

# Virtual Mentor

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## CLINICAL PEARL

### The Spectrum of Autism—From Neuronal Connections to Behavioral Expression

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Autism spectrum disorders are defined behaviorally by the *Diagnostic and Statistical Manual (DSM) IV-TR* based on abnormal development in social interaction and communication and restricted, repetitive, and stereotyped patterns of behaviors and interests that are evident before the age of 3. After decades of debate, research has demonstrated that the distinctions among autism, Asperger disorder, and pervasive developmental disorder not otherwise specified are neither clinically reliable nor based on valid neurobiological or genetic differences. The fifth edition of the *DSM* therefore proposes to collapse all of the clinical syndromes under the single diagnosis of autism spectrum disorder (ASD).

#### Etiology

There will continue to be no separate category of ASD diagnoses for cases with a known etiology in *DSM-5*. These etiologies are typically discovered after the diagnosis is made, though autism spectrum disorder sometimes manifests after an early diagnosis of a primary disorder such as Down syndrome, neurofibromatosis, or inborn errors of metabolism. Currently, the most common identifiable causes of ASD are tuberous sclerosis and fragile X syndrome. Many other disorders are infrequently associated with ASD. ASD cases co-occurring with recognizable genetic syndromes are classified as syndromic autism spectrum disorder, and those without a recognizable syndrome are termed nonsyndromic or idiopathic [1].

The list of identifiable causes is growing as a result of the rapid pace of genetic discoveries about autism spectrum disorder [1]. At present, about 15 or 20 genes or chromosomal syndromes have been identified that each account for a small percentage of cases. The distribution of these genes over the genome explains why ASD has been “nonspecifically” associated with chromosomal abnormalities. The study of families with these rare genes has shown that they are associated with autism, ASD, and intellectual disability without ASD, all of which can occur within the same family. Genes code for protein formations, which, in this context, affect brain development; disorders with similar manifestations likely have overlapping brain differences. Likewise, a number of the genes associated with autism spectrum disorder have also been associated with attention deficit disorder/hyperactivity (ADHD), depressive disorders, schizophrenia, and obsessive compulsive disorder (OCD).

## **Pathophysiology**

Major strides have also been made in understanding the pathophysiology of ASD. Alterations in cortical connectivity are now widely accepted as a central pathophysiologic mechanism [2, 3]. The alteration is typically characterized as (functional) underconnectivity of cortical systems (cortico-cortical intra-hemispheric connectivity) and (functional) overconnectivity of local cortical connections [4]. In many respects, ASD could be conceptualized as a failure or underdevelopment of the specialization of cortical systems and organization responsible for both voluntary and automatic functions [5].

The idea that ASD stems from genes that guide neuronal development is supported by “neuropathologic studies indicating malformations in the minicolumnar structure of the cortex, volumetric studies indicating early brain overgrowth and a subsequent abnormal trajectory of brain growth, and the functional imaging studies that indicate abnormalities in the functional connections between brain regions during cognitive processing” [6]. The importance of this pathophysiologic characterization is that it provides a framework for interpreting all of the clinical manifestations of ASD: selective underdevelopment of higher-order abilities with or without enhanced basic abilities in the same domain of function. This perspective makes it possible to understand why ASD not only affects the social, communication, and reasoning domains (those with the highest information processing demands) but also higher cortical sensory and motor abilities, balance, and memory. Altered connectivity also appears to explain the co-occurrence of anxiety disorder, affective disorder, and OCD with ASD.

## **Diagnosis**

Despite autism spectrum disorder’s neurobiological and genetic basis, diagnosis remains focused on behavior. The behavioral manifestations of ASD are variable in nature and degree, as would be expected from the underlying pathophysiology and genetics described above. Even among individuals of the same age and similar IQ with rigorously diagnosed autistic disorder, there are variations in everything from motor apraxia to developmental trajectory of head and brain growth. The most noticeable phenotypic heterogeneity is in IQs, which can range from severely impaired to superior, and in language, which can vary from nonverbal to overly verbose. Many comorbid medical conditions or associated psychiatric disorders and symptoms also contribute to ASD’s heterogeneity [7].

Further, even the most common symptoms of ASD are not definitive in isolation or universal (e.g., while poor eye contact is frequently considered indicative of ASD, it is present in other disorders such as ADHD, and some individuals with ASD do make natural eye contact or learn to do so through intervention). Therefore, evaluation by a specialist in autism spectrum disorder (usually a psychologist, psychiatrist, neurologist, or related team) is typically needed to make a formal diagnosis. Nonetheless, all physicians should be aware of the common presentations and refer individuals for further assessment when ASD is suspected.

### **Lower-Functioning and Younger Children**

A recent summary of research on the infant siblings of children with autism has provided new insights into the early development of ASD, with some surprising findings [8]. Few differences are apparent at 6 months in children who eventually receive ASD diagnoses despite the social nature of infants of this age. In fact, at 9 months old, most infants who go on to receive ASD diagnoses demonstrate some social engagement and many normal social behaviors, such as anticipation during peekaboo and orienting to their name and others' voices. Onset patterns are variable, but the infant research suggests that the earliest signs for many children with ASD are differences in motor development and unusual visual interest in objects.

Most differences in development become more apparent between 12 and 24 months, including general developmental delays (including dramatic decreases in IQ for some children), more prominent repetitive behaviors, atypical sensory responsivity (e.g. being either hyper- or hyposensitive to touch, sounds, and so on), and increasingly difficult temperaments. Social and communicative impairments certainly still play a major role, but they are only two of many domains impacted in ASD and tend to appear later. This is consistent with principles governing the presentation of neurologic disorders of brain development in childhood. Specifically, signs and symptoms manifest when development reaches the point at which the defective mechanism is called into operation to support brain development and function.

While symptoms in the three diagnostic domains (social, communication, and repetitive behaviors) are not necessarily the first signs, they do remain the principal considerations for the differential diagnosis of autism spectrum disorder. The best predictors of later ASD diagnosis are lack of response to one's name at 14 months and lack of self-initiated and spontaneous use of eye contact to direct someone's attention to an object or activity of interest ("joint attention") [8]. Several practice parameters have been developed to aid in the early diagnosis of ASD [9, 10] due to research supporting the benefit of early, intensive intervention [11, 12]. Both routine developmental surveillance and ASD-specific screening (particularly at 18 months or when risk factors are present) are supported by both the Child Neurology Society [10] and the American Academy of Pediatrics [9]. Each has a detailed algorithm for when and how to make referrals, as well as key warning signs that warrant an immediate referral for further assessment. For example, the Child Neurology Society notes that the following developmental patterns should be considered abnormal [10]:

- No babbling by 12 months;
- No gesturing by 12 months;
- No single words by 16 months;
- No 2-word spontaneous phrases by 24 months;
- Any loss of language or social skills at any age.

### **Higher-Functioning and Older Children, Adolescents, and Adults**

ASD diagnoses for children in the average or greater range of intellectual ability and with on-time language development often go undetected or misdiagnosed until later

childhood, or even adulthood, in some cases. Many of these individuals are thought of as “weird” or eccentric and go without a diagnosis. Alternatively, emotional or behavioral concerns may be what draws clinical attention to higher-functioning individuals with ASD [13]. A red flag for a missed ASD diagnosis in older children, adolescents, or adults is a history of other psychiatric diagnoses. Common previous diagnoses include combinations of ADHD, oppositional defiant disorder, bipolar disorder, OCD, and schizophrenia-spectrum disorders. Often individuals have received treatment for these other concerns without much success or are on a medley of medications and still have poor functioning.

The presentation of individuals with high-functioning ASDs changes over the course of their development [14]. In 3- to 6-year-olds, poor peer relationships may emerge, though attention problems and difficulty regulating emotions and arousal may be the prominent features. They may have a limited range of play skills and exhibit unusual sensory sensitivity.

Over the next few years, peers further notice and highlight their differences. Some higher-functioning children with ASD may self-isolate, whereas others have great interest in making friends, but are awkward or pushy in their attempts. As high-functioning children with autism spectrum disorder go through elementary school, a perseverative interest, disruptive behaviors, and problems with social speech may emerge or worsen. Even among children with ASD who are thought to have normal language development, many higher-order language concerns become evident as they get older, including problems with conversational speech (especially a tendency to be “one-sided”), atypical prosody, overly literal comprehension, and formal or stilted speech [6].

Learning difficulties also often emerge, particularly as academic demands become more integrative. Individuals with ASD have a characteristic pattern of cognitive development that includes intact or enhanced skills in some areas (attention, sensory perception, elementary motor movement, simple memory, formal language, rule-learning, and visuospatial processing), and deficits in higher-order skills involved in complex information processing (e.g., concept formation, aspects of abstract reasoning, face recognition, skilled motor movements, higher cortical sensory perception, and complex memory) [15].

Increased social isolation is also likely to occur throughout adolescence and adulthood and may be accompanied by depression and disorganized thinking. Particularly as their peers mature, the level of social and emotional immaturity in the adolescent or adult with high-functioning autism spectrum disorder becomes more noticeable. This, combined with poor problem solving, lack of flexibility, and difficulty with perspective taking, often leads to many functional challenges in achieving independence.

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## Further Reading

Autism Speaks ([www.autismspeaks.org](http://www.autismspeaks.org)) and First Signs ([www.firstsigns.org](http://www.firstsigns.org)) offer a variety of resources, including an ASD Video Glossary with video clips to aid in understanding ASD presentation.

The Centers for Disease Control ASD Information for Healthcare Providers (<http://www.cdc.gov/ncbddd/autism/hcp.html>) includes a health care provider resource kit, guidelines and recommendations for screening, links to download recommended screening measures, and research summaries.

The Organization for Autism Research (<http://www.researchautism.org/resources>) offers a series of research-based guides, additional links to other resources, and a DVD series focused on higher-functioning individuals with ASD and adults with ASD in particular.

The National Institutes of Health (<http://health.nih.gov/topic/Autism>) offers links to each institute's relevant information on ASD, with information on both clinical and biological aspects of ASD and information on the latest and ongoing research.

*The Woman Who Thinks Like a Cow*, the HBO movie about Temple Grandin, a highly successful adult with high-functioning autism, also provides helpful insight into understanding the perspective and thinking of individuals with ASD.

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