The Early Origins of Autism

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KEYWORDS

• Autism spectrum disorder • Diagnosis • Genetics • Early childhood development

KEY POINTS

- The autism spectrum disorders (ASDs) are strongly genetically determined, and the clinical identification of deleterious genetic variants that influence the development of ASD in individual patients is becoming increasingly achievable for personalized approaches to care, including specification of recurrence risk in families.
- The ability to reliably identify most cases of ASD far earlier than the average age of community diagnosis presents a novel opportunity for implementation of early intervention.
- New waves of necessary research on the efficacy of early intensive behavioral intervention, and on the development of personalized approaches whose specificity is predicated on knowledge of the particular mechanisms of causation of the condition in individual patients, will ultimately transform the clinical approach to these conditions in early childhood.

INTRODUCTION

The diagnostic conceptualization of autism has shifted with the publication of Diagnostic and Statistical Manual of Mental Disorders (DSM)–5; language deficits, previously a core feature of autism, are no longer an independent criterion domain; instead they are inextricably linked to the characteristic social impairments of autism in a construct referred to as social communication.[1] Asperger syndrome and pervasive developmental disorder (PDD) not otherwise specified, once subtypes of PDDs, have been eliminated as separate diagnoses; most individuals who previously held these diagnoses are now in the broader diagnostic category of autism spectrum disorders (ASDs), except for (usually) milder cases that better fit the new DSM-5 diagnosis of social communication disorder. These changes reflect major advances in knowledge about symptom structure, patterns of familial transmission in the ASDs, the importance of specifying degree of impairment in adaptive functioning (which is imperfectly correlated with symptom burden), and comorbidity of ASD with neuropsychiatric impairments that range from epilepsy to intellectual disability to

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attention-deficit/hyperactivity disorder (ADHD) or almost any psychiatric disorder. These comorbidities and the wide range of severity of symptom burden and impairment in adaptive functioning reflect the marked diversity of genetic pathways to ASD and other neurodevelopmental susceptibilities represented by individual children and families. This diversity presents unique challenges and opportunities for comprehensive intervention planning at each successive stage of development. Overwhelmingly, the ASDs are influenced by genetic factors,[2] as reflected in a sibling recurrence rate that is 20 times higher than the population prevalence, and in twin and family studies of ASD conducted around the world, now cumulatively totaling more than 4 million subjects.[3]

EPIDEMIOLOGY

ASD is a recent addition to the DSM, having been introduced in DSM-3 in 1980, and until a little more than decade ago was considered rare. Between 1992 and 2001, the prevalence was estimated at 12.7 in 10,000.[4] In the United States, the most recent prevalence estimate of 1 in 68 is an order of magnitude greater.[5] Several reasons for this steep upswing in prevalence are at play. First, diagnostic criteria have become progressively more inclusive. DSM-5 now defines ASD as a spectrum that explicitly encompasses a range of core symptom severity, in contrast with prior definitions, which often invoked significant cognitive and language delays.[1] A greater variety of standardized assessment tools, including rapid developmental screeners that facilitate earlier detection of risk, are now available. Increasing rates of research citations and media coverage have promoted awareness of ASD, among both parents and clinicians. Furthermore, diagnostic substitution, whereby the same developmental disability receives a different diagnosis, previously contributed to reduced ASD diagnoses, particularly with respect to historical diagnoses of intellectual disability.[6,7]

Throughout the diagnostic evolution of ASD, one consistent epidemiologic feature has been the male/female sex ratio of 4:1. Observations of quantitative trait distributions and recurrence studies in later-born infant siblings confirm that this pronounced disparity is evident by the second year of life.[8] Failure to incorporate sex-specific norms in the diagnostic process has contributed to significant differences in the rates of community diagnosis for girls versus boys who manifest precisely the same level of quantitative symptom burden.[9–11] Furthermore, there is evidence that female sex can often moderate the phenotypic expression of inherited susceptibility to ASD and that a female protective effect is responsible for protecting young girls against the expression of inherited ASD susceptibility.[12–14]

Over the past decade it has become clear that social and cultural factors may influence the likelihood of individuals receiving a clinical diagnosis of ASD in the community.[15] For example, underdiagnosis has been linked to social disadvantage as related to parental education, income, socioeconomic status, and ethnic/minority status.[16–18]

Early Childhood Diagnosis

The largest body of evidence for diagnostic stability applies to children between 2 and 3 years of age. Diagnostic stability of more than 80% has repeatedly been shown among 2-year-olds 1 to 7 years from the initial diagnosis.[19–24] Factors associated with less stability of an ASD diagnosis include age less than 30 months at time of diagnosis,[23,25] lower severity of core symptoms,[26] and reliance on psychometric tools rather than clinical judgment to formulate a diagnosis.[20,22,27]

A related consideration is whether early evaluations for ASD in toddlers frequently miss diagnoses that can be identified later in the toddler period. In a recent longitudinal