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Altered Growth Trajectory of Head Circumference During Infancy and Schizophrenia in a National Birth Cohort

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Abstract

Identification of abnormalities in the developmental trajectory during infancy of future schizophrenia cases offers the potential to reveal pathogenic mechanisms of this disorder. Previous studies of head circumference in pre-schizophrenia were limited to measures at birth. The use of growth acceleration of head circumference (defined as the rate of change in head circumference) provides a more informative representation of the maturational landscape of this measure compared to studies based on static head circumference measures. To date, however, no study has examined whether HC growth acceleration differs between pre-schizophrenia cases and controls. In the present study, we employed a nested case control design of a national birth cohort in Finland. Cases with schizophrenia or schizoaffective disorder (N=375) and controls (N=375) drawn from the birth cohort were matched 1:1 on date of birth (within 1 month), sex, and residence in Finland at case diagnosis. Longitudinal data were obtained on head circumference from birth through age 1. Data were analyzed using a new nonparametric Bayesian inversion method which allows for a detailed understanding of growth dynamics. Adjusting for growth velocity of height and weight, and gestational age, there was significantly accelerated growth of

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Dr. Brown contributed to the study design, data analysis, data interpretation, writing, and literature search

Dr. Gyllenberg contributed to the study design, data analysis, data interpretation, and writing

Dr. Hinkka-Yli-Salomäki contributed to the study design, data analysis, and data interpretation

Dr. Sourander contributed to the study design, data analysis, data interpretation, and writing

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head circumference in females with schizophrenia from birth to 2 months; the findings remained significant following Bonferroni correction ($p < 0.0125$). This is the first study to report abnormal HC growth acceleration, a more sensitive measure of somatic developmental deviation of this measure, in schizophrenia.

Keywords

schizophrenia; head circumference; growth trajectory; infancy-development

Introduction

Abnormalities in the trajectory of early development during infancy and childhood among individuals who later develop schizophrenia, compared to controls, have supported the neurodevelopmental hypothesis of this disorder (Cannon et al., 1997; Isohanni et al., 2004; Jones et al., 1994; Walker et al., 1994). To date, there is evidence that head circumference (HC) at birth is abnormal in pre-schizophrenia. Small HC was related to an increased risk of later schizophrenia, independent of other factors (Cantor-Graae et al., 1998; Hultman et al., 1997) though other studies found no association, or relationships that were restricted to females (Wahlbeck et al., 2001; Welham et al., 2009). However, in contrast to other indices of development which delineate trajectories, including developmental milestones, neurocognition, and behavior prior to schizophrenia onset (Cannon et al., 1997; Isohanni et al., 2004; Keskinen et al., 2015; Khandaker et al., 2011), the pattern of HC growth among pre-schizophrenia cases following birth has not been well investigated because those studies utilized measures of HC that were isolated to birth. Growth trajectory of HC can more optimally be studied by examining growth velocity, which is defined as the rate of change in HC per unit change in time. The assessment of growth velocity of HC after birth, using frequent, longitudinal measures and a statistical approach developed specifically to calculate growth velocity, provides essential information on cumulative development, thereby addressing the question of whether there are somatic deviations of the growth trajectory of this measure during childhood among individuals who later develop schizophrenia.

We addressed these questions using a powerful new nonparametric Bayesian inversion method for reconstructing growth velocity curves from sparse temporal data (Lopez-Pintado and McKeague, 2013; McKeague et al., 2011). In particular, this approach allows for a detailed understanding of growth patterns, taking into account large fluctuations in growth velocity and high between-subject variability.

We applied this method to examine the relationship between growth velocity of HC in pre-schizophrenia cases and controls in a national birth cohort investigation, the Finnish Prenatal Study of Schizophrenia (FiPS-S). We hypothesized that there would be deviations of HC growth velocity during infancy in pre-schizophrenia cases compared to controls.

Methods

The Finnish Prenatal Study of Schizophrenia (FiPS-S) is based on a nested case-control design. All offspring were derived from the Finnish Maternity Cohort (FMC), consisting of

virtually all pregnancies in Finland beginning in 1983 (total sample size is over 1 million). The computerized nationwide Finnish Population Registry was created in 1971. The registry includes comprehensive data on place of birth, place of residence, and biological parents, including their birth dates. The Finnish Hospital and Outpatient Discharge Registry (FHDR) was used to identify all diagnoses for psychiatric hospital admissions and outpatient treatment visits. The FHDR computerized data are available from 1969 to the present.

The sample of the FiPS-S consisted of all offspring born in Finland from 1983–1998, and subjects were followed up until 2009 (see “Case and control identification”). While these birth and follow-up years led to potential inclusion of some relatively young onset cases, childhood/adolescent onset schizophrenia, though rare, has been well described (Rapoport and Gogtay, 2011). To identify the cases, we conducted a registry linkage between the FMC and the FHDR, using personal identification numbers. Cases were defined as having schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) (heretofore, these cases are referred to as “schizophrenia”). This protocol led to the identification of 1,514 cases of schizophrenia or schizoaffective disorder (N=1,226 with schizophrenia, 288 with schizoaffective disorder). The age at first treatment was recorded by the first contact for a schizophrenia diagnosis by a psychiatric facility. In a prior study, the validity of schizophrenia diagnoses according to the FHDR was excellent: 93% of subjects with a diagnosis of schizophrenia in the FHDR were assigned a consensus diagnosis of schizophrenia following interview (Mäkikyrö et al., 1998).

The schizophrenia cases in the FiPS-S were matched 1:2 to controls (N=3,028) drawn from the birth cohort who were without schizophrenia, other nonaffective psychotic disorders, and bipolar disorder, by date of birth (within 1 month), sex, and residence in Finland at the time of case diagnosis.

The study was approved by the ethical committees of the hospital district of Southwest Finland, the 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 1–2 months until 15 months (Ministry of Social Affairs and Health, 2009). Physicians and registered nurses complete a nationally standardized form, including HC, height, and weight measurements at every visit. The examinations are conducted on 99% of all children in Finland. Archived longitudinal data were abstracted manually in record rooms from the well baby centers by public health or research nurses highly trained and experienced in data acquisition. At least one HC measurement was obtained on 2,127 subjects (1,066 cases and 1,061 controls).

Measures

The primary measure was growth velocity of HC at *a priori* selected time points during the first year of life. The analyses were limited to the first year of life because insufficient HC

measurements were available beyond that age (see “Statistical analysis” for criteria of subjects selection based on availability of HC measurements).

Covariates

Covariates, representing potential confounders, consisted of height growth velocity, weight growth velocity, maternal age, paternal age, gestational age at time of birth, maternal education, province of birth, degree of urbanization at birth, and maternal and parental history of schizophrenia spectrum disorders and any psychiatric disorder (lifetime prevalence) (Table 1). All covariates other than height and weight growth velocity and gestational age were obtained from the Finnish Population Registry. Gestational age was abstracted from the same records containing HC, height, and weight data.

Statistical Analysis

In order to provide accurate and complete reconstructions of the growth velocity trajectories, sufficient and biologically plausible data on each subject and his/her matched control were necessary. For that purpose, the following inclusion criteria were used: 1) HC and height measurements did not decrease between subsequent time points, 2) maximum age at first visit was 40 days, 3) at least 6 visits by 12 months of age, 4) age at the 6th visit was at least age 9 months and 5) there were no extreme outliers (Supplemental Material). There were 375 cases and 375 matched controls with data abstracted on HC growth measures in the study and who fulfilled the inclusion criteria. The numbers of HC growth measurements in each one-month age window by age 12 months was similar in cases and controls (see Supplemental Information and Supplemental Figure 2).

Growth velocity trajectories were reconstructed using the Bayesian inversion method developed by Lopez-Pintado and McKeague (Lopez-Pintado and McKeague, 2013; McKeague et al., 2015). The full text of the analytic method is provided in the supplement. This approach was utilized in an earlier study based on the same birth cohort, in which we demonstrated a significant association between autism and accelerated HC growth in early infancy (McKeague et al., 2015). Supplemental Figure 1A shows the reconstructed HC growth trajectories of the subjects in the study. The uncertainty around the reconstructed curves can reasonably be ignored in our analyses below since it is negligible compared to the variation among subjects (see Supplemental Figure 1B). Multivariable generalized estimating equations (GEE) were used to assess differences between mean (reconstructed) HC growth velocities of pre-schizophrenia cases and controls, accounting for the possibility of dependence of growth velocity in cases and controls due to the matching. The mean difference with estimated 95% confidence intervals (CI) from the GEE analyses were used to plot the mean difference of HC growth velocities between cases and controls. Appropriate to the matched design, conditional logistic regression analyses were used to estimate the association between pre-schizophrenia and HC growth velocities adjusting for height and weight at the same age, and gestational age. Statistical significance was judged at $\alpha=0.05$. In order to further address confounding, we conducted bivariate analyses of other covariates in relation to schizophrenia using Chi square and t-tests. Covariates that differed between cases and controls ($\alpha = 0.20$) were adjusted in the statistical models. Statistical adjustment was also made for all covariates that were associated at $\alpha < 0.20$ with inclusion of the study

subjects in the final dataset (Supplemental Table 1), in order to control for potential selection bias (Rothman et al., 2012). Statistical analyses were performed using SAS (SAS Version 9.4; SAS Institute Inc., Cary, NC) and R statistical software; the R package growthrate (Lopez-Pintado and McKeague, 2013) was used to carry out the growth velocity reconstructions. We used the same multivariate models to test for interactions between sex and growth velocity (Rothman et al., 2012).

Results

Demographics and cumulative HC measures

The demographic characteristics of the cases and controls are presented in Table 1. Family history of psychiatric disorders, variously defined, were associated with schizophrenia in offspring. The relationships between inclusion versus exclusion status of study subjects to the covariates are presented in Supplemental Table 1. We found that province of birth, degree of urbanization and the family history categories were all significantly associated with a subject's being included in the study sample. Among the case-control pairs, 210 were males and 165 were females (Table 1). Summary statistics concerning HC measured at birth and age 12 months by sex are provided in Supplemental Table 2.

Growth velocity

As there was a sex by HC growth velocity interaction (birth, $p=0.024$; 1 month, $p=0.022$; 2 months, $p=0.02$), we conducted all analyses stratified by sex. The plots representing differences in mean HC growth velocities between pre-schizophrenia cases and controls as a function of age between birth and 12 months are depicted in Figure 1A for females and in Figure 1B for males. In the GEE analyses accounting for the matching but no other covariates, the 95% point-wise confidence bands from birth to age 2 months among females did not include 0 (Figure 1A), indicating a significant acceleration of HC growth, or a greater rate of change in HC growth per unit of time, among female cases compared to female controls over that age period. From age 2 to 12 months, this difference between pre-schizophrenia cases and controls in females was not observed. Table 2 reports the monthly mean (SD) HC growth velocities in pre-schizophrenia cases and controls from birth to 12 months. The last two columns of Table 2 give P-values of the regression coefficients of HC growth (based on conditional logistic regression), with adjustment for gestational age at birth, height/weight growth velocities at the same age, urbanization of birth, province of birth, and maternal schizophrenia. These analyses show that HC growth velocity is significantly increased in females from birth to age 2 months (birth, $p=0.005$; 1 month, $p=0.004$; 2 months, $p=0.006$). To account for the implicit multiple testing, we applied the Bonferroni correction for analyses in the four 3-month-intervals in year 1 (for 4 independent t-tests, $\alpha=0.05/4=0.0125$); the associations between accelerated HC growth at 0–2 months and pre-schizophrenia in females remained statistically significant. The estimated effect sizes (cases minus controls) at ages 0, 1, 2, and 3 months for females, relative to the SD in controls are, respectively, 0.25, 0.25, 0.26, 0.19. For further assurance we also adjusted for parental history of schizophrenia; the findings persisted for HC growth velocity at 1 month ($p=0.012$) though did not survive Bonferroni correction for birth ($p=0.013$) and 2 months

($p=0.027$). No increases in acceleration of HC growth were observed for male pre-schizophrenia cases at any time point (Figure 1B and Table 2).

Exclusion of preterm and small for gestational age (SGA) infants

The findings were similar following exclusion of preterm births and SGA infants ($N=9$). Increased growth velocity of HC in female pre-schizophrenia cases was observed at birth ($p=0.01$), 1 month ($p=0.01$), and 2 months ($p=0.02$), adjusting for height growth velocity, weight growth velocity, gestational age, urbanization and province of birth, and maternal schizophrenia.

Exclusion of schizoaffective disorder

In order to assess whether the findings were present only among pre-schizophrenia cases, we excluded cases of pre-schizoaffective disorder ($N=69$). Growth velocity of HC was significantly increased in pre-schizophrenia females at birth ($p=0.03$) and at 1 month ($p=0.028$), adjusting for the same covariates as above.

Discussion

We found significantly accelerated growth of HC in female pre-schizophrenia cases between birth and age 2 months. This difference was not observed from 3 to 12 months suggesting that this difference fades with time. The findings were not accounted for by confounding factors. The findings were also present excluding pre-term and small for gestational age births and schizoaffective disorder cases, though these results became marginally significant and occasionally non-significant in these analyses possibly due to the smaller sample sizes.

In previous studies, measures of HC and schizophrenia were documented at a single time point during early life. In contrast to those studies, we utilized a dynamic measure of growth throughout the first year of life, employing a novel method for analysis of longitudinal data in which growth velocity curves were obtained. Our findings indicate for the first time that accelerated growth of HC may be a developmental precursor for schizophrenia, with an effect that appears restricted to very early life. Interestingly, prior studies of autism have shown increases in HC from birth to about age 2 (Chawarska et al., 2011; Constantino et al., 2010; Courchesne and Pierce, 2005; Dawson and Bernier, 2013; Hazlett et al., 2005). In a study of autism in the same Finnish birth cohort investigated in the present study, we showed accelerated growth of HC in autism cases at postnatal months 2–4, adjusting for growth velocity of height and weight (McKeague et al., 2015). We and other groups have shown that several early developmental risk factors (Abel et al., 2013; Brown et al., 2004; Lampi et al., 2013; Malaspina et al., 2001; Polo-Kantola et al., 2014; Reichenberg et al., 2006) are shared between the two disorders and certain copy number variants (Grayton et al., 2012) are also found at higher frequencies in both disorders. While schizophrenia is more often characterized as a disorder of reduced overall volume(s) of total brain and several specific brain regions, it is conceivable that disrupted cortical development due to overactive brain growth during the fetal and early postnatal period, a time during which rapid synapse development occurs, alters the trajectory of brain growth and connectivity (Gilmore et al., 2010). These developmental deviations may increase vulnerability for development of

psychotic, neurocognitive, and behavioral symptoms of schizophrenia, when functional networks related to the expression of these characteristics become activated (Karlsgodt et al., 2014).

The findings might be explained in part by vitamin D deficiency, which has been related to bone growth measures (Bikle, 2012) and also to schizophrenia (Cui et al., 2012). Unfortunately, maternal vitamin D levels were not available.

While further studies are necessary to understand the sex difference, females have increased levels of insulin-like growth factor-I (IGF-I), which plays a major role in the regulation of both prenatal and postnatal growth (Le Roith et al., 2001), compared to males (Ong et al., 2002) and increased IGF-I is related to increased HC at birth (Ong et al., 2002).

As noted above, some studies have reported diminished HC at birth in schizophrenia, and thus the question of ‘catch-up growth’ should be considered (Cantor-Graae et al, 1998; Hultman et al, 1997). However, this was not found in our sample. We observed only slight decreases in cumulative HC at birth between female cases and controls (0.3 cm less in cases compared to controls) and at age 12 months the difference in HC was similar (0.2 cm less in cases compared to controls) (Supplemental Table 2). There were no differences in HC between male cases and controls at birth, and nearly identical HC between the two groups at age 12 months. Hence, these results are not consistent with catch-up growth in either sex.

The present study benefits from several advantages. First, the statistical model allows for analysis of growth velocities. Second, our sample size was considerable relative to other studies of HC measures in pre-schizophrenia. Third, the present study was based on a national birth cohort that is representative of the source population which gave rise to the cases, while many previous studies were based on cohorts from selected regions or clinical samples, with greater potential for selection bias (Raznahan et al., 2013).

Limitations of the study include: 1) the data beyond age 1 were too sparse to follow up the growth trajectories into childhood; 2) no data were available on nutritional intake or vitamin levels; 3) diagnoses were based on a psychiatric registry, although the agreement with consensus interview diagnoses was high (Mäkikyrö et al., 1998). While some schizophrenia cases may have been diagnosed as “other psychoses” in the hospital discharge register (Moilanen et al., 2003), the comprehensive ascertainment offers substantial advantages regarding representativeness of cases; 4) since the oldest subjects were age 26, it is possible that the findings may be specific to earlier onset schizophrenia; 5) power to detect associations between HC growth and pre-schizophrenia may be reduced beyond age 2 months due to diminished variance in these measures (see Supplemental Figure 1A); 6) as noted above, the subjects included represented a subsample of the overall sample in the FiPS-S due the requirement of availability of HC data and of their meeting the inclusion criteria for analysis. While included and excluded subjects differed with regard to province of birth, urbanization, and family history of psychiatric disorder (Supplemental Table 1), the findings persisted after adjustment for these covariates, indicating that the findings were not biased by differential selection.

Conclusions and Relevance

We have found novel evidence for accelerated growth of HC during very early life in female patients with pre-schizophrenia. This work provides novel data indicating that deviations in the trajectory of brain growth may play a role in the pathogenesis of schizophrenia, and offers the promise of identifying specific neurobiological disruptions and preventive approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Mean difference of growth velocity of head circumference in females (panel A) and males (panel B). The black solid lines represent the mean difference estimates, the black dotted lines represent 95% confidence intervals from generalized estimation models and the red dotted lines represent mean differences at zero; the finding is significant if the confidence interval does not include 0.

Table 1

Demographic characteristics in relation to schizophrenia case-control status

	Cases (N=375)	Controls (N=375)		
	Mean (SD)	Mean (SD)	t	P-value
Gestational age (weeks) ^a	39.4 (1.7)	39.4 (1.5)	0.1	0.92
	N (%)	N (%)	χ^2	P-value
Sex			N/A	N/A
Females	165 (44)	165 (44)		
Males	210 (56)	210 (56)		
Maternal age (years)			3.6	0.61
19 or less	16 (4.3)	12 (3.2)		
20–24	74 (19.7)	70 (18.7)		
25–29	130 (34.7)	138 (36.8)		
30–34	97 (25.9)	108 (28.8)		
35–39	48 (12.8)	42 (11.2)		
40 or more	10 (2.7)	5 (1.3)		
Paternal age (years) ^b				1.00
19 or less	4 (1.1)	4 (1.1)		
20–24	40 (10.8)	44 (11.9)		
25–29	120 (32.5)	122 (32.9)		
30–34	109 (29.5)	105 (28.3)		
35–39	64 (17.3)	65 (17.5)		
40–49	31 (8.4)	29 (7.8)		
50 or more	1 (0.3)	2 (0.5)		
Province of birth			4.2	0.24
Eastern Finland	44 (11.7)	42 (11.2)		
Northern Finland	49 (13.1)	61 (16.3)		
Southern Finland	185 (49.3)	160 (42.7)		
Western Finland	97 (25.9)	112 (29.9)		
Degree of urbanization			2.7	0.26
Rural	83 (22.1)	95 (25.3)		
Semi-Urban	37 (9.9)	46 (12.3)		
Urban	255 (68)	234 (62.4)		
Maternal education ^c			2.2	0.53
Secondary school	92 (24.7)	81 (21.7)		
High-school	218 (58.4)	230 (61.7)		
College/bachelor degree	40 (10.7)	45 (12.1)		
Master/doctoral degree	23 (6.2)	17 (4.6)		
Maternal SSD ^d	42 (11.2)	8 (2.1)	23.3	< 0.001

	Cases (N=375)	Controls (N=375)		
	Mean (SD)	Mean (SD)	t	P-value
Maternal any psychiatric disorder ^e	116 (30.9)	57 (15.2)	25.3	< 0.001
Parental SSD ^d	63 (16.8)	11 (2.9)	39.0	< 0.001
Parental any psychiatric disorder ^e	178 (47.5)	92 (24.5)	41.8	< 0.001

Abbreviations: SSD, schizophrenia spectrum disorder.

^aMissing data for 63 cases and 45 controls.

^bMissing data for 6 cases and 4 controls.

^cMissing data for 2 cases and 2 controls.

^dICD-10 codes F20–25, F28–29, ICD-9 codes 295, 297, 298.9X, 301.2C, and ICD-8 codes 295, 297, 298.20, 298.30, 298.99, 299.

^eIn addition to the above this includes ICD-10 codes F10–19, F30–34, F38–39, F40–45, F48, F50–53, F55, F59–66, F68–69, F84, F99, ICD-9 codes 296, 298.8A, 299, 300–301.1, 301.2 excluding 301.2C, 301.3–301.9, 302, 307.1A, 307.4A, 307.4F, 307.4H, 307.5A, B, C & E, 307.8A, 307.9X, 309–309.1, 309.2 excluding A&B, 309.2D, E & F, 309.3–309.9 excluding 309.3A & 309.4A, 312.0A, 312.1–312.2, 312.3 excluding 312.3D, 312.4–312.9, 291–292, 303–305, and ICD-8 codes 291, 296, 298.00, 298.10, 303–304, 300.0–302.9, 305, 306.40, 306.50, 306.98, 307.99, and 308.

Table 2

Mean (SD) head circumference (HC) growth velocity (cm/year) by month and by sex in pre-schizophrenia cases and matched controls and P-values for the effect of HC growth velocity based on conditional logistic regression analyses

Age (Months)	Mean (SD) HC growth velocity				Conditional logistic regression ^a	
	Females		Males		Females	Males
	Case (N = 165)	Control (N = 165)	Case (N = 210)	Control (N = 210)		
0	20.7 (4.6)	19.7 (4.1)	20.8 (4.8)	21.6 (4.8)	0.005	0.73
1	20.1 (4.4)	19.1 (4.0)	20.3 (4.6)	20.9 (4.5)	0.004	0.94
2	17.9 (2.9)	17.3 (2.6)	18.3 (3.1)	18.6 (2.9)	0.006	0.94
3	15.4 (2.2)	15.0 (1.9)	15.8 (2.4)	16.1 (2.2)	0.05	0.97
4	12.9 (1.7)	12.8 (1.6)	13.3 (1.8)	13.5 (1.8)	0.68	0.44
5	11.0 (1.5)	11.1 (1.3)	11.3 (1.5)	11.6 (1.7)	0.72	0.26
6	9.3 (1.4)	9.3 (1.2)	9.5 (1.3)	9.7 (1.6)	0.57	0.72
7	7.9 (1.3)	8.0 (1.1)	8.1 (1.3)	8.1 (1.3)	0.91	0.38
8	6.8 (1.4)	6.8 (1.1)	6.8 (1.2)	6.8 (1.3)	0.85	0.13
9	6.0 (1.2)	6.0 (1.1)	6.0 (1.1)	5.9 (1.2)	0.53	0.12
10	5.1 (1.2)	5.2 (1.1)	5.2 (1.3)	5.0 (1.2)	0.54	0.16
11	4.7 (1.2)	4.7 (1.0)	4.8 (1.4)	4.6 (1.2)	0.67	0.19
12	4.3 (1.1)	4.4 (1.0)	4.5 (1.4)	4.3 (1.1)	0.74	0.21

^a Adjusted for growth velocity of height (missing data on 46 cases, 46 controls) and weight (missing data on 1 case, 1 control) at the same age, gestational age, urbanization of birth, province of birth, and maternal schizophrenia.