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Definition, Epidemiology, Etiology, and Clinical Assessment of Autism Spectrum Disorder

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Abstract: *The neuro developmental illness known as autism spectrum disorder (ASD) is typified by difficulties with social communication, limited interests, and repetitive activities. In light of current worries about rising prevalence, this article aims to clarify the variables that could affect prevalence rates, such as modifications to the diagnostic standards. The authors list the variables that are correlated with the risk of ASD and discuss the data supporting the theory that ASD is a neurobiological illness influenced by both genetic and environmental factors impacting the developing brain. In conclusion, the paper outlines the steps involved in a clinical evaluation, starting with developmental screening and concluding with a referral for a final diagnosis and screening recommendations for co-occurring diseases*

Keywords: Autism spectrum disorder (ASD); prevalence; etiology; screening; evaluation; medical comorbidity

I. INTRODUCTION

Neurodevelopmental disorders such as autism spectrum disorder (ASD) are typified by deficiencies in social communication, limited interests, and repetitive behaviors. The diagnostic criteria for ASD were updated from the previous 4th edition (DSM-IV) in 2013 with the release of the Diagnostic and Statistical Manual of Mental Disorders—5th edition (DSM-5) (Table 1)

The DSM-IV classified four different pervasive developmental disorders (PDDs) as separate diagnoses: autism disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS). These diagnoses were combined into one concept known as a "spectrum" ASD diagnosis in the DSM-5. Since Rett syndrome is now recognized as a distinct neurological condition, it is no longer classified as an ASD in the DSM-5. For people who struggle with social communication but do not exhibit repetitive or restricted behaviors, a distinct disorder known as social (pragmatic) communication disorder (SPCD) was created. Severity level descriptors were also included to aid in classifying the degree of assistance required by an individual with ASD.

The goal of this revised definition is to improve accuracy and facilitate the early diagnosis of ASD. Studies assessing the possible effects of switching from the DSM-IV to the DSM-5, however, have projected a decline in the prevalence of ASD, and there has been worry that children who have previously been diagnosed with PDD-NOS may not match the requirements for an ASD diagnosis. Different reports estimate the impact and scope of this shift. According to one study, the DSM-5 criteria detected 91% of children with clinical DSM-IV PDD diagnosis when parents reported their child's ASD symptoms alone.

However, a comprehensive analysis indicates that only 50% to 75% of people continue to receive a diagnosis (9) and additional research has also indicated a lower diagnosis rate for people with ASD using the DSM-5 criteria (10). People who did not fit the criteria were frequently labeled as having PDD-NOS and high functioning Asperger's syndrome in the past. There is a greater number of children whose ASD diagnosis is missed, especially older children, adolescents, adults, or those with a previous diagnosis of Asperger's disorder or PDD-NOS. Overall, most studies suggest that the DSM-5 provides increased specificity and decreased sensitivity compared to the DSM-IV. However, there seems to be a gradual decrease in the proportion of individuals who would receive a diagnosis under the DSM-IV but not under the new DSM-5, most likely as a result of improved behavior documenting and raised awareness.

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Table 1 Changes in ASD criteria from the DSM-IV to DSM-5

Changes	DSM-IV	DSM-5
Location in manual	Disorders usually first diagnosed in infancy, childhood, or adolescence	Neurodevelopmental disorder
Sub-criteria	3 sub-criteria	2 sub-criteria
	Qualitative impairment in social interaction	Persistent deficits in social communication and social interaction across multiple contexts
	Qualitative impairments in communication	Restricted, repetitive patterns of behavior, interests, or activities
	Restricted repetitive and stereotyped patterns of behavior, interests, and activities	
Needed to diagnose	Triad: 3/3 diagnostic criteria must be met	Dyad: 2/2 diagnostic criteria must be met
Diagnostic criteria	Qualitative impairment in social interaction, manifested by at least 2 of the following:	Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following:
	Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction	Deficits in social-emotional reciprocity, (including abnormal social approach and failure of reciprocal conversation, reduced sharing of interests, emotions, or affect, failure to initiate or respond to social interactions)
	Failure to develop peer relationships appropriate to developmental level	Deficits in nonverbal communicative behaviors used for social interaction (poorly integrated verbal and nonverbal communication, eye contact and gesture/body language abnormalities
	A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people	Deficits in developing, maintaining, and understand relationships (including adjusting behavior in various social contexts, difficulties in sharing imaginative play or in making friends, or lack of interest in peers)
	Lack of social or emotional reciprocity	Restricted, repetitive patterns of behavior, interests, or activities, manifested by at least two of the following:
	Qualitative impairments in communication as manifested by at least one of the following:	Stereotyped or repetitive motor movements, use of objects, or speech
	Delay in or total lack of, the development of spoken language	Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
	In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others	Highly restricted, fixated interests that are abnormal in intensity or focus

Table 1 (*continued*)

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Table 1 (*continued*)

Changes	DSM-IV	DSM-5
	Stereotyped and repetitive use of language or idiosyncratic language	Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment
	Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level	
	Restricted repetitive and stereotyped patterns of behavior, interests, and activities, manifested by at least one of the following:	
	Encompassing preoccupation with one or more stereotyped patterns of interest that is abnormal either in intensity or focus	
	Apparently inflexible adherence to specific, nonfunctional routines or rituals	
	Stereotyped and repetitive motor mannerisms	
	Persistent preoccupation with parts of object	
Age of development	Onset prior to age 3 years	Symptoms must be present in early developmental period but may not manifest until social demands exceed limited capacities or may be masked by learned strategies
Not better explained by	Rett's disorder or childhood disintegrative disorder	SPCD
Sensory symptoms	Not addressed	Sensory symptoms are a new criterion introduced in DSM-5 under the sub-criteria of restricted, repetitive patterns of behavior, interests, or activities

ASD, autism spectrum disorder; SPCD, social (pragmatic) communication disorder.

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The influence of the new SPCD diagnosis on the prevalence of ASD is still unknown. According to one study, the new SPCD diagnosis includes people with significant needs who do not meet the criteria for an ASD diagnosis but who have subthreshold autistic features. Moreover, children who satisfied DSM-IV criteria for PDD-NOS may now receive an SPCD diagnosis.

Epidemiology

The prevalence of ASD is estimated by the World Health Organization (WHO) to be 0.76% worldwide; however, this figure only represents about 16% of all children. According to estimates from the Centers for Disease Control and Prevention (CDC), 1 in 59 children in the US, or roughly 1.68% of children aged 8 years, have been diagnosed with ASD. In the United States, the average number of parent-reported ASD diagnoses in 2016 was 2.5%. The Autism and Developmental Disabilities Monitoring Network (ADDM) has estimated that between 2000–2002 and 2010–2012, the prevalence of ASD in the United States more than doubled. Although it may be too early to remark on trends, in the US, the prevalence of ASD has appeared to stabilize with no statistically significant increase from 2014 to 2016. It is still too early to tell how the DSM-5 diagnostic criteria may affect prevalence in its entirety.

The rise in ASD prevalence estimates and the rise in the diagnosis of milder cases of ASD in the US are probably due to increasing awareness and insurance regulations requiring commercial plans to include services for ASD. Even while the mandates only slightly increased prevalence at first, as health care providers gained more knowledge about the regulatory and reimbursement processes, prevalence continued to rise. Modifications in reporting procedures could potentially be the cause of the rise in prevalence. According to a Danish study, rather than a real rise in the frequency of ASD, the bulk of the increase in the condition's prevalence between 1980 and 1991 was caused by modifications to the diagnostic criteria and the addition of outpatient data.

All racial, cultural, and socioeconomic groups experience ASD, although diagnoses vary greatly among them. Compared to black or Hispanic children, Caucasian children are routinely diagnosed with ASD at a higher rate. Even while the discrepancies seem to be closing, stigma, limited access to healthcare services, and patients' native language being a language other than English could all be contributing factors to the persistent imbalance.

Although ASD is more common in men, a recent meta-analysis found that, despite not following the DSM-5 criteria, the true male-to-female ratio is closer to 3:1 than the previously stated 4:1. Additionally, this study revealed that girls who fit the criteria for ASD are more likely to go undiagnosed. It is possible that the autism phenotype in women contributes to misdiagnosis, delayed diagnosis, or missed diagnosis in girls. In addition to being less likely to exhibit overt symptoms, women are also more inclined to "camouflage" their social deficiencies, which makes an early diagnosis even more difficult. Similar to how gender prejudices and the idea that ASD is only a male condition may hinder diagnoses in girls.

Rett syndrome, Down syndrome, fragile X, and tuberous sclerosis are among the genetic diagnoses that have a higher rate of co-occurring ASD than the general population; nevertheless, the total number of ASD cases is much lower for these established genetic illnesses (27–30). Research on kids with sex chromosomal aneuploidy reveals a certain social functioning profile in men that may indicate a higher risk of autism. A number of locations (namely chromosomes X, 2, 3, 7, 15, 16, 17, and 22) have been linked to an elevated risk of ASD with the growing usage of chromosomal microarray.

Prematurity and older parents are two additional risk factors for ASD (33–35). This may be explained by the idea that older gametes are more likely to have mutations that increase the risk of developing preterm and other obstetrical issues.

Causes

ASD is a neurobiological condition that is impacted by environmental and genetic variables that have an impact on the growing brain. Our knowledge of probable etiologic pathways for ASD is still expanding as a result of ongoing research, but no single, overarching cause has yet been identified.

Though there have been few neuropathologic investigations, those that have been conducted have identified modest malformations, aberrations in the limbic system, variations in the cerebellar architecture and connections, and changes in the frontal and temporal lobe cortical modifications. A short exploratory study of young children's neocortical

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architecture found that most of the participants had focal disruption of cortical laminar architecture, indicating issues with cortical layer creation and neuronal differentiation. Children with ASD have been found to have brain overgrowth in terms of both cortical size and extra-axial fluid volume. These areas are currently being studied to learn more about the etiology of the disorder and to determine whether they could be biomarkers.

ASD susceptibility is influenced by genetic variables; siblings of ASD patients have a greater diagnosis risk than the general population, and autism diagnoses are significantly more likely, though not always, to coincide in monozygotic twins.

Our knowledge of the genes that predispose people to ASD has expanded thanks to genome wide association studies and whole exome sequencing techniques. Understanding the roles played by these genes may also provide insight into possible biological processes. Genes that influence neuronal excitability, neurotransmitter function, or brain development are a few examples of potential genes linked to ASD. Numerous genetic abnormalities linked to autism spectrum disorders (ASD) include proteins, including regulatory proteins like transcription factors, that are important at the neural synapse or involved in activity-dependent alterations in neurons. Neurotransmission and neuroinflammatory pathways are plausible "networks" of ASD genetic risk convergence. There could be a role for dysregulation of transcription and splicing or changes in epigenetic mechanisms such DNA methylation or histone acetylation and modification. A recent study reports 16 newly discovered genes linked to ASD, bringing to light novel potential mechanisms such as ion transport and cellular cytoskeletal structure. Ultimately, with uncommon de novo and inherited mutations in over 700 genes, ASD continues to be one of the most genetically diverse neuropsychiatric illnesses.

The etiology of ASD is undoubtedly influenced by genetics, yet the phenotypic manifestation of genetic predisposition within ASD is still highly heterogeneous. In certain cases, prenatal, perinatal, and postnatal environmental variables may alter genetic risk. Prenatal folic acid supplementation may lower risk in patients exposed to antiepileptic medicines, however prenatal exposure to thalidomide and valproic acid has been shown to raise risk. It's unclear from research if a modest but promising trial of folinic acid in autism can be utilized to support a larger recommendation for supplementation. It has been demonstrated that there is a higher chance of having a kid with ASD in older parents. There has been speculation about a maternal history of autoimmune diseases like psoriasis, diabetes, or thyroid conditions, but research findings are still conflicting. Another area of interest and possible risk factor, based on current research, is maternal infection or immunological activation during pregnancy. It has also been noted that longer and shorter interpregnancy periods raise the incidence of ASD. Premature babies have been shown to have an increased risk of ASD as well as other neurodevelopmental problems. Preterm delivery, low birthweight, caesarian delivery, uterine hemorrhage, and low Apgar scores were among the few obstetric variables that were found to be more consistently linked to autism in a previous epidemiologic assessment (67). Many prenatal, perinatal, and postnatal risk variables were shown in a recent meta-analysis to be associated with an increased relative risk of ASD in offspring. However, the results also showed high heterogeneity, making it difficult to determine the precise significance of these factors.

There is no proof that vaccinations, thimerosal, or mercury are linked to autism spectrum disorders (ASD), despite the panic surrounding the now-retracted Lancet article that was first published in 1998. In the biggest single study to date, a statewide cohort analysis of Danish children showed no increased risk following the measles, mumps, and rubella (MMR) immunization.

In the end, research keeps surfacing variables that are correlated with the likelihood of ASD, but no conclusions about causality have been drawn. This provides ample opportunity for exploration, as researchers persist in uncovering novel variations that indicate genetic susceptibility or novel environmental factors that necessitate additional investigation.

Assessment

In order to identify children who are at-risk or exhibiting symptoms suggestive of ASD, screening of the general pediatric population is the first step in the evaluation process. A diagnostic evaluation is then advised. According to AAP standards, developmental surveillance should be done at nine, fifteen, and thirty months during well-child visits. Additionally, autism-specific screening should be done at eighteen months and again at twenty-four or thirty months. Early indicators of Autism Spectrum Disorder (ASD) include low eye contact, a lack of response to name, sharing and showing, no gestures by the age of one year, and a loss of language or social skills. The Modified Checklist for Autism in Toddlers, Revised, with Follow-up (M-CHAT-R/F) and the Survey of Wellbeing of Young Children (SWYC) are

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two screening tests for ASD in this demographic. Preschoolers who exhibit restricted pretend play, peculiar or highly focused hobbies, and rigidity may be warning signs. Children of school age may exhibit literal or concrete thinking, struggle to understand emotions, and even show interest in their peers despite lacking the social skills or verbal abilities to engage in proper social interactions. The Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS), and Autism Spectrum Screening Questionnaire (ASSQ) are screening measures that can be used if there is a suspicion of ASD in these groups.

Primary care physicians are advised to refer children who exhibit concerns during screening to early intervention if they are younger than three years old, or to the public school system for a psychoeducational evaluation so that an individual education plan (IEP) can be established if the child is older than three. For a conclusive diagnosis and thorough evaluation, clinicians should also refer the patient to a specialist (pediatric neurologist, developmental-behavioral pediatrician, child psychiatrist, or certified child psychologist). A thorough physical examination that evaluates for dysmorphic traits, a thorough neurologic examination that includes measuring head circumference, and a Wood's lamp examination of the skin should all be part of an extensive evaluation. This thorough evaluation should include a parent interview, gathering of any outside informant observations, and a direct clinician observation of the child's present cognitive, linguistic, and adaptive functioning by a clinician with experience with ASD.

Furthermore, primary care physicians must be aware of co-occurring conditions in children with ASD and assess for them. In a surveillance study involving more than 2,000 children diagnosed with ASD, 83% of the children also had a developmental diagnosis, 10% had a psychiatric diagnosis, and 16% had a neurologic diagnosis. Intellectual disability (ID) co-morbid with ASD has been observed in patients as high as 50% to 70% in the past; the most recent estimate from the CDC is 31.0% (26.7% to 39.4%), with ID being defined as intelligence quotient (IQ) $\leq$70. Obesity, sleep disorders, seizures, and gastrointestinal (GI) diseases, including dietary limitations and food selectivity, are other typical co-occurring medical conditions. Research employing electronic health record (EHR) analysis demonstrated a prevalence of GI diseases [without inflammatory bowel disease (IBD)] at 10-12% and epilepsy at approximately 20% (82). Research has demonstrated that individuals with ASD who also have comorbid ID and high-risk medical conditions such tuberous sclerosis complex (TSC) are more likely to have epilepsy. Numerous studies have indicated that GI issues or GI symptomatology, such as reflux, constipation, diarrhea, or restricted eating, are common in ASD. Depending on how sleep symptoms are defined or how the assessment technique is employed, the prevalence of sleep disorders in patients with ASD has been reported to range from 50% to 73% (90-92). According to reports, the prevalence of overweight and obesity in children with ASD is approximately 33% and 18%, respectively, higher than that of typically developing children.

Anxiety, attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder, mood disorders, and other disruptive behavior disorders are additional behavioral or mental co-occurring problems in autism spectrum disorders (ASD). There are reports of co-occurring ADHD ranging from 25% to 81%. Despite a high degree of heterogeneity from the current literature, a recent meta-analysis of 30 studies measuring rates of anxiety and 29 studies measuring rates of depression found that the pooled lifetime prevalence for adults with ASD was 42% for any anxiety disorder and 37% for any depressive disorder, though estimates could be influenced by the use of self-report measures and the presence of ID (95). According to this study, co-occurring mood disorders (at 8%) and oppositional defiant disorder (at 46%) were also common in children with ASD seeking treatment; in fact, 66% of the sample, which included over 600 patients, had more than one co-occurring condition.

At this time, there are no well-defined biomarkers or diagnostic tools for ASD; instead, the diagnosis is established by meeting descriptive criteria. Clinical genetic testing is advised in view of the relatively high yield in ASD patients. It can aid with family planning and provide information about any essential medical interventions or work up. As first tier genetic testing in the work up of ASD, the American College of Medical Genetics and Genomics (ACMGG) guidelines currently prescribe chromosomal microarray for all children, fragile X testing in males, and further gene sequencing, including PTEN and MECP2 in some cases. Recent consensus recommendations no longer support the routine use of high resolution G-banded karyotype, which was once advised for all patients with ASD. However, it may still be done in patients whose reproductive or family history suggests chromosomal rearrangements, or who have specific syndromes like Trisomy 21 or sex chromosome anomalies. The American Academy of Neurology, the AAP, the ACMGG, and the American Academy of Child and Adolescent Psychiatry are among the professional societies that

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advocate genetic testing for ASD. Depending on the results of the testing, a child may need to be referred to a geneticist and/or genetic counselor in the future. Recent research indicates that whole exome sequencing might eventually replace other methods as the method of choice for clinical genetic testing in people with ASD, as the field of genetics continues to progress quickly.

For each patient diagnosed with ASD, no more laboratory testing is generally advised beyond genetic testing. However, patients with certain findings or risk factors can benefit from additional testing. Patients who exhibit any of the following concerning symptoms or signs should have a metabolic work-up: hypotonia; recurrent episodes of vomiting, lethargy, or hypoglycemia; microcephaly or poor growth; coarse features; concern for seizures or ataxia; or a history of clear developmental regression, including loss or plateau of motor skills. A metabolic laboratory evaluation could include the complete blood count (CBC), liver and renal function tests, lactate, pyruvate, carnitine, amino acids, an acylcarnitine profile, urine organic acids, and/or urine glycosaminoglycans, depending on the patient's history and presentation. Lead levels in children with a history of pica should be evaluated. A laboratory assessment of nutritional status should be taken into consideration for a youngster whose food intake is markedly reduced. A referral for a potential sleep study may be necessary if there are symptoms of restless sleep. If iron insufficiency is suspected, especially if dietary rigidity restricts iron intake, an examination is reasonable if these symptoms are present.

While neuroimaging is not always advised for children with ASD, it might be suitable in those who have microcephaly, a suspicious neurologic exam (spasticity, severe hypotonia, unilateral abnormalities), or a suspicion of TSC or other neurocutaneous disorders. It is recommended to obtain an electroencephalography (EEG) for patients who appear to be having seizures. When testing results are available, it may be best to send kids who show signs of other genetic, metabolic, or neurological disorders right away to a professional who can get and analyze the aforementioned tests. For those without a history of severe food selectivity, there is currently insufficient evidence to recommend routine testing for intestinal permeability studies, immunologic or neurochemical markers, mitochondrial disorders, allergy testing, hair analysis, uriney peptides, intestinal permeability studies, erythrocyte glutathione peroxidase studies, or vitamin and mineral deficiencies.

II. CONCLUSION

ASD is a neurodevelopmental disease marked by repetitive behaviors, limited interests, and difficulties in social communication. With the adoption of the new diagnostic manual (DSM-5), there have been recent modifications to the diagnostic criteria, which will probably have an effect on prevalence, which is currently 1 in 59 children in the US. ASD is a neurobiological condition that is impacted by environmental and genetic variables that have an impact on the growing brain. Although no clear ultimate causative pathway has been identified, research keeps identifying characteristics that are correlated with the risk of ASD, and these discoveries may direct future etiologic exploration. In order to identify children who may be at risk, developmental screening of the general pediatric population is the first step in the clinical evaluation process. A thorough neuropsychological assessment and a referral to a specialist are then conducted for a final diagnosis. Common co-morbid diagnoses should also be checked for in children with ASD. Clinical genetic testing is advised as a part of the initial medical examination even if there are no reliable biomarkers or diagnostic tools available. Referrals to subspecialists or additional medical testing may be undertaken in response to particular patient characteristics.

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