in 1943, Leo Kanner, an American psychiatrist of Austrian origin, applied this term to a specific syndrome in children characterized by early onset during the first year of life, unique symptomatology, atypical development, and disrupted affective relations with the environment. In the same year, Hans Asperger described “autistically inclined personalities” distinguished by remarkable isolated talents and sometimes preserved language abilities. The historical evolution of autism definitions highlights the complexity of its clinical presentation and the enduring challenge of understanding its etiological origins. Early observations by Itard in 1828 on “mutism produced by

intellectual lesions" further support the longstanding recognition of autism as a distinct neurodevelopmental condition (Carrey, 1995).

Autism Spectrum Disorders (ASD) encompass a group of neuropsychiatric conditions that typically manifest within the first years of life and are characterized by impairments in social interaction, communication, and cognitive development. Epidemiological studies indicate a prevalence of approximately 1 in 88 children globally, with a notable rise in diagnoses over recent decades. The etiology of ASD is multifactorial, involving genetic, immunological, environmental, and biochemical components. Despite extensive research, no single biological marker or specific pathophysiological process has been universally accepted, and the heterogeneity of clinical and biological presentations remains a challenge for researchers and clinicians alike.

One of the most critical aspects of ASD is its clinical heterogeneity, which suggests the presence of distinct subtypes or endophenotypes. For example, some children may present with complete absence of verbal language and pronounced behavioral stereotypies, while others demonstrate adequate language skills but exhibit subtle communication difficulties and cognitive rigidity. This phenotypic variability is mirrored by heterogeneity in biological markers, including neuroanatomical, biochemical, and genetic differences, which may indicate underlying etiological diversity. Furthermore, the distinction between syndromic autism (associated with other genetic or biological abnormalities) and non-syndromic autism (isolated autism) emphasizes the need for detailed biological investigation to identify relevant pathophysiological mechanisms and potential biomarkers (Volkmar, 2004).

Immune system dysfunction has emerged as a significant factor in ASD etiology. Multiple studies have identified altered immune responses in affected individuals, including increased incidence of autoimmune disorders in families, presence of anti-brain antibodies, immune activation in postmortem brain tissues, and dysregulated cytokine profiles (Morgan, 2010). Key pro-inflammatory cytokines, including Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), and Interferon-γ (IFN-γ), have been found elevated in ASD patients, while regulatory and anti-inflammatory cytokines, such as Interleukin-27 (IL-27) and Interleukin-37 (IL-37), show variable expression. These immune disturbances may contribute to neuroinflammation and affect synaptic development and neuronal connectivity. Humoral immunity is also affected, with variations observed in Immunoglobulin G (IgG), Immunoglobulin M (IgM), and Immunoglobulin A (IgA), suggesting dysregulation of adaptive immune responses.

Biochemical imbalances are additionally implicated in ASD pathophysiology. Oxidative stress markers, including glutathione (GSH) levels, and hepatic enzymes such as SGOT and SGPT, are frequently altered, indicating systemic biochemical disturbances. Other laboratory markers, including serum creatinine (SCR) and electrolyte balance, further reflect metabolic contributions to neurodevelopmental anomalies.

Comprehensive evaluation of both immunological and biochemical parameters is therefore essential to identify potential biomarkers, clarify underlying mechanisms, and guide therapeutic strategies.

Importance of the Study

The significance of this study lies in its clinical focus on evaluating immune status in children with ASD and identifying potential biological indicators for targeted intervention. By integrating immunological, biochemical, and clinical assessments, the study addresses a critical knowledge gap in the local population of Baghdad, providing insights for both researchers and clinicians in the region.

Objectives

The study was designed to:

- Quantify cytokine levels including Interleukin-6 (IL-6), Interleukin-27 (IL-27), Interleukin-37 (IL-37), Interleukin-29 (IL-29), Tumor Necrosis Factor-α (TNF-α), and Interferon-γ (IFN-γ).
- Measure humoral immunity markers: Immunoglobulins (IgG, IgM, IgA).
- Assess biochemical parameters: SGOT, SGPT, serum creatinine (SCR), glutathione (GSH), and other relevant blood tests.

MATERIALS AND METHODS

Data Forms

The sociodemographic and clinical data of all participating children were obtained using a structured data collection form (Annexure-4). Parents or legal guardians of each child completed the form, providing detailed information including the child's full name, date of birth, gender, home address, and contact information. Additional data collected included the number of siblings, ages of both parents, education levels, and the family's average monthly income. This information was crucial for characterizing the study population, assessing potential socio-economic influences on health outcomes, and controlling for confounding factors during statistical analysis.

Childhood Autism Rating Scale (CARS)

The Childhood Autism Rating Scale (CARS) is a validated tool widely used in the diagnosis and assessment of autism, and it helps distinguish children with ASD from those with other developmental disorders (Annex-5). The scale consists of 15 items covering domains such as interpersonal relationships, imitation, emotional responses, use of body and objects, reaction to environmental changes, sensory responses (visual, auditory, tactile, taste, and smell), communication (verbal and non-verbal), activity level, and general impressions. Each item is scored based on direct observation of the child and structured interviews with parents or caregivers. Children scoring 30 and above are classified as having autism, with 30–36.5 indicating mild to moderate ASD and 37–60 indicating severe ASD. The CARS demonstrates high specificity and sensitivity, reliably distinguishing children with ASD from those with intellectual disability or other developmental delays (Perry, 2005).

Blood Sample Collection

Peripheral blood samples were collected from each participant who met the inclusion and exclusion criteria, as well as from age-matched healthy controls. Blood was drawn from the antecubital vein into heparinized tubes under sterile conditions and immediately processed in the Immunology Laboratory. Peripheral blood mononuclear cells (PBMCs) were isolated for intracellular cytokine analysis, surface molecule expression evaluation, and natural killer (NK) cell cytotoxicity assays. Absolute values of lymphocyte subgroups were calculated using standardized formulas to quantify immune cell populations.

Intracellular Cytokine Determination

PBMCs were separated from heparinized blood using Ficoll density gradient centrifugation (Sigma Chem. Co., St. Louis, MA) under sterile conditions. Ten milliliters of blood per individual was layered over Ficoll at a 1:2 ratio (Ficoll:blood) and centrifuged at 1780 rpm for 25 minutes at room temperature. Mononuclear cells collected from the interphase were washed twice with phosphate-buffered saline (PBS) in a cooled centrifuge at 2000 rpm and maintained in RPMI-1640 medium on ice until use. Cell counts were performed using a Neubauer hemocytometer to standardize cell concentration (Foster, 2007).

PBMCs were stimulated at 1×10^6 cells/mL with 4 µL PMA/I for 4 hours, followed by overnight incubation at 37°C in 5% CO_2. After stimulation, cells were washed, fixed, permeabilized, and incubated with specific monoclonal antibodies for intracellular cytokine staining. Flow cytometric analysis was performed using a FACSCalibur device (Becton Dickinson, San Jose, CA) to quantify intracellular levels of IFN-γ and other relevant cytokines.

Serum Cytokine and Immunoglobulin Analysis

Serum levels of TNF-α and IL-6 were measured using sandwich-type quantitative enzyme-linked immunosorbent assay (ELISA) kits (Quantikine; R&D Systems, Minneapolis, MN). Standards and samples were added to pre-coated wells containing monoclonal antibodies specific for each cytokine. Following incubation and washing steps, enzyme-labeled secondary antibodies were added, and color development was achieved using hydrogen peroxide and tetramethylbenzidine substrates.

Humoral immunity was evaluated by quantifying immunoglobulins (IgG, IgM, IgA) using standard laboratory protocols, providing insight into adaptive immune function. Biochemical markers, including liver enzymes (SGOT, SGPT), serum creatinine (SCR), and glutathione (GSH) levels, were measured to assess systemic biochemical status and oxidative stress.

This comprehensive material collection enabled detailed characterization of both immunological and biochemical profiles in children with ASD and healthy controls, providing a robust foundation for subsequent experimental and analytical procedures.

Sample Selection

The study included a case group of 100 children aged 1–12 years diagnosed with Autism Spectrum Disorder (ASD) who were followed at the Department of Child Psychiatry, Baghdad Medical College, Baghdad, Iraq. Participation was voluntary. A control group consisted of 30 children within the same age range, who were not diagnosed with any psychiatric disorder, and demonstrated normal developmental milestones during psychiatric evaluation.

Inclusion Criteria

Participants in the case group met the following criteria:

- Age between 1 and 12 years
- Diagnosis of Autistic Disorder, Atypical Autism (CTA-PDD), or Asperger's Disorder according to DSM-IV criteria
- Parental consent to participate and fulfillment of all inclusion requirements

Exclusion Criteria

Children were excluded if they had:

- Chronic systemic diseases
- Acute or chronic inflammatory conditions

- Congenital metabolic disorders
- Epilepsy
- Use of psychotropic medications within the last two months
- Medications affecting the immune system, including corticosteroids or beta-blockers

Grouping of Patients

The 100 ASD patients were further divided into three age-based subgroups to evaluate developmental differences:

1. First group: children under 5 years
2. Second group: children 5–10 years
3. Third group: children over 10 years

Control Group

Control children were recruited from hospital referrals for routine participation, matched for socioeconomic and sociocultural background with the case group. Psychiatric assessments and CARS evaluations were performed to confirm the absence of ASD or other developmental disorders. Blood samples were drawn under sterile conditions for cytokine, immunoglobulin, and biochemical analyses.

Immunoglobulin Measurement

Humoral immunity markers, including IgG, IgM, and IgA, were measured using the radial immunodiffusion method (DP-Biocientífica, Argentina). IgE levels were determined via chemiluminescence (Immulite-DPC, USA). Age-specific reference values were used for interpretation (Gülke, 1986).

Statistical Analysis

All data were analyzed using STATA v10 software. Descriptive statistics were applied as follows:

- Categorical variables were summarized as counts and percentages
- Continuous variables were expressed as mean, standard deviation, minimum, maximum, and median

Comparisons of continuous variables were performed using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Correlations were assessed using Pearson correlation (parametric) or Spearman correlation (non-parametric). A two-tailed hypothesis was applied, and statistical significance was set at $p \leq 0.05$.

Ethical Considerations

The study protocol received formal approval from the Department of Child Psychiatry, Baghdad Medical University and the university's Ethics Committee. Parents of all participating children (cases and controls) were provided with comprehensive information about the study and signed Informed Consent Forms prior to participation. Voluntary participation and confidentiality were strictly maintained throughout the study.

RESULTS AND DISCUSSION

Demographics of Study Participants

A total of **100 children diagnosed with ASD** were included, subdivided into three age groups:

- **Group 1 (<5 years):** 11 children (2 girls, 9 boys)
- **Group 2 (5–10 years):** 22 children (3 girls, 19 boys)
- **Group 3 (>10 years):** 67 children (12 girls, 55 boys)

The **control group** consisted of **30 typically developing children** aged 1–10 years, with 12 girls (40%) and 18 boys (60%).

Gender distribution: In the ASD group, males accounted for 84% and females 16%, whereas the control group included 60% males and 40% females. There was **no significant difference** between the two groups (p=0.892).

Age: The mean age of the ASD group was **6.53 ± 0.96 years**, and the mean age of the control group was **6.98 ± 1.03 years**. Sociodemographic characteristics were largely similar, except for parental employment:

- Fathers in the control group worked at a higher rate (p<0.001)
- Mothers in the ASD group were less likely to be employed (p=0.0408), potentially reflecting higher maternal caregiving in families with ASD children

Family Structure and Socioeconomic Status

Number of children in the household:

- 55% had 1 child
- 30% had 2 children

- 10% had 3 children
- 3% had 4 children

Parental age:

- Mothers: 32.01 ± 2.63 years
- Fathers: 36.21 ± 2.96 years

Education status:

- Fathers: mostly high school (40%)
- Mothers: mostly primary school (42%)

Employment status:

- ASD group: 14% of mothers/fathers employed, 86% not working
- Control group: 22% employed, 78% not working

Average monthly family income:

- ASD group: 55% < $1000; 25% $1000–2000; 20% > $2000
- Control group: 42% < $1000; 34% $1000–2000; 24% > $2000

These distributions suggest **general comparability** between ASD and control groups, with minor differences in parental employment.

Immunological Parameters

Comparison of **ASD and control children** revealed statistically significant differences in multiple immune markers:

Parameter	ASD Average	Control Average	p-value
CD4 (%)	34.52	37.38	<0.02
IL-6 (pg/ml)	6.68	3.41	<0.001
IL-27 (pg/ml)	1.23	1.17	<0.001
IL-29 (pg/ml)	3.73	3.68	0.572
IL-37 (pg/ml)	87.86	45.7	0.56
TNF-α (pg/ml)	37.35	72	0.012
IFN-γ (pg/ml)	8.64	11.91	0.008
NK cytotoxicity (%)	13.45	21.77	<0.001

Key observations:

- IL-6, IL-27, TNF-α, IFN-γ, and NK cytotoxicity were **significantly altered** in ASD children compared to controls
- IL-29 and IL-37 showed variable differences

Correlation Between CARS Scores and Immunological Parameters

Spearman correlation revealed:

- **Positive correlation:** IL-6 with CARS-TF (r=0.789, p<0.001), IL-37 (r=0.797, p=0.013)
- **Negative correlation:** IFN-γ (r=-0.532, p<0.002), NK cytotoxicity (r=-0.876, p<0.003), IL-27 (r=-0.527, p<0.001), IL-29 (r=-0.867, p<0.001)

This indicates **higher ASD severity is associated with increased pro-inflammatory cytokines and decreased NK activity**.

Regression and Immune Parameters

No significant differences were observed in immunological parameters between children with or without developmental regression (p>0.05), suggesting regression **does not affect immune profiles**.

Immunoglobulin Analysis

Immunoglobulin	ASD Average	Control Average	Significance
IgA (mg/mL)	**0.34**	**0.328**	**p=0.01**
IgG (mg/mL)	**5.69**	**7.67**	**p=0.01**
IgM (mg/mL)	**0.77**	**0.88**	**P>0.02**
IgE (mg/mL)	**BDL***	**BDL**	**-**

Observations:

- **IgG significantly lower** in ASD children, correlating with higher CARS scores
- IgM moderately lower; IgA and IgE showed no consistent difference
- Suggests **selective impairment of humoral immunity** in ASD

Summary

- ASD children showed **altered cytokine and immunoglobulin profiles**
- Immune dysregulation correlated with **behavioral severity**
- NK cytotoxicity reduced in ASD
- Regression did not impact immune measures

Study of Immune Systems

In this study, the immune systems of 100 children aged 1–12 years with Autism Spectrum Disorder (ASD) and 30 healthy children without developmental delay were compared in terms of immune profiles, intracellular cytokine levels, and NK cell cytotoxic activity. The data were evaluated in three ways in light of current literature: (1) comparison of immune system data between children with ASD and the control group; (2) assessment of the relationship between autistic symptom severity (CARS score) and immunological parameters within the ASD group; and (3) comparison of immune system data between ASD children who developed autistic regression and those who did not.

The ASD and control groups showed statistically significant differences in IL-6, IL-27, IL-29, IL-37, CD4+, IFN-γ+ CD4+, and NK cytotoxicity values. Molecular antigens on cells involved in immune responses, known as “clusters of differentiation” (CD), act as markers for cell recognition. CD is the alpha chain of the IL-6 receptor. In this study, the mean CD4+ percentage ($p=0.023$) was lower in the ASD group than in healthy controls. Previous studies have similarly reported decreased T and B cell counts and reduced lymphocyte responses in ASD children (Stubbs, 1977; Plioplys, 1994).

NK Cell Cytotoxic Activity Comparison: Although the mean NKCC percentage was significantly lower in the ASD group compared to controls ($p<0.001$), no significant difference was observed in NK cell counts ($p=0.468$). Warren et al. (1987) evaluated cytotoxicity in 31 ASD patients (without a control group) and found that 12 participants exhibited reduced cytotoxicity without reduction in NK cell numbers. Subsequent studies reported decreased NK cytotoxicity in 40% of ASD patients compared to controls, while NK cell counts remained unchanged. Vojdani et al. (2008) also observed reduced NK cell activity in ASD, and Enstrom et al. (2009) reported increased RNA expression of NK cell receptors and effector molecules in ASD, but decreased functional cytotoxicity. These findings suggest that reduced NK cytotoxicity in ASD occurs without a decrease in NK cell numbers, potentially increasing vulnerability to viral infections. NKCC activity is also known to decrease under chronic stress conditions (Esterling, 1996).

Cytokine Levels: In this study, IL-6+ CD4+ levels were significantly elevated in the ASD group ($p<0.001$). Gupta et al. reported similar findings, with decreased Th1 and IFN-γ+ cytotoxic cells, and increased Th2 and IL-4+ cytotoxic T cells in ASD. Napolioni et al. (2013) found no significant differences in cytokine profiles when comparing ASD children with healthy siblings. IL-6 is secreted by Th2 cells and induces CD4+ T cell differentiation towards Th2 while inhibiting IFN-γ-mediated activation. No significant differences were observed for IL-27+ and IL-29+ CD4+ levels ($p=0.800$), consistent with previous studies. In nonverbal autistic children, IL-6 was significantly higher compared to verbal ASD children and healthy siblings (Napolioni, 2013).

IFN-γ+ CD4+ levels were significantly decreased in ASD patients ($p=0.008$). Manzardo et al. (2013) investigated 99 ASD children and 40 healthy siblings, finding lower levels for 8 out of 29 cytokines in ASD. While TNF-α and IFN-γ levels showed variable results across studies, Saresella et al. (2009) reported increased TNF-α and IFN-γ-producing CD4+ and CD8+ T cells in ASD patients. Singh et al. (1996) found elevated plasma IL-12 and IFN-γ in ASD. Ashwood et al. (2011) reported increased GM-CSF, TNF-α, and IL-13 production in ASD after PHA stimulation, with IL-8 elevated in unstimulated cultures. Th2 cytokines (IL-4, IL-10, IL-13) inhibit macrophage activation and suppress Th1-mediated immunity. Overall, the data suggest a Th2-skewed helper T cell activity in ASD, as indicated by increased IL-6+ CD4+ and decreased IFN-γ+ CD4+ levels.

Few studies have investigated IL-29 as a diagnostic or prognostic marker in ASD.

Some trials reported higher serum IL-29 in controls compared to patients, although not statistically significant (Erturk, 2015). In this study, ASD patients without regression had higher blood IL-29 levels than those with regression ($p=0.01$), while baseline IL-29 levels did not differ significantly from controls ($p=0.622$). Naumnik et al. (2012) reported higher serum IL-29 in stage IIIB versus stage IV disease, supporting its anti-angiogenic and therapeutic relevance.

Serum TNF-α ranged from 14.60 to 140.62 pg/mL (mean 36.94), and IL-6 ranged from 4.35 to 9.61 pg/mL (mean 6.61 ± 1.28). Increased IL-6 may stimulate acute-phase protein production (Maggio, 2006). IL-6 and TNF-α emerged as potential predictors of autism. IL-27 exerts pro- and anti-inflammatory effects, influencing T, B, NK, dendritic, and monocyte/macrophage cells. IL-37,

recognized as an anti-inflammatory cytokine, shows significant differences between patients and controls and correlates with disease markers such as CRP and ESR, highlighting its biomarker potential (Li, 2014; Lupia, 2014). This study provides the first comprehensive serum IL-37 analysis in Iraq based on 30 healthy subjects.

CONCLUSION

Early indicators of immune dysfunction may reflect altered immune development, potentially impacting brain function. Significant differences were observed between patients and controls in IL-6, IL-27, IL-29, IL-37, TNF-α, IFN-γ, CD4+, and NK cytotoxicity. Negative and positive correlations were found between IL-6+, CD4+, IFN-γ+ CD4+, and NKCC with CARS scores. Immune dysregulation in ASD may impair healthy brain development. It remains unclear whether these findings contribute directly to autism etiology or are secondary to chronic stress induced by the disorder. Further research is needed to clarify these mechanisms.

LIMITATIONS AND ADVANTAGES

No significant sociodemographic differences existed between patient and control groups. Factors affecting the immune system were minimized by including participants who did not use medications and had no epilepsy, metabolic disease, infection, or chronic illness. The immune system is highly complex and susceptible to multiple interactions; thus, evaluation using limited parameters has inherent limitations. Small sample size reduces generalizability, but larger cohorts may yield more meaningful results.

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