Review Article

Exploring the Multifactorial Nature of Autism Spectrum Disorder: A Review of Genetic, Environmental, and Neurobiological Findings

P.A D G Lakshmi*, RVS Anvesh, Dua Mishra, Pawan Kiran, Sri Sowmya
Department of Pharmacology, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad – 500090, India.
***Corresponding author's E-mail:** ahalyapati8087@grcp.ac.in

Received: 06-12-2024; **Revised:** 23-02-2025; **Accepted:** 10-03-2025; **Published online:** 20-03-2025.

ABSTRACT

Autism Spectrum Disorder (ASD) is a multifaceted neurodevelopmental disorder marked by difficulties in social interaction and communication, restricted sensory sensitivities and repetitive behaviours. While the exact causes of ASD remain unclear, it is believed to result from a combination of genetic and environmental factors. Genetic studies have revealed numerous gene variations associated with ASD, with conditions like Rett syndrome and fragile X syndrome providing insights into the disorder's genetic underpinnings. Environmental factors, such as older parental age, prenatal exposure to toxins, maternal health issues, and birth complications, are also linked to an increased risk of ASD, though these factors alone are not sufficient to cause the disorder. Neuropathological studies indicate structural brain abnormalities, particularly in the cerebellum and limbic system, which may contribute to the social and behavioural deficits observed in individuals with ASD. Additionally, gastrointestinal issues are commonly reported in ASD, with disruptions in the gut-brain axis potentially influencing symptom severity. Recent research has also highlighted the role of acetylcholinesterase and its inhibitors in ASD. While individuals with ASD often face challenges related to epilepsy and comorbid conditions, early intervention and personalized treatment plans can significantly improve outcomes. Continued research into genetic, environmental, neurobiological, and pharmacological factors, including acetylcholinesterase, is crucial for advancing understanding and treatment of ASD.

Keywords: Autism Spectrum Disorder (ASD), genetic studies, acetylcholinesterase, neuropathological studies, gut-brain axis, pharmacological factors.

INTRODUCTION

According to the 2019 Global Burden of Disease (GBD) Mental Disorder Collaborators, Mental disorders remain among the top ten leading causes of global burden. They account for a significant proportion of years lived with disability (YLDs), contributing 125.3 million YLDs in 2019[1]. Among mental disorders, autism spectrum disorders (ASDs) stand out as persistent and disabling neuro-developmental conditions. ASD is characterized by "a range of conditions characterized by some degree of impaired social behaviour, communication and language, and a narrow range of interests and activities that are both unique to the individual and carried out repetitively." First described in 1943, ASDs have shown a significant global increase in incidence over the decades. It is estimated that the global prevalence of autism is approximately 1 in 132 individuals. A study conducted in India found comparable prevalence rates, with 1% of children aged 2–6 years and 1.4% of those aged 6–9 years being affected. A 2018 study further estimated that 1.2 million children under the age of 5 in South Asia are living with autism, accounting for over a quarter of the global prevalence[2].

ASD is a neuro-developmental condition that persists throughout childhood and adulthood. Most cases are identified within the first five years of life. Individuals with ASD often face co-occurring medical Conditions such as epilepsy, depression, anxiety, and attention deficit hyperactivity disorder (ADHD) are associated with ASD. Individuals with ASD exhibit a wide range of intellectual functioning, from mild cognitive impairments to severe intellectual disabilities. ASD is a neurobiological disorder influenced by both genetic and environmental factors that impact brain development (Fig 1). The diagnosis of ASD is based on behaviour al observations in two primary domains: social communication and interaction, and restricted and repetitive behaviour. Currently, no definitive genetic, chemical, or neurological test exists for ASD. However, early detection and the initiation of appropriate therapies are critical to improving the long-term functioning and quality of life for individuals with ASD and their families[3]. The purpose of this article is to provide an overview of the current knowledge surrounding autism spectrum disorders.

Types of neuro-developmental disorders:

Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder (ASD) is a neuro-developmental condition characterized by deficits in social communication, repetitive behaviour, and sensory processing abnormalities. It manifests across a wide spectrum of severity, with individuals displaying varying cognitive and functional abilities. Etiology involves a complex interplay of genetic predispositions, environmental factors, and prenatal influences. Treatment typically includes behaviour al interventions, speech and occupational therapy, and tailored educational strategies to improve adaptive functioning and communication skills[4].

Attention-Deficit/Hyperactivity Disorder (ADHD):

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neuro-developmental disorder marked by inattention, hyperactivity, and impulsivity, often impairing daily functioning. Individuals with ADHD struggle with focus in task completion, organization, and impulse control. Hyperactivity involves restlessness and difficulty remaining seated, while impulsivity may lead to interrupting others or acting without consideration. The exact causes are unclear, but genetic factors, brain structure differences, and prenatal exposures to toxins are believed to be contributing factors. Treatment typically involves stimulant medications (e.g., methylphenidate), behaviour al therapy, and environmental modifications to improve attention and self-regulation[5].

Intellectual disability (ID)

Intellectual Disability (ID) is a condition characterized by substantial limitations in intellectual functioning (IQ below 70). Adaptive behaviour, which impacts skills like reasoning, learning, problem-solving, and more, daily living tasks. It arises before the age of 18 and can be caused by genetic conditions (e.g., Fragile X syndrome, Down syndrome), prenatal factors (e.g., infections, malnutrition), or birth complications (e.g., oxygen deprivation). Treatment involves specialized education, speech and occupational therapy, and social skills training to enhance independence and quality of life. Early intervention and continued support are crucial for improving outcomes[6].

Specific Learning Disorders (SLD)

Specific Learning Disorders (SLD) are conditions that impact a person's ability to learn specific academic skills, despite having normal intelligence and access to education. These difficulties are due to differences in how the brain processes information, but not due to the lack of efforts. Common types include dyslexia (reading difficulties), dysgraphia (writing difficulties), and dyscalculia (math difficulties). Treatment typically includes specialized educational strategies, Individualized Education Plans (IEPs), tutoring, and tailored teaching methods[7].

Communication disorders

Communication disorders are conditions that make it difficult for a child to understand, produce, or use language effectively. These disorders can affect how a child speaks, comprehends language, or uses language in social situations. Common types include Language Disorder (difficulty with vocabulary, sentence structure, and expressing thoughts), Speech Sound Disorder (difficulty pronouncing words correctly), Childhood-Onset Fluency Disorder (stuttering), and Social Communication Disorder (difficulty using language in social contexts). The causes can vary, including genetics, brain injury, or developmental delays. Treatment typically involves speech and language therapy, social skills training, and parent education[8].

Motor disorders

Motor disorders are conditions that affect a person's ability to control their physical movements or coordinate actions, making tasks like walking, writing, or using utensils challenging. Types of motor disorders include Developmental Coordination Disorder (DCD), where individuals struggle with coordinating movements like tying shoelaces or riding a bike; Stereotypic Movement Disorder, characterized by repetitive, non-purposeful movements such as hand-flapping or rocking; and Tic Disorders, which involve sudden, involuntary movements or sounds, with Tourette's syndrome being a common example. These disorders may stem from genetic factors, brain development issues, or complications during pregnancy or birth. Treatment often involves physical and occupational therapy to improve motor skills and coordination, along with behaviour al interventions to manage repetitive movements or tics[9].

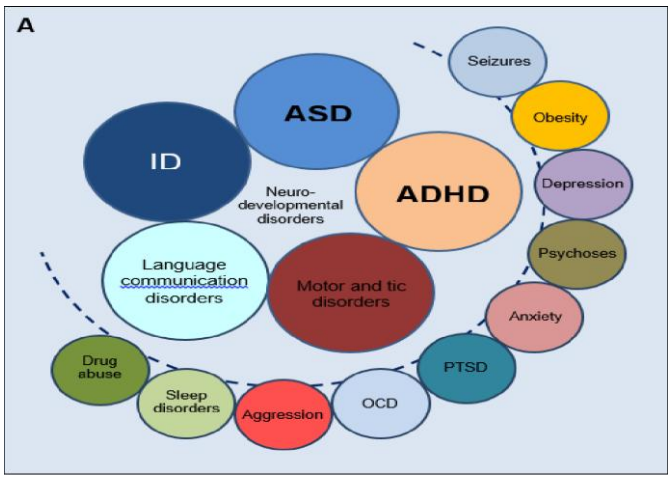

Figure: 1

Autism

Autism spectrum disorder (ASD) is a major public health issue. Autism Spectrum Disorder (ASD) is a term used to describe a group of conditions where people have certain challenges. These challenges include difficulty with repetitive actions, social communication, and having very specific or limited interests. Some people with autism may also experience unusual sensory reactions, like being overly sensitive to sounds or lights. Autism signs typically manifest early in life. Around 1 in 100 people worldwide have autism, but the number is higher in richer countries[10]. Scientists have found that while there is no major brain damage or obvious brain disease in people with autism, there are small differences in the brain's structure and function. For example, babies without autism naturally make eye contact, use sounds to express their intentions, and communicate their emotions with facial expressions. These abilities often come more easily to young children without autism than to older children or adults with autism. The potential to discover links between brain function and the development of basic social behaviour s is part of the reason there's been a growing interest in researching autism in neuroscience[11].

Etiology

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition influenced by a combination of genetic and environmental factors. Although the exact mechanisms underlying ASD remain unclear, it is widely accepted that both hereditary and non-hereditary elements contribute to its development (Fig 2). ASD can be categorized into two main categories: syndromic and non-syndromic forms. Syndromic ASD is often associated with identifiable chromosomal abnormalities or mutations in single genes, as seen in conditions like Rett syndrome, fragile X syndrome, and MECP2 duplication syndrome. In contrast, non-syndromic ASD has a more ambiguous cause due to its genetic variability [12]. It is believed that a combination of spontaneous genetic mutations and various environmental factors, both before and after birth, play a significant role in its onset, reinforcing the idea that the origins of ASD are intricate and multifactorial. Research has shown that prenatal exposure to drugs such as thalidomide and valproic acid may increase the risk of ASD among new-borns, a theory that is supported by multiple animal studies. Furthermore, maternal health issues— including autoimmune diseases, psoriasis, thyroid problems, or diabetes—as well as infections during pregnancy, can also impact the likelihood of ASD developing in children. The disorder is observed more frequently in children born prematurely, via caesarean delivery, or those with low birth weights or poor Apgar scores. While these findings enhance our understanding of potential ASD triggers, further research is crucial to fully uncover the disorder is true causes.[13]

Epidemiology

Geographical and methodological considerations have an influence on the prevalence rates of autism spectrum disorder (ASD), which vary significantly as of 2024. The World Health Organization (WHO) estimates that 1 in 100 children worldwide are on the autistic spectrum, though regional differences in diagnostic practices, awareness, and access to healthcare may cause this figure to fluctuate [14]. In India**,** estimating the exact prevalence of autism remains challenging, while recent estimates place the number at about 1 in 100 youngsters, with some research going as high as 1 in 68. ASD affects children from all racial, ethnic, and socioeconomic backgrounds, though diagnosis rates are not evenly distributed. White children are diagnosed more often than Black or Latino children, potentially due to factors such as stigma, access to healthcare, or language barriers. Boys are diagnosed with ASD at a rate of 4:1 compared to girls. However, girls may be underdiagnosed because their symptoms are less obvious or masked by behaviour s like “camouflaging,” which helps them hide social challenges. Over the past few decades, improved screening, expanded diagnostic criteria, and increased awareness have contributed to a rise in ASD diagnoses[15].

History

Signs and symptoms

A history of mental health problems or neurodevelopment disorders, such as learning difficulties and ADHD, frequent communication or social interaction problems, repetitive or restricted behaviours (often referred to as "stimming"), resistance to change or limited interests, difficulties finding or keeping a job or attending school, difficulties making or maintaining social connections, and connections to mental health services or learning disabilities. Some autistic individuals exhibit remarkable or uncommon abilities, such as splinter skills (such memorizing trivia) or uncommon aptitudes in music, mathematics, or artistic replication, which in rare instances are regarded as a component of the savant syndrome. Even when it comes to things they enjoy, people with this combination of autism symptoms are more likely to refuse to comply with requests or expectations. About three-quarters of children with ASD exhibit unusual or aberrant eating behaviour, to the point where it was once used as a diagnostic sign. The most prevalent issue is selectivity, though food refusal and eating rituals often happen[16].

Figure 2

Pathophysiology

Research in ASD has predominantly concentrated on understanding brain development and function over the years. Experimental and post-mortem studies have identified (CNS) abnormalities both at the gross morphological level and at the cellular level, including in neurons and glial cells. These findings suggest that neuropathology’s are present in ASD. However, recent research on immune responses and gut-brain signalling has shown that pathologies in ASD extend beyond the CNS[17].

The genetic causes of autism are complex. There is no single specific gene variation associated with autism. Multiple gene variations have been associated with the autism. One of the most significant genetic discoveries related to autism is the identification of the gene responsible for Rett syndrome (Rett syndrome, a neurodevelopmental disorder characterized by intellectual disability, loss of communication skills, and symptoms similar to autism). Autism is observed in a small minority with complete

mutations of the fragile X gene (FMR1 - fragile X messenger ribonucleoprotein 1). These mutations occur in less than 1% of the recent studies of children diagnosed with autism. Autism develops by the decreased FMR1 expression of the fragile X gene leading to mental retardation and social communication difficulties. Genetic factors, including copy number mutations and rare variant mutations, play a significant role in ASD, accounting for 25% of cases. Mitochondrial dysfunction, which may be linked to mitochondrial DNA mutations, has been implicated in ASD and other neurological disorders[18].

Neuropathology The earliest formal reports of autism emerged in the early 1980s, during which approximately 30 brains were subjected to study. However, numerous reports have suggested that the brains of autistic individuals exhibit structural enlargement compared to those of neurotypical individuals. Regional neuropathology studies have also indicated potential alterations in specific brain regions, including the brainstem, cerebellum, and a set of limbic structures, such as the hippocampi formation, amygdala, septal nuclei, and anterior cingulate gyrus. These structures in autistic subjects are characterized by smaller dimensions and a higher density compared to the typical human brain[19].

Gastrointestinal abnormalities in ASD: Studies have suggested a possible link between gastrointestinal issues and ASD, although the evidence remains inconclusive. The gut-brain interaction may play a role in the development or severity of ASD. M-cells, found in the intestinal mucosa, engulf larger molecules and transfer them to antigen-presenting cells for immune response. Cholera toxin-B subunit can bind to ganglioside M1 receptors in intestinal epithelial cells, facilitating the entry of small proteins into the bloodstream. Increased intestinal permeability, often resulting from infections or inflammatory conditions, can lead to the absorption of larger molecules and potentially cause ASD. Several factors, including infections and intestinal permeability, contribute to the pathogenesis of Crohn's disease and ASD. Further research is necessary to comprehend the gastrointestinal mucosal environment and immune response in individuals with ASD[20].

Evaluation

Impact on the Brain

Neuro-imaging techniques, like Magnetic Resonance Imaging (MRI), are one of the few ways to directly look at the brain while it's still active (in vivo). Over the past decade, structural MRI studies have shown that people with ASD often have differences in both grey matter and white matter. These differences can vary by brain region when comparing people with ASD to typically developing (TD) individuals. Many of these studies have focused on volumetric (size) and morphometric (shape) measurements of the brain to understand how ASD affects brain structure. In simpler terms, MRI studies are helping us understand the physical differences in the brains of people with autism and how these differences might relate to the challenges them face[21].

Regional Brain Structure

The exact cause of the brain enlargement observed in ASD remains unclear. However, recent research suggests that, before the age of 2, the brain of a child with ASD grows faster than usual, particularly in the cortical surface area. This early brain growth seems to be linked to ASD but not due to thicker brain tissue. Additionally, there are differences in the white matter, which might explain why the brain is not as well connected in people with ASD. Many studies have also looked at the specific parts of the brain that might be linked to the core symptoms of ASD [21-22].

Some of these key brain areas include:

- Frontotemporal lobe (involved in thinking, decision-making, and social behaviour)
- Amygdala (involved in emotion and social processing)
- Hippocampus (involved in memory)
- Basal ganglia (involved in movement and behaviour regulation)
- Anterior cingulate cortex (ACC) (linked to emotion and decision-making)

1. Difficulties in regions such as Broca's area, which plays a key role in speech and language production, Wernicke's area, which is crucial for language comprehension, and the superior temporal sulcus (STS), may account for the challenges individuals with ASD face in interpreting social language and cues in social interactions.

2. Variations in the frontal lobe, superior temporal cortex, parietal cortex, and amygdala may be associated with challenges in social interactions, such as maintaining eye contact and interpreting emotional cues.

3. Changes in the orbitofrontal cortex (OFC) and caudate nucleus are thought to be related to the repetitive behaviours and restricted interests seen in ASD.

However, it's important to note that these brain differences are not unique to autism. Some of these abnormalities can also be found in other conditions, which means they are not specific only to ASD. In simpler terms, researchers are finding that the brain of someone with ASD develops differently in certain areas. These differences could help explain some of the difficulties experienced by individuals with autism.[23]

Cortical area

Brain overgrowth during childhood in ASD leads to differences in the shape and structure of the brain. Several studies have looked at how the cerebral cortex changes in people with autism, focusing on things like the shape of the brain and the pattern of folds (called sulcal patterns). One explanation for these changes is that the brain's white matter fibres, which help different parts of the brain

communicate, may pull on the cortex, affecting how it folds. Normally, the brain folds in specific ways to allow the outer layers to grow and expand. In children with ASD, researchers have found abnormal cortical folding—meaning the way the brain folds is different from typical patterns[24].

Total brain volume Research shows that kids with ASD have faster brain growth between ages 2 and 4. Their brains are usually larger than those of typically developing kids at this age and this changes upon aging. In older kids and adults with ASD, their brain size either stays the same or even gets smaller compared to kids without autism. This suggests that while their brains grow quickly early on, the growth slows down or stops later. The frontal and temporal lobes of the brain are especially affected in young children with autism. In short, kids with autism have bigger brains when they're younger, but the growth slows down or stops as they grow older[25].

Mitochondrial Dysfunction and Autism

Mitochondrial dysfunction significantly impacts autism spectrum disorder (ASD), manifesting in abnormalities within mitochondrial complexes that lead to defects in intracellular systems. These defects contribute to the development of autism-like behaviours. Mitochondrial dysfunction has been observed in ASD patients, although primary mitochondrial disease has been genetically confirmed in a limited subset of cases. Mitochondrial DNA (mtDNA) alterations are more prevalent in ASD patients compared to control individuals. Mitochondrial deletions, which are not isolated genetic alterations exclusive to ASD, primarily result from alterations in the causative genes for autism or genes involved in mtDNA maintenance, or from the detrimental effects of environmental factors. They frequently occur alongside other genetic risk elements associated with ASD or changes in genes that are crucial for communication between genomes. These findings suggest that mitochondrial dysfunction is common in ASD. Moreover, various research studies have pointed to certain mitochondrial complexes as playing a role in the development of autism. Mitochondrial dysfunction may occur due to a primary issue stemming from a mutation in a gene that directly contributes to ATP production, or it can be a secondary effect caused by other genetic, metabolic, or biochemical irregularities that hinder the mitochondria's ability to generate ATP. Mitochondrial dysfunction has been utilized to identify patient-risk genes associated with complex traits, including autism. This method has been implemented in studies of autism due to the ongoing inconsistency of biomarkers associated with the disorder[26].

1) **ROS Production**: Mitochondria generate reactive oxygen species (ROS) as a redox signal that integrates their function with the rest of the cell. ROS signalling can originate from mitochondria releasing hydrogen peroxide, which modulates the action of target proteins by reversibly oxidizing crucial protein thiols. This alteration affects enzymes, kinases, phosphatases, and transcription factors within mitochondria, the cytosol, or the nucleus. Autism spectrum disorder (ASD) has been associated with alterations in the primary targets of ROS and membrane phospholipid levels. Elevated ROS levels consistently resulted in a depletion of the Reserve Capacity (RC) of mitochondria in autism-A (abnormal mitochondria) lymphoblastic cell lines (LCLs). ROS attacks polyunsaturated fatty acids, which are integral to cell membranes, leading to the secretion of lipid peroxidation (LPO) end products[27].

2) **Oxidative Stress**: It refers to a pathological state resulting from the imbalance between ROS and the cell's capacity to detoxify. Any form of obstruction in this process leads to extreme damage to all macromolecules and interferes with numerous communication pathways. The brain exhibits a high vulnerability to oxidative injury compared to other organs, which has led to its involvement in the pathophysiology. Numerous reports have indicated accumulated levels of different LPO markers in autism, confirming an elevation in oxidative stress in this condition[28].

3) **Apoptosis**: As numerous cellular mechanisms participate in the normal development of the nervous system, programmed cell death (apoptosis) occurs due to spatial or temporal errors in stimuli or errors within the apoptosis pathway itself. Numerous active factors influence foetal brain development in adults and infants, leading to abnormalities in apoptosis. Apoptosis may play a role in the development of autism, and it has been hypothesized that exogenous cyclic dipeptides could interfere with neural development at an early stage, potentially resulting in psychiatric disorders such as schizophrenia and autism. The apoptotic protein and elevated expression of Caspase 3, along with an impaired anti-apoptotic pathway, have been observed in autistic children[29].

EFFECT OF ACETYLCHOLINE IN ASD

ASD is characterized by impairments in communication and interaction, as well as repetitive patterns of behaviour and interests. Current interventions don't completely eliminate ASD features. Acetylcholine, a neurotransmitter involved in attention, novelty seeking, and memory, has been investigated as a potential contributor to ASD symptomatology. Acetylcholinesterase inhibitors (ACEIs), such as donepezil, galantamine, and rivastigmine, inhibit acetylcholinesterase and have varying modes of action and biological availability. Their effectiveness and side effects on core ASD features across the lifespan and possible adverse effects remain[30].

Treatment/Management

Currently, there is no cure for Autism Spectrum Disorder (ASD), nor is there a one-size-fits-all treatment for individuals with autism. The interventions available for ASD are diverse, encompassing both pharmacological and non-pharmacological approaches. Non-pharmacological therapies often focus on educational interventions that aim to improve academics, social skills, adaptation, and communication abilities[31].

Treating autism with medication: If behaviour al and educational interventions are not sufficient, medications may help an individual with autism better manage their symptoms. There are various medications used with ASD patients as detailed below.

Antidepressant and anxiety medications: They can be beneficial for individuals with ASD in managing persistent anxiety and obsessive behaviour s. Certain medications, such as Zoloft or Prozac, can enhance mood, thoughts, and behaviour s [32].

Atypical Antipsychotics: Which is used in treating motor restlessness, repetitive behaviour and insomnia in offspring with autism medications like aripiprazole, quetiapine fumarate. FDA-approved for treating behaviour s associated with autism.

Differential Diagnosis

Doctors will look for signs of developmental delays during regular check-ups. ASD varies widely in symptoms and severity, making diagnosis challenging. There isn't a specific medical test to diagnose the disorder. One way to diagnose ASD is by observing and asking how people socially interact and communicate, as well as how their communication skills and behaviour s have developed and changed over time. Tests such as hearing, speech, language, developmental levels, and social and behaviour al issues can also be helpful. Clinicians primarily diagnose adults with ASD by observing and interacting with them, or by observing their experiences [33].

1. **Persistent Deficit in Social Communication**: This includes difficulty in reciprocating emotions, communicating with others, sharing emotions, processing group communications, and eye contact, body language, non-verbal communication, and gesture communication using facial expressions. Additionally, there may be a lack of development in maintaining understanding relationships, friendships, and the ability to maintain peers.

2. **Restricted Pattern of Behaviour:** This category encompasses repetitive motor movements like palilalia, peculiar moments, and repeated hand movements (motor stereotypes). Individuals with autism may be preoccupied and engrossed in unusual activities, such as excessive smelling or touching of objects. They may also have highly restricted fixated interests that are abnormal in intensity or focus. Additionally, they may exhibit hyper or hypo-reactive responses to sensory input or have an unusual interest in sensory aspects of their environment. These symptoms must be present during the early developmental period and can cause clinically significant impairments in social, occupational, or other important areas of functioning [34].

Complications

Epilepsy often develops with an increased risk of seizures throughout childhood, particularly during adolescence when the seizure frequency is highest. Selective serotonin reuptake inhibitors (SSRIs) and neuroleptics can also trigger seizures and should be used cautiously.

While it has been reported that the life expectancy of individuals with autism spectrum disorders is generally normal, this is primarily due to complications associated with epilepsy. Notably, the mortality rate for people with ASDs is twice that of the general population. Stimulants, while effective in treating ADHD, can have side effects. The most common side effects include decreased appetite and sleep disturbances. In rare cases, autistic children may experience heightened irritability or withdrawal, or they may develop tics or repetitive movements, such as arm waving[35].

Risk Factors: The etiology of autism spectrum disorder (ASD) is multifaceted, and no single environmental factor can fully account for its increased prevalence. Numerous environmental risk factors have been proposed based on human studies and animal research, but it is evident that numerous more, potentially the most significant, remain to be identified. The most promising risk factors currently identified are drugs, dietary factors, environmental chemicals, infectious agents and other stressors that may be physical or psychological [36].

Navigating the Difficulties of Longitudinal Research

A comprehensive review and meta-analysis of 56 longitudinal studies demonstrated that challenging behaviour s exhibited by autistic individuals tend to diminish over time. However, further research is warranted to elucidate the underlying mechanisms and specific factors contributing to this observed trend[37].

Adaptive behaviour

Adaptive behaviour, a collection of skills acquired over time for everyday life, poses significant challenges. A research study involving 64 people diagnosed with ASD revealed critical findings. The study found that adaptive behaviour was notably impaired, assessed through standardized measures of communication, socialization, and day-to-day living activities. These skills enable independent personal and practical management. Surprisingly, adaptive behaviour showed no significant improvement over time, suggesting targeted interventions and support are needed. Executive function and self-monitoring behaviour s emerged as significant predictors of later adaptive behaviour. Executive functions include problem-solving, flexible thinking, and impulse control, while self-monitoring involves real-time behaviour observation and regulation for social interactions and decision-making[38].

Fostering Effective Teamwork in Autism Healthcare

Effective teamwork in autism healthcare requires integrating diverse professional expertise to meet the complex needs of individuals with ASD. Interdisciplinary collaboration is key to enhancing intervention outcomes by leveraging the unique skills and perspectives of various disciplines. However, challenges such as differing treatment approaches and communication barriers must be addressed. The following outlines key strategies for fostering successful teamwork in autism healthcare[39].

Collaborative Expertise for Comprehensive Care

Collaboration across fields like behaviour analysis, education, and healthcare ensures a holistic approach to ASD care. Professionals must value each other's contributions and communicate interventions in clear, accessible terms for all team members[40].

Building Strong Communication Channels

Training in soft skills, such as active listening and conflict resolution, is essential for team members, especially behaviour analysts, to collaborate effectively. Strong communication between schools, families, and healthcare providers is also vital for ensuring successful interventions, as emphasized in studies on inter-professional teamwork.

Effective Collaboration Models in Practice

Structured collaboration models, such as team teaching or scheduled consultation sessions, improve communication and engagement, particularly in school environments for learners with ASD. Programs like Project DATA provide practical frameworks for working together with children and families to address ASD needs.

Navigating Common Challenges

Common barriers to collaboration include communication challenges, lack of administrative support, and scheduling conflicts. Addressing these issues is crucial for fostering effective teamwork. Setting clear guidelines for inter-professional collaboration can help prevent conflicts and improve coordination among team members from different disciplines.

Promoting Harmony and Respect

While clear standards for collaboration and fostering mutual respect among team members can mitigate these challenges and lead to more effective, integrated.

Future prospects of autism

Although predicting the long-term trajectory of an autistic individual's life presents significant challenges, research indicates several reliable indicators that can serve as valuable predictors of their future.

- ASD: A lifelong developmental condition affecting behaviour, communication, and social interaction, with varying symptoms and severity.
- Prevalence and Hospitalization Rates: Around 700,000 people in the UK are on the autism spectrum, with a significant portion at risk of hospital admission and long-term stays.
- Genetic research

Scientific research suggests that certain inherited genes contribute to an individual's susceptibility to autism spectrum disorder (ASD). A comprehensive understanding of the genetic underpinnings of ASD is crucial for the development of efficacious treatment strategies. Notably, researchers have identified a mutated human Arid1b gene in genetically modified mice that disrupts GABA neurons, leading to an imbalance in brain communication. These cognitive and social deficits observed in the mice indicate that a drug that modulates GABA receptors may hold potential as a therapeutic intervention[41].

New medicines autism

There's currently no pharmaceutical treatment available for autism score symptoms, such as social skills and communication challenges, restrictive interests, and repetitive behaviours.

Balovaptan is a vasopressin receptor antagonist that inhibits the binding of a molecule influencing social behaviour to brain receptors. The Food and Drug Administration (FDA) approved the medication based on efficacy data from a second-phase trial conducted in adults with autism spectrum disorder (ASD). The trial demonstrated the medication's safety and well-tolerability, with significant improvements in social interaction and communication. A study involving children and adolescents is currently underway[42].

Visual Supports

Language comprehension is a significant obstacle to skill development. If children don't understand what's being said to them, they can't fully benefit from their parents' teaching. In such situations, it's crucial to supplement verbal communication with visual aids. A particularly useful visual support is a visual schedule, which outlines the different steps involved in completing a specific skill. This provides the child with a clearer understanding of the steps and, over time, ASD children will be able to use these visual supports to complete the task more independently[43].

Prevention

Preventing ASD involves addressing both environmental and genetic factors. While complete prevention isn't possible, understanding these factors can help reduce risks and improve outcomes for children with ASD. Prevention strategies focus on three stages: before birth, early childhood, and later life [44].

Several factors may increase the risk of ASD:

1. **Parental Age**: Older parents or very young mothers may have a slightly higher risk.
2. **Environmental Factors**: Exposure to pollution, chemicals, and smoking during pregnancy can raise the risk.
3. **Maternal Health**: Conditions like obesity, diabetes, and hypothyroidism during pregnancy are linked to higher ASD risk. Proper healthcare can help mitigate this.
4. **Infections and Immune Reactions**: Infections like rubella may increase risk, but vaccines and treating fever during pregnancy can help reduce it.

5. **Nutrition**: Deficiencies in omega 3 fatty acid, folic acid and vitamin D during pregnancy may increase risk, and supplements can be helpful.
6. **Breastfeeding**: Breastfeeding for at least a year may support brain development and reduce ASD risk.
7. **Medications during Pregnancy**: Certain medications, like some antidepressants or anti-seizure drugs, may slightly increase the risk. Safer alternatives can be explored with a doctor.
8. **Ultrasounds**: Frequent or high-intensity ultrasounds in early pregnancy may impact brain development; limiting unnecessary ultrasounds may reduce this risk.
9. **Vaccinations**: There is no scientific evidence linking vaccines, such as the MMR vaccine, to ASD. Vaccines are safe and protect against serious diseases.[45,46,47]

For children with ASD to acquire critical abilities, early detection and intervention are essential. Results can also be enhanced by lifelong support, which includes methods for dealing with issues like depression or social difficulties. Although it is impossible to completely prevent ASD, risks can be considerably decreased by taking actions like promoting brain development, preventing hazardous exposures, and enhancing maternal health.[48]

CONCLUSION

This review explores the complex behavioural and psychiatric conditions commonly associated with ASD such as irritability, ADHD, anxiety, and mood disorders. It highlights genetic factors, including gene variants and chromosomal defects that contribute to ASD. The role of acetylcholinesterase activity is also discussed, as altered cholinergic function has been implicated in ASD, potentially affecting neurotransmitter balance and brain connectivity. Despite increasing prevalence, there are no effective treatments for ASD's core symptoms. Current review focuses on understanding genetic mutations, molecular pathways, and brain connectivity abnormalities. While co-occurring conditions are often overlooked, addressing these in research is crucial for developing targeted therapies. Further studies are needed to unravel the genetic, environmental, and co-morbid factors to improve ASD treatment outcomes.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Whiteford H.A., Ferrari A.J., Degenhardt L., Feigin V., Vos T. The global burden of mental, neurological and substance use disorders: An analysis from the Global Burden of Disease Study 2010. PLoS ONE. 2015;10:e0116820. doi: 10.1371/journal.pone.0116820.
2. Olusanya BO, Davis AC, Wertlieb D, Boo N-Y, Nair MKC, Halpern R, Kuper H, Breinbauer C, de Vries PJ, Gladstone M, Halfon N, Kancherla V, Mulaudzi MC, Kakooza-Mwesige A, Ogbo FA, Olusanya JO, Williams AN, Wright SM, Manguerra H, et al. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet Global Health. 2018;6(10):e1100–e1121. doi: 10.1016/S2214-109X(18)30309-7.
3. Francis, Konstantinos & Karantanos, Georgios & Al-Ozairi, Abdullah & AlKhadhari, Sulaiman. (2021). Prevention in Autism Spectrum Disorder: A Lifelong Focused Approach. Brain Sciences. 11. 151. 10.3390/brainsci11020151.
4. Hens, K. (2019), The many meanings of autism: conceptual and ethical reflections. Dev Med Child Neurol, 61: 1025-1029. https://doi.org/10.1111/dmcn.14278
5. Antshel KM, Zhang-James Y, Faraone SV. The comorbidity of ADHD and autism spectrum disorder. Expert Rev Neurother. 2013 Oct;13(10):1117-28. doi: 10.1586/14737175.2013.840417. PMID: 24117274.
6. Sinzig J, Lehmkuhl G. Komorbiditäten bei Autismus-Spektrum-Erkrankungen - Stand der Forschung und Aufgaben für die Zukunft Comorbidities with autism spectrum disorders - present state of research and future outlook. Z Kinder Jugendpsychiatr Psychother. 2011 Mar;39(2):91-8; quiz 99. German. doi: 10.1024/1422-4917/a000095. PMID: 21442597.
7. Conant, L. L., & Miller, L. E. (2024). Intellectual developmental disorder, autism spectrum disorder, attention-deficit/hyperactivity disorder, and specific learning disorders across the lifespan. In M. W. Parsons & M. M. Braun (Eds.), *Clinical neuropsychology: A pocket handbook for assessment* (4th ed., pp. 587–617). American Psychological Association. https://doi.org/10.1037/0000383-022
8. Félix, J., Santos, M.E. & Benitez-Burraco, A. Specific Language Impairment, Autism Spectrum Disorders and Social (Pragmatic) Communication Disorders: Is There Overlap in Language Deficits? A Review. Rev J Autism Dev Disord 11, 86–106 (2024). https://doi.org/10.1007/s40489-022-00327-5
9. Pringsheim T, Hammer T. Social behaviour and comorbidity in children with tics. Pediatr Neurol. 2013 Dec;49(6):406-10. doi: 10.1016/j.pediatrneurol.2013.08.005. Epub 2013 Oct 2. PMID: 24095577.
10. Sesay, M. M., McCracken, C. E., Stewart, C., Simon, G., Penfold, R., Ahmedani, B., Rossom, R. C., Lu, C. Y., Beck, A., Coleman, K. J., Daida, Y., Lynch, F. L., Zeber, J., Copeland, L., & Owen-Smith, A. (2024). Short report: Transition to International Classification of Diseases, 10th Revision and the prevalence of autism in a cohort of healthcare systems. Autism, 28(5), 1316-1321. https://doi.org/10.1177/13623613231220687

11. Sauer AK, Stanton JE, Hans S, et al. Autism Spectrum Disorders: Etiology and Pathology. In: Grabrucker AM, editor. Autism Spectrum Disorders Internet. Brisbane (AU): Exon Publications; 2021 Aug 20. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK573613/ doi: 10.36255/exonpublications.autismspectrumdisorders.2021.etiology

12. Taylor MJ, Rosenqvist MA, Larsson H, Gillberg C, D'Onofrio BM, Lichtenstein P, Lundström S. Etiology of Autism Spectrum Disorders and Autistic Traits Over Time. JAMA Psychiatry. 2020 Sep 1;77(9):936-943. doi: 10.1001/jamapsychiatry.2020.0680. PMID: 32374377; PMCID: PMC7203675.

13. GUINCHAT, V., THORSEN, P., LAURENT, C., CANS, C., BODEAU, N. and COHEN, D. (2012), Pre-, peri- and neonatal risk factors for autism. Acta Obstetricia et Gynecologica Scandinavica, 91: 287-300. https://doi.org/10.1111/j.1600-0412.2011.01325.xBaxter A.J., Brugha T.S., Erskine H.E., Scheurer R.W., Vos T., Scott J.G. The epidemiology and global burden of autism spectrum disorders. Psychol. Med. 2015;45:601–613. doi: 10.1017/S003329171400172X.

14. Nadeem, Muhammad & Murtaza, Bibi & Al-Ghamdi, Maryam & Ali, Akbar & Zamzami, Mazin & Khan, Jalaluddin & Ahmad, Aftab & Rehman, Mujaddad & Kazmi, Imran. (2021). Autism - A Comprehensive Array of Prominent Signs and Symptoms. Current Pharmaceutical Design. 27. 10.2174/1381612827666210120095829.

15. Sicherman, N., Charite, J., Eyal, G. *et al.* Clinical signs associated with earlier diagnosis of children with autism Spectrum disorder. *BMC Pediatr* **21**, 96 (2021). https://doi.org/10.1186/s12887-021-02551-0

16. Samsam M, Ahangari R, Naser SA. Pathophysiology of autism spectrum disorders: revisiting gastrointestinal involvement and immune imbalance. World J Gastroenterol. 2014 Aug 7;20(29):9942-51. doi: 10.3748/wjg.v20.i29.9942. PMID: 25110424; PMCID: PMC4123375.

17. Genovese, A.; Butler, M.G. The Autism Spectrum: Behaviour al, Psychiatric and Genetic Associations. Genes 2023, 14, 677. https://doi.org/ 10.3390/genes14030677

18. Blatt, Gene. "autism". Encyclopedia Britannica, 17 Jan. 2025, https://www.britannica.com/science/autism. Accessed 24 January 2025.

19. Madra M, Ringel R, Margolis KG. Gastrointestinal Issues and Autism Spectrum Disorder. Child Adolesc Psychiatr Clin N Am. 2020 Jul;29(3):501-513. doi: 10.1016/j.chc.2020.02.005. Epub 2020 Apr 2. PMID: 32471598; PMCID: PMC8608248.

20. Ha S, Sohn IJ, Kim N, Sim HJ, Cheon KA. Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. Exp Neurobiol. 2015 Dec;24(4):273-84. doi: 10.5607/en.2015.24.4.273. Epub 2015 Dec 16. PMID: 26713076; PMCID: PMC4688328.

21. Ecker, Christine et al, Neuroimaging in autism spectrum disorder: brain structure and function across the lifespan. The Lancet Neurology, Volume 14, Issue 11, 1121 - 1134

22. Frith, Chris. Is autism a disconnection disorder? The Lancet Neurology, Volume 3, Issue 10, 577

23. Harden AY, Jou, RJ, Keshavan MS, Varma R, Minsbew NJ (2004) Increased frontal cortical folding in autism: a preliminary MRI study. Psychiatry Res 131:263-268.Van Essen DC (1997) A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385:313-318.

24. Wang, L.; Wang, B.; Wu, C.; Wang, J.; Sun, M. Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. Int. J. Mol. Sci. 2023, 24, 1819. https://doi.org/ 10.3390/ijms24031819

25. Varga NÁ, Pentelényi K, Balicza P, Gézsi A, Reményi V, Hársfalvi V, Bencsik R, Illés A, Prekop C, Molnár MJ. Mitochondrial dysfunction and autism: comprehensive genetic analyses of children with autism and mtDNA deletion. Behav Brain Funct. 2018 Feb 20;14(1):4. doi: 10.1186/s12993-018-0135-x. PMID: 29458409; PMCID: PMC5819172.

26. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17:290–314. doi: 10.1038/mp.2010.136

27. Lombard J. Autism: a mitochondrial disorder? Med Hypotheses. 1998;50:497–500. doi: 10.1016/S0306-9877(98)90270-5

28. Dong, D., Zielke, H.R., Yeh, D. and Yang, P. (2018), Cellular stress and apoptosis contribute to the pathogenesis of autism spectrum disorder. Autism Research, 11: 1076-1090. https://doi.org/10.1002/aur.1966

29. Karvat G, Kimchi T. Acetylcholine elevation relieves cognitive rigidity and social deficiency in a mouse model of autism. Neuropsychopharmacology. 2014 Mar;39(4):831-40. doi: 10.1038/npp.2013.274. Epub 2013 Oct 7. PMID: 24096295; PMCID: PMC3924518.

30. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

31. Hurwitz R, Blackmore R, Hazell P, Williams K, Woolfenden S. Tricyclic antidepressants for autism spectrum disorders (ASD) in children and adolescents. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD008372. DOI: 10.1002/14651858.CD008372.pub2. Accessed 24 January 2025.

32. Barnard-Brak L, Richman DM, Chesnut SR, Little TD. Sch Psychol Q. Social communication questionnaire scoring procedures for autism spectrum disorder and the prevalence of potential social communication disorder in ASD. 2016;31:522–533. doi: 10.1037/spq0000144.

33. Okoye C, Obialo-Ibeawuchi CM, Obajeun OA, Sarwar S, Tawfik C, Waleed MS, Wasim AU, Mohamoud I, Afolayan AY, Mbaezue RN. Early Diagnosis of Autism Spectrum Disorder: A Review and Analysis of the Risks and Benefits. Cureus. 2023 Aug 9;15(8):e43226. doi: 10.7759/cureus.43226. PMID: 37692637; PMCID: PMC10491411.

34. Pan, P.-Y., Bölte, S., Kaur, P., Jamil, S., & Jonsson, U. (2021). Neurological disorders in autism: A systematic review and meta-analysis. Autism, 25(3), 812-830. https://doi.org/10.1177/1362361320951370

35. Craig J. Newschaffer, Daniele Fallin, Nora L. Lee, Heritable and Nonheritable Risk Factors for Autism Spectrum Disorders , Epidemiologic Reviews, Volume 24, Issue 2,

December 2002, Pages 137–153, https://doi.org/10.1093/epirev/mxf010

36. Dawn Adams, Nicole Dargue, Jessica Paynter, Longitudinal studies of challenging behaviours in autistic children and adults: A systematic review and meta-analysis, Clinical Psychology Review, Volume 104, 2023, 102320, ISSN 0272-7358, https://doi.org/10.1016/j.cpr.2023.102320.

37. Kanne, S.M., Gerber, A.J., Quirmbach, L.M. et al. The Role of Adaptive Behaviour in Autism Spectrum Disorders: Implications for Functional Outcome. J Autism Dev Disord 41, 1007–1018 (2011). https://doi.org/10.1007/s10803-010-1126-4

38. Sandbank, M., Bottema-Beutel, K., Crowley, S., Cassidy, M., Dunham, K., Feldman, J. I., Crank, J., Albarran, S. A., Raj, S., Mahbub, P., & Woynaroski, T. G. (2020). Project AIM: Autism intervention meta-analysis for studies of young children. *Psychological Bulletin, 146*(1), 1–29. https://doi.org/10.1037/bul0000215

39. Lord C. The future of autism: Global & local achievements & challenges. Indian J Med Res. 2020 Apr;151(4):263-265. doi: 10.4103/ijmr.IJMR_874_20. PMID: 32461386; PMCID: PMC7371055.

40. Jacob, S., Anagnostou, E., Hollander, E. et al. Large multicenter randomized trials in autism: key insights gained from the balovaptan clinical development program. Molecular Autism 13, 25 (2022). https://doi.org/10.1186/s13229-022-00505-6

41. Hong M.P., Erickson C.A. Investigational drugs in early-stage clinical trials for autism spectrum disorder. Expert Opin. Investig. Drugs. 2019;28:709–718. doi: 10.1080/13543784.2019.1649656.

42. Francis K, Karantanos G, Al-Ozairi A, AlKhadhari S. Prevention in Autism Spectrum Disorder: A Lifelong Focused Approach. Brain Sci. 2021 Jan 24;11(2):151. doi: 10.3390/brainsci11020151. PMID: 33498888; PMCID: PMC7911370.

43. Brewer N, Young RL and Lucas CA (2020) Autism Screening in Early Childhood: Discriminating Autism From Other Developmental Concerns. Front. Neurol. 11:594381. doi: 10.3389/fneur.2020.594381

44. Rudenstine, S.; Galea, S. Preventing brain disorders: A framework for action. Soc. Psychiatry Psychiatr. Epidemiol. 2015, 50, 833-41. doi: 10.1007/s00127-015-1007-4. Epub 2015 Jan 17. PMID: 25595136.

45. Dawson, G. Early behaviour al intervention, brain plasticity, and the prevention of autism spectrum disorder. Dev. Psychopathol. 2008, 20,775-803. doi: 10.1017/S0954579408000370. PMID: 18606031.

46. Casanova, M.F. The neuropathology of autism. Brain Pathol. 2007, 17, 422–433. doi: 10.1111/j.1750-3639.2007.00100.x. PMID: 17919128; PMCID: PMC8095561.

47. Sandin, S.; Schendel, D.; Magnusson, P.; Hultman, C.; Suren, P.; Susser, E.; Gronborg, T.; Gissler, M.; Gunnes, N.; Gross, R.; et al. Autism risk associated with parental age and with increasing difference in age between the parents. Mol Psychiatry. 2016 May;21(5):693-700. doi: 10.1038/mp.2015.70. Epub 2015 Jun 9. PMID: 26055426; PMCID: PMC5414073.

48. Estes, A.; Munson, J.; Rogers, S.J.; Greenson, J.; Winter, J.; Dawson, G. Long-Term Outcomes of Early Intervention in 6-Year-Old Children With Autism Spectrum Disorder. J. Am. Acad. Child. Adolesc. Psychiatry 2015, 54, 580–587. doi: 10.1016/j.jaac.2015.04.005. Epub 2015 Apr 28. PMID: 26088663; PMCID: PMC4475272.