Autism Spectrum Disorder: From Underlying Causes To Evidence-Based Therapies

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ABSTRACT

Autism, as a neurodevelopmental disorder with a complex etiology, continues to be a priority area of multidisciplinary research. Current evidence indicates a complex interaction between genetic, epigenetic, and environmental factors that contribute to the heterogeneous manifestation of the autism spectrum. Autism Spectrum Disorder (ASD) is characterized by: (1) impairments in the quality of communication and social interactions, and (2) restricted and repetitive behaviors, interests, and activities. In Romania, data collected by the Help Autism Association on individuals registered with social assistance services as of July 1, 2021, show the following: 13,992 children (ages 0–18) were diagnosed with ASD, of whom: 6,152 were enrolled in mainstream education, 3,446 were in special education, and 4,394 were not enrolled in any form of education. Additionally, 1,095 individuals with ASD exited social services in the last two years after reaching the age of 18. Early screening of young children is crucial for the timely detection of ASD, as various atypical behaviors often become apparent before the age of 3. These may include hand-flapping (similar to waving a flag), self-biting, head-banging, and other repetitive or self-injurious behaviors. Parental and caregiver

education plays a critical role in the early identification and long-term management of ASD. Among the evidence-based interventions currently showing positive outcomes are: Applied Behavior Analysis (ABA), verbal behavior therapy, and animal-assisted therapy. Some studies have demonstrated that improvements in social communication and social cognition remained significant at both 8 weeks and 6 months after the end of therapeutic interventions. Although the etiology of autism is not yet fully understood, advances in the field are evident and essential for improving the quality of life of affected children, who cannot be held responsible for the onset of this neurobiological disorder.

KEYWORDS:
Autism spectrum disorder, neurodevelopmental disorders, genetic and environmental factors, early intervention, behavioral therapies, evidence-based treatment.

Autism Spectrum Disorders (ASD) are defined by a series of abnormalities in brain development that lead to impaired social interactions, difficulties in concentration, repetitive behaviors, and restricted areas of interest. This spectrum encompasses several conditions: (1) genetic disorders that exhibit certain autistic features, such as Fragile X syndrome, Rett syndrome, and tuberous sclerosis; and (2) idiopathic forms of autism, which are referred to by various names and display a wide range of manifestations. Among the latter, Asperger's syndrome is the most notable. Although it was once considered a separate clinical entity, it is now recognized as a form of high-functioning autism that typically appears in children over the age of three. In addition to impaired communication skills, it is characterized by a strong interest in fields that require high intellectual capacity—such as mathematics, physics, computer science, and music—and the development of remarkable abilities in these areas. (1)

ASD is characterized by the following core features: (1) impaired quality of communication and social interactions, and (2) restricted, repetitive behaviors, interests, and activities (RRBs). A diagnosis of ASD requires the presence of both criteria. The condition typically manifests in early childhood, usually before the age of three, and occurs more frequently in males. It is often associated with cognitive abnormalities, comorbidities, and self-injurious behaviors, all of which can profoundly impact daily life. These factors underscore the urgent need for the development and implementation of effective treatment strategies, including pharmacological interventions. (2)

In 2022, the prevalence of Autism Spectrum Disorder (ASD) among 8-year-old children in the United States was 32.2 cases per 1,000 children, equivalent to approximately 1 in 31 children. The condition was 3.4 times more common in boys than in girls. Compared to previous years—1 in 36 (2.8%) in 2020 and 1 in 44 (2.3%) in 2018—the prevalence of ASD continued to rise in 2022. (3)

Over time, a higher number of ASD cases has been recorded among non-Hispanic White children compared to non-Hispanic Black children or Hispanic children. However, in 2016, no significant differences were identified in the proportion of diagnosed cases between non-Hispanic White and non-Hispanic Black populations. Nevertheless, the prevalence of ASD among Hispanic children has remained lower compared to the other racial and ethnic groups. (4)

In Romania, scientific studies on the prevalence of autism are limited, and up-to-date official data remain insufficient. The most recent available estimates date back to 2016, when the Help Autism Association conducted a study on a sample of 300 children from daycare centers in Bucharest, estimating a prevalence of 1 case per 51 children. In 2023, a report by the National Institute of Public Health (INSP) estimated that 14.3% of primary school children in Romania were diagnosed with Autism Spectrum Disorder. However, the National Institute of Public Health (INSP) emphasizes that these figures do not reflect the entire population, as Autism Spectrum Disorders remain underdiagnosed in Romania, and there is no official national registry of individuals with autism. Data collected by the Help Autism Association regarding the number of children with pervasive developmental disorders (including autistic disorder, Asperger's disorder, atypical autism/PDD-NOS), childhood disintegrative disorder, and infantile autism—registered with social assistance services as of July 1, 2021—indicated a total of 13,992 children (aged 0 to 18 years) nationwide. Additionally, 1,095 individuals with ASD were reported to have exited the social assistance system in the past two years upon reaching the age of 18. Of the 13,992 children, 6,152 were enrolled in mainstream education, 3,446 were attending special education institutions, and 4,394 were outside of any formal educational system (either below school age or not enrolled in school). (5)

A Danish study identified a link between maternal use of valproate during pregnancy and an increased incidence of Autism Spectrum Disorder (ASD), along with a higher risk of congenital malformations and lower intelligence in the child. Between 1996 and 2006, in Denmark, a large-scale study involving 655,615 children reported 5,437 cases of ASD, of which 2,644 children had been exposed to antiepileptic drugs due to maternal intake during pregnancy. Among these, 508 women were exposed to valproate, and their children were found to have a threefold increased risk of developing autism compared to those not exposed. (6)

Another significant risk factor is severe hypothyroxinemia during the early weeks of pregnancy. A study conducted on 5,100 women and their 4,039 children found a fourfold increased risk of Autism Spectrum Disorder (ASD) in the offspring, along with more pronounced symptoms and signs of autistic spectrum impairment up to the age of six. (7)

Previous studies have demonstrated that the pathogenesis of Autism Spectrum Disorder (ASD) is influenced by genetic factors, the maternal environment during pregnancy, and the perinatal immune status. In 1970, it was proposed that maternal infection with the rubella virus is associated with the development of autism in offspring. In recent years, numerous studies have confirmed the link between maternal infections during pregnancy and an increased risk of ASD in children. Fetal neurodevelopment can be affected through multiple mechanisms during pregnancy, including active infections and the maternal immune response to these infections. (8)

Maternal immune activation (MIA), triggered by infections or inflammation during pregnancy, has been associated with an increased risk of Autism Spectrum Disorder (ASD) in offspring. MIA leads to elevated levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-17 (IL-17), which can cross the placental barrier and affect fetal neurophysiological development.

Placental inflammation, mediated through the activation of toll-like receptors, contributes to alterations in the fetal microenvironment, influencing brain connectivity and cognitive functions. Experimental models have demonstrated that exposure to maternal immune activation induces behavioral phenotypes resembling Autism Spectrum Disorder (ASD), including deficits in behavioral inhibition and social interactions. Specific blockade of the cytokines IL-6 and IL-17 prevents the emergence of these phenotypes, highlighting the crucial role of maternal inflammation in the etiology of ASD. Additionally, optimal maternal levels of vitamins and antioxidants appear to mitigate the impact of maternal immune activation on fetal neurodevelopment. These findings support the hypothesis that maternal inflammation is a significant risk factor for the development of Autism Spectrum Disorders, and that controlling the inflammatory response during pregnancy may represent an important avenue for prevention. (9)

A population-based study conducted in Denmark found that viral infections requiring hospitalization during the first trimester of pregnancy—including influenza, gastroenteritis, and other unspecified viral infections—were associated with a 2.8-fold increased risk of Autism Spectrum Disorder (ASD). In contrast, bacterial infections during the second trimester were linked to a 1.4-fold increased risk of ASD. Within the same cohort, exposure exclusively to the influenza virus during pregnancy was correlated with a 2.3-fold increased risk of ASD, regardless of the trimester of exposure. Rubella and cytomegalovirus infections thus appear to enhance fetal vulnerability to the subsequent development of disorders within the autism spectrum. (10)

A genome-wide association study (GWAS) conducted on a large population identified a correlation between the genetic profile of mothers with a history of infections during pregnancy and the subsequent incidence of Autism Spectrum Disorder (ASD) in their children, compared to mothers without such a history. Although the reported genetic association between maternal infections and ASD was relatively modest, cases of ASD associated with maternal infections may have distinct genetic etiologies. Validating the locations, types, and timing of infections during pregnancy remains a major challenge, limiting the accurate assessment of the role of maternal infections in the development of Autism Spectrum Disorders (ASD). Further research is needed to differentiate the direct pathogenic effects of infection from the indirect effects of maternal inflammation during pregnancy. (11)

Family-based analyses suggest the importance of genetic factors in Autism Spectrum Disorder (ASD). There is a possibility that first-degree relatives of affected individuals carry the same abnormalities in serotonin structures and other related substances. Neurogenetic evaluations of affected children reveal genetic dysfunctions, with mutations in the SHANK3 gene being associated with the development of ASD. (12)

Some epidemiological studies have concluded that autism has a higher incidence when either parent is over the age of 35. If the mother is above this age, there is a 1.52-fold increased risk of developing Autism Spectrum Disorder (ASD) compared to mothers younger than 29 years. Similarly, fathers over the age of 50 have been observed to have a 2.2-fold higher risk of having a child with ASD compared to those under 29 years. (13)

The severity of autism-specific symptoms has been significantly correlated with certain regional differences in neuroanatomy. For example, deficits in language and communication have been linked to dysfunctions in the frontal and temporal lobes. Postmortem studies conducted on brain tissue from 11 children with Autism Spectrum Disorder (ASD) and 11 control subjects revealed abnormalities in the laminar cortical structure in 10 of the children with autism compared to only one control subject, suggesting that these irregularities may have a prenatal origin. Additionally, regions with atypical neurons were identified in brain areas responsible for communication, language, socialization, and emotion. (14)

A link has been demonstrated between GABA and the specific manifestations and alterations associated with Autism Spectrum Disorder (ASD): its reduced levels contribute to various anomalies observed in this condition. This decrease in GABA was detected using magnetic resonance spectroscopy in a study involving ASD patients and control subjects. Behavioral quantification of inhibition was correlated with the low concentration of GABA. (15)

Studies have shown a connection between dysfunctions in serotonin, oxytocin, and vasopressin and abnormalities in various behaviors. Neurophysiological dysregulations involving at least one of these substances may also be present in individuals affected by Autism Spectrum Disorder (ASD). Elevated blood serotonin levels have been identified in one-third of patients with ASD, as well as in their parents and siblings. Additionally, abnormalities in other neurotransmitters, such as acetylcholine and glutamate, were also present. Comparing data from various neuroimaging modalities, significant differences have been identified between the neurobiological profiles of individuals with Autism Spectrum Disorder (ASD) and those with typical development (TD), alongside substantial variability. (16)

Early screening of young children is crucial for the detection of Autism Spectrum Disorder (ASD). In the United Kingdom, Baron-Cohen and colleagues observed in longitudinal studies of young children that abnormalities in play behavior and other specific elements were associated with a significantly increased rate of accurate early prediction of ASD onset in these subjects. Baron-Cohen developed the most widely used and accurate screening questionnaires tailored to different age groups, including the Checklist for Autism in Toddlers (CHAT), the Modified CHAT (M-CHAT), and the Quantitative CHAT (Q-CHAT) for newborns and infants, as well as the Autism-Spectrum Quotient (AQ) for young children, adolescents, and adults. (17)

Typically, various anomalies become evident before the age of three. There are always qualitative impairments in social interaction, manifested as inappropriate interpretations of social or emotional cues, including lack of response to others' emotions and/or a failure to modulate behavior according to the social context. There is a lack of creativity, as well as impaired use of variations in intonation and stress for modulating vocal messages. The condition is further characterized by a restricted, repetitive, and stereotyped pattern of behaviors, interests, and activities. Certain nonspecific problems may arise, including fears/phobias, sleep disturbances, temper tantrums, and aggressive outbursts. All levels of IQ can be associated with autism, but significant intellectual disability is present in approximately three-quarters of cases. The diagnosis encompasses autistic disorder, infantile autism, childhood psychosis, and

Kanner's syndrome. Differential diagnosis should be made with expressive language disorder, secondary socio-emotional difficulties, reactive attachment disorder, intellectual disability with some associated emotional/behavioral disorders, and very early-onset schizophrenia. (18)

Atypical movements include "flapping" of the hands, resembling a flag, with a loose wrist—especially occurring during states of happiness, excitement, or impatience—often combined with whole-body movements such as jumping and rotation around a vertical axis. Motor tics are also observed in children with Autism Spectrum Disorder (ASD), including rapid movements of the fingers or mouth, as well as repetitive leg movements or facial expressions, without the intent to communicate any sensation. Self-injurious behaviors may take various forms: skin picking, biting different parts of the body, hitting the head against objects or surfaces, punching, slapping or hitting different body areas, pressing on the eyes or other body parts, hair or nail pulling, and teeth grinding. These types of behaviors can lead to higher rates of mortality. (19, 20, 21)

Table. Recommended Instruments for the Diagnostic Procedure of Autism Spectrum Disorder (ASD) in Children. (22, 23, 24)

Signs of Autism Spectrum Disorder (ASD)	Characteristics + Instructions
1. The child does not smile when interacting with others	- Smiles in response (8 weeks = 2 months). - Thoroughly investigate this sign. - This characteristic can be observed as early as 8 weeks.
2. The child does not respond when spoken to	• Responds to verbal commands (52 weeks = 12 months). • Thoroughly investigate this sign.
3. Babbling	- Babbles during play (52 weeks = 12 months). Thoroughly investigate this sign.
4. Does not use gestures (such as pointing and waving) (Imperative signal)	• Makes communicative gestures (waves goodbye) (If the score is negative, repeat at 15 months)
5. Lack of interest in other people (Declarative signal)	- Repeatedly puts in and takes out blocks from a box; Also consider the child's engagement of others in their experiences (at 15 months), as this is an important sign of possible deficits/abnormalities in joint attention, a common sign of ASD. - If the child scores negatively on engaging others: Review the previously evaluated characteristics. If one or more of them also have low scores, administer a CoSoS/ESAT test. - Take into account the low score on this aspect when assessing the next three characteristics below. If the scores for the first two are negative, administer the CoSoS/ESAT test.
Does not use words functionally	Says three words (18 months = 1.5 years). - At this point, seek professional evaluation for further investigation, possibly related to hearing issues.

Does not use two-word phrases (other than echolalia).	Speaks two-word "phrases" (24 months = 2 years).
Loss of language/social skills at any age	It is not necessary to consider this characteristic separately if other characteristics have already been evaluated.

Education of the family and caregivers is of paramount importance, yet it is often overlooked. Patients with autism lack the capacity to fully comprehend their condition; therefore, their well-being heavily depends on the understanding and support provided by those closest to them. Furthermore, the mental health of caregivers, especially family members, may deteriorate due to the chronic stress and challenges associated with caregiving. Unusual and demanding situations frequently encountered can overwhelm them. Consequently, every family member directly involved in caring for a patient with autism should receive targeted training, guidance, and counseling tailored to address their specific needs and emerging challenges.

Family and caregiver education is of critical importance, yet it is frequently neglected. The patient often lacks the capacity to fully understand their condition; therefore, their well-being depends largely on how well those close to them comprehend the situation and are able to provide appropriate support. Moreover, the mental health of caregivers, particularly family members, may deteriorate over time due to the ongoing challenges and the unusual situations they frequently encounter, which can be overwhelming. For this reason, every family member directly involved in the care of a patient with autism should receive targeted training, advice, and counseling tailored to their specific needs and the difficulties that arise. (25)

The ABA method is a learning program designed to systematically and intensively modify the autistic behavior of the child, with the ultimate goal of achieving the child's social integration. The system is well-structured, with clear objectives, implemented through small, manageable tasks that allow continuous monitoring and measurement of the child's progress. Rewards play a significant role and may include material or social reinforcers. The program is intensive and conducted throughout the entire day. Although these strict rules have faced criticism and skepticism, it is precisely this structured approach that provides the child with a sense of security, predictability, and a stable routine. Therapeutic goals are established based on the patient's age and abilities and include improvements across various domains such as communication and language, social skills, self-care (personal hygiene, dressing, etc.), play, as well as academic and learning skills. (26)

Some advantages of ABA therapy include gaining independence and self-care skills, significant improvement in IQ, academic performance, and language competencies, maintaining proper hygiene, enhancement of cognitive and behavioral acquisitions, assimilation of diverse useful and functional knowledge, strengthening language abilities, reduction of undesired behaviors (such as stereotypes and aggressive behaviors), improvement of fine and gross motor skills, recognition and naming of surrounding objects and people, and the ability to narrate personal experiences.(27)

Verbal Behavior (VB) therapy is an enhanced form of ABA therapy that focuses specifically on the child's ability to acquire functional

language and represents an applied analytic behavioral approach. Initially, due to its complexity and higher level of difficulty, it was largely overlooked for many years. It was only in 1998, when Dr. Sundberg and Dr. Partington published three books on the subject, that parents of children with autism began to show interest in Verbal Behavior therapy. The most popular among these tools is the Assessment of Basic Language and Learning Skills (ABLLS), which has become both a working plan and an assessment tool, as well as a tracking form for skills development (where an adult familiar with the child marks off multiple checkboxes). For a patient or caregiver without any prior ABA training, this assessment can be overwhelming, and completing the questionnaire may pose comprehension challenges. In the Verbal Behavior approach, the child begins immediately by receiving items, and soon thereafter, is encouraged to request them independently. (28)

Children with autism spectrum disorder (ASD) exhibit a distinct stress response profile, characterized by elevated cortisol levels compared to unaffected children. Studies such as those by Corbett et al. (2006) and Spratt et al. (2012) have demonstrated that these children not only have higher baseline cortisol levels but also show an increased response to stressors and a prolonged maintenance of elevated cortisol levels following stress exposure. These findings indicate a heightened vulnerability of children with ASD to the adverse effects of stress and to cognitive impairments associated with cortisol dysregulation. (28, 29, 30)

The inclusion of animals in interventions for autism is increasingly recognized in both research and clinical practice. This approach is known as Animal-Assisted Interventions (AAI) and is categorized into three types: targeted therapeutic services (Animal-Assisted Therapy, AAT), visitation programs (Animal-Assisted Activities, AAA), and educational programs (Animal-Assisted Education, AAE). The presence of animals in the lives of individuals with autism is associated with enhanced social interaction; the animal serves as a social facilitator, connecting individuals with ASD to those around them. Moreover, it influences psychobiological processes by reducing stress levels and diverting attention away from negative emotions. (31)

The most common animal species involved in animal-assisted activities were horses (accounting for 55% of studies), followed by dogs, guinea pigs, and dolphins. The personnel conducting the therapy included therapists, riding instructors, animal trainers, and volunteers. Most interventions were carried out over a period of 8 to 12 weeks, with 3 to 4 sessions per week, each lasting between 50 and 75 minutes. Evaluation methods primarily consisted of behavioral observation, psychological assessment, or a combination of both. Information regarding the therapeutic impact was gathered from parents, teachers, and the children with autism participating in the studies. Psychological assessments included measures such as electrodermal activity (EDA), electro-encephalography (EEG), electromyography (EMG), and salivary assays for cortisol and progesterone levels. (32, 33, 34)

Some studies have demonstrated that improvements in social communication and social cognition remained significant at both 8 weeks and 6 months after the conclusion of the intervention. The interventions analyzed were similar to those in previous studies, with durations ranging from 8 to 12 weeks and involving an average of approximately 10 hours of direct contact per participant. (35)

Autism, as a neurodevelopmental disorder with a complex etiology, continues to represent a priority area for multidisciplinary research. Current evidence points to a complex interplay of genetic, epigenetic, and environmental factors contributing to the heterogeneous manifestation of the autism spectrum. Early, personalized, and evidence-based interventions have proven essential in improving long-term outcomes for individuals with autism. Nevertheless, further research is needed to elucidate the underlying neurobiological mechanisms and to develop more effective intervention strategies tailored to the individual needs of those on the spectrum. Promoting social inclusion and fostering rigorous scientific understanding remain fundamental goals in the global approach to autism.

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