AN UPDATE ON AUTISM SPECTRUM DISORDER PART 1: THROUGH A CLINICAL LENS

Abstract

During the past 30 years, autism spectrum disorder (ASD) has emerged as one of the faster growing diagnosed disorders of childhood. Its growth in prevalence among children has led to the need for a much greater focus on this area from not only a clinical lens, but also an insurance one.

Autism is also not just a disorder of children. According to the CDC, more than 5.4 million adults (>2% of the population) in the U.S. alone have ASD. In addition, a 2022 study found that adults with autism comprise 0.6% of the world's adult population.

An additional concern with ASD is the many comorbidities linked to it that are known to impact the health and wellbeing of those with the disorder.

Assessing risk for ASD, however, is still inherently difficult due to the heterogeneity of its manifestations, as well as gaps in the clinical understanding of its pathogenicity, its potential comorbidities, and its variable long-term prognosis. This usually means that in addition to clinical information, social, educational, and behavioral information is routinely required in order to develop a comprehensive assessment when reviewing applications indicating ASD in the medical history.

This article, the first of two parts, provides a clinical review of ASD, and the second part, in the September issue, will focus on insurance medicine's view and assessment of ASD.

Introduction

Autism spectrum disorder (ASD) is commonly described as a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction together with restricted and repetitive patterns of behavior, interests, and activities.[1]

It is estimated that since the 1990s, prevalence of ASD has steadily increased due to a multitude of factors. According to the U.S. Centers for Disease Control and Prevention (CDC), in 2000, U.S. prevalence in children was approximately 1 in 150. By 2018, that number rose to approximately 1 in 44.[2] Worldwide prevalence has also seen a substantial uptick. Estimated global prevalence as of 2022, according to the World Health Organization (WHO), was 1 in 100 children,[3] a number nearly double that of 10 years ago, when worldwide prevalence was 62 in 10,000.[43]

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With the combination of ASD's increased prevalence, medicine's greater understanding of it as well as of its growing health and social impact, it is not surprising to see that insurance customers, who are the main care providers for these individuals, are seeking broader and more targeted coverage for ASD healthcare needs. The market's greater focus on providing more tailored juvenile products is contributing to improving coverage options for persons with ASD as well.

Understanding the Disorder

The most recent update of the International Classification of Diseases (ICD), version 11, describes ASD as "Characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behavior, interests, or activities that are clearly atypical or excessive for the individual's age and sociocultural context."[4]

Certain behavioral actions can be indicative of ASD. Commonly expressed social deficits include lack of social-emotional reciprocity, difficulty in interpreting nonverbal communication, and challenges in initiating and maintaining human relationships.

Those with ASD also prefer repetitive, stereotyped movements or experiences. Introducing anything new into customary routines can be challenging both for the patient and the caregiver. ASD individuals can also be very sensitive to certain neurosensory inputs, such as particular sounds.

These signs and symptoms typically first emerge in early childhood, but some manifestations may not be overt in situations where the social interactions are not new and therefore not challenging to the child.

ASD can also occur alone or with other neurodevelopmental, mental, or behavioral conditions. Language or learning impairments may also be associated but do not necessarily occur in all cases.[5]

Table 1: Medical Syndromes With Symptoms Similar to ASD

Williams Syndrome	Fragile X Syndrome
Tardive Dyskinesia	Angelman Syndrome
Prader-Willi Syndrome	Rett Syndrome
Landau-Kleffner Syndrome	

Source: https://www.autism.org/related-disorders/[6]

Pathogenesis

The underlying etiologies of ASD have not yet been fully elucidated. The current accepted understanding is that many cases may have a genetic component. This is supported by evidence that shows differences in sex distribution (far more prevalence among males than females) and increased prevalence among siblings and family members.

Many genes known to be associated with ASD are also associated with neurological development or function in some way (e.g., neurogenesis or synaptic functioning) and are expressed in the central nervous system. Despite these associations, no genetic linkage has yet been identified that is specific to ASD. Most likely, its genetic component involves interplay among certain genes, their variants, how they are expressed, and other external influencing factors.[7, 8]

Environmental and perinatal factors have also been determined to increase the risk of developing ASD. Many of these factors center around the conception or perinatal period, which indicates how impacts on neurogenesis can increase the likelihood of development of ASD. Older parental age, for example, has been shown to be a factor in increased ASD risk, likely due to the greater potential for spontaneous mutations or alterations in genetic expression due to age.[9] Perinatal risks have also been studied, but to date no single specific risk has been identified.

What the evidence has shown so far is that conditions that adversely affect neonatal or maternal health can lead to an increased risk profile for ASD. Neonatal conditions such as low birth weight and prematurity,[10] and maternal conditions such as diabetes, preeclampsia,[11] and obesity, can all potentially contribute to ASD development.[12, 13] Exposure to certain medications taken by the mother during pregnancy, such as valproic acid[14] and selective serotonin reuptake inhibitors (SSRIs), have been shown to increase ASD risk as well. Whether it is the exposure to medications, or the combination of such exposure with the possible genetic linkage to the underlying neurological or psychiatric indication for use, there seems to be an increase in ASD risk in children of mothers who continued these medications during pregnancy.[15] However, in many cases, the risk to the mother and child of stopping certain medications might outweigh the potential ASD risk, and so would not preclude use of these medications.[16]

A note about vaccines: Although vaccines had been controversially linked to ASD by some reports in the past, a large body of epidemiological research and evidence has since conclusively shown there is no link at all between vaccines and development of ASD.[17, 18]

Prevalence

Prevalence of ASD varies from country to country and region to region, depending on the methodology used and the area studied. However, one well-recognized worldwide trend in ASD is fast-rising prevalence. Current approximate overall prevalence (children and adults) ranges from 1 in 40 to 1 in 500 across the U.S., Europe, and Asia.[19]

This increased prevalence is due to many factors. Most ascribe it mainly to the better understanding and awareness of this disorder by the public and medical communities. With this has come better and earlier detection of cases through screening and referrals for clinical assessment, as well as the development of more dedicated services for individuals with ASD and their caregivers and families. However, the lack of access to testing and care services in some regions may mean a number of children are undetected until later in life; sometimes not until adulthood.[20, 21] This situation was made even more difficult during the past few years, as some

studies suggest the COVID-19 pandemic may have contributed directly to delayed screenings for younger children with ASD.[44]

There is also the likelihood that the increased prevalence may be due to a truer representation and clearer understanding of the condition. In the past, many ASD cases may have been misdiagnosed as either a learning disorder or an intellectual disability but can now be more accurately recognized. There may also be a true increased prevalence of ASD, as multiple social, economic, and environmental factors have been linked to a rise in prevalence for childhood developmental disorders overall.[22]

Prevalence among children and adults is similar, and the higher concordance among siblings points to a genetic pathophysiology in many cases.[24] Males are also known to be more likely to be diagnosed with ASD than females, with some studies show prevalence among males to be as much as four times that of females. However, other comprehensive studies indicate that this number may be overestimated, and that females may be underdiagnosed.[23]

Clinical Assessment

Early diagnosis and intervention are critical to enabling those with ASD to receive appropriate treatment and improve prognoses. For proper evaluation and diagnosis, however, there needs to be an awareness of the condition by the primary caregivers as well as opportunities to screen for the disorder.

It is of vital importance as well that primary caregivers are educated about early signs and symptoms that may suggest the presence of ASD. Most commonly, a primary caregiver will be aware something is "off" due to the differences in the progression of a child's social skills compared to their cognitive skills. For very young children, normal social milestones such as eye contact, smiling, and showing affection can be impacted, and early pathological repetitive behaviors (such as hand flapping) and fixations (certain obsessive behaviors) can also be present.

Screening through various community health services, routine check-ups, and reports from teachers are other vital ways of picking up cases among younger individuals.[25]

Table 2: Early ASD Indicators in Children

Age	Signs/symptoms
<6 months	• Decreased visual fixation
6-12 months	• Reduced response to name • Reduced gaze to faces • Lack of shared smiles • Limited to no vocalizations • Fixations on certain things or actions
12-24 months	• Limited sharing, interests, or attention • Problems with eye contact • Initiative and receptive language delay • Lack of response to name • Lack of imaginative and imitative play • Verbal and non-verbal communication deficits

Source: https://pubmed.ncbi.nlm.nih.gov/31843864/[26]

Table 3: Early Manifestions Reported by Caregivers	
Social, language, behavior delays or deficits	Lack of pretend play or gesturing
Frequent tantrums or intolerance to change	Repeating words, phrases, actions over and over
Does not respond to name, prefers being alone	Obsessive over certain things, dislikes change
Avoids eye contact	Unusual sensitivities to sounds, smells, tastes

Clinical Intervention

After initial determination of the possibility of ASD, referral for a comprehensive evaluation is the next critical step. This is usually done by a specialist clinician with expertise in ASD evaluation and treatment. The evaluation should incorporate a thorough medical history, physical examination, and investigational bloodwork, to determine the following: if the child meets the diagnostic criteria for ASD (usually according to DSM 5-TR criteria); the child's neurodevelopmental status as well as strengths and weaknesses; whether there may be an underlying organic cause of the ASD symptoms; and if any other associated conditions or comorbidities are present. The severity of each of the symptoms is also assessed, and graded, using the three levels of severity described in the DSM 5 criteria.

Table 4: ASD Severity Levels		
Level 1	Requiring support	• Difficulty initiating social interactions • Organization and planning problems can hamper independence
Level 2	Requiring substantial support	• Social interactions limited to narrow special interests • Frequent restricted/negative behaviors
Level 3	Requiring very substantial support	• Severe deficits in verbal and nonverbal social and communication skills • Great distress/difficulty changing actions or focus

Source: https://www.verywellhealth.com/what-are-the-three-levels-of-autism-260233[42]

Assessment of severity is crucial to determining what type of care support may be required going forward and may also be an important indicator of future prognosis.[27] The assessment process may require multiple consultations and, in many cases, the assistance of a multidisciplinary team. Through this, a proper diagnosis can be arrived at and a thorough and individualized treatment and management plan can be formulated for a child's specific needs and severity level.[28]

Associated Comorbidities

An important part of the comprehensive assessment is screening for associated conditions such as genetic disorders, neurological or psychiatric pathologies, and other medical issues.

Developmental conditions commonly found include global or specific learning and language delays. ADHD as well as anxiety, depression, or other mood disorders may also be present in young to

adolescent children. Older children or young adults may exhibit aggression or self-harming behaviors. In terms of medical conditions, ASD is linked with epilepsy, fine and gross motor incoordination, feeding problems, gastrointestinal issues, and sleep disorders.[29]

Apart from the medical history and physical examination, additional investigations are often required to complete the full diagnostic picture. This includes referrals for formal genetic testing as well as metabolic and biochemical screening to rule in or out any organic causes. Focused neurological diagnostic tests such as MRI or EEG may also be useful in cases with certain associated conditions such as epilepsy.[30]

Treatments/Therapies

ASD is a chronic condition. Once a diagnosis is confirmed, a multidisciplinary holistic management plan needs to be developed for the patient according to their age and specific needs.

Chronicity also means management plans and therapies will need to evolve over time as the individual ages.

The current goal of ASD management is not curative. Rather, it is to optimize quality of life by facilitating improvements, if possible, in independence and social functioning. Often, an individual's entire family, including siblings, will be involved in the caregiving and therapies. Support should be provided to the main caregivers so that specific interventions can be implemented where necessary. This also extends to other settings such as schools, as the child is likely to need specialized care and attention for their educational needs.[31]

Overall goals of ASD therapy may include[32, 33] promoting and developing positive behaviors, such as social and communication skills, independent and adaptive skills, and education and cognitive skills. Goals may also include helping to manage negative behaviors such as non-functional or maladaptive behaviors and rigidity in thinking and behaviors.

To best achieve the goals of therapy, some key factors that may maximize outcomes are:[34, 35]

- **Timing.** Research has shown that early diagnosis and early intervention can positively impact ASD children and be crucial for their longer-term prognosis. Intensive therapy and treatments may foster improvements that over time can minimize the impacts to the child's quality of life. Together with improving existing symptoms, there is also evidence to show early diagnosis and intervention may prevent other problematic behaviors from developing.
- **Multidisciplinary team approach.** Individualized and targeted therapy for the child needs to be addressed in a holistic manner, as multiple aspects may require intervention through various specialists, including:
  - Developmental pediatrician
  - Child psychiatrist and psychologist
  - Speech pathologist
  - Occupational therapist
  - Social worker
  - School teachers

Behavioral Interventions

Behavioral interventions have been extensively studied in the two-year-old to adolescent age range and have been found to be some of the most effective treatments for ASD.[36] Within this age range, the most efficacious treatments, according to evidence, have been:

- Behavioral approaches
- Developmental approaches
- Naturalistic Behavioral Developmental Interventions (NBDI)
    - NDBI integrates therapy into the child's everyday life through a developmental systems approach, to ensure development of skills in one domain (e.g., learning a symbol, such as a new word or gesture, in one activity) are integrated with development of skills in other domains (e.g., using the word or gesture to sustain engagement with another person and in other activities). Skills are taught in the course of a child's typical daily interactions, experiences, and routines, with multiple materials and by multiple people[1,41]
- Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH)[38]
    - The TEACCH program is used to promote learning and development – in particular, communication and social skills, independence, coping skills and skills for daily life, such as dressing, washing, cleaning teeth, and so on. Tailored to each child's individual needs, it centers around structured teaching in a classroom setting through using schedules and physically organized spaces to make daily life predictable for children and help them understand their daily activities.
- Psychotherapy (e.g., cognitive behavioral therapy [CBT])
- Group-based Social Skills Interventions (GSSIs) (effective for adolescents)

The current goal of ASD management is not curative.

For children under age two, an integrative developmental behavioral model focusing on social, speech, and communication skills through exploratory play and sensory stimulation has proven beneficial.

Among older adolescents, the treatment/therapy focus should shift to helping them learn skills to maintain desirable behaviors and reduce maladaptive behaviors. Training in developing the ability to perform adult activities should also start at this age range to prepare them for adulthood.

Pharmacological Treatment

ASD has no known cure, and no currently known efficacious pharmacological treatment. That being said, certain pharmacological options for psychiatric or neurodevelopmental conditions that co-occur with ASD should be considered, especially when these conditions and other behaviors lead to a severely impacted quality of life and interference with other therapies and treatments. They should only be started when other treatment modalities are in place and maximized.[37]

A careful analysis of the risk and benefit of each pharmaceutical treatment option should be undertaken, then closely monitored and consistently followed. The potential for polypharmacy reactions is also present and the attempt to minimize interactions should be reviewed.

Table 5: Current Pharmacological Interventions and Indications of Usage			
Indications	**Medications**	**Actions**	**Adverse Effects**
Irritability, aggression, emotional instability	aripiprazole, risperidone	Atypical antipsychotic, acts mainly at dopamine and serotonin receptors	Drowsiness, gastrointestinal (vomiting, appetite changes, constipation), extrapyramidal effects
ADHD	methylphenidate (MPH), atomoxetine, extended release guanfacine	Noradrenaline and dopamine effects	Appetite changes, irritability, headaches, sleep problems, emotional disturbance
Restricted, repetitive behaviors	SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline)	Affects serotonin reuptake	Mood and energy changes, insomnia, gastrointestinal upset
Sleep	melatonin	Impacts sleep/wake cycle	Drowsiness, headache
Hyperactivity, irritability	N-Acetylcysteine	Acts as an antioxidant and contributes to production of glutathione, one of the main central nervous system antioxidants	Gastrointestinal upset, drowsiness
Social, communication challenges	oxytocin	Acts as a neuropeptide, potentially affecting neural pathways that play roles in social/communication	Increased appetite, energy, restlessness

Source: https://pubmed.ncbi.nlm.nih.gov/36625807/[38]

Complementary Therapies

Not surprisingly, a large number of caregivers (and patients) pursue alternative or complementary therapies to treat, cure, or alleviate the symptoms of ASD. While many therapies are available (treatments, medications, and supplements), unequivocal evidence showing efficacy over existing treatments and/or placebo is still lacking. It is important that before a complementary approach is considered, the primary clinician treating the child is consulted.[39]

A healthy lifestyle should still be encouraged for ASD children. This includes a well-balanced and nutritious diet, avoidance of neurotoxins, a good amount of physical and social activity, and adequate sleep. All of these support the goal of having an overall better functioning child or adult who can live with and function better with their ASD.[40]

Conclusion

As ASD continues to rise in prevalence, it will require a persistent effort to continue vital research into its pathogenesis and pathophysiology in order to further break down the mysteries of this difficult and disabling disorder. In parallel, greater screening and awareness means that the potential to implement early intervention treatment in young children is increased, and with that hopefully an improvement in

the quality of life through the utilization of multiple modes of therapy. However, despite the advances in knowledge and treatment of ASD during the last 20 years, it remains a chronic lifelong condition that is associated with increased morbidity. Therefore, the need for better access to care and having the resources to initiate and maintain care is vital, and it is within this space that insurers can find themselves playing an invaluable role in helping a person with ASD journey towards a better and longer life.

Part 2, which will cover the insurance implications in depth, will be in the September 2023 edition of ReFlections.

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