Autism Spectrum Disorder

DEFINITION, EPIDEMIOLOGY, ETIOLOGY, EVALUATION.

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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental illness marked by social communication difficulties as well as restricted interests and repetitive activities. There have recently been worries regarding growing prevalence, and this article aims to expand on issues that may impact prevalence rates, such as recent revisions to diagnostic criteria. The authors examine evidence that ASD is a neurobiological condition impacted by both hereditary and environmental variables impacting the developing brain, and they list risk factors for ASD. Lastly, the article outlines how clinical assessment begins with developmental screening and progresses to referral for a conclusive diagnosis, as well as offers advice on screening for concomitant diseases.

Keywords: Medical comorbidity, screening, evaluation, prevalence, etiology, Autism Spectrum Disorder (ASD)

DEFINITION:
A neurological illness called autism spectrum disorder (ASD) is characterised by limitations in social communication, the existence of narrow interests, and repetitive activities. Asperger's disorder, childhood disintegrative disorder, autistic disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) were all independent pervasive developmental disorder (PDD) diagnoses in the DSM-IV. The notion of a "spectrum" ASD diagnosis was developed in the DSM-5. As Rett syndrome is regarded as a distinct neurological illness, it is no longer classified as an ASD in the DSM-5. For those who struggle with social communication but don't exhibit repetitive, constrained behaviours, a distinct social (pragmatic) communication disorder (SPCD) was created. To assist classify the type of support an ASD patient needs, severity level descriptors were also added. This revised definition aims to be more precise and advances the early detection of ASD (3). Although there has been worry that children with a prior PDD-NOS diagnosis may not fulfill criteria for ASD diagnosis, studies predicting the possible impact of switching from the DSM-IV to the DSM-5 have indicated a drop in ASD prevalence (4,5). (5-7) The size and implications of this alteration have been estimated differently in several papers. In one research, the DSM-5 criteria identified 91% of children with clinical DSM-IV PDD diagnosis based only on parental reporting of ASD symptoms (8). However according to a comprehensive analysis, only 50% to 75% of people keep their diagnoses (9), and other research has similarly indicated a declining incidence of ASD diagnoses using the DSM-5 criteria (10). Frequently, persons who didn't fit the criteria were previously labelled as having PDD-NOS and high functioning Asperger's syndrome (11,12). While those with ASD are more likely to have the condition, there are more children whose ASD diagnosis is missed, especially older children, adolescents, adults, or those with a previous diagnosis of Asperger's disorder or PDD-NOS (5,13), as well as those who have a former diagnosis of Asperger's disorder or PDD-NOS (14).

How the new SPCD diagnosis would affect the prevalence of ASD is yet unknown. According to one research, the subthreshold autistic persons who do not meet the criteria for an ASD diagnosis but nevertheless have significant requirements are included in the new SPCD diagnosis (15). Moreover, youngsters who had previously satisfied DSM-IV PDD-NOS eligibility requirements may now be given the SPCD label.

EPIDEMIOLOGY:
The World Health Organization (WHO) estimates that there are 0.76% ASD cases worldwide, while only around 16% of children worldwide fall into this category (16). According to the Centers for Disease Control and Prevention (CDC), 1 in 59 American children aged 8 have an Autism Spectrum Disorder (ASD) diagnosis (6,17). Parent-reported ASD diagnoses in the US were somewhat higher on average in 2016 at 2.5%. (18). According to estimates from the Autism and Developmental Disabilities Monitoring Network (ADDM), the prevalence of ASD more than doubled in the US between 2000-2002 and 2010-2012. (6). Notwithstanding the possibility that it is too soon to make predictions about trends, the prevalence of ASD in the US seems to have stabilised, with no statistically significant rise from 2014 to 2016. (19). The complete effect of the DSM-5 diagnostic criteria has not yet been determined, however changing the diagnostic criteria might affect prevalence (17).

ASD prevalence estimates and the number of milder instances of ASD being diagnosed in the US have likely grown as a result of insurance laws mandating commercial plans to include therapies for ASD and increasing awareness (6,20,21). Even while there wasn't much of an increase in prevalence right away following the regulations, there have been subsequent rises as medical practitioners become more familiar with the regulatory and payment procedures. The rise in prevalence can also be brought on by modifications to reporting procedures.
According to a Danish research, changes in diagnostic criteria and the addition of outpatient data, rather than an actual rise in the incidence of ASD, were mostly responsible for the increase in prevalence from 1980 to 1991. (21).

All racial, cultural, and socioeconomic groups experience ASD, yet the diagnosis varies widely amongst them. Children who have ASD are consistently more likely to be White than Black or Latino (6). Although there still seems to be a gap, it may be because of stigma, a patient's inability to get treatment, or the fact that their native language is not English.

ASD is more prevalent among men (22,23) Nevertheless, a recent meta-analysis (24), which did not use the DSM-5 criteria, found that the real male-to-female ratio is closer to 3:1 than the previously reported 4:1. According to this study, girls who fit the criteria for ASD are more likely to go without a clinical diagnosis. Girls with autism may experience misdiagnosis, delayed diagnosis, or non-diagnosis due to the feminine phenotype. In addition to being less likely to exhibit overt symptoms, women are also more inclined to "camouflage" their social deficiencies, which makes it more difficult to make a prompt diagnosis (25). Similarly, misconceptions about ASD being a male condition and gender biases might prevent diagnosis in females (26).

Fragile X, tuberous sclerosis, Down syndrome, Rett syndrome, and other genetic illnesses all have higher rates of co-occurring ASD than the general population, although they only make up a very tiny percentage of all instances of ASD (27-30). A certain social functioning profile in men is described in studies of children with sex chromosomal aneuploidy, which predicts a greater susceptibility to autism (22,23,31,32). ASD risk has been linked to a number of locations, including those on chromosomes X, 2, 3, 7, 15, 16, and 22, thanks to the growing usage of chromosomal microarray (28).

Prematurity and older parental figures are additional risk factors for ASD (33-35). This could be because, according to the notion, older gametes are more likely to have mutations that increase the risk of preterm and other obstetrical issues (36).

ETIOLOGY:

ASD is a neurobiological disease that is impacted by environmental and genetic variables that have an impact on the developing brain. Although no one, overarching explanation for ASD has yet been identified, ongoing research is expanding our understanding of various etiologic processes that may contribute to the disorder.

Despite the paucity of these research, cerebellar architecture and connection discrepancies, limbic system abnormalities, frontal and temporal lobe cortical changes, as well as other modest anomalies, have all been identified (28,37,38). Focused disruption of cortical laminar architecture was seen in the majority of participants in a short exploratory investigation of young children's neocortical architecture, pointing to issues with cortical layer creation and neuronal differentiation (39). Children with ASD have been documented to have enlarged brains in terms of cortical size as well as an increase in extra-axial fluid; these findings are the subject of continuing research to help us better understand the genesis of the disorder as well as to identify a possible biomarker (40,41).

Siblings of individuals with ASD have a greater likelihood of diagnosis compared to the general population, and monozygotic twins have a substantially higher, but not 100%, concordance of autism diagnosis. Genetic variables play a role in ASD susceptibility (42-44).

Our understanding of ASD susceptibility genes has been expanded by genome wide association studies and whole exome sequencing techniques, and knowing the function of these genes might provide insight into probable biological pathways (45). For instance, potential genes for ASD include those that impact neuronal excitability, brain development, or neurotransmitter function (46,47). The majority of the genetic flaws linked to ASD encode regulatory proteins like transcription factors, which are important at the neural synapse or involved in activity-dependent alterations in neurons (42,48). ASD genetic risk convergence "networks" may comprise neurotransmission and neuroinflammatory signalling pathways (49). Alterations in epigenetic processes, such as DNA methylation or histone acetylation and modification, or dysregulation of transcription and splicing might be involved (42,49-51). In a recent research, 16 newly discovered genes linked to ASD were described. These genes suggest novel possible processes, such as cellular cytoskeletal organisation and ion transport (52). ASD has uncommon de novo and inherited variations in approximately 700 genes, making it one of the most genetically diverse neuropsychiatric illnesses (53).

Although genetics undoubtedly contribute to the aetiology of ASD, the phenotypic manifestation of genetic predisposition within ASD is nonetheless incredibly heterogeneous (54). Prenatal, perinatal, and postnatal environmental variables in some individuals may modify genetic risk (35). Studies show that prenatal folic acid supplementation in patients exposed to antiepileptic medicines may lower risk, although prenatal exposure to thalidomide and valproic acid have been observed to increase risk (55-57). It has not been shown by research if a modest, successful trial of folic acid in autism may be used to suggest supplementation more generally (58). An increased chance of having a child with ASD has been demonstrated for both older mothers and fathers (59). It has been hypothesised that autoimmune diseases such as diabetes, thyroid illness, or psoriasis run in the maternal family, however research findings are still conflicting (60,61). Another area of concern is maternal illness or immunological activation during pregnancy, which may be a possible risk factor, according to recent studies (62-65). There has also been evidence that both shorter and longer inter-pregnancy intervals raise the incidence of ASD (66). Premature babies have a higher chance of developing ASD as well as other neurodevelopmental abnormalities, according to research (34). Obstetric variables such as uterine haemorrhage, caesarian deliveries, low birthweight, preterm birth, and low Apgar scores were revealed to be the few factors more consistently related with autism in a previous epidemiologic analysis (67). A recent meta-analysis showed a number of prenatal, perinatal, and postnatal risk variables that contributed to an increased relative risk of ASD in children (35), but it also revealed high heterogeneity, making it impossible to accurately assess the significance of these factors.

There is no proof that vaccinations, thimerosal, or mercury are linked to ASD, notwithstanding the panic surrounding the now-retracted Lancet paper that was initially published in 1998. (68-70). A statewide cohort study of Danish children found no evidence of an elevated risk following the measles, mumps, and rubella (MMR) vaccine, making it the biggest single research to date (70).

In the end, research will continue to identify variables that are associated with an increased risk of ASD, but no causative links have been shown. This gives a lot of potential for discovery as researchers work to identify novel genetic risk variants or new environmental factors that need additional investigation (52).

EVALUATION:

A diagnostic examination is then advised after screening the general paediatric population for children who may be at risk or who are exhibiting symptoms indicative of ASD. Guidelines from the American Academy of Pediatrics (AAP) include developmental monitoring during well-child visits at 9, 15, and 30 months, as well as autism-specific screening at 18 months and again at 24 or 30 months (28,71). Poor eye contact, inadequate name response, lack of sharing and displaying, no gestures by 12 months, and loss of language or social abilities are some early indicators of ASD. The Modified Checklist for Autism in Toddlers, Revised, with Follow-up (M-CHAT-R/F) and Survey of
Wellbeing of Young Children (SWYC) are screening instruments for ASD in this demographic (72,73). Limited pretend play, unusual or extremely concentrated hobbies, and rigidity are all warning signs in toddlers. Children of school age may think logically or literally, have difficulty comprehending emotions, and may exhibit interest in their friends, but they may lack social graces or conversational abilities. The Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS), and Autism Spectrum Screening Questionnaire (ASSQ) are accessible screening instruments if there is a suspicion of ASD in these populations (74-76).

If issues are discovered during screening, it is advised that primary care clinicians refer the child to early intervention if they are under three years old or to the public school system for a psychoeducational evaluation in order to create an individual education programme (IEP) if they are three years old or older. Also, for a thorough evaluation and clear diagnosis, clinicians should send the child to a specialist (paediatric neurologist, developmental-behavioral paediatrician, child psychiatrist, or certified child psychologist) (71). A thorough evaluation should consist of a thorough physical examination, which should include a check for dysmorphic characteristics, a full neurologic examination with a head circumference, and a skin Wood's lamp examination. This thorough evaluation should include a parent interview, the gathering of any informant observations from the outside world, and a direct clinician observation of the child's present cognitive, linguistic, and adaptive functioning by a clinician with ASD experience. (28,71,77,78).

The possibility of co-occurring disorders in children with ASD should also be considered by primary care providers. A surveillance study of more than 2,000 ASD patients found that 83% also had a developmental diagnosis, 10% had a psychiatric diagnosis, and 16% had a neurologic diagnosis (79). The most current CDC estimate placed the rate of co-morbid intellectual impairment (ID) in patients with ASD at 31.0% (26.7% to 39.4%), with ID being defined as an IQ of less than 70. In the past, rates of co-morbid ID in individuals with ASD were reported at 50% to 70%. (6,80). GI (gastrointestinal) issues, including dietary limitations and food preferences, sleep disorders, obesity, and seizures are some other frequent co-occurring medical diseases (81-84). Epilepsy was shown to be prevalent in studies employing electronic health record (EHR) analysis at 20%, while GI illnesses [without inflammatory bowel disease (IBD)] were found to be prevalent at 10-12%. (82). It has been demonstrated that ASD with comorbid ID and medical conditions carrying a higher risk, such as tubercous sclerosis complex (TSC), have higher prevalence rates of epilepsy (85-87). Depending on how sleep symptoms are defined or the measuring method employed, persons with ASD have been reported to experience sleep issues in anywhere between 50% and 73% of cases (90-92). Overweight and obesity are more common in ASD children than normally developing children, with rates of about 33% and 18%, respectively (81-84,93). Anxiety, attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder, mood disorders, and other disruptive behavioural disorders are additional behavioural or mental co-occurring illnesses in ASD (81).

There have been reports of co-occurring ADHD rates ranging from 25% to 81%. (81,94). Despite the high degree of heterogeneity in the current literature, a recent meta-analysis of 30 studies measuring anxiety rates and 29 studies measuring depression rates found that the combined lifetime prevalence for adults with ASD was 42% for any anxiety disorder and 37% for any depressive disorder, though the use of self-report measures and the presence of ID may have affected estimates (95). This study indicated co-morbid oppositional defiant disorder at a rate of 46% and mood disorders at 8%, with 66% of the sample of over 600 patients having more than one co-occurring disease. Among children with ASD seeking treatment, the prevalence of any anxiety disorder was found to be comparable at 42%. (94).

Currently no clear ASD biomarkers or diagnostic measures exist, and the diagnosis is made based on fulfillment of descriptive criteria. In light of a relatively high yield in patients with ASD, clinical genetic testing is recommended and can provide information regarding medical interventions or work up that might be necessary and help with family planning (96). The American College of Medical Genetics and Genomics (ACMG) guidelines currently recommend chromosomal microarray for all children, fragile X testing in males, and additional gene sequencing, including PTEN and MECP2, in certain patients as first tier genetic testing in the work up of ASD (97).

According to recent consensus recommendations, high resolution G-banded karyotyping, which was once advised for all ASD patients, is no longer routinely indicated. However, it may still be done for patients who have a family or reproductive history suggesting chromosomal rearrangements or specific syndromes like sex chromosome anomalies or Trisomy 21. (96-98). Several professional societies, including the American Academy of Neurology, the AAP, the ACMGG, and the American Academy of Child and Adolescent Psychiatry, recommend genetic testing for ASD. Depending on the results of the test, a child may need to be referred further to a geneticist and/or genetic counsellor (25,28,97,99). Recent studies indicate whole exome sequencing may replace other clinical genetic testing methods as the science of genetics continues to develop quickly in people with ASD (100,101).

No further laboratory testing, save genetic testing, is typically advised for every patient with an ASD diagnosis. More testing, however, could be necessary for people with specific results or risk factors. Patients who present with any of the following worrying symptoms or signs should be evaluated for a metabolic condition: a history of obvious developmental regression, such as loss or plateauing of motor abilities, hypotonia, repeated vomiting, lethargy, or hypoglycemic episodes, microcephaly or poor growth, concern for other organ involvement, coarse features, or worry about seizures or ataxia. A metabolic laboratory assessment may include a 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 (97,102). Lead levels in kids with a history of pica should be checked (28,103). A laboratory assessment of a child's nutritional status should be taken into consideration if their food consumption is considerably reduced. An examination for iron insufficiency is not unreasonable if restless sleep symptoms are present, especially if dietary rigidity restricts iron intake. Sleep complaints may call for a referral for a potential sleep study (104). For individuals with ASD, neuroimaging is not always advised (28,99), but it may be useful if there is a suspicion of TSC or other neurocutaneous abnormalities, microcephaly, or an abnormal neurologic exam (spasticity, severe hypotonia, unilateral findings). Electroencephalography (EEG) should be performed on patients who appear to be having seizures (102). Whenever possible, it may be best to refer children who may have further genetic, metabolic, or neurological issues very early to a specialist who can order and interpret the aforementioned testing. Without a history of extreme food selectivity, there is currently insufficient evidence to recommend routine testing for vitamin and mineral deficiencies, celiac disease, immunologic or neurochemical markers, mitochondrial disorders, allergy testing, hair analysis, intestinal permeability studies, erythrocyte glutathione peroxidase studies, stool analysis, or urinary peptides.

**SUMMARY:**
The neurodevelopmental condition known as ASD is marked by difficulties with social interaction, as well as by narrow interests and repetitive activities. The transition to the new diagnostic manual (DSM-5) resulted in recent revisions to the diagnostic criteria, which are expected to have an effect on prevalence, which is now estimated to affect 1 in 59 children in the US. ASD is a neurobiological disease that is impacted by environmental and genetic variables that have an impact on the developing brain. A complete causal route has not yet been identified, but research is still revealing variables that are associated with an increased risk of ASD. These findings may serve as a roadmap for early intervention and diagnosis.
For future etiologic research. Clinical examination begins with developmental screening of the general paediatric population to identify children who are at risk, then is followed by a specialist referral for a precise diagnosis and thorough neuropsychological evaluation. Moreover, prevalent co-morbid disorders should be checked for in children with ASD. The first medical examination should include clinical genetic testing even if there are no obvious biomarkers or diagnostic techniques. Based on certain patient features, additional medical testing or subspecialty referrals may be requested.

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