Early Head Growth in Infants at Risk of Autism: A Baby Siblings Research Consortium Study

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Objective: Although early brain overgrowth is frequently reported in autism spectrum disorder (ASD), the relationship between ASD and head circumference (HC) is less clear, with inconsistent findings from longitudinal studies that include community controls. Our aim was to examine whether head growth in the first 3 years differed between children with ASD from a high-risk (HR) sample of infant siblings of children with ASD (by definition, multiplex), HR siblings not diagnosed with ASD, and low-risk (LR) controls. **Method:** Participants included 442 HR and 253 LR infants from 12 sites of the international Baby Siblings Research Consortium. Longitudinal HC data were obtained prospectively, supplemented by growth records. Random effects nonlinear growth models were used to compare HC in HR infants and LR infants. Additional comparisons were conducted with the HR group stratified by diagnostic status at age 3: ASD (n = 77), developmental delay (DD; n = 32), and typical development (TD; n = 333). Nonlinear growth models were also developed for height to assess general overgrowth associated with ASD. **Results:** There was no overall difference in head circumference growth over the first 3 years between HR and LR infants, although secondary analyses suggested possible increased total growth in HR infants, reflected by the model asymptote. Analyses stratifying the HR group by 3-year outcomes did not detect differences in head growth or height between HR infants who developed ASD and those who did not, nor between infants with ASD and LR controls. **Conclusion:** Head growth was uninformative as an ASD risk marker within this HR cohort. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(10):1053–1062. **Key Words:** autism spectrum disorder, head circumference, high-risk design, longitudinal study, early detection

Autism spectrum disorders (ASD) are among the most common neurodevelopmental disorders, with recent US prevalence estimates at greater than 1 in 100 children.[1] Current early detection strategies focus on behavioral signs that can be reliably detected in the second year of life.[2] However, the identification of biomarkers for ASD could improve the predictive accuracy of behavioral signs alone and help shift surveillance to the first year.[3,4] Several lines of evidence, including results from neuroimaging[5-8] and post mortem studies,[9] have identified early brain overgrowth as a distinguishing feature of ASD. Indeed, increased head size has been described in children with autism since Kanner's original case series.[10] Head circumference (HC), available from physician growth records, is correlated with brain volume[11] and thus represents a potential biomarker for ASD. In fact, macrocephaly (HC >97th percentile) has been reported in many cross-sectional studies of children with ASD, with rates averaging about 20%.[12-22] Some longitudinal studies have suggested a unique trajectory of head growth in ASD, with a normal or slightly reduced HC at birth,[18,23-26] followed by accelerated growth and macrocephaly by around the first birthday,[7,23,27,28] in some cases coinciding with symptom onset[28] and/or correlating with

This article is discussed in an editorial by Dr. Armin Raznahan on page 1045.

parent-reported developmental regression.[29,30] Elder *et al.*[31] reported that infants from a high-risk sample (younger siblings of children with ASD) were more likely to be diagnosed with ASD if they had increased HC at 12 months and decelerating HC growth rate from 12 to 24 months.

Recent studies, however, suggest the need to re-examine the evidence for head overgrowth in ASD, which is based largely on comparisons with published population norms. A systematic review by Raznahan *et al.*[32] identified 5 independent longitudinal cohorts of typically developing children that demonstrate trajectories in HC z scores that deviate from Centers for Disease Control and Prevention (CDC) norms[33] in ways similar to those reported in children with ASD, suggesting general norm biases rather than disease-specific biomarkers. The few longitudinal studies of head growth in children with ASD that have incorporated community controls rather than relying on population norms identify only modest differences. Hazlett *et al.*[7] used a nonlinear (exponential) mixed model to compare head growth trajectories from birth to 35 months in 51 children with ASD, 11 with developmental delay (DD), and 14 typically developing (TD) controls, finding increased growth in the group with ASD relative to the other 2 groups combined. Dissanayake *et al.*[34] reported increased head growth in 28 children with ASD and IQ >70 compared to 19 TD children of similar mental age, although this reached statistical significance using only a 1-tailed test. In both studies, divergence in head size between groups with and without ASD was not apparent until after the first year.[7,34] Similarly, a recent birth cohort study from Norway[35] (n = 106,082) that compared children with ASD (n = 376) to others in the population in the first year using mixed effects models found no overall group differences in head growth, although rates of macrocephaly were elevated among boys with ASD (8.7%) compared to other boys (3.3%), presumably because of increased variability in the group with ASD. A US birth cohort study that included 100 children with ASD found no overall ASD-related differences in head growth based on measurement of HC at 9, 24, and 36 months, based on cross-sectional comparisons at each time point.[36] There is also uncertainty as to whether increased head growth in ASD, when detected, is a component of generalized somatic overgrowth,[34,37,38] or is independent of group differences in height and/or weight.[7,28,39,56] In addition, 2 recent studies also reported similar head growth in children with ASD compared to children other developmental or mental health diagnoses[23,25]; notably, in 1 of these studies, both groups would have been regarded as having accelerated head growth in the first 18 months if assessed relative to CDC norms.[25] Thus, evidence for increased HC as an ASD-specific risk marker remains inconsistent.

Another key question is whether increased head growth is specific to ASD or, rather, is also expressed in relatives without ASD who share genetic vulnerability. Macrocephaly has been reported in 19% to 31% of parents of probands with ASD[16,20] and 12% to 16% of siblings.[16,40] Indeed, a recent analysis of HC from the California Autism Twin Study indicates that rates of macrocephaly are 20% to 27%, with no differences among probands with ASD, concordant and discordant co-twins.[52] Studies reporting HC in relatives have generally not included data regarding other relevant phenotypes (e.g., subthreshold symptoms), so it is difficult to know whether increased rates of macrocephaly are due to nonspecific familial correlations in HC[41] or represent co-segregation of macrocephaly and behavioral symptoms of the "broader autism phenotype,"[42,43] presumably due to the expression of genes involved in susceptibility to ASD.

The objective of this study was to examine whether head growth in the first 3 years differed between high-risk infants who developed ASD versus high-risk infants who did not and low-risk controls. Our longitudinal design allowed prospective as well as retrospective measurement of HC in 1 of the largest samples of children with ASD and nondiagnosed siblings studied to date.

METHOD

Participants

The Baby Siblings Research Consortium (BSRC) is an international network dedicated to studying early development in infants at increased risk of ASD. The present analyses included data from 12 BSRC sites (University of Alberta, Dalhousie University, Kennedy Krieger Institute, McMaster University, University of California, Davis, University of California, Los Angeles, University of California, San Diego, University of Miami, University of Pittsburgh, University of Toronto, Vanderbilt University, and Washington University in St. Louis). Institutional review board approval to collect and analyze de-identified data from

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