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A Modern Perspective on the Immunological Aspects of Autism Spectrum Disorder (ASD)

Farangisbonu Alisher qizi Doniyorova

PhD., Associate Professor of the Nervous Diseases, Alternative Medicine of the Tashkent State Dental Institute, Tashkent, Uzbekistan

Abstract Autism Spectrum Disorder (ASD) is increasingly recognized as a multifactorial condition where neurodevelopmental anomalies are intricately linked to immune system dysfunction. While the diagnostic framework of ASD has traditionally centered on behavioral manifestations, a growing body of evidence points to immunological abnormalities—including chronic inflammation, cytokine dysregulation, and altered microglial activity—as playing a substantial role in the disorder's pathogenesis.

Keywords Autism Spectrum Disorder, Neuroinflammation, Cytokines, Immune dysregulation, Interleukins, Neuroimmunology, Biomarkers, Neurodevelopment

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social interaction, communication, and repetitive behaviors. Recent advancements in neuroscience and immunology have highlighted that ASD is not merely a result of altered brain development but is also closely linked with immune system dysfunction [1,2].

Emerging research suggests that neuroinflammation, characterized by activated microglia and dysregulated cytokine levels, plays a central role in ASD pathophysiology [3]. Maternal immune activation (MIA), systemic inflammation, and gastrointestinal immune responses contribute to altered neurodevelopmental trajectories [4,5]. Consequently, a paradigm shift is occurring—from purely genetic or behavioral models to integrative frameworks involving immune-neural interactions [6].

2. Purpose of the Research

This review aims to explore recent findings on the immunological mechanisms involved in ASD, particularly focusing on cytokine dysregulation, microglial activation, maternal immune influence, and peripheral biomarkers. The goal is to synthesize key immunological insights to guide future diagnostic and therapeutic interventions relevant to clinical practice and research.

* Corresponding author:
fdoniyorova91@mail.ru (Farangisbonu Alisher qizi Doniyorova)
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3. Materials and Methods

This narrative review was based on articles published from 2013 to 2024, using databases such as PubMed, Scopus, and Web of Science. Search terms included “autism spectrum disorder,” “immune dysfunction,” “cytokines in autism,” “maternal immune activation,” and “microglial inflammation.” Ninety-seven peer-reviewed articles were selected, including original studies, clinical trials, meta-analyses, and systematic reviews, ensuring methodological rigor and contemporary relevance.

4. Results

Multiple lines of evidence indicate that immune system dysregulation is a recurring and robust feature of Autism Spectrum Disorder (ASD). Across several independent studies, children diagnosed with ASD exhibit elevated concentrations of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, IFN-γ, and monocyte chemoattractant protein-1 (MCP-1) in both plasma and cerebrospinal fluid (CSF) [1,3,4]. These elevations are often found to correlate with core ASD symptom severity, including impaired communication skills, increased irritability, and restricted behaviors [2,5].

A large meta-analysis conducted in 2022 across 27 studies ($n > 4,500$ ASD participants) demonstrated a consistent pattern of heightened Th1 and Th17 cytokine responses, while anti-inflammatory cytokines such as IL-10 and TGF-β were significantly reduced [4,6]. These cytokine profiles suggest a skewed immune response with ongoing systemic inflammation and impaired resolution mechanisms.

In postmortem brain tissue, persistent microglial activation and astroglial reactivity were observed in the cerebellum, frontal cortex, and temporal lobes, suggesting chronic

neuroinflammation [3,6]. Immunohistochemical studies further revealed increased expression of HLA-DR markers and CD68+ macrophages, which are indicators of CNS immune activation.

Peripheral immune abnormalities have also been reported, including reduced natural killer (NK) cell cytotoxicity, abnormal Treg/Th17 ratios, and increased numbers of plasma B cells, all suggesting dysregulated immune tolerance in ASD [2,9].

Moreover, maternal immune activation (MIA)—induced by prenatal infections or autoimmune flare-ups—has been shown to elevate fetal brain cytokines, disrupt neuronal migration, and alter microglial maturation. In rodent models, a single injection of poly(I:C) during gestation resulted in offspring with autism-like behaviors, such as social deficits, repetitive grooming, and reduced ultrasonic vocalizations, alongside marked increases in IL-6 and TNF-α in fetal brains [6,7].

Emerging research also indicates a strong relationship between gastrointestinal (GI) inflammation and ASD. In one study, over 40% of children with ASD exhibited evidence of mucosal inflammation, which was positively correlated with behavioral regression and sensory processing dysfunction [8]. Elevated zonulin and lipopolysaccharide-binding protein (LBP) levels suggest increased intestinal permeability ("leaky gut"), which may contribute to peripheral immune activation.

5. Discussion

The accumulation of immunological evidence points toward a chronic inflammatory state in a significant subset of individuals with ASD. The elevated pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) not only serve as potential biomarkers but may also play causal roles in the disruption of neurodevelopmental processes [1,3,5]. For instance, IL-6 is known to interfere with synaptic plasticity and long-term potentiation, mechanisms essential for learning and memory. In animal models, blocking IL-6 during gestation prevented ASD-like behaviors in offspring [6].

Similarly, TNF-α, while essential in normal immune surveillance, when chronically elevated, induces oxidative stress, disrupts blood-brain barrier (BBB) integrity, and promotes neuronal apoptosis, all of which are observed in ASD [2,5].

The immune cell profile of ASD individuals also supports a state of imbalance. Decreased function of regulatory T cells (Tregs) impairs immune tolerance and enhances susceptibility to autoimmune reactions [4]. At the same time, an overrepresentation of Th17 cells—which produce IL-17—has been implicated in cortical malformations and behavioral abnormalities in both human and animal studies [3].

An important emerging concept is the gut-brain-immune axis, where intestinal dysbiosis and inflammation influence CNS function. Short-chain fatty acids (SCFAs) produced by beneficial gut bacteria play a key role in modulating microglial activity, but in ASD, butyrate levels are often decreased, which may facilitate excessive immune activation [9]. Probiotic intervention trials have shown moderate behavioral improvements, though data remain preliminary [9,10].

Therapeutically, the field is cautiously exploring immune-modulating strategies. Early-phase clinical trials have evaluated anti-inflammatory agents like pioglitazone and minocycline, showing reductions in irritability and hyperactivity, although larger trials are needed for validation. Similarly, intravenous immunoglobulin (IVIG) and stem cell therapies have been tested in small ASD cohorts with mixed outcomes [10].

One challenge that persists is the heterogeneity within ASD itself. Not all individuals with autism exhibit immune alterations, and not all immune-altered individuals benefit from immunological interventions. Thus, future research must aim to define immune-based ASD subtypes and validate biomarker panels for clinical stratification.

6. Conclusions

In summary, the data collectively support that immune dysregulation is not merely an epiphenomenon of ASD but likely contributes causally to neurodevelopmental dysfunction. Longitudinal and mechanistic studies are urgently needed to clarify these associations and unlock novel treatment paradigms.

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