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Invited Commentary: Male Reproductive System Congenital Malformations and the Risk of Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is a prevalent developmental disorder. Studies indicate that while ASD etiology has a genetic component, the risk is polygenic, with gene-environment interactions being likely. The prenatal period is a critical exposure window for nongenetic risk factors. Previous studies have found positive associations between congenital malformations (all types) and ASD; a few also found specific associations between genitourinary system malformations and ASD; and one study found an association between hypospadias and ASD. In the accompanying article, Rotem et al. (*Am J Epidemiol*. 2018;000(00):000–000) describe how they conducted a comprehensive analysis focusing on the shared risk of ASD with hypospadias or cryptorchidism, using existing data from a large Israeli health services system, which afforded several advantages because of the large sample size and low attrition of the patient population. The authors conducted a careful analysis, including sensitivity analyses, to account for risk factor and case misclassifications that might have occurred had they relied solely on preexisting diagnostic codes to define exposures and outcome. They observed positive associations between both hypospadias and cryptorchidism and ASD that were independent of numerous sociodemographic and pregnancy health factors. This study advances our understanding of ASD etiology and illustrates how existing data might be used to assess some ASD risk factors.

Keywords

autism spectrum disorder; congenital malformations; cryptorchidism; hypospadias

Autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by impairments in social interaction and communication and restricted, repetitive, and stereotyped patterns of behavior, is a prevalent disability, affecting an estimated 1.5%–2.5% of US children (1–3). While ongoing systematic tracking of ASD is lacking in many countries, periodic assessments indicate that prevalence rates in various countries are comparable to rates reported from US systems (4–7).

Research on ASD etiology has seen significant advances only during the past decade or two. Autism has been recognized as a condition distinct from childhood schizophrenia only since

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1943 (8), and the understanding that autism encompasses a spectrum of severity levels emerged gradually throughout the 1980s and early 1990s (9). Moreover, early twin studies found very high heritability estimates for autism (10), and thus the prevailing view was that genetics explained most ASD cases. However, while several recent twin studies (with more rigorous case ascertainment than earlier studies) still strongly supported a genetic component (11, 12), heritability estimates were lower than those from earlier studies, and the estimated influence of nongenetic factors was as high as or higher than the estimated genetic component. Moreover, ASD has been positively associated with numerous chromosomal abnormalities and genetic syndromes, and studies have revealed the involvement of hundreds of gene variants in autism, including both single gene variants and larger copy number variants comprising both inherited and de novo mutations (13, 14). The composite evidence thus supports a complex polygenic risk and likely gene-environment interactions.

Both epidemiologic and neurobiological studies indicate that the prenatal period is probably the most critical time frame for nongenetic risk factors for ASD (15–17). While biological mechanisms are not completely understood, research to date points to several general areas of interest: immune dysregulation, inflammation and oxidative stress, endocrine disruption, neurotransmitter alterations, and epigenetic effects (15–17). Risk factors associated with ASD in various studies include maternal preconception health conditions that might affect a woman's pregnancy, prenatal and perinatal health conditions and outcomes, and prenatal and perinatal exposures (15–17).

In an accompanying article, Rotem et al. (18) describe how they conducted a comprehensive assessment of the relationship between ASD and congenital abnormalities of the male reproductive system—hypospadias (abnormal positioning of the opening of the urethra) and cryptorchidism (undescended testes). Using data from Israel's second-largest integrated health-care organization, Maccabi Health Services, they analyzed associations between ASD and both hypospadias and cryptorchidism in a large sample comprised of over 200,000 male singleton births. They observed moderate associations between both conditions and ASD that were not explained by various sociodemographic factors, use of infertility treatments, pregnancy complications, or gestational age or birth weight at delivery.

Elucidating the relationship between male genitourinary tract malformations and ASD is potentially important to furthering our understanding of the underlying causes of ASD. Cryptorchidism is a common congenital malformation affecting an estimated 2%–9% of male infants (reviewed by Toppari et al. (19)), although there is significant variation in observed prevalence depending on the birth weights of boys included in the sample and the age of ascertainment. Hypospadias is also relatively common, with mean prevalence estimates varying from 5.2 per 10,000 live births in South America to 34.2 per 10,000 live births in North America (20), although true prevalence is difficult to estimate because of the extremely broad severity of the defect and the high prevalence of mild or glandular forms that may not be recognized at birth or in early infancy (21). Given the very large male predominance in the prevalence of ASD (1–3), it is important to study perinatal factors affecting male births. Moreover, both genetic and endocrine-related factors are implicated in the etiology of ASD, hypospadias, and cryptorchidism.

There has been little previous study of this association and arguably no study as comprehensive as the current study. Several previous studies examined associations between congenital malformations (all types) and ASD, and the majority found positive associations (22, 23). While some of these studies further examined more specific types of malformations, small sample sizes limited these assessments to groupings of malformations by organ system rather than assessment of individual malformations. Moreover, even organ system assessments were limited, as evidenced by imprecise risk estimates in some studies. The findings from studies that assessed genitourinary system malformations were inconsistent. Two studies (both population-based studies of Swedish children (different birth cohorts)) found statistically significant associations between genitourinary malformations and ASD (24, 25); 2 studies found moderately increased risk estimates (odds ratios of 1.6 and 1.7) that did not reach statistical significance (26, 27); and 3 studies found no association (22, 28, 29). However, one of the investigative groups reporting no association did observe a positive association with genitourinary malformations in the subset of ASD cases with co-occurring intellectual disability (22).

Only 1 previous study evaluated hypospadias specifically; Butwicka et al. (30) reported modest positive associations between hypospadias and several neurodevelopmental disorders, including ASD. Interestingly, they also reported an increased risk for ASD among the unaffected brothers of boys with hypospadias in comparison with randomly selected brothers of boys without hypospadias (30), which suggests that the underlying mechanism was genetics or shared familial environment. However, Butwicka et al. did not assess other genitourinary malformations, such as cryptorchidism; this was a limitation of their study, given that these 2 conditions, while both related to androgen signaling, differ in the timing of onset and thus the estimated critical exposure period during pregnancy (31).

Several facets of the current study are noteworthy. Rotem et al. took advantage of a wide array of clinical data available through a large electronic medical record system, which included linkages to important sociodemographic data captured by Israel’s Central Bureau of Statistics (18). In addition to the large sample size, a central feature of this data source is its completeness, as attrition from Maccabi Health Services is very low. The system thus allowed for longitudinal assessments of children from pregnancy and birth through childhood, which is critical given that ASD diagnoses typically lag behind the onset of symptoms by several years. In this population, the average age at diagnosis was approximately 5 years.

The authors also carefully considered the complexities of developing a case definition for a condition like ASD that currently has no biological marker (thus diagnoses are made via behavioral observation). In clinical practice, ASD is diagnosed using a variety of diagnostic instruments, with varying degrees of rigor. Moreover, diagnoses made at young ages are not always stable. For example, a recent analysis from a US population-based case-control study found that 17% of preschool-aged children who had received a previous ASD diagnosis from a community health-care provider did not meet the study’s ASD case criteria based on in-person developmental assessments using standardized instruments considered “gold standard” for ASD ascertainment; additionally, 15% of children who met the study case criteria had not been previously diagnosed as having ASD (32). In the current study, while

the authors defined ASD cases using *International Classification of Diseases, Ninth Revision*, diagnostic codes, they also conducted a validation assessment for a random sample of cases, which confirmed the diagnosis 90% of the time (18). Additionally, they conducted secondary analyses in which they restricted ASD cases to those that met stringent criteria for receipt of ASD developmental services—a high bar given that these services are provided as a government benefit, and eligibility is based on strict criteria spelled out in a national health insurance law that, among other things, requires detailed medical assessments and independent psychological assessments.

Rotem et al. were also thoughtful in defining the risk factor of interest. They analyzed hypospadias and cryptorchidism separately, which (as noted above) is important given that hypospadias is linked to androgen deficiency in the first trimester and cryptorchidism is linked to androgen deficiency in the third trimester. Additionally, while they initially assessed all cases with hypospadias and cryptorchidism diagnoses as indicated in *International Classification of Diseases, Ninth Revision*, codes, they also conducted analyses in which they limited their risk factor definition to hypospadias and cryptorchidism diagnosed in the first year of life (18). This restriction eliminates many milder cases more prone to misclassification. However, the authors could have perhaps taken this assessment a step further by also restricting their sample to cases requiring surgical repair. This restriction might have excluded additional mild and miscoded cases.

The authors conducted a thorough analysis in which they assessed various potential explanations for the associations they observed. They adjusted risk estimates for numerous potential sociodemographic confounding factors, including birth year, which is important given the notable secular trends that have been reported for diagnoses of both the outcome and risk factors of interest in this study. They further adjusted for several pregnancy-related factors—preterm delivery, birth weight, maternal preeclampsia, maternal diabetes, and conception via infertility treatment—and demonstrated that the observed associations between hypospadias and cryptorchidism and ASD were independent of these factors as well (18). They conducted a series of sensitivity analyses in which they 1) restricted their sample to cases least likely to have been influenced by risk factor detection bias (i.e., the aforementioned restriction to hypospadias and cryptorchidism detected in the first year and separate analyses with restriction to hypospadias and cryptorchidism detected prior to ASD evaluation and restriction to boys without co-occurring chromosomal or central nervous system malformations) and 2) restricted their sample to cases least likely to have been influenced by outcome selection bias (i.e., the aforementioned restriction to children meeting strict criteria for receipt of government services for ASD) (18). These sensitivity analyses demonstrated that the associations originally observed for both hypospadias and cryptorchidism were robust.

Finally, the authors separately assessed unaffected brothers of children with hypospadias or cryptorchidism to control for family effects. In contrast to the findings reported by Butwicka et al. (30), they found that the brothers did not have an elevated ASD risk in comparison with general population controls (18). Thus, the associations they observed did not appear to be linked to familial aggregation of both male reproductive system disorders and ASD.

However, given that only 2 studies have assessed this issue and they had contradictory findings, further research is warranted.

Despite the many strengths of the study by Rotem et al., several important questions could not be answered. While the authors acknowledged that their study design did not allow for estimation of genetic versus environmental effects, they posit that given the links between hypospadias and cryptorchidism and in-utero androgen deficiency, these malformations might be proxies for fetal exposure to environmental endocrine-disrupting chemicals (18). They lacked data with which to empirically assess this hypothesis. They also lacked data with which to subdivide ASD cases into phenotypic subtypes, such as ASD symptom severity scores (33), and they did not assess neurodevelopmental conditions other than ASD. Thus, they could not disentangle ASD effects from more general neurodevelopmental effects. While we agree with the authors that this study provides important novel data on ASD risk factor associations, their assertion that the findings implicate environmental exposures may be overstated. Investigators examining associations between endocrine disrupters and male reproductive system malformations have reported inconsistent findings; moreover, the magnitude of risk estimates reported has been modest (34, 35). Additionally, while human and animal studies link endocrine disrupters to various neurodevelopmental symptoms, the data on specific disorders, such as ASD, are yet sparse (36), and limited data on fetal testosterone and ASD in males suggest associations with high levels of testosterone rather than deficits (37).

Nonetheless, this study advances our understanding of ASD etiology. Moreover, even though the underlying mechanisms are yet unknown, the findings reported in this study have implications for providing follow-up of boys born with genitourinary malformations who might have subsequent developmental delays, potentially representing early symptoms of ASD. While the American Academy of Pediatrics already currently recommends universal autism screening at ages 18 and 24 months (38), recognizing which groups of children might face higher-than-average risk for ASD will also be helpful, such that both parents of these children and their health-care providers can be particularly attentive to ASD screening, with the ultimate goal of getting early developmental intervention services for children with ASD symptoms. Finally, this novel analysis of secondary data highlights the value of such data in furthering our understanding of ASD epidemiology. It also illustrates how consideration of all data available can help overcome and/or assess and inform some of the limitations that secondary data sets pose in terms of both exposure and outcome misclassification.

Abbreviation

ASD	autism spectrum disorder

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