REVIEW ARTICLE

A REVIEW OF CAUSES, PHYSIOLOGY, IMMUNITY AND PROPOSED DRUG STRATEGIES OF AUTISM SPECTRUM DISORDERS

Ali Mohammed Al-Rawi[1], Suhaib M. Ibrahem[2], Yousry Sadoon Rasheed[3] and Ahmed AbdulJabbar Suleima[1]

[1,] Department of Biotechnology, College of Science University of Anbar, Ramadi, Iraq.
[2] College of Pharmacy, University of Anbar, Ramadi, Iraq
[3] Department of Biology, College of Science, University of Anbar, Ramadi,Iraq

Corresponding author:
Ahmed A. Suleiman

Mobile: +9647904774532
e.mail: **:**

Ahmed.suleiman@uoanbar.edu.iq

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ABSTRACT:

Early infancy repetitive behavioral patterns and social communication issues are hallmarks of autism spectrum disorder (ASD). Numerous genetic, environmental, and immunological variables are thought to have a role in the pathogenesis of ASD, but its etiology has remained a mystery in spite of intensive research. This review tries to clarify the main causes of ASD and investigate the most recent developments in its care. ASD pathogenesis has been linked to a number of genes related to synaptogenesis in neurons. Additionally, environmental elements and ailments like immunological imbalances and gastrointestinal (GI) abnormalities have been connected to the pathogenesis of ASD. Despite the fact that ASD has a solid hereditary foundation, various factors may either directly advance the disease or act as modifiers, aggravating its symptoms. Given the strong relationship between the immune system and the GI tract, abnormal immunological responses seen in autistic children may be caused by autoimmune diseases or infections in the mother. Furthermore, ASD has frequently been linked to mitochondrial malfunction, a common metabolic condition. It is thought that oxidative stress, a characteristic of many neurological illnesses, contributes to the development or occurrence of autism and autonomic dysfunction. Drug therapy have been shown to be inefficient in treating the primary symptoms of ASD, hence non-drug methods should be given priority first when it comes to treatment. But treating comorbidities and related symptoms like irritability and aggression may be helped by drugs.

Keywords: *autism spectrum disorder, oxidative stress, mitochondrial dysfunction, immune dysregulation*

INTRODUCTION:

Autism is a neurodevelopmental condition that manifests in children as early as the first 36 months of life and is strongly linked to anomalies in prenatal and postnatal brain development [1]. ASD sufferers struggle with a variety of issues, such as impaired social interaction and engagement, stereotyped gestures, repetitive behaviors, difficulty reading social cues, a preference for consistency and routine, and issues with language acquisition [1]. Additionally, sensory abnormalities, such as increased sensitivity to sensory stimuli that results in avoidance behaviors, are frequently seen [2]. ASD is more common in men than in women, with a male-to-female ratio of about 4:1[3].

Neurotransmitters are essential for maintaining healthy brain development as well as for controlling motor, behavioral, and cognitive functions [4]. Thus, a malfunction in the neurotransmitter system may play a role in the etiology of autism by interfering with procedures including synaptogenesis, differentiation, and

migration of neuronal cells, which in turn affects brain development [5].

Autism is characterized by severely impaired social interaction and communication skills, as well as restricted and repetitive behaviors and interests [6]. People with autism may seem uninterested in social interaction or they may desire to engage in social interaction but struggle to exhibit appropriate social behaviors. Their responses to social situations could seem repetitive or strange. In certain situations, people with autism may exhibit great sociability and affection for strangers. People with autism spectrum illnesses typically have poor social skills and difficulty understanding implicit social rules. They frequently don't fully understand societal mores and manners. Communication issues, both verbal and nonverbal, are typically present in people with ASD. Others may have weak verbal abilities or repeat words or phrases that others have said, while some persons may speak very little or at all. Non-verbal communication issues are also frequent, making it challenging to interpret gestures, facial expressions, body language, and voice tone [6].

A child with autism may manifest in one or more of the ways listed below. (1) If he makes friends, they won't stay with him since he won't be able to converse with children his own age. (2) He will always feel the desire to withdraw from the outer world. (3) They have a hard time deciphering the emotions and sentiments of those around them. Understanding gestures, facial expressions, and different speech tones may be difficult for kids with autism. Autism sufferers also have trouble focusing on others' faces, making it challenging for them to identify or pick up on socially acceptable behavior patterns. (4) Additionally, children with autism show a lack of emotional stimulation, social interaction, sharing with their parents, and comfort in them. (5) Their verbal and nonverbal communication skills are inadequate. Many people never learn how to speak [7].

Autism Causes:

Research reveals that ASD development may be influenced by both genetics and environment [8] The precise genes involved in this situation have not yet been identified by researchers. Given that a significant percentage of people with ASD have not named any family members who also have the disease, the person at risk is likely to be impacted by environmental variables and unique genetic problems. It's crucial to realize that a mutation is any alteration to the ordinary genetic code, whether it develops naturally or is passed down through the family. Changes may be advantageous, harmful, or have no effect at al [9]. Although a child may be genetically predisposed to autism, this does not guarantee a diagnosis. According to research, ASD may be influenced by both heredity and environment [8]. The particular genes involved in this situation still remain unknown. The person at risk is likely to be impacted by environmental circumstances and unique genetic difficulties given that a substantial percentage of persons with ASD have not noted autism in their families. A mutation is any alteration to the ordinary genetic code, whether it happens spontaneously or is inherited. This is crucial to comprehend. Changes might be positive, negative, or have no effect at al [9]. A child's genetic propensity for autism does not guarantee a definitive diagnosis. Air, water, food, and even prescription drugs fall under this category. Additionally, everything that surrounds us is present in the environment while the fetus is developing within the confines of the mother's womb [11].

Numerous environmental factors are included when examining their links to autism, including parental age, family medical history, exposure to risky medicines while pregnant, and any challenges that might have arisen during pregnancy or

delivery [12]. Recent study suggests that dangerous chemicals and environmental variables may potentially have a significant impact, despite the well-established significance of genetic abnormalities in ASD. There hasn't yet been a systematic evaluation of studies examining toxicants in relation to ASD. The estimation of toxicant doses presents in the environment before conception, during pregnancy, and in early childhood; the detection of toxicants through biomarkers; and the investigation of genetic susceptibility to toxicants are the three main categories of research that look into the relationship between environmental toxicants and ASD. It is very likely that a number of variables contribute to the increased risk of autism. But it's crucial to remember that many people who are exposed to environmental risk factors don't show any symptoms of getting an ASD [13].

Genetic Causes:

The specific pathomechanics of ASD are yet unknown, despite the fact that several causes can cause autistic illnesses. Among these, genetic causes have been the subject of in-depth study and are accepted as a legitimate etiology [14]. Co-occurring or related conditions in ASD individuals typically include Rett syndrome, Tuberous sclerosis, and Fragile X syndrome [15]. The relevance of inheritance is shown by the fact that siblings of those with ASD are more likely than the general population to have autism [16]. Twin studies have also provided evidence that genetic factors play a crucial role in the emergence of ASD [17]. Notably, clinical symptoms vary less among ASD patients who are more genetically connected to one another [18]. A thorough study of various genetic studies has revealed significant genetic anomalies in ASD, including dysregulation of genes involved in synaptogenesis, synaptic maintenance, and the signaling pathways of synapse formation. These modifications mostly impact scaffolding and transmembrane proteins [19]. Despite the identification of a large number of genes involved in ASD as well as the understanding of gene-gene interactions, epigenetic impacts, and environmental modifiers, 25% of individuals with ASD have genetic origins, such as recognized medical problems, single-gene deficiencies, and chromosomal abnormalities. As a result, a number of clinical traits and concurrent illnesses have been related to ASD [20].

Neuropathology of ASD:

The frontal cortex, cerebellum, hippocampus, amygdaloid nucleus, and cerebello-thalamocortical circuits are only a few of the brain regions that exhibit abnormalities in postmortem, neuroimaging, and animal models of ASD [21]. One of the neuropathological characteristics of ASD is the presence of focal cortical dysplasias, which are believed to be caused by heterochronic division of germinal cells and aberrant daughter cell migration to their allocated places [22]. Because of this abnormal neuronal migration inside the ASD human brain, there are isolated, thin cortical areas, particularly in the frontal lobe, which are distinguished by fewer pyramidal neurons and interneurons. In addition to epileptic seizures, these pathological anomalies in ASD have also been linked to sensory and motor deficits [23]. An association between an autism-epilepsy phenotype and macrocephaly, an abnormality resulting from rapid brain growth during early childhood and associated with ASD, has recently been discovered. Research suggests an overall increase in brain size in some ASD individuals [24].

Given the significance of orexins (A and B) in the control of wake-sleep circadian rhythm, it is likely that individuals with ASD have dysregulation in orexinergic neurotransmission, which has been associated to a number of neuropsychiatric illnesses, including neurodevelopmental

disorders. Reduced 5-HT and melatonergic system activity is complemented by elevated orexinergic system activity in individuals with ASD, which may be brought on by amygdala dysfunction. Sleep patterns are disrupted as a result of this [25,26&27]. Despite the fact that only associative studies have been conducted to demonstrate a potential connection between this measurement and health issues like obesity, orexin evaluation may be a promising novel biomarker in the etiology of ASD [28].

According to a growing body of studies, industrial chemicals may contribute to the onset of neurobehavioral diseases like ASD, whose incidence has been gradually increasing in recent years. Heavy metals in particular are recognized as neurodevelop-mental poisons because of their ability to harm fetuses and cause neurological abnormalities, developmental delays, learning impairments, and behavioral abnormalities. Metal exposure during pregnancy and the first few years of life has been linked to an increased risk of autism in numerous studies. Furthermore, it is important to consider the possible effects of co-exposure to many metals when assessing children who reside in underdeveloped countries or areas that are highly contaminated with these substances [29]. EDCs, such as metals, organochlorine insecticides, perfluoroalkyl substances (PFAS), and polychlorinated biphenyls, have been demonstrated in studies to have detrimental effects on embryonic neurodevelopment [30].

Autism Implication:

Other diseases linked to ASD include gastrointestinal issues, inflammation, environmental factors, infection, toxins, nutrition, and medicines [31].

1. Gastrointestinal Abnormalities:

Numerous studies have demonstrated that individuals with ASD have a higher prevalence of gastrointestinal (GI) issues, including symptoms including nausea, vomiting, gastroesophageal reflux disease, constipation, chronic diarrhea, and stomach discomfort [16]. No definitive association between GI issues and ASD, however, was found in a nested case-control investigation utilizing a UK database [32]. However, more research is needed before conclusive evidence of GI immune/inflammatory-mediated illness or elevated intestinal permeability, also referred to as "leaky gut," in ASD can be drawn [33] due to the study' shortcomings and underlying assumptions. Similar research exploring the possibility that dietary casein, gluten, or its metabolites can cross the intestinal barrier into the bloodstream and trigger immune-related reactions in the brain has shown inconsistent results [34&35]. Contrary to other articles, providing autistic children with GI symptoms intravenous secretin did not improve their linguistic deficiencies, according to studies examining the prevalence of diarrhea in autistic children [36]. These unresolved issues highlight the requirement for competently powered investigations with sufficient power. The severity of behavioral ASD symptoms is strongly correlated with GI abnormalities, and recent evidence suggests that GI issues may contribute to the development or progression of ASD [24].

2. Microbiota:

Researchers looking at possible links between behavioral problems and gastrointestinal (GI) bacteria have been increasingly interested in the microbiota. The discovery of decreased disaccharidase enzymatic activity in kids with ASD and GI symptoms [37] has sparked additional research into the function of intestinal mucosal flora in glucose metabolism. Children with ASD have been found to have abnormal carbohydrate digestion, transport, and mucosal dysbiosis (perturbation of the gut microbial ecology) [38]. Gut dysbiosis may have an impact on how some diseases

develop. Notably, the gut microbiota of people with ASD is less abundant with fermenting bacteria [39]. The ability of the gut microbiota to communicate with the brain and affect behavior is known as the microbiota-gut-brain axis [40]. Fecal microbiota transplantation has demonstrated promise in the treatment of a number of GI illnesses, but further study and rigorous clinical testing are still required before it can be widely used [41]. In contrast, several studies [42] have not been able to distinguish between ASD children with and without GI difficulties in terms of their GI microbiota. Immunological imbalances, immune reactivity, inflammation, abnormal digestion, injuries, infections, and cross-reactions in other organs, such as the brain, can all be made worse by imbalances in the gut microbial population. The focus of ongoing study remains in this area [24].

3. Imbalance in the immune system:

The pathophysiology of ASD has long been considered to be influenced by comorbid conditions associated with the condition, such as inflammation, an inflammatory response, and immunological activation, even though the results of recent study are still unclear [20]. The peripheral immune system has been found to be aberrant in numerous investigations, indicating that the immune system may play a part in ASD. In the brain and cerebrospinal fluid (CSF), immunological abnormalities in ASD patients have been observed, including the activation of microglia, the innate neuroimmune system, and neuroinflammation [43]. Recently, another investigation addressing neuroimmune issues in ASD was reported [44]. The blood-brain barrier (BBB), a crucial regulator of brain homeostasis and linked to neurological inflammation, immunological dysregulation, and other ASD symptoms, is altered in children with ASD due to higher levels of inflammatory cytokines [45&46]. Patients with ASD have immune dysregulation in the gastrointestinal tract, peripheral circulation, and central nervous system (CNS). Immune issues in ASD infants have been connected to maternal infection or inflammation as well as autoimmune illnesses in the relatives of ASD children. Autism is linked to certain CD4+ and CD8+ cell subsets, as well as an imbalance of Th1- and Th2-like cytokines [47]. Peripheral blood has been discovered to contain a number of interleukins (ILs), an imbalanced amount of IFN-gamma, increased levels of both the Th1 and Th2 pathways activated, and a predominance of the Th2 pathway in children with ASD [48]. Immunoglobulins are also unbalanced in the serum of kids with ASD. The amount of albumin, gamma globulin, serum IgG, IgG2, and IgG4 is higher in autistic people, which may be related to underlying autoimmune illnesses and/or increased susceptibility to infections. Total serum protein levels are significantly higher in autistic people. ASD has a number of immunological disorders associated with it [49]. The immune system has the ability to both exacerbate and ameliorate neurological and behavioral conditions, including those brought on by genetic defects. According to recent studies, many neurological disorders get worse when the immune system is activated [50]. However, immune cells can also be useful. Patients with ASD were shown to have Th1 and Th2 pathways active, with the Th2 arm predominating. Due to this, some antigens, possibly those that pass via the gastrointestinal tract, may lead to tolerance while simultaneously having an impact on many organs, including the brain. More investigation is necessary in order to fully comprehend the immune system's function in ASD [24].

4. Mitochondrial Malfunction:

The most prevalent metabolic issue linked to ASD is mitochondrial malfunction, which has been found to have a high incidence in children with the diagnosis. The true prevalence of mitochondrial

dysfunction in ASD is still unknown, though, because it might be underestimated by conventional diagnostic standards. Individuals with ASD commonly show signs of mitochondrial malfunction and poor electron transport chain activity, indicating a strong link [51].

Furthermore, new types of mitochondrial dysfunction in ASD have been revealed by recent investigations, which may make it difficult to diagnose them using traditional diagnostic standards [51]. Numerous investigations have revealed that many individuals with ASD also have genetic abnormalities related to ASD and mitochondrial dysfunction [52&53]. The most common metabolic abnormality associated with ASD seems to be mitochondrial malfunction [54].

An excessively high rate of lactic acidosis was seen in a case series of children with ASD from more than 25 years ago, and this served as a diagnosis for mitochondrial malfunction. This finding supports the hypothesis that problems in glucose metabolism may contribute to ASD. Notable more investigations have connected mitochondrial dysfunction and ASD [55]. The HEAD syndrome, which is characterized by the confluence of hypotonia, epilepsy, autism, and developmental delay, has been specifically identified as affecting a subset of ASD children with respiratory chain issues. Despite the apparent prevalence of this association between ASD and mitochondrial dysfunction in children with mitochondrial disease, the HEAD acronym has not yet been extensively adopted in clinical practice or research [56].

In recent years, evidence linking ASD, mitochondrial malfunction, and vaccinations has emerged. In one illustrative case, a girl with an underlying mitochondrial condition went from receiving multiple immunizations on the same day to a feverish episode before regressing and being diagnosed with ASD. A group of 28 children who also had ASD were the subject of additional research, which further substantiated the involvement of infectious/inflammatory triggers in the development of ASD and mitochondrial dysfunction. Unexpectedly, in this case series, 71% of the children who experienced a return of ASD symptoms did so within two weeks of having a temperature greater than 101°F, and 33% of these occurrences were linked to routine childhood vaccinations [57]. the association between infections and metabolic decompensation in children with underlying metabolic diseases, such as mitochondrial illness, has been shown in research involving kids with mitochondrial malfunction [58]. This finding supports this theory. However, not many people are aware of this association.

Many medical practitioners recommend vaccination as a preventive measure against serious illnesses because it does not appear to trigger neurodegenerative events in the majority of persons with mitochondrial malfunction [57]. It is important to keep in mind that, despite the intriguing link between ASD and the conventionally accepted mitochondrial problem, children who have both illnesses don't appear to be common. According to a recent meta-analysis, just 5% of children with ASD met the rigorous criteria for a typical diagnosis of mitochondrial illness disease [51].

Conclusion:

Autism Spectrum Disorder (ASD) is a complex neurological condition characterized by unique behaviors, social challenges, communication difficulties, and sensory issues. Diagnosis relies on persistent, impactful symptoms from childhood. Recent evidence suggests that ASD is heterogeneous due to genetic and environmental influences. Gut microbiota and metabolites are linked to ASD, offering new research avenues. Research also links ASD to immune system dysfunction, oxidative stress, and environmental toxin exposure. Genetics, oxidative stress,

immune issues, and neuroimaging are emerging research areas. Non-drug therapies focusing on support, social skills, and education are primary treatments. Medications like risperidone are used for aggressive behaviors. Understanding ASD's physiological mechanisms is crucial for better treatments.

Conflict of Interest:

The authors declare that there is no conflict related to this work

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مقال مراجعة للتعريف بالاسباب والأمراض العصبية والآثار المترتبة على اضطراب طيف التوحد

علي محمد الراوي[1] , صهيب محمد ابراهيم[2] , يسري سعدون رشيد[3], احمد عبد الجبار سليمان[1]

1, قسم التقنيات الاحيائية , كلية العلوم , جامعة الانبار, الانبار , العراق
2 كلية الصيدلة , جامعة الانبار, الانبار , العراق
3 قسم علوم الحياة , كلية العلوم , جامعة الانبار , الانبار , العراق

تتميز اضطرابات طيف التوحد، في مرحلة الطفولة المبكرة، بصعوبات التواصل الاجتماعي وأنماط السلوك المتكررة. خلال العقود القليلة الماضية وبسبب تغير النظريات حول مسببات اضطرابات طيف التوحد ، لا يوجد علاج مناسب لهذا الاضطراب. كان الهدف من هذه المراجعة هو الكشف عن أهم أسباب هذا الاضطراب، وكذلك الخوض في معرفة أحدث طرق العلاج لهذا الاضطراب. هناك العديد من الجينات المتهمة في التسبب في مرض اضطرابات طيف التوحد ، يشارك معظمها في تكوين المشابك العصبية في الخلايا العصبية. إن الفيزيولوجيا المرضية لاضطراب طيف التوحد مرتبطة بالعوامل والظروف البيئية مثل تشوهات الجهاز الهضمي والاختلالات المناعية. على الرغم من أن اضطرابات طيف التوحد له ارتباط وثيق بالعامل الوراثي، إلا أن العديد من العوامل المرتبطة بها يمكن أن يكون لها دور مباشر في التسبب في المرض أو تعمل كمعدلات للجينات، مما يؤدي إلى تفاقم المرض. إن الأطفال المصابين بالتوحد عادة ما يكون لديهم استجابة مناعية غير متوازنة لأن الجهاز الهضمي متصل مباشرة بجهاز المناعة. يشتبه أن الأم قد تكون مصابة بعدوى أو مرض مناعي ذاتي. إن خلل الميتوكوندريا هو الاضطراب الأيضي الأكثر انتشارًا والمرتبط باضطراب طيف التوحد. كذلك ترتبط العديد من الاضطرابات العصبية بالإجهاد التأكسدي. ومع ذلك، فإن العلاقة بين الإجهاد التأكسدي وحدوث أو تطور مرض التوحد والخلل اللاإرادي غير مفهومة بشكل جيد. يجب استخدام العلاجات غير الدوائية في المقام الأول. بالنسبة للأعراض الرئيسية لمرض طيف التوحد، فإن العلاج الدوائي غير فعال. من ناحية أخرى، قد تكون الأدوية مفيدة في علاج الأمراض المصاحبة وأعراضها، مثل التهيج والعنف .