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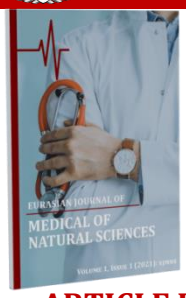

CHILDHOOD AUTISM: CURRENT INSIGHTS INTO PATHOGENESIS AND NEUROLOGICAL COMORBIDITY

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https://doi.org/10.5281/zenodo.16255668

ARTICLE INFO
Received: 16th July 2025
Accepted: 20th July 2025
Online: 21st July 2025
KEYWORDS
Autism spectrum disorder, ASD, pathogenesis, genetic factors, neurodevelopment, neuroinflammation, neurological comorbidity, epilepsy, sensory processing disorder, sleep disturbances, gut-brain axis, early intervention, pediatric neurology, neuroimaging, immune dysfunction.

ABSTRACT
Autism spectrum disorders (ASD) are complex neurodevelopmental conditions with increasing prevalence worldwide. This review aims to summarize the latest data on the multifactorial pathogenesis of ASD, with emphasis on genetic, neuroimmune, and environmental influences. Additionally, the article explores the wide spectrum of neurological comorbidities often observed in children with ASD, such as epilepsy, sensory processing disorders, motor dysfunction, and sleep disturbances. Modern trends in therapeutic strategies and the importance of early, multidisciplinary intervention are also discussed. The review highlights the need for continued research into biomarkers and personalized approaches to autism treatment.

ДЕТСКИЙ АУТИЗМ: СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О ПАТОГЕНЕЗЕ И НЕВРОЛОГИЧЕСКОЙ КОМОРБИДНОСТИ

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https://doi.org/10.5281/zenodo.16255668

ARTICLE INFO
Received: 16th July 2025
Accepted: 20th July 2025
Online: 21st July 2025
KEYWORDS
РАС, аутизм, патогенез, генетические факторы, нейроразвитие, нейровоспаление, неврологические коморбидности, эпилепсия, сенсорные нарушения, расстройства сна, ось кишечник-мозг, раннее вмешательство, детская неврология,

ABSTRACT
Расстройства аутистического спектра (РАС) представляют собой сложные нейроразвивающиеся состояния с растущей распространённостью во всём мире. В обзоре представлены современные данные о многофакторной патогенезе РАС с акцентом на генетические, нейроиммунные и экологические влияния. Дополнительно рассматриваются распространённые неврологические коморбидности, такие как эпилепсия, сенсорные нарушения, моторные и речевые отклонения, а также расстройства сна. Освещаются современные терапевтические подходы и значение раннего мультидисциплинарного вмешательства. Подчёркивается необходимость

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нейровизуализация, иммунная дисфункция.

дальнейших исследований биомаркеров и персонализированных методов лечения аутизма.

BOLALARDA AUTIZM: PATOLOGENEZ VA NEVROLOGIK KOMORBIDLIK BO‘YICHA ZAMONAVIY YONDASHUVLAR

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https://doi.org/10.5281/zenodo.16255668

ARTICLE INFO

Received: 16th July 2025
Accepted: 20th July 2025
Online: 21st July 2025

KEYWORDS

ASB, patogenez, genetik omillar, neyro-rivojlanish, neyroinflammatsiya, nevrologik komorbidlik, epilepsiya, sezgi muammolari, uyqu buzilishi, ichak-miya o‘qi, erta aralashuv, bolalar nevrologiyasi, neyrotasvirlash, immun tizim disfunktsiyasi.

ABSTRACT

Autizm spektridagi buzilishlar (ASB) butun dunyoda keng tarqalib borayotgan murakkab nevro-rivojlanish holatlaridir. Ushbu sharhda ASBning ko‘p omilli patogeneziga oid so‘nggi ilmiy ma’lumotlar, xususan genetik, neyroimmun va ekologik omillarning roli yoritiladi. Shuningdek, maqolada bolalarda uchraydigan nevrologik komorbidliklar, jumladan epilepsiya, sezgi buzilishlari, harakat muammolari va uyqudagi buzilishlar muhokama qilinadi. Terapiyadagi zamonaviy yondashuvlar va erta, ko‘p sohalik aralashuvning ahamiyati ta’kidlanadi. Tadqiqotlar davomida autizmning biomarkerlari va individuallashtirilgan davolash strategiyalarini rivojlantirish zarurligi ko‘rsatib o‘tiladi.

Introduction

Autism spectrum disorders (ASD) represent a significant clinical and public health concern, especially in pediatric neurology and psychiatry. The increasing awareness and diagnostic capabilities have led to a rise in identified cases worldwide. As reported by the Centers for Disease Control and Prevention (CDC) in 2023, the estimated prevalence of ASD in the United States reached 1 in 36 children aged 8 years, a notable increase compared to previous years [1].

ASD is characterized by impairments in social communication, restricted interests, and stereotyped behaviors, with a wide range of symptom severity. The clinical heterogeneity of ASD often coexists with other neurodevelopmental and neurological disorders, complicating diagnosis and management. Understanding the multifactorial etiology and comorbidities associated with ASD is crucial for developing effective interventions and support systems.

Pathogenesis: Genetic, Neurobiological, and Environmental Mechanisms

ASD is widely recognized as a genetically influenced neurodevelopmental condition. Genome-wide association studies (GWAS) and whole-exome sequencing have identified numerous gene variants associated with ASD. Among them, **CHD8**, **SCN2A**, **SHANK3**, **NRXN1**, and **SYNGAP1** are consistently linked to synaptic transmission, neuronal excitability, and chromatin remodeling [2,3]. These genes are critical for brain development and plasticity, and mutations can result in altered synaptogenesis and connectivity.

Epigenetic regulation also plays a vital role in ASD pathogenesis. DNA methylation and histone modification patterns have been found to differ in children with ASD, suggesting that environmental factors may alter gene expression without changing the DNA sequence. For example, maternal stress, infection, or toxic exposures during pregnancy can affect fetal gene expression profiles and increase autism risk.

Neuroimaging findings support atypical brain development in ASD. Studies using magnetic resonance imaging (MRI) show that early brain overgrowth is often followed by a deceleration in growth, especially in the frontal and temporal cortices. Abnormalities in cortical thickness, white matter integrity, and connectivity between regions such as the **default mode network** (DMN), **salience network**, and **social brain areas** are widely documented [4].

Furthermore, **immune dysregulation** has been increasingly implicated in ASD. Children with ASD often show elevated levels of **pro-inflammatory cytokines** (e.g., IL-6, TNF-α), abnormal **T-cell profiles**, and **microglial activation**, suggesting ongoing neuroinflammation [5]. Maternal immune activation (MIA) during pregnancy—such as infection or autoimmune disorders—has been shown to increase ASD risk in offspring, possibly through disruption of fetal brain development.

Gastrointestinal (GI) dysfunction is another aspect frequently reported in ASD. Altered gut microbiota composition, often termed "dysbiosis", may affect brain function through the **gut-brain axis**. Short-chain fatty acids (SCFAs), microbial metabolites, and immune interactions in the gut may influence neurodevelopment via systemic inflammation and neurotransmitter regulation [6].

Environmental risk factors, while less significant than genetic ones, can act as triggers in genetically predisposed individuals. These include **prenatal exposure to valproic acid**, **air pollutants**, **heavy metals (e.g., lead, mercury)**, and **perinatal hypoxia**. Cumulative exposure to multiple minor stressors may converge on common neurodevelopmental pathways, leading to clinical manifestations of autism.

Neurological Comorbidity: Scope and Implications

Comorbid neurological conditions are reported in up to 70–80% of individuals with ASD. Among the most prevalent are:

- **Epilepsy**: Occurs in 20–30% of children with ASD, particularly in those with co-occurring intellectual disability. Seizure onset often follows a bimodal distribution—infancy or adolescence—and may require long-term antiepileptic therapy [7].
- **Sleep disturbances**: Affects up to 80% of ASD patients, significantly impacting behavior and cognitive function. Melatonin secretion abnormalities and circadian rhythm gene mutations (e.g., **CLOCK**, **BMAL1**) have been implicated.
- **Motor abnormalities**: Including **hypotonia**, **dyspraxia**, **clumsiness**, and delayed gross/fine motor milestones, which may result from cerebellar dysfunction. Structural MRI frequently reveals cerebellar hypoplasia, especially of the vermis [8].
- **Sensory processing disorders (SPD)**: Children may exhibit hyperreactivity (e.g., sound sensitivity), hyporeactivity, or sensory seeking behaviors. SPD can manifest as distress in crowded environments, refusal to wear certain clothes, or fascination with spinning objects.

- **Cognitive impairments and developmental delays**: Nearly half of children with ASD have below-average intellectual functioning. Executive dysfunction, impaired theory of mind, and weak central coherence are cognitive hallmarks.
- **Attention-deficit/hyperactivity disorder (ADHD)** symptoms**: Present in over 50% of children with ASD, complicating behavioral regulation and learning. Differentiation between ASD and ADHD is important for treatment selection.

The recognition of comorbidities is essential not only for symptomatic management but also for prognostic evaluation. For example, the presence of epilepsy and severe intellectual disability is often associated with poorer long-term outcomes.

Therapeutic Approaches and Future Perspectives

The treatment of ASD is individualized and must address both core symptoms and associated comorbidities. **Early intensive behavioral intervention (EIBI)**, particularly programs based on **Applied Behavior Analysis (ABA)**, has been shown to improve social, communication, and adaptive functioning.

Pharmacotherapy is generally used for managing comorbid symptoms. Antipsychotics such as **risperidone** and **aripiprazole** are FDA-approved for treating irritability and aggression. Melatonin is often prescribed for sleep disorders, and antiepileptic drugs for seizure control.

Emerging strategies include:

- **Neurofeedback therapy** and **transcranial magnetic stimulation (TMS)**, targeting abnormal brain networks.
- **Probiotic supplementation** and **fecal microbiota transplantation (FMT)** for modulating gut-brain interactions.
- **Oxytocin-based therapies**, aimed at enhancing social cognition.
- Research into **biomarkers** (e.g., microRNAs, neuroinflammatory markers, metabolomics profiles) holds promise for early diagnosis and subtyping.

In the long term, integration of **genetic data**, **neuroimaging**, and **behavioral assessments** may enable precision medicine approaches in ASD.

Conclusion

Autism spectrum disorder is a multifaceted neurodevelopmental condition with a complex interplay of genetic, neurobiological, immune, and environmental factors. The high rate of neurological comorbidities underscores the need for comprehensive and multidisciplinary evaluation. Advancements in genomics, neuroimaging, and systems biology are gradually paving the way toward precision diagnostics and individualized therapies. Continued investment in early screening, family-centered care, and translational research is essential to improve quality of life and long-term outcomes for individuals with ASD and their families.

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