Boys' Club: Sexual Dimorphism in Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a complex and heterogeneous disorder of development. Its heterogeneity presents a challenge for the creation of diagnostic criteria that will encompass all affected individuals without misdiagnosing other developmental disorders, or missing individuals entirely. Our current definition recognizes a spectrum of persistent deficits in socialization, communication, and restricted interests/repetitive behaviors.[1] Even though *DSM* guidelines for diagnosis of autism have changed over time, there is a persistent sexual dimorphism in the ASD population, with far more males receiving the diagnosis than females. Sex ratios vary from one study to the next, with an average 4:1 male-to-female ratio across the spectrum.[2] However, there is great variation in this sex ratio when patients with ASD are subdivided based on level of function. The high-functioning ASD population, formerly diagnosed with Asperger's disorder, has a male-to-female ratio of 10:1,[3] while children with intellectual disability in addition to ASD have male-to-female ratios much closer to 1:1.[3,4] Many explanations for this sexual dimorphism have been proposed, but no single factor can account for this phenomenon.

When trying to understand what may underlie the sexual dimorphism of ASD, we must look at sexual dimorphism within the general population. The Social Responsiveness Scale (SRS) surveys quantitatively measure deficits in reciprocal social behavior.[5] Across multiple studies, SRS scores from unaffected and affected individuals demonstrated a mean score 3 points higher for males (0.17 SD) than females.[6,7] This difference may seem trivial, but a small shift toward the pathological end of the spectrum in males combined with an absolute threshold for diagnosis of ASD across both sexes creates a significant difference in the number of males diagnosed with ASD relative to females. Normalizing the data based on sex differences may help to correct for this bias. This baseline difference in reciprocal social behavior between the sexes may explain part of the sex difference seen in ASD-diagnosed populations, but it is clear that other factors contribute to the sexual dimorphism of this complex disorder.

The female protective effect (FPE) is a widely held theory that females are inherently protected from certain ASD traits, leading to reduced rates of ASD diagnosis in females. Genetic studies support this theory by revealing a higher burden of de novo mutations in females with ASD compared to males with ASD.[8,9] Constantino *et al*. used ASD multiplex families (i.e. two or more family members meeting criteria for ASD diagnosis) to look at whether common allelic variations in the pseudoautosomal region of the X chromosome might serve as protective factors for females (relative to males) when present in a homozygous state. No single allele met a threshold for genome-wide significance for such a protective function. Constantino *et al*. were able to demonstrate a sex difference in the distribution of autistic trait scores among siblings of affected individuals in multiplex families. Their work revealed a bimodal distribution in the female ASD population, in contrast to a unimodal distribution among males, demonstrating that a protective effect may exist among multiplex females.[10] Similar bimodal distributions of affected females have been identified in other research in ASD multiplex families, reproducibly demonstrating two distinct populations of females, separating an affected group from an unaffected group.[11] The nature of sex-specific reduction in phenotypic expression of genetic susceptibility to autism is further qualified by findings of Dworzynski *et al*., which demonstrated a significantly higher rate of ASD diagnosis in girls when they also had intellectual disability or behavioral problems.[12] These data suggest that some highly deleterious genetic influences may override the protective phenomenon unique

to females. Further research will be required to elucidate the specific biological mechanisms that protect females; discovery of such mechanisms may aid in the development of more effective diagnostic tools and therapeutic interventions in the future.

Familial inheritance of autistic traits supports the existence of a strong genetic component to ASD, but we must also acknowledge the impact of clinical practice on diagnosis. The higher rate of ASD diagnosis among males may be influenced by a community diagnostic bias against females. Dworzynski *et al*. demonstrated that boys with ASD have a higher rate of comorbid behavioral abnormalities, thus preferentially bringing more boys with ASD to clinical attention than girls with the same level of ASD symptom burden.[12] Even after controlling for symptom burden, boys were more likely to be given a community diagnosis of ASD compared to girls.[10,13] Addressing this bias is not likely to lead to complete resolution of this sex difference, but it is important to acknowledge and address its contribution.

To address the issue of community diagnostic bias against female diagnosis of ASD, a number of studies have attempted to identify and quantify differences between male and female ASD phenotypes. Some studies demonstrate higher rates of restricted interests and repetitive behaviors among males[14,15] or greater social deficits in males.[16] In contrast, other studies demonstrate no statistically significant differences between ASD phenotypes of males versus females.[17-19] This inconsistency across studies may reflect the heterogeneity of ASD and subsequent differences in the populations studied by each research group; however, it is more likely that the difficulty to identify unique "feminine" or "masculine" autistic traits reflects an absence of genuine subtypes based on sex. Therefore, efforts to create ASD criteria that are unique to each sex may not be particularly helpful.

Instead, we are more likely to diagnose ASD with higher specificity and sensitivity by acknowledging that this disorder spans a heterogeneous spectrum, and following a few simple guidelines. First, increase the use of quantitative measures in the context of multidisciplinary, biopsychosocial diagnostic assessment to limit clinical bias and subjectivity of diagnosis. Second, acknowledge that male and female populations do not have equal distributions of ASD traits and use sex-normed thresholds for diagnosis based on the distribution of autistic traits for each sex. Third, continue to study the roles of biological mechanisms that contribute to ASD inheritance or protection from inheritance. By increasing our understanding of the biological and clinical factors that contribute to the sexual dimorphism of ASD, we can improve the accuracy of diagnosis and develop novel therapeutic treatments, thus improving outcomes for all people along the autism spectrum.

Take Home Summary

On average, boys outnumber girls 4:1 in the diagnosis of autism spectrum disorders (ASD). This is likely due in part to sexual dimorphism at the level of basic biology. However, it is also likely influenced by biases that exist in the way ASD is clinically diagnosed. Understanding the clinical and biological factors that contribute to this sexual dimorphism in ASD prevalence among boys and girls will help us improve the accuracy of diagnosis.

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