Autism with Intellectual Disability Related to Dynamics of Head Circumference Growth during Early Infancy

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ABSTRACT

BACKGROUND: It is not yet definitively known whether dynamic features of head circumference growth are associated with autism. To address this issue, we carried out a nested matched case-control study using data from national well baby clinics in Finland; autism cases were identified from the Finnish Hospital and Outpatient Discharge Registry.

METHODS: A nonparametric Bayesian method was used to construct growth velocity trajectories between birth and 2 years of age in autism cases and matched control subjects ($n = 468$ in main analyses, 1:1 matched control subjects). Estimates of odds ratios for autism risk in relation to the growth velocities were obtained using conditional logistic regression.

RESULTS: Growth velocity of head circumference at 3 months of age, adjusting for gestational age at birth and maternal age, is significantly associated with autism ($p = .014$); the finding was observed in subjects with comorbid intellectual disability (ID) ($p = .025$) but not in those without ID ($p = .15$). Height growth velocity among subjects with autism and without ID is significantly associated with autism at 6 months ($p = .007$), and weight growth velocity at 18 months without ID ($p = .02$) and 24 months without ID ($p = .042$) and with ID ($p = .037$).

CONCLUSIONS: Acceleration in head circumference growth is associated with autism with comorbid ID at 3 months but not subsequently. This association is unrelated to acceleration in height and weight, which are not strongly associated with autism until after 6 months.

Keywords: Autism, Development, Epidemiology, Growth Velocity, Head Circumference, Trajectories

http://dx.doi.org/10.1016/j.biopsych.2014.08.008

Evidence is accumulating of a strong association between autism and extreme growth of head circumference (HC) during early infancy. We studied the association between HC growth and autism with the aim of shedding light on the dynamic features of HC growth that relate to autism. We focus on rates of growth (i.e., growth velocity) rather than cumulative growth, and we also take into account growth velocities of height and weight. The main difficulty in studying dynamic features of HC growth related to autism has been a lack of sufficiently large cohorts to allow accurate comparisons of growth velocity trajectories between cases and control subjects. The main contribution of the article is to utilize high-quality longitudinal well baby clinic data from a large nested matched case control study, the Finnish Prenatal Study of Autism (FiPS-A), along with a novel statistical technique to allow direct comparisons of HC growth velocities between cases and control subjects.

In an intriguing study, Chawarska *et al.* (1) examined the trajectory of early growth in boys with autistic disorder compared with typically developing boys. Cases were found to have significantly larger HC in the first year of life, reflecting a generalized process that also included elevated height and weight. General morphologic between-group differences, however, may not be apparent until after accelerated growth has had time to accumulate, so the present study is complementary: our focus is on growth velocity. Indeed, growth rate acceleration is distinct from cumulative growth—for example, depending on the starting point, children who were smaller at birth may be able to catch up with typical peers and never lead to macrocephaly or macrosomy. Earlier studies that found elevated HC growth in autism are complementary to our study in the same way. Dawson *et al.* (2) found a significant increase in HC from birth to 12 months in autism spectrum disorder (ASD) cases, adjusting for height. Fukumoto *et al.* (3) reported significantly larger HC in the ASD group at 6 and 9 months after birth. Courchesne *et al.* (4) observed markedly increasing separation of HC in ASD and control subjects from 6 to 14 months. Hazlett *et al.* (5) found increased HC beginning at 12 months, adjusting for body mass index. Accelerated HC growth was also found in the first year of life (6) and from 2 to 3 years (7).

In addition to Chawarska *et al.* (1), other studies found no differences in HC either alone or after adjusting for height and/or weight. Mraz *et al.* (8) reported larger HC in ASD beginning at 6 months, persisting at every age interval until

ISSN: 0006-3223
Biological Psychiatry May 1, 2015; 77:833–840 www.sobp.org/journal

25 months, though significance was lost controlling for length and weight. van Daalen *et al.* (9) found no significant difference in HC from 4 to 11 months. Constantino *et al.* (10) found increases in head growth from birth to 15 months in ASD cases compared with sibling cases and control subjects, but the findings fell short of statistical significance. No differences were found in HC in another study (11). In a Norwegian birth cohort, Suren *et al.* (12) found similar mean head growth in boys with autism as for control subjects, though variability and the proportion with macrocephaly were greater in boys with autism. Among girls, HC was smaller at birth and mean head size was lower in the first year, though there were no significant differences with control subjects. Schrieken *et al.* (13) found a smaller HC relative to height over the first year in autistic cases. Nordahl *et al.* (14) found a pronounced increase in cross-sectional HC in male ASD cases with regression relative to typically developing control subjects starting at 4 to 6 months of age, persisting through 19 months. There was no difference in cross-sectional HC between ASD cases without regression and typically developing (TD) control subjects. In analyses of longitudinal changes in HC, the rate of HC growth was larger in the autism with regression group than TD and autism without regression groups. The rates of HC growth relative to TD before 4.5 months were only slightly but statistically significantly increased in the ASD groups without regression and with regression. There were no differences in HC growth trajectory from birth to age 3 in girls alone. Webb *et al.* (15) found no differences in rate of growth between ASD cases with and without regression. Gray *et al.* (16) found no difference in HC between autism cases and the Centers for Disease Control and Prevention norm median up to 18 months of age; an increase in HC was observed at 18 months in male subjects. These analyses were restricted to male subjects given the small number of female subjects. No differences in HC were found between autism cases and subjects with developmental delay but without autism. The pattern of HC growth was significantly increased in probands with ASD compared with siblings (17). In that study, subjects with increasingly extreme HC demonstrated increasingly lower mean IQ scores. Moreover, autism symptom severity increased with HC. Probands with larger HC also had earlier onset of first words and were more likely to have had regression. Early generalized overgrowth of HC, height, and weight in boys was related to more severe symptoms and greater deficits in adaptive social functioning (1).

Some previous studies suggest that increased body growth is also a feature of autism. In a previous study, the rates of height growth in ASD were significantly increased compared with control subjects up to age 2 (8). In another study, increased growth in height was found in boys with ASD versus control subjects, with significant effects from 4.8 to 24 months (1). Significantly increased height was also observed from 100 to 400 days postnatally (9). ASD male subjects were significantly heavier than control subjects at 3 to 12 months (3).

Our analytical strategy involved a new nonparametric modeling approach that brings greater flexibility, as well as ease of implementation, to growth trajectory analysis. Repeated measurements of HC were available on most subjects in the FiPS-A study, but it was challenging to gain a detailed understanding of growth patterns. The problem was exacerbated by large fluctuations in growth velocity during early infancy and high between-subject variability. To address this problem, we used a powerful new nonparametric Bayesian inversion method for reconstructing growth velocity curves from sparse temporal data (18,19) (see Supplement 1). We applied this method to examine the relationship between the growth dynamics of head circumference, as well as height and weight, in a large sample of cases and control subjects from a national birth cohort in Finland with longitudinal data on these measures.

METHODS AND MATERIALS

The study used a nested matched case-control design (FiPS-A) described in detail in Lampi *et al.* (20) and summarized here. In this design, the cases and matched control subjects are drawn from the same birth cohort. The cohort consisted of all offspring born in Finland from 1987 to 2005 ($n = 1.2$ million pregnancies). To identify the autism cases, we conducted a record linkage between the Finnish Medical Birth Register and the Finnish Hospital Discharge and Outpatient Register (FHDR), using personal identification numbers assigned at birth. Cases with childhood autism (ICD-10 F84.0, ICD-9 299.0) in the cohort were followed up from 1987 to 2007. The total number of childhood autism cases in the entire study sample was 1132 (only 7 cases with ICD-9 299.0, the remainder with ICD-10 F84.0). Registry diagnoses of infantile autism from the FHDR were very well validated with the Autism Diagnostic Interview-Revised in a previous study (21). The childhood autism cases were matched 1:1 to control subjects drawn from the birth cohort who were without ASD or severe/profound intellectual disability on date of birth, sex, birthplace, and residence in Finland.

The study was approved by the ethical committees of the hospital district of Southwest Finland, National Institute for Health and Welfare, and the Institutional Review Board of the New York State Psychiatric Institute.

Collection of Data on Head Circumference, Height, and Weight from Well Baby Health Clinics

Parents in Finland have their children evaluated with nationally standardized developmental assessments at well baby centers throughout the country at age 1 month and every 1 to 2 months until 15 months. Toddlers are seen at age 2. Physicians and registered nurses complete a nationally standardized form, including HC, height, and weight measurements at every visit. The clinics where all cases and control subjects received care were identified by registry linkages with the Finnish Medical Birth Register and FHDR. These archived longitudinal data were abstracted manually by public health or research nurses highly trained and experienced in the data acquisition.

Measures

The primary measure was growth velocity of HC at selected intervals from birth to age 2. The analyses were limited to 2 years based on findings from the prior literature (reviewed in