

Genetics of Childhood Disorders: XLII. Autism, Part 1: Diagnosis and Assessment in Autistic Spectrum Disorders

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Autism is a developmental disorder that is evident in infancy or early childhood and results in a broad range of behaviors and, often, lifelong impairments. Now conceptualized as a spectrum of related diagnostic categories, autistic spectrum disorders (ASD) involve severe difficulties in basic aspects of social behavior and communication, such as eye contact, facial expressions, and the development of spontaneous, reciprocal language, which, for reasons not well understood, are associated with behaviors characterized by repetition and restriction, ranging from finger-flicking to compulsive touching to complex preoccupations with electrical appliances or highly circumscribed interests such as names of radio stations or Scottish clans. Such patterns, which often change with development, occur in individuals who function intellectually from profound mental retardation to the superior range of intelligence. Regardless of the level of functioning, all these cases share basic disturbances in social interaction and communication.

Manifestations of the severity of the disorder also range from severe to relatively mild. The spectrum includes classical cases of autism, as defined by the presence of severe deficits in the three relevant domains, to cases that include significant social

impairment, but without communication disorder or without repetitive behaviors. There are also differences in developmental trajectories, both between ASD and within them. Thus childhood disintegrative disorder is defined by normal development until at least age 2 years, followed by loss of skills across multiple areas of functioning. Asperger's disorder is defined by severe social deficits and restricted interests or behaviors that are not accompanied by language delay or mental retardation. Asperger's disorder is typically diagnosed later; it is not clear if behavior patterns actually develop later, or if there is later recognition of the abnormality of these behaviors as they begin to cause impairment in social situations.

The assumption, as discussed in more detail below, is that ASD are of neurobiological origin beginning before birth or in very early development, related to complex genetics. It is estimated that in about 10% of cases, ASD is associated with another identifiable medical condition, the most common being tuberous sclerosis.

Recently, the epidemiology of ASD has been of particular interest. Estimates of prevalence, based on school and state health systems, have skyrocketed, as have demands for services.

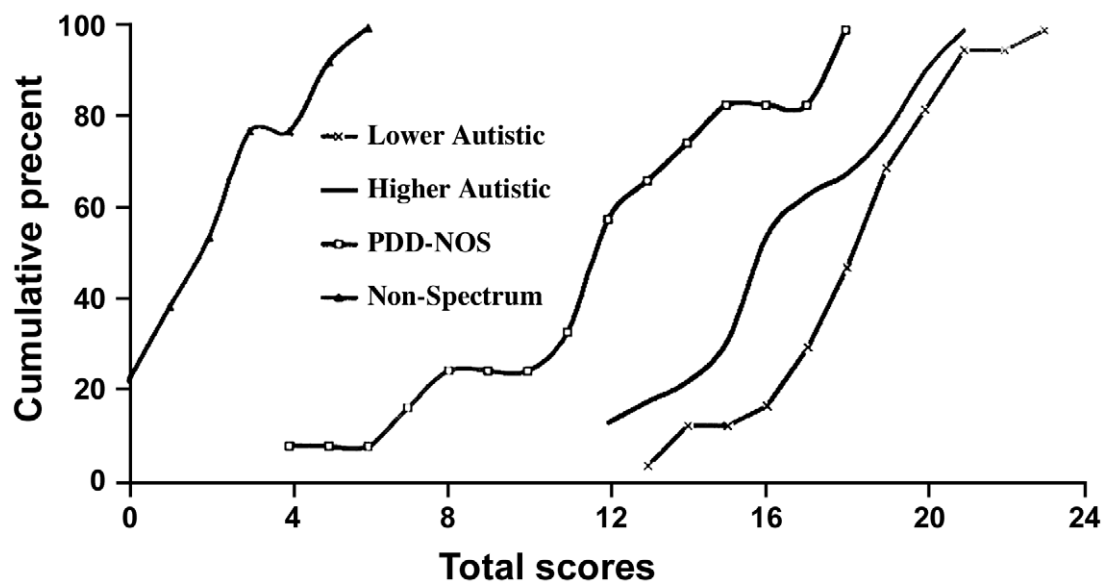


Fig. 1 Cumulative distribution of total Autism Diagnostic Observation Schedule (ADOS) algorithm scores for module 1. PDD-NOS = pervasive developmental disorder-not otherwise specified.

Until about 1999, well-designed, large-scale epidemiological studies indicated that the prevalence of autism had increased from earlier estimates of 4 to 5 per 10,000 to about 7 per 10,000 for narrowly defined cases and from 2 per 10,000 to 5 per 10,000 for additional, more broadly defined cases of ASD. However, in the past year or so, there have been a number of independent, smaller-scale studies that have yielded even higher prevalence rates for ASD. For example, a recent study in the United Kingdom reported prevalence rates of nearly 17 per 10,000 for autism and 63 per 10,000 of all ASD, including autism. Patterns of intellectual deficits have also changed, from earlier estimates of mental retardation in association with autism in 75% to 80% of individuals, to the most recent U.K. study, which reported associated mental retardation in only 26% of children with ASD. Together, the broadening of the conceptualization of ASD to include milder difficulties as well as severe social deficits without mental handicap, better ascertainment, and the expanded number of referrals of children have converged to result in a very different characterization of ASD than might have been made even 10 years ago.

In addition, our understanding of the nature of the social deficits associated with ASD, particularly in young and school-age children, has become more focused than it was 50 years ago when Leo Kanner first used the term *autism*. Numerous studies have shown that although ASD affects the acquisition of social relationships, difficulties do not lie in typical measures of attachment (e.g., strange situation). Rather, they are found in very basic social-communicative behaviors, such as use of gaze and facial expression; in specific contexts in which the coordination of these behaviors results in a “social-cognitive event,” such as pointing to express interest in something (e.g., “protodeclarative pointing”); and in reciprocal relationships, most easily seen in the absence of friendships with peers. Lorna Wing’s characterization of three forms of social deficits, ranging from aloof to passive to active, but odd, also provided a conceptualization of a complex deficit that affects social and communicative behaviors on multiple levels and in different ways for different children, though there are some strong similarities (e.g., in deficits in eye contact and facial expression) that appear across age and intellectual level.

Characterizations of a unique and specific social-communicative deficit associated with ASD in adolescence and adulthood have been more difficult. When ASD is associated with cognitive and language delays, individuals with autism, compared to those with equivalent levels of retardation but without autism, have more difficulty with both basic and more contextual aspects of social interaction and relationships as a group. In particular, when ASD is not associated with language deficit or mental retardation, there are a number of compensatory “strategies,” as well as comorbidity with anxiety disorders, depression, and other psychiatric disorders, which affect the manifestation of the disorder. While standardized diag-

nostic instruments such as the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) have been able to operationalize the definitions of ASD described in *DSM-IV* and *ICD-10*, a current goal is to modify these tools to be able to quantify the severity of the disorder as a whole, or at least for the primary domains of the disorder (social reciprocity, communication, restrictive behaviors), independent of chronological age, developmental level, or degree of mental handicap/language impairment. An example of this process is the work of Tanguay and Robertson, identifying factors within the social deficit as measured on the ADI-R and the ADOS. In our own research, as shown in Figure 1, we have been able to discriminate clearly between children with nonspectrum disorders and children with various ASD on measures such as the ADOS social and communication scales. However, there is very significant overlap among groups of children with clinical diagnoses of pervasive developmental disorder-not otherwise specified and those with clinical diagnoses of autism, both with and without mental retardation. A challenge for the future is to generate scores that are meaningful beyond the broad differentiations.

Recent research in neuroimaging and neuropsychology has contributed to a better understanding of the synergy between social and cognitive models of deficits in ASD. From recent empirical findings by Schultz indicating different areas of brain activation for adults with ASD during an observation of a social situation, to the finding of Dawson and her colleagues of poor response to their names in infants in whom autism is later diagnosed, research has highlighted the intersection of deficits in specific behaviors (e.g., looking at faces) and more holistic processing of social “presses,” such as in orienting to someone’s voice. The forerunners of such hypotheses, including the concept of autism as rooted in delayed or failed acquisition of a “theory of mind” and even earlier deficits in joint attention, have been shown to be part of developmental processes that are crucial aspects of the overall pattern of ASD throughout childhood.

There have also been attempts to generate separate measures of various aspects of the phenotype. Standard diagnostic instruments yield scores in each of three defining domains, but, on the whole, factor analyses and other statistical techniques, all with relatively small samples, have tended to yield one clear “autism spectrum” factor and often a strong effect of the degree of cognitive impairment and/or verbal skills. Some studies have found less robust factors that include various repetitive behaviors, but these are less internally consistent and less consistent across populations. Consideration of these issues, as well as the clinical observation of the enormous diversity within ASD, has led to various proposals of subtypes that differ from those proposed in *DSM-IV* and *ICD-10* and that might be tied more closely to differences in neurobiological factors. Such subtypes include distinctions related to IQ, language level, presence of seizures, early developmental trajectory, and comorbidity with

other childhood psychiatric disorders. To date, none of these potential subtypes has been consistently replicated beyond features that are already part of the defining variable. However, some findings of different family history data for nonverbal versus verbal individuals and for individuals with normal versus delayed language milestones are quite intriguing. This is an area of intense interest for genetics that will require large samples, the development of sophisticated measures, and complex statistics to yield replicable findings.

One question that remains to be addressed is whether familial transmission is different for social deficits, language abnormalities, and repetitive behaviors. Twin studies have found that there is almost as much variation in IQ and autistic symptoms within monozygotic twin pairs as within dizygotic pairs. Families with a child with Asperger's disorder show an increased rate of autism as well as Asperger's disorder and milder phenotypes. Although a significant proportion of children with autism have mental retardation, the rates of mental retardation without autism are not increased in families of children with ASD, suggesting that the mental retardation that occurs in some cases of autism is a part of the disorder, rather than a separately transmitted phenomenon.

In summary, substantial progress has been made in the ability to describe accurately the social-communicative and behavioral deficits that comprise ASD. Measurement tools that allow the categorization of autism and the autistic spectrum in reliable and valid ways are available. There is a strong empirical basis for the treatment of many of the symptoms of autism as continuous dimensions. Categorical approaches do not fully represent the range or the significance of these behaviors. Replicable thresholds can be set, using specific methods, such as the ADI-R and the ADOS, for the presence of ASD, based on observation or report of a constellation of behaviors. Yet boundaries are not yet well defined among the ASD or between individual behaviors. Identifying in relatives those behaviors that are clearly associated with impairment and measurable personality characteristics, which may or may not be pathological, in order to define a unique broader common variant has been difficult. Much work remains for those seeking to understand better the psychological and developmental nature of these disorders and to provide better methods of quantification of the disorder or, ideally, aspects of the disorder, for neurobiological and genetic studies.

WEB SITES OF INTEREST

Autism Society of America: <http://www.autism-society.org>
 Cure Autism Now: <http://www.canfoundation.org/>
 Yale Child Study Center: <http://info.med.yale.edu/chldstdy/autism/>
 TEACCH: <http://www.teacch.com>
 Centers for Disease Control: <http://www.cdc.gov/ncbddd/dd/ddautism.htm>

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