ORIGINAL ARTICLE

Early Generalized Overgrowth in Boys With Autism

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Context: Multiple studies have reported an overgrowth in head circumference (HC) in the first year of life in autism. However, it is unclear whether this phenomenon is independent of overall body growth and whether it is associated with specific social or cognitive features.

Objectives: To examine the trajectory of early HC growth in autism compared with control groups; to assess whether HC growth in autism is independent of height and weight growth during infancy; and to examine HC growth from birth to 24 months in relationship to social, verbal, cognitive, and adaptive functioning levels.

Design: Retrospective study.

Setting: A specialized university-based clinic.

Participants: Boys diagnosed as having autistic disorder (n=64), pervasive developmental disorder–not otherwise specified (n=34), global developmental delay (n=13), and other developmental problems (n=18) and typically developing boys (n=55).

Main Outcome Measures: Age-related changes in HC, height, and weight between birth and age 24 months; measures of social, verbal, and cognitive functioning at age 2 years.

Results: Compared with typically developing controls, boys with autism were significantly longer by age 4.8 months, had a larger HC by age 9.5 months, and weighed more by age 11.4 months ($P=.05$ for all). None of the other clinical groups showed a similar overgrowth pattern. Boys with autism who were in the top 10% of overall physical size in infancy exhibited greater severity of social deficits ($P=.009$) and lower adaptive functioning ($P=.03$).

Conclusions: Boys with autism experienced accelerated HC growth in the first year of life. However, this phenomenon reflected a generalized process affecting other morphologic features, including height and weight. The study highlights the importance of studying factors that influence not only neuronal development but also skeletal growth in autism.

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AUTISM IS A COMPLEX DEVELOPMENTAL disorder characterized by marked impairments in social interaction and communication accompanied by a range of repetitive behaviors and restricted interests.[1] Along with pervasive developmental disorder–not otherwise specified (PDD-NOS), which is typically characterized by less severe impairments and a more atypical presentation, autism belongs to the class known as autism spectrum disorders (ASDs). Although the diagnosis of ASDs can be reliably assigned at approximately the second birthday,[2,3] the symptoms typically emerge when the individual is aged 6 to 18 months.[4-9] There are no known biological markers for ASDs; the etiology of ASD is unclear, and the wide heterogeneity of its expression has led to a hypothesis of multiple subtypes that might be linked to different etiologic factors with varying phenotypic features and outcomes.[10,11]

Macrocephaly (head circumference [HC] >97th percentile) is one of the better-established phenotypic features characterizing a subset of individuals with autism.[12-20] Although estimates vary among studies, on average, approximately 20% of individuals with autism are macrocephalic.[12,16] In most cases, macrocephaly in autism is not apparent prenatally[21] or at birth but emerges as the result of an abnormally rapid growth velocity in the first year of life.[13,22-25] Although the studies vary somewhat as to when the extreme overgrowth becomes noticeable, the evidence converges that by the end of the first year, the difference in HC between infants with autism and either population norms[13,22,25] or typically developing community samples[23,25] becomes apparent. Studies estimate that 35%[26] to 59%[13] of children with ASDs experience extreme HC growth (ie, increasing >2 SD between birth and the first birthday) compared with 6% of typi-

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cally developing infants.[13] The phenomenon of extreme overgrowth has been considered by some as a potential indicator of risk of autism in infancy,[13,27] although this claim has been challenged lately.[28]

Considering the high correlation between total brain volume and HC, particularly in infants and young children,[23,29,30] the early acceleration of HC growth in autism has attracted considerable attention as a potential indicator of abnormal neural development. Neuroimaging studies[13,23,30-35] suggest that enlarged HC in children with autism is, indeed, associated with increased total brain volume rather than with increased nonneural tissue volume, cerebrospinal fluid, or intracranial blood volume. Enlargement in young children seems to extend to the frontal, temporal, and parietal lobes in gray and white matter[13,23,33] and to subcortical structures, such as the amygdalae and the caudate nucleus.[34,35] Although a variety of candidate processes have been proposed, including increased neurogenesis, gliogenesis, or both; altered myelination; atypical synaptic pruning; inflammatory process; or altered cortical connectivity,[36-39] no specific mechanisms responsible for the observed brain overgrowth in autism have been identified.

The relationship between accelerated HC growth and the rate of weight and length/height increase in infancy also has been examined in some detail. The results of several studies[13,22,23] suggest that enlarged HC is independent of other body parameters. However, other studies have reported associations between HC, body weight, and height overgrowth in various combinations. Mraz et al[25] reported that in 35 children with ASD aged 5 to 25 months, HC, length, and weight were increased compared with Centers for Disease Control and Prevention (CDC) norms and a community sample. A similar pattern was noted in a high-functioning sample of 85 boys and girls with autism in Japan but only at ages 3 and 6 months.[24] However, in an Australian high-functioning autism and Asperger syndrome sample (N=28), this phenomenon was reported at approximately 2 to 3 years of life only.[40] To further complicate matters, 2 studies report only excessive increase in height or weight growth in the first year, with HC remaining in the normative range[41] or appearing macrocephalic in a few cases but without signs of unusual acceleration.[42] Thus, the evidence regarding an association between HC and other growth parameters remains conflicted. Differences among studies regarding the type of reference norms used, approaches to data analysis, and issues associated with small sample sizes, limited data density, and often high heterogeneity of the samples are likely to contribute to such disparate patterns of results. Regarding norms against which growth patterns of children with ASDs were compared, some studies[13,22] standardize their growth measurement using CDC norms, others compare their unstandardized growth parameters with community samples, and still others standardize ASDs and typical samples using CDC norms and compare them with one another.[25] Considering that the growth patterns of typically developing infants raised in optimal environments can deviate from CDC norms, the use of a normative community sample for comparisons is preferable.[23] Furthermore, several different approaches have been used to model growth data and test for between-group differences. Some approaches compared growth data directly at successive time points using simple *t* tests[13,24,25] or repeated-measures analysis of variance.[25] The simple *t* test, however, does not consider correlations among successive measurement points, whereas the analysis of variance might be affected by the presence of missing measurements for individual participants. Only a few studies used growth curve analysis in the form of hierarchical linear models[4] or nonlinear mixed models.[23] However, these models make strong assumptions regarding the shape of growth curves that can be advantageous if the assumed shape matches the structure of the data but can bias results if it does not. In the present study, we use a less assumption-laden method for modeling growth curves in hopes of disambiguating the nature of the association between enlarged HC and other morphologic features in infants who later develop autism.

Despite largely consistent findings regarding macrocephaly in autism, identifying a unique pattern of behavioral correlates of this particular phenotypic feature has been difficult. Two studies[13,16] have reported higher rates of macrocephaly in autism than in PDD-NOS samples, suggesting an association between brain overgrowth and a more severe form of ASDs. An association with lower adaptive functioning and increased motor stereotypes in older macrocephalic children also has been reported.[19,20,43] Associations between HC and IQ seem to be limited,[16,18,44] although in higher-functioning individuals with autism, macrocephaly seems to be associated with better verbal functioning.[20] Studies linking the rate of HC growth in infancy and later symptom severity also have yielded mixed results. Several studies[13,25,27] have suggested that infants with ASDs who experience a more rapid rate of HC growth have greater social impairments. However, a study[26] focused on a high-functioning sample that was more homogeneous regarding IQ demonstrated better adaptive functioning in individuals with autism who exhibited faster rates of HC growth.

Thus, although strong evidence supports an early atypical head growth pattern in autism, several issues remain to be clarified, including the association between HC overgrowth and the rate of increase in height and weight in the same early developmental period and examination of the overgrowth phenomenon as a potential marker of a phenotypic subtype in ASDs. In the present study, we compare a large sample of male toddlers with autism and PDD-NOS with samples of typically developing (TD) boys and boys with various developmental delays seen for a diagnostic evaluation at approximately their second birthday. Longitudinal growth data were collected retrospectively from medical records from birth to 24 months. We examined whether children with autism and PDD-NOS evidence accelerated HC growth in the first year compared with TD and developmental delay controls, whether HC growth acceleration represents an independent morphologic feature or is a part of generalized body overgrowth, and whether children who exhibit atypical growth in infancy show greater impairments in social, cognitive, verbal, and adaptive skills at the age of 2 years.

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Table 1. Characteristics of the 184 Study Participants by Group[a]

Characteristic	Autism (n = 64)	PDD-NOS (n = 34)	GDD (n = 13)	Other[b] (n = 18)	TD (n = 55)	*P* Value
GA, mean (SD), wk	39.0 (1.6)*†	38.5 (2.2)*	38.7 (2.4)*†	38.9 (1.9)*†	39.7 (1.2)†	.02
Maternal age, mean (SD), y	34 (4)	35 (5)	31 (5)	33 (5)	34 (4)	.34
Paternal age, mean (SD), y	35 (5)	36 (5)	31 (5)	37 (8)	36 (6)	.09
First diagnosis: visit 1, mean (SD)						
Age, y	2.2 (.5)*	2.0 (.6)*†	2.4 (1)*	1.7 (.5)†	2.0 (.7)*†	.02
Verbal DQ	46 (21)*	70 (32)†	49 (18)*	72 (25)†	98 (19)‡	<.001
Nonverbal DQ	77 (16)*	92 (20)†	73 (13)*	103 (11)†‡	102 (11)‡	<.001
Social Affect	15.9 (3.2)*	12.4 (4.5)‡	9.3 (6.5)†‡	5.9 (2.6)†	NA	<.001
RRB	4.5 (1.8)*	3.1 (1.9)†	3.0 (2.2)†	1.1 (1.1)‡	NA	<.001
Confirmatory diagnosis: visit 2, mean (SD)						
Age, y	3.7 (.7)	3.9 (.6)	3.5 (.7)	3.3 (.9)	NA	.09
Verbal DQ	62 (28)*	98 (18)†	56 (29)*	97 (24)†	NA	<.001
Nonverbal DQ	71 (20)*	97 (14)†	62 (20)*	100 (13)†	NA	<.001
Social Affect	14.2 (3.7)*	7.8 (3.7)†	6.3 (6.8)†	4.8 (5.0)†	NA	<.001
RRB	5.5 (1.4)*	3.5 (1.8)†	4.0 (3.1)*†	1.7 (2.0)‡	NA	<.001

Abbreviations: DQ, developmental quotient (based on the Mullen Scales of Early Learning); GA, gestational age; GDD, global developmental delay; NA, not applicable; PDD-NOS, pervasive developmental disorder–not otherwise specified; RRB, Autism Diagnostic Observation Scale–Generic repetitive and restrictive behaviors algorithm score; Social Affect, Autism Diagnostic Observation Scale–Generic social affect algorithm score; TD, typically developing.

[a] In each row, values that do not share a common superscript symbol (*, †, or ‡) are significantly different at $P < .05$ by the Tukey-Kramer test.

[b] For explanation of "Other" see "Participants" subsection of the "Methods" section.

METHODS

This study was approved by the Human Investigations Committee of Yale University School of Medicine, New Haven, Connecticut; informed written consent was obtained from all the parents before testing. Diagnosis and assessment were conducted at the Toddler Developmental Disabilities Clinic at the Child Study Center at Yale University School of Medicine.

PARTICIPANTS

Participants consisted of 184 boys enrolled consecutively in studies on early social cognition at the Yale Toddler Developmental Disabilities Clinic before their third birthday (**Table 1**). Considering the 4:1 male to female ratio in ASDs, the number of girls was insufficient for the planned analyses; thus, girls were excluded from the present study. Children with any clinical symptoms were assessed using the Mullen Scales of Early Learning[45] and the Autism Diagnostic Observation Scale–Generic.[46] Parents were interviewed using the Vineland Adaptive Behaviors Scales–Expanded Form.[47] In 90% of cases, the diagnosis was based on a consensus best-estimate diagnosis between 2 expert clinicians at 4 years based on all relevant background and evaluation data. The remaining 10% were lost to follow-up, of which only 11 (4 with an autistic disorder [AUT] diagnosis) received their diagnosis before age 30 months (eg, an age when diagnostic assignment might be less stable).[3] The diagnostic status of TD boys was confirmed through parent interview and standard assessment of verbal and nonverbal skills. The final sample included boys with AUT (n=64), PDD-NOS (n=34), global developmental delay (GDD, n=13), and other difficulties (including language or motor delays, anxiety, and attention deficits) (Other, n=18) and TD controls (n=55). Toddlers with major comorbid health problems (eg, seizure disorder or uncorrected visual or auditory abnormalities), known chromosomal disorders, encephalitis, and hydrocephalus and those with gestational age younger than 32 weeks were excluded from the study.

Gestational age in the overall sample ranged from 32 to 42 weeks, although 97.3% of children had a gestational age 36 weeks or older. The PDD-NOS group had a lower gestational age than did the TD group; no other pairwise comparisons were statistically significant (Table 1). Children were evaluated, on average, near their second birthday, with a confirmatory diagnosis performed near their fourth birthday. The groups differed in levels of verbal and nonverbal functioning and severity of social impairments in a predictable manner (Table 1). The groups did not differ in racial distribution (white/nonwhite, $\chi^2_4=3.92$, $P=.42$); 79% of the boys were white and 13% were African American, Asian, or of mixed racial heritage; in 8% of cases, the parents did not provide information regarding race. The mean (SD) age of mothers was 33.7 (4.5) years and of fathers was 35.4 (5.7) years at the time of the child's birth, and the groups did not differ. A high proportion of mothers (76%) and fathers (73%) completed college, and the groups did not differ in parental educational status (college/no college, $\chi^2_4=3.14$, $P=.53$ for mothers and $\chi^2_4=3.15$, $P=.53$ for fathers). Participants in all the groups were drawn primarily from the same geographic area in the northeastern United States (Connecticut, New York, New Jersey, and Massachusetts).

PROCEDURES

Head circumference and height and weight data were obtained via medical record review at the following 10 time points: birth, 2 weeks, and 2, 4, 6, 9, 12, 15, 18, and 24 months. These time points coincide with the standard recommended pediatric visit schedule for healthy children (ie, well-child visits). The mean (SD) number of HC measurements per child was 7.2 (2.1); no significant differences were noted between groups in the number of valid data points ($P=.90$). Ninety-eight percent of boys had 2 or more HC measurements available, and 81% had 5 or more. There were a mean (SD) of 8.62 (1.9) measurements for weight and 8.17 (2.1) measurements for height per child, and the numbers were comparable across groups ($P=.41$ and $P=.47$, respectively). There was a notable decline in data density from 12 to 24 months: at 12 months, 83% of boys had HC measurements (compared with 91% for weight and 90% for height); by 24 months, this number dropped to 25% for HC measurements (and 63% for weight and 60% for height), reflecting the standard pediatric practice of less frequent HC measurement during well-baby visits by 24 months. Considering that the HC, height, and weight measures were collected in various pediat-

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ric offices, the reliability of the measurements in this study has not been established.

STATISTICAL ANALYSIS

The primary analysis was based on fitting Bayesian multilevel growth curve models to the raw data measurements, not transformed through CDC[48] or World Health Organization norms. Additive effects at the overall, group, and individual levels were modeled as spline functions[49] implemented as low-rank thin-plate splines[49] in Just Another Gibbs Sampler,[50] an open-source program for Bayesian analysis of hierarchical models using Markov chain Monte Carlo simulation. These simulations produced samples drawn from the posterior distributions for all model parameters, and statistical inferences were derived by analyzing these samples using the statistical computing software R.[51] Estimated mean curves for each group were calculated as pointwise means of all sampled mean curves for that group, and 95% credible bands were found by calculating 2.5% and 97.5% quantiles from the sample of fitted group curves. For interpretative purposes, the credible bands derived from a Bayesian model are analogous to confidence intervals.

After the models were fit for HC, height, and weight individually, combinations of the 3 variables were generated using principal component analysis (PCA), a standard technique in which a set of correlated variables is linearly transformed into a new set of orthogonal variables called *principal components* (PCs).[52] Toward this end, a spline curve was fit to each of the original variables, HC, height, and weight, based on the entire sample. Subtracting these 3 fitted curves from the respective original variables gave residuals interpretable as age-corrected HC, height, and weight measurements. Applying PCA to these residuals produced 3 PCs, each defined as a linear combination of the 3 age-corrected variables. Subsequently, individual PC scores were derived by multiplying the coefficients for the given PC by the individual's growth values (eg, HC) recorded at a given time point. The PC scores are combinations of the age-corrected measurements that capture the variability of these measurements in an optimal way; for example, PC_1 is the linear combination that accounts for the maximal proportion of variability in the joint distribution of age-corrected HC, height, and weight. The individual PC scores were analyzed using the same spline models and procedures as used for the original growth variables (HC, height, and weight). The use of PCA was guided by a desire for such combinations of variables to emerge from the data without previous assumptions as to what those combinations are. However, to facilitate comparability with previous studies, we also report rates of absolute macrocephaly ($z_{HC}>2$ SD) in the diagnostic groups and examine between-group differences in relative macrocephaly ($z_{HC}-z_{height}>2$ SD) based on CDC norms.

The choice of spline function modeling was motivated by the desire to build a general growth model with minimal assumptions. Diverse functions can be closely approximated using spline basis functions, and because the true functions that explain the growth in this population are unknown, splines provide a versatile modeling tool. Using more restricted models that assume that the growth curves follow quadratic or exponential forms, for example, would be simpler if such models were accurate but could obscure the true behavior and give misleading results if the unknown underlying growth curves did not adhere to the assumed form. In addition, splines allow the detection and estimation of possible subtle effects in the growth curves, such as acceleration in growth over months followed by deceleration. Discovering such effects using more assumption-laden models would require specifying when such effects may occur and, thus, would add parameters to the model. Furthermore, a spline model makes derivatives and second derivatives of the growth curves easy to calculate should such analyses be desired. This type of modeling also easily accommodates irregular patterns of missing measurements because conditional probability distributions of all ingredients in the model can be derived at arbitrary time points using the Markov chain Monte Carlo samples of fitted spline curves.

To enhance comparability with other studies using growth curve approaches, in a secondary analysis, we analyzed data using a mixed-models approach. Following closely the model in the study by Hazlett et al,[23] a nonlinear mixed-effects growth model was fit using the exponential growth function, with b_0 as a random effect. Each parameter was crossed with the diagnostic group so that differences between groups for each parameter could be assessed statistically. Following the strategy adopted by Hazlett et al, race, maternal education, and body mass index (BMI) were included as covariates; subsequent models replaced BMI with height, weight, or height and weight together.

RESULTS

HC GROWTH

Figure 1A shows growth curves for HC in all 5 groups. Subsequently, we conducted a set of planned comparisons between each clinical group and TD controls.

As shown in **Figure 2**A, boys with autism had a similar HC as TD boys shortly after birth but experienced faster growth such that their HC became significantly larger than that of TD controls by 9.5 months ($P=.05$) and remained significantly larger at 12 ($P=.02$), 15 ($P=.009$), and 18 ($P=.02$) months. The difference seemed no longer significant by 24 months ($P=.10$), which most likely is due to a lower data density at this age level, as indicated by estimated mean and credible band limits. The HC growth curve of boys with PDD-NOS was not significantly different from that of the AUT or TD group (Figure 2B). Finally, no significant differences in HC growth rate were noted between boys with GDD and Other disorders and TD controls (Figure 2C and D). Together, these results suggest that by age 9 to 10 months, boys with autism display an atypical increase in HC.

HEIGHT AND WEIGHT GROWTH

Using an identical approach as that of the HC analysis, we examined whether the abnormally rapid growth in autism is specific to HC or represents part of a general overgrowth pattern (Figure 1B and C). Boys with autism showed accelerated body growth, with significant departure from TD controls occurring at approximately 4.8 months for height and 11.4 months for weight ($P=.05$ for both) (**Figure 3**A). Their height remained significantly above that recorded in TD controls at 6 ($P=.02$), 9 ($P=.002$), 12 ($P=.002$), 15 ($P=.002$), 18 ($P=.001$), and 24 ($P=.02$) months. Significant departure from the weight curves of TD controls occurred in boys with autism at 11.4 months ($P=.05$) and remained significant throughout 12 ($P=.04$), 15 ($P=.03$), 18 ($P=.02$), and 24 ($P=.02$) months. Boys with PDD-NOS also experienced accelerated growth, which began manifesting in height at 7.3 months and weight at 19.4 months ($P=.05$ for both)

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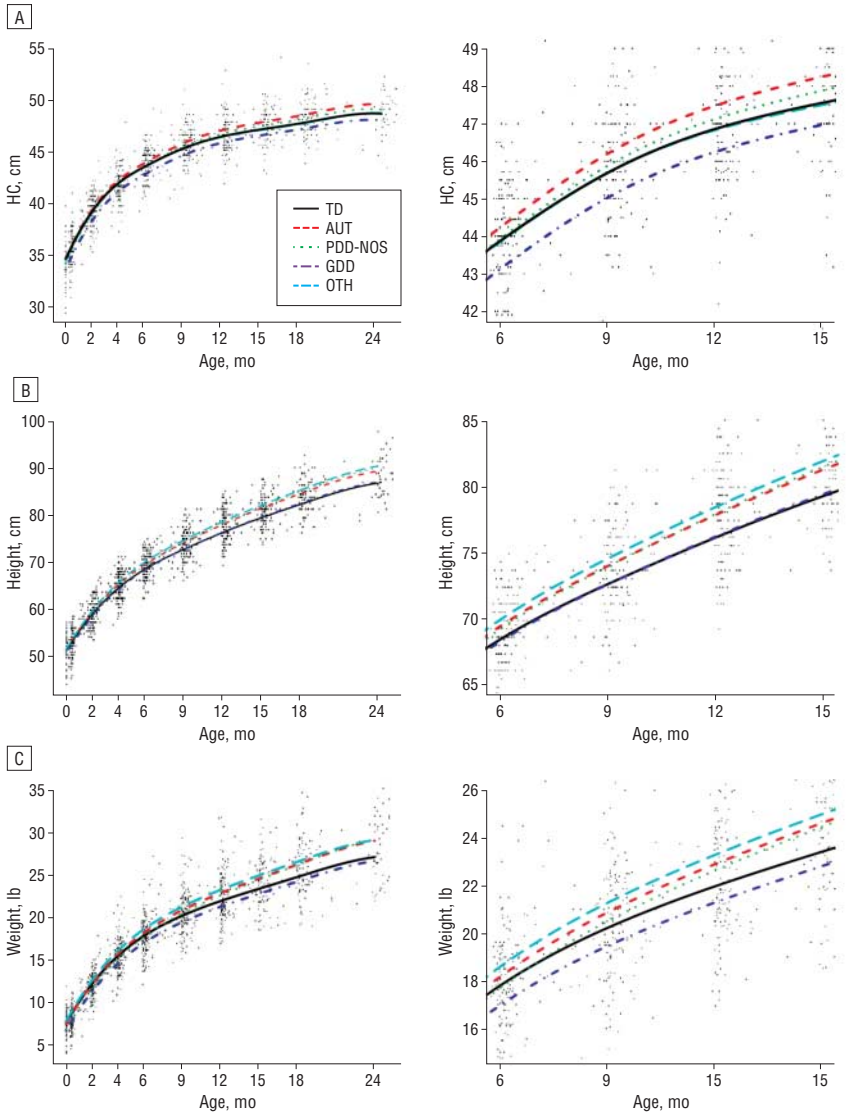

Figure 1. Spline-based Bayesian multilevel growth curves showing group means for head circumference (HC) (A), height (B), and weight (C) for the autism (AUT), pervasive developmental disorder–not otherwise specified (PDD-NOS), global developmental delay (GDD), Other (OTH), and typically developing (TD) groups from birth to 24 months (left) and zoomed in from 6 to 15 months (right). (For explanation of "Other" see "Participants" subsection of the "Methods" section).

(Figure 3B). Accelerated height but not weight growth was also noted in the Other group arising at approximately 4.5 months ($P=.05$) (Figure 3C). In comparison, the GDD group exhibited no significant differences from the TD group (Figure 3D). Thus, accelerated HC growth in autism seems to be accompanied by height and weight overgrowth, although manifesting at different developmental time points.

ASSOCIATIONS AMONG HC, HEIGHT, AND WEIGHT

Based on the analyses of the 3 growth parameters at the group level, it was unclear whether boys with autism who evidenced HC overgrowth also showed rapid growth of weight and height and whether the observed HC overgrowth was associated with specific phenotypic features, including level of language, cognitive functioning, and symptom severity. To clarify this issue, we conducted a PCA on HC, height, and weight data for the autism, PDD-NOS, and TD groups combined (**Table 2**). (The latent structure based on the entire sample was nearly identical to that obtained in the subsample of interest.) Three PCs were identified. PC_1 accounted for 70% of the variability and reflected an average of the 3 growth variables and, thus, represented the overall body size. PC_2 accounted for an additional 19% of the variability and represented large HC values combined with small height and weight values (ie, large head and small body). PC_3 captured the remaining 11% of the variability and represented increased height relative to body size (ie, long and lanky body) and the residual random noise.

Individual scores for the first and second PCs at each time point were fit using the same penalized spline model used previously for HC, height, and weight. Analysis of the mean scores on PC_1, representing overall body size,

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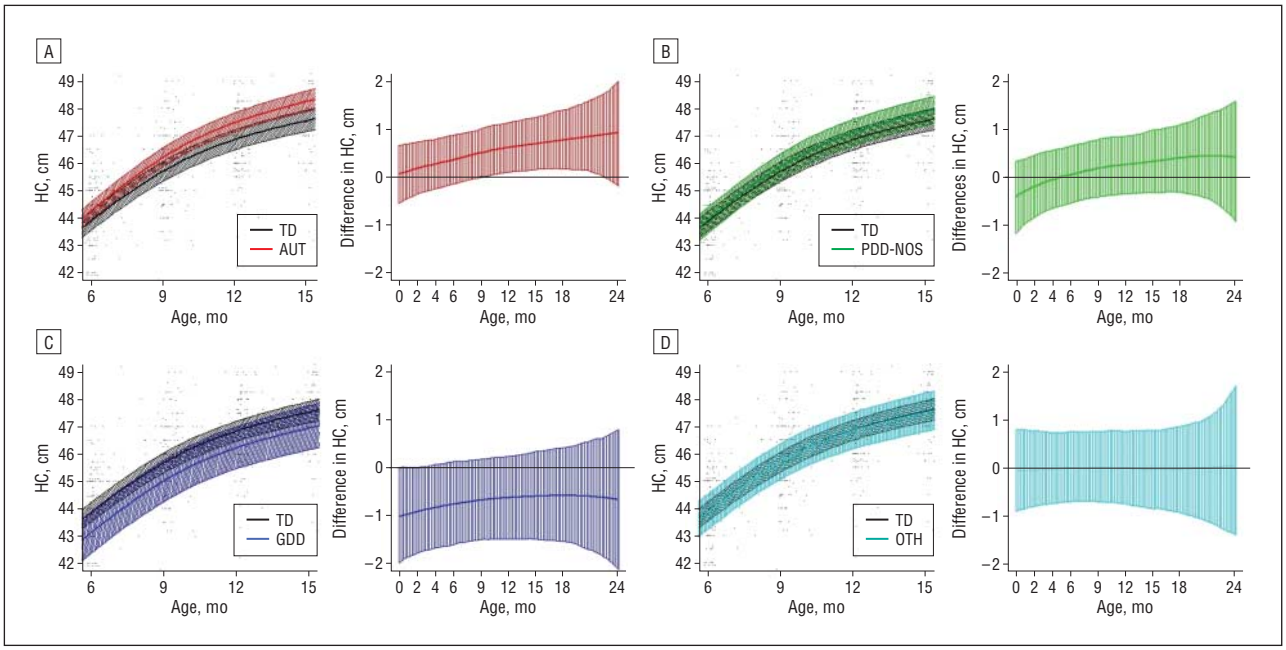

Figure 2. Head circumference (HC) data for the autism (AUT) and typically developing (TD) groups (A), pervasive developmental disorder–not otherwise specified (PDD-NOS) and TD groups (B), global developmental delay (GDD) and TD groups (C), and Other (OTH) and TD groups (D). For each pair, graphs on the left illustrate spline-based Bayesian multilevel growth curves for each of the clinical groups and TD controls. The boundaries represent 95% credible bands. Graphs on the right describe differences between means of a given clinical group and TD controls from birth to 24 months. Divergence of the credible band from 0 represents a significant difference between the means at $P \leq .05$ (2-sided). (For explanation of "Other" see "Participants" subsection of the "Methods" section.)

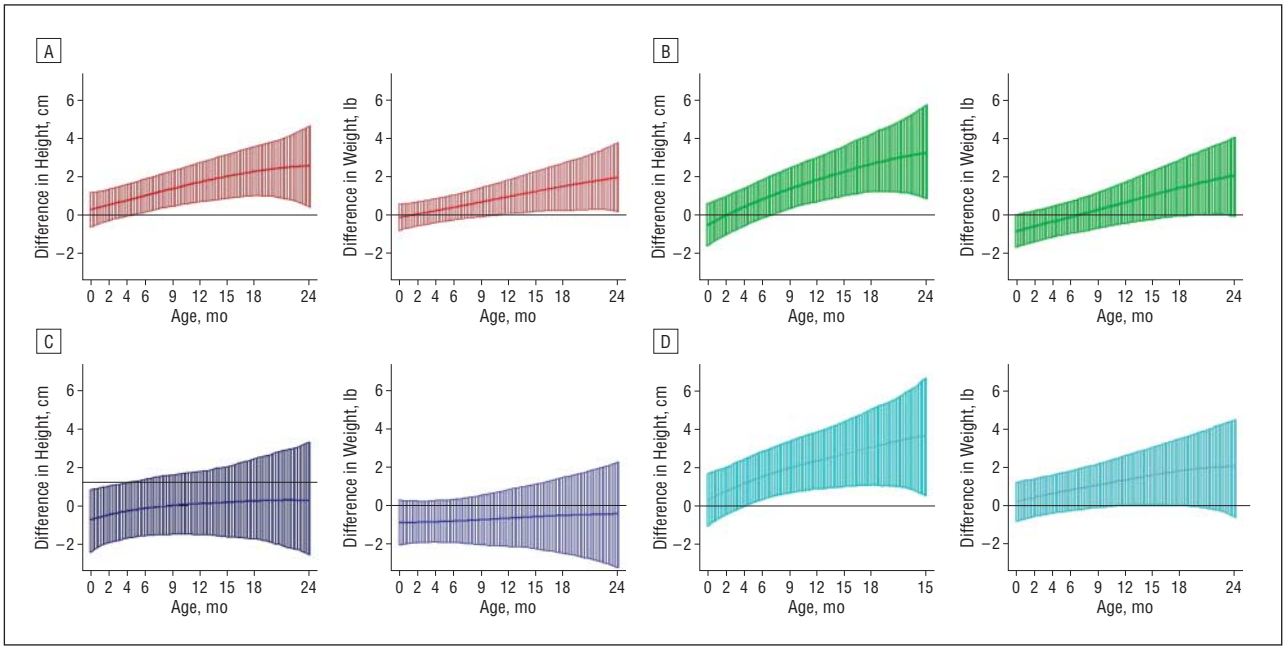

Figure 3. Differences between means of a given clinical group and typically developing controls for height (left) and weight (right) for autism (A), pervasive developmental disorder–not otherwise specified (B), global developmental delay (C), and other delays (D) from birth to 24 months. Divergence of the credible band from 0 represents a statistically significant difference between the means at the $P \leq .05$ level (2-sided).

shows that as a group, boys with autism experienced generalized overgrowth, with their growth curves diverging significantly from those of TD controls by 6.5 months ($P = .05$) and remaining significant at 9 ($P = .009$), 12 ($P = .002$), 15 ($P = .001$), 18 ($P = .001$), and 24 ($P = .01$) months (**Figure 4**A). A similar pattern was noted in the PDD-NOS group, with the divergence from the TD sample occurring later than in autism, at 11.5 months ($P = .05$) (Figure 4B). A direct comparison of the AUT and PDD-NOS PC_1 scores yielded no significant results.

Given the hypotheses of the study, PC_2, representing a large HC relative to body size, was the most interesting because any differences in this feature between boys with autism and TD controls would be due to HC overgrowth itself and unexplained by an overall increase in body size. An analogous analysis of PC_2 scores yielded

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Table 2. Principal Component (PC) Analysis of Height, Weight, and Head Circumference Variables in the Autism, PDD-NOS, and TD Groups Combined

Morphologic Feature	Coefficient		
	PC_1	PC_2	PC_3
Head circumference	0.54	0.78	0.29
Height	0.57	−0.60	0.55
Weight	0.61	−0.13	−0.78
Proportion of variance	0.704	0.188	0.109

Abbreviations: PC_1, an average of the 3 growth variables (ie, overall body size); PC_2, large head circumference and small height and weight values (ie, large head and small body); PC_3, increased height relative to body size (ie, long and lanky body); PDD-NOS, pervasive developmental disorder–not otherwise specified; TD, typically developing.

no significant differences among any of the 3 groups (**Figure 5**).

These results were consistent with standard analyses of macrocephaly rates. Based on CDC norms, the rate of absolute macrocephaly in the autism group was 21% by 15 to 18 months, which approximates those reported previously in infants[26] and older individuals with autism[16,53] and was higher than that in TD (1.5%) and PDD-NOS (2.2%) children (χ^2=19.74, P=.001). However, rates of relative macrocephaly ($z_{HC}-z_{height}>2$ SD) did not differ between boys with autism (13.6%) and boys with PDD-NOS (6.7%) and TD controls (11.8%) (χ^2_2=1.39, P=.50).

GENERALIZED OVERGROWTH AND PHENOTYPIC FEATURES

Subsequently, we explored whether generalized overgrowth was associated with specific phenotypic features in boys with autism and PDD-NOS at the time of their first diagnostic assessment (mean [SD] = 2.2 [0.5] years). First, we examined linear relationships between PC_1 scores at various ages (birth and 3, 6, 9, 12, 18, and 24 months) and characterization variables. No significant linear effects were found. In an exploratory analysis of nonlinear associations between overgrowth in the first year and clinical phenotypic features at 2 years, we used a thresholding approach and compared boys whose PC_1 scores fell in the extreme 10% of the distribution with the rest of the sample. We refer to this population of boys in the upper 10% of the distribution on PC_1 as the children with "extreme overgrowth." Note that this approach is different from that used in other studies where extreme overgrowth was operationalized as an increase in z scores of 2 SD or greater from birth into late infancy.[13,26] In the AUT group, we identified 6 boys whose PC_1 scores fell into this category at 6, 9, and 12 months. The period between 6 and 12 months was chosen as critical for the onset of HC growth acceleration and the emergence of the first behavioral symptoms of autism.[9,54] Boys who exhibited the most extreme generalized overgrowth did not differ from the remaining autistic sample regarding maternal (P=.10) or paternal (P=.21) age at birth, gestational age (P=.69), age at first concern (P=.09), or age at independent walking (P=.77). Based on parental report, there were no differences between groups regarding the prevalence of gestational diabetes (P=.40). Results of chromosome and fragile X testing were available on all but 1 of the 6 extreme overgrowth boys, and the results were negative. In the sixth boy, only chromosomal screening was performed, and the results were within the norm. However, the boys exhibited more severe symptoms of autism at age 2 years. Their Autism Diagnostic Observation Scale–Generic social affect algorithm scores were higher by a mean of 3.58 points (P=.009) and their Autism Diagnostic Observation Scale–Generic total algorithm scores were higher by a mean of 4.37 points (P=.01) than those of boys with autism with a less extreme growth pattern. They also showed greater deficits in adaptive social functioning, as expressed by their Vineland Adaptive Behaviors Scales–Expanded Form socialization scores being lower on average by 8.86 points (P=.03), and there was also a trend for these boys to have lower verbal developmental quotient scores by a mean of 16.25 points (P=.08). There was no evidence of an association between extreme overgrowth and nonverbal cognitive functioning. An analogous analysis of the top 10% of boys scoring high on PC_2 in the same developmental period suggests that those with exaggerated head growth have marginally higher Vineland Adaptive Behaviors Scales–Expanded Form adaptive communication skills by 8.65 points (P=.08) than the remaining sample with autism. Analysis of the top 10% of the PDD-NOS sample regarding PC_1 and PC_2 scores yielded null results.

NONLINEAR MIXED-MODEL ANALYSIS

Using nonlinear mixed-effects models showed that the effects of race and maternal education were not statistically significant and led to a similar pattern of results as using spline models. A similar pattern of results emerged when community sample measurements were transformed using CDC and World Health Organization norms and entered into the model. The estimated b_0 coefficient for the autism group was larger than that for the TD group (6.34 vs 5.54, P=.005), and the b_1 parameter was smaller (−14.43 vs −13.67, $P<.001$). The b_1 parameter for the PDD-NOS group was also smaller than that for the TD group (−14.21 vs −13.67, P=.02). Predicted curves for each group showed that at birth, there were no apparent differences between groups but that between 9 and 24 months of age, the HC of the autism group was larger than that of the TD group by approximately 1 cm and that of the GDD group was smaller by approximately 1 cm. When height, weight, and BMI were added to the model as covariates, differences between the AUT and PDD-NOS groups and the TD group disappeared, whereas differences between the GDD and TD groups remained significant. These results suggest that the differences in HC between the AUT and PDD-NOS groups and the TD group are related to other morphologic changes, including height and weight, whereas the differences in HC between the GDD and TD groups were evident beyond changes in their height and weight.

COMMENT

This study presented data from a large and prospectively characterized sample of children with develop-

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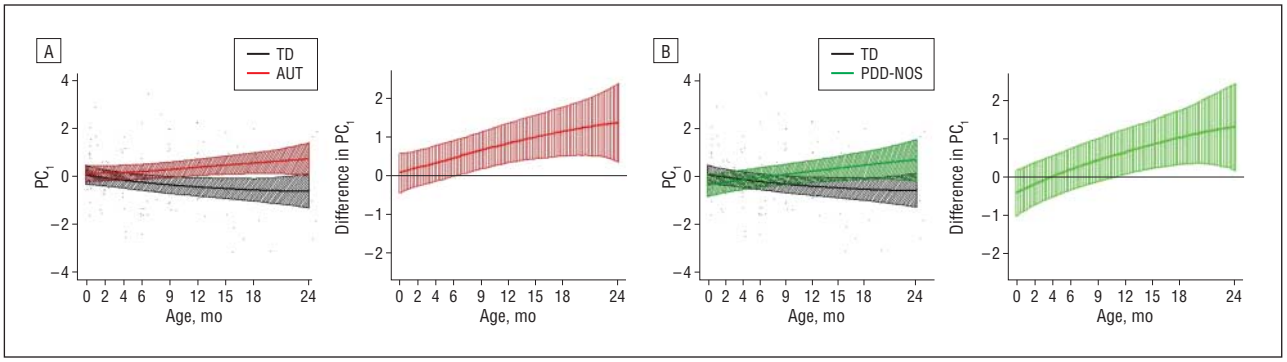

Figure 4. Comparison between the autism (AUT) (A) and pervasive developmental disorder–not otherwise specified (PDD-NOS) (B) groups and typically developing (TD) controls on overall body size principal component scores (PC_1). Graphs on the left illustrate spline-based Bayesian multilevel growth curves of the first PC for each comparison group. The boundaries represent 95% credible bands. Graphs on the right show a difference between means for 2 groups from birth to 24 months. Divergence of the 95% credible band from 0 represents a significant difference between the means at $P \leq .05$ (2-sided).

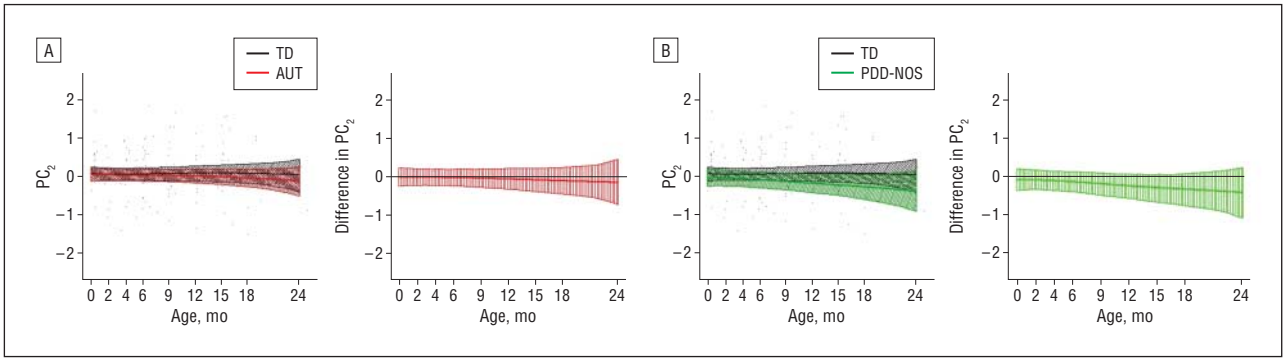

Figure 5. Comparisons between the autism (AUT) (A) and pervasive developmental disorder–not otherwise specified (PDD-NOS) groups and typically developing (TD) controls on the relative head size principal component scores (PC_2). Graphs on the left illustrate spline-based Bayesian multilevel growth curves of the second PC derived by principal component analysis for each comparison group. The boundaries represent 95% credible bands. Graphs on the right show a difference between means for 2 groups from birth to 24 months. Divergence of the 95% credible band from 0 represents a significant difference between the means at the $P \leq .05$ level (2-sided).

mental disorders, including autism and PDD-NOS. Assembling the sample at the time of the first diagnosis allowed for the inclusion of children with rapid and slow improvement rates and with a range of severity of symptoms and cognitive impairments, enhancing the generalizability of the results to the broader population of toddlers experiencing developmental delays. Regardless of the diagnosis, most of the sample was drawn from the same geographic area, and the parents had comparable racial and ethnic backgrounds, age at birth of the child, and educational level. Children were observed regularly for their well-baby visits, as indexed by the high density of the growth data collected in the 24-month period.

The results of this study suggest that although, as a group, boys with autism were normocephalic and normosomic at birth (consistent with results of other studies[22-24,26,41]), they experienced accelerated growth of HC, height, and weight in the first year of life. In autism, the increase in skeletal growth occurred between 4 and 5 months and preceded acceleration in HC growth, which became apparent between 9 and 10 months, with weight curves diverging from typical trajectories shortly thereafter between 11 and 12 months. Thus, although we find evidence of an increased HC in autism, we find no evidence of the presence of disproportionately increased HC in relation to overall body size. Although an atypical skeletal and weight growth spurt also was noted in the PDD-NOS group, no clear evidence of an increased rate of HC growth was found. Boys with mixed developmental delays (Other) showed accelerated skeletal growth but without evidence of overgrowth in HC or weight. There was no evidence of overgrowth in the GDD group along any of the dimensions. In fact, infants with GDD seemed to have a smaller HC at birth, which normalized later in infancy. These results illustrate the complexity of early growth patterns in disabled populations and highlight that accelerated growth along all 3 dimensions seems to occur only in those with severe social disabilities due to autism.

Although these results are consistent with those of several previous studies,[24,25,40] we did not replicate the finding of selective HC enlargement in relation to stature in infancy reported by others.[13,22,23] The present study reports on a larger and more homogeneous sample of children with autism and relies on a statistical treatment of the data that allows for fewer a priori assumptions regarding the shape of the growth curves and more flexibility in modeling of the data. Specifically, the studies were based on relatively small and often heterogeneous samples combining individuals with autism and PDD-NOS into a single ASD category.[13,22] Regarding growth curve modeling, an alternative approach to ours included nonlinear mixed models.[23] Although we replicated the HC differences between target groups, considering that morphologic measurements, such as height,

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weight, and BMI, are themselves exponential functions of age, we found that including them as covariates in the nonlinear mixed model removed exponential components of HC, leaving the assumed model poorly designed for modeling age-related changes in HC growth in autism.

The fact that the generalized overgrowth was found primarily in autism suggests its association with a more severe form of social disability in the autism spectrum. Furthermore, boys with autism who exhibited the most extreme body overgrowth between 6 and 12 months had more severe symptoms of autism at age 2 years and had lower levels of adaptive socialization skills compared with the remaining boys with autism. A history of neither gestational diabetes nor fragile X syndrome was associated with generalized overgrowth. These results generate an exciting hypothesis suggesting the presence of a subtype of autism characterized by extreme overgrowth and severe social impairments. This hypothesis needs to be verified empirically, and potential factors linking the overgrowth to autistic psychopathology need to be examined.

Furthermore, although pronounced and statistically significant overgrowth along all 3 dimensions was found in the AUT group only, in many respects, the growth curves of PDD-NOS infants deviated from those of the TD group in a similar manner. The PDD-NOS is considered a residual diagnostic category encompassing individuals with atypical features, and, thus, the group was not only smaller than the AUT group but also more heterogeneous. It is not clear whether the observed patterns of growth regarding the timing and magnitude of differences in the TD and AUT groups are due to the true nature of their physical growth or to limited power to detect differences from the AUT or the TD group. This question should be addressed through a more comprehensive subtyping of growth trajectories in a larger sample.

When considering potential underlying mechanisms for enlarged total brain volume and acceleration of HC growth in autism, most researchers have focused on factors that affect neuronal development. The present study, however, highlights the importance of examining factors that affect not only brain but also skeletal growth. In fact, considerable evidence suggests that many of the factors that affect neuronal growth also affect nonneural tissue and cell development. For example, fibroblast growth factor 2, which has a role in memory consolidation and neurogenesis,[55] also affects angiogenesis, vascular remodeling, and skeletal development.[56] Insulin–like growth factor 1 level, which has been reported to be elevated in the plasma of children with autism[53] and is known to affect body size,[57] is linked to brain overgrowth in animal models as well.[58] Brain-derived neurotrophic factor, reported to be altered in ASDs,[59-62] not only has an important role in early brain development[63] but also is associated with metabolic syndrome and obesity.[64,65] Vascular endothelial growth factor, found at higher levels in plasma of adults with autism,[66] also regulates organ and body growth in early postnatal development.[67,68] In terms of genetic factors, the phosphatase and tensin homologue mutations have been associated with macrocephalic individuals with ASDs.[69,70] In animal models, phosphatase and tensin homologue mutations also have been associated with body size determination and regulation of metabolism.[71] Finally, the neurotransmitter and neurohormone serotonin, which has been found at higher levels in individuals with autism,[72] has an important role in neuronal development[73] but also is crucially involved in embryogenesis[74] and in bone and skeletal development.[75] Considering the present findings, efforts should be advanced to examine factors responsible for the entire constellation of neural and nonneural growth-related phenotypic traits because it is possible that these 2 phenomena share a common etiology. Simultaneous assessment of the morphologic and phenotypic features; neuroimaging parameters, including brain structure and chemical concentrations; immunologic and endocrine factors; and genetics combined with the study of changes across early development will be essential for discovery of the mechanisms that underlie atypical growth in autism.

This study has some limitations. The samples were not drawn by formal random processes to support the generalizability of findings in the samples to their respective populations; however, the realities of clinical research limit the feasibility of such an approach. Future studies should examine long-term sequelae of early overgrowth into adolescence and beyond and determine whether the results observed in boys extend to girls with autism as well. Analysis of the association between overgrowth and clinical characteristics in autism was exploratory, and confirmatory analyses with larger samples and more extensive biological measures will be helpful to further our understanding of the etiologic factors associated with physical overgrowth in autism. Finally, the sample of children with non-ASD disorders was relatively small, and future studies should further evaluate the specificity of the findings to autism and PDD-NOS.

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