Early Generalized Overgrowth in Autism Spectrum Disorder: Prevalence Rates, Gender Effects, and Clinical Outcomes

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Objective: Although early head and body overgrowth have been well documented in autism spectrum disorder (ASD), their prevalence and significance remain unclear. It is also unclear whether overgrowth affects males and females differentially, and whether it is associated with clinical outcomes later in life. **Method:** To evaluate prevalence of somatic overgrowth, gender effects, and associations with clinical outcomes, head circumference, height, and weight measurements were collected retrospectively between birth and 2 years of age in toddlers with ASD (n = 200) and typically developing (TD; n = 147) community controls. Symptom severity, verbal, and nonverbal functioning were assessed at 4 years. **Results:** Abnormalities in somatic growth in infants with ASD were consistent with early generalized overgrowth (EGO). Boys but not girls with ASD were larger and exhibited an increased rate of extreme EGO compared to community controls (18.0% versus 3.4%). Presence of a larger body at birth and postnatal overgrowth were associated independently with poorer social, verbal, and nonverbal skills at 4 years. **Conclusion:** Although early growth abnormalities in ASD are less common than previously thought, their presence is predictive of lower social, verbal, and nonverbal skills at 4 years, suggesting that they may constitute a biomarker for identifying toddlers with ASD at risk for less-optimal outcomes. The results highlight that the search for mechanisms underlying atypical brain development in ASD should consider factors responsible for both neural and nonneural tissue development during prenatal and early postnatal periods, and can be informed by the finding that early overgrowth may be more readily observed in males than in females with ASD. J. Am. Acad. Child Adolesc. Psychiatry, 2014; 53(10):1063–1073. **Key Words:** autism, infancy, head circumference, overgrowth, gender

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by severe impairments in social communication and interaction and a range of restricted, repetitive patterns of behaviors, interests, or activities.[1] Although as a group, children later diagnosed with ASD are normocephalic at birth, their head circumference (HC) growth rate subsequently accelerates, leading to an enlarged HC in early preschool age.[2-9] Because of the high correlation between HC and total brain volume (TBV), HC growth rate in ASD has been considered an index for abnormal brain development in infancy.[10] Recent work suggests that early HC enlargement is accompanied by increased extra-axial fluid volume by 6 to 9 months and increased total cerebral volume by 12 to 15 months in infants later diagnosed with ASD.[11] By preschool age, children with ASD exhibit increased cortical surface area[12] and enlargements of the frontal, temporal, and parietal lobes[12-15] involving both gray and white matter.[5,12] Initial reports suggested that HC overgrowth is independent of growth rates in other morphological features[2,3]; however, more recent work indicates that atypical growth patterns in ASD are also observed in height and weight.[4,5,7,16-18] Despite high heritability of physical body parameters, the increase in HC in affected children does not appear to be accounted for entirely by parental head size or height.[22,25,29] Simultaneous analysis of individual growth curves along all 3

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dimensions suggests that infants with rapid HC growth rates also experience increased growth in height and weight, suggesting an early generalized overgrowth (EGO).[7] A comparison with other disabled groups suggests that EGO may be specific to infants with ASD.[7]

Not surprisingly, considering the 4:1 male-to-female ratio in ASD,[19] relatively few studies have examined gender effects on early growth in ASD. Those studies suggest that somatic overgrowth in the first year of life is more common in boys than in girls with ASD, although specific patterns differ across studies. In a study of Japanese infants with ASD, boys showed overgrowth in HC, height, and weight compared to community controls throughout the first year, but girls were larger only shortly after birth.[8] A population-based Norwegian study suggested that boys but not girls were larger and heavier than the community controls in the first year of life.[18] The 2 studies have the advantage of including community-based comparison samples, which is particularly important given the reported secular and ancestral biases in population norms (e.g., Centers for Disease Control).[7,20-22] However, growth data in these studies were available only for a limited age range (birth to 12 months), and, given markedly smaller sample sizes in girls than in boys, it was not clear whether the null results in girls were due to limited power to detect the gender effects. Moreover, neither of the studies attempted to directly examine the relationship between HC, height, and weight growth trajectories on an individual level. Although gender effects on the prevalence of macrocephaly or megalencephaly have been more frequently investigated, the results also remain inconclusive. Macrocephaly rates have been reported to be higher in boys than in girls with ASD[23] or comparable between the 2 sexes.[22,24-26] Evidence for enlargement in total brain volume (TBV) in young females with ASD is also mixed, with some reporting presence of TBV enlargement,[15,27,28] and others reporting none.[9] Thus, sex effects on head and somatic growth patterns in early development remain to be further examined.

ASD is a highly heterogeneous disorder with regard to its behavioral expression as well as increased variability in head size[29] and somatic growth patterns.[7,18] Estimates of prevalence of HC overgrowth in infants later diagnosed with ASD have ranged from 35% to 59%,[2,3] which inspired a discussion of whether HC overgrowth might constitute an early marker of risk for ASD.[30,31] However, considering recent reports that the previously reported macrocephaly rates in older individuals with ASD (11%–27%) may be inflated because of ancestral or secular biases in the normative samples used in these studies,[21,22,32] there is a pressing need to reexamine the rates of early HC and somatic overgrowth among infants later diagnosed with ASD, using community-based comparison samples.[7,20,21] Otherwise, reliance on questionable norms may lead to overidentification of outliers and thus may thwart the discovery of more homogenous and meaningful subgroups of children with ASD based on their growth patterns.

Although early overgrowth may signal a pathological process leading to disproportions in brain architecture in older individuals with ASD, its associations with clinical outcomes are unclear. Although some studies report that early HC overgrowth is more pronounced in children with a more severe form of ASD (autism versus pervasive developmental disorder–not otherwise specified [PDD-NOS]),[2,7,17] language impairment,[7] and regression,[9] others link overgrowth with higher adaptive and verbal skills.[3] Thus, verification and elaboration of any predictive relationships with clinical outcomes are needed. Considering the progressive nature of atypical brain development in ASD, the effects of early overgrowth on behavior might depend on the amount of time elapsing between the period of growth acceleration and the time when its putative effects on the phenotype are examined. Consequently, measurement of outcomes within a relatively narrow age range should help to clarify predictive links between growth patterns and later levels of functioning.

The aims of this study were to examine the following: EGO patterns in ASD within gender; the prevalence of EGO in the first 2 years of life; and predictive associations between features of EGO in infancy and clinical outcomes at 4 years.

METHOD

This study was approved by the Human Investigations Committee of the Yale University School of Medicine, and informed written consent was obtained from all parents before testing.

Study Participants

Study participants (n = 347) consisted of children enrolled consecutively in studies of social cognition or referred for a differential diagnosis of ASD to a