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Fetal head circumference growth in children with specific language impairment

Andrew J O Whitehouse^{1,2}, Stephen R Zubrick³, Eve Blair¹, John P Newnham⁴, and Martha Hickey⁵

¹Centre for Child Health Research, University of Western Australia, Perth, Australia

²Neurocognitive Development Unit, School of Psychology, University of Western Australia, Perth, Australia

³Centre for Developmental Health, Curtin University of Technology, Perth, Australia

⁴School of Women's and Infants' Health, University of Western Australia, Perth, Australia

⁵Department of Obstetrics and Gynaecology, University of Melbourne, Victoria, Australia

Abstract

Objective—To characterise fetal brain growth in children with specific language impairment (SLI).

Design—A nested case-control study.

Setting—Perth, Western Australia.

Participants—Thirty children meeting criteria for SLI at age 10 years were individually matched with a typically developing comparison child on sex, non-verbal ability, fetal gestational age, maternal age at conception, smoking and alcohol intake during pregnancy.

Main outcome measures—Occipitofrontal head circumference (HC) was measured using ultrasonography at approximately 18 weeks gestation. Femur length provided a measure of fetal length. Occipitofrontal HC was measured at birth and at the 1-year postnatal follow-up using a precise paper tape measure, while crown-heel length acted as an index of body length at both time points. Raw data were transformed to z-scores using reference norms.

Results—The SLI group had a significantly smaller mean HC than the typically developing comparison children at birth, but there was no group difference at 18 weeks gestation or at the 1-year postnatal follow-up. Individual analyses found that 12 SLI children had an HC z-score less than -1 at birth, with three of these cases meeting criteria for microcephaly. There was no group difference in the indices of overall body size at any time point.

Correspondence to Dr Andrew Whitehouse, Telethon Institute for Child Health Research, Centre for Child Health Research, PO Box 855, University of Western Australia, West Perth 6872, Western Australia; awhitehouse@icmr.uwa.edu.au.

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Ethics approval This study was conducted with the approval of the King Edward Memorial Hospital (Perth, Western Australia) and Princess Margaret Hospital (Perth, Western Australia).

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Conclusions—Children with SLI are more likely to have a small HC at birth but not at 18 weeks gestation or infancy, suggesting growth asynchrony in brain development during the second half of pregnancy.

Specific language impairment (SLI) is a neurodevelopmental condition characterised by a clinically significant language delay that is not associated with low intelligence, hearing impairment or limited educational opportunities. There are several reasons to hypothesise that atypical brain development in SLI may commence prenatally. First, the only gene that has been successfully associated with the SLI phenotype, contactin-associated protein-2 (*CNTNAP2*) on chromosome 7q,¹ is a member of the neuroligin family, a set of proteins implicated in synaptic adhesion during the early stages of neurodevelopment. Second, perisylvian structures found to be anomalous in children with SLI, including the planum temporale, the pars triangularis and the inferior frontal gyrus,² are known to develop in the third prenatal trimester. Third, there is preliminary evidence that auditory processing deficits in SLI are present during the first year of life,³ suggesting an alteration in the typical course of brain development, rather than damage occurring subsequent to normal prenatal development. However, by its very nature, SLI cannot be identified until language milestones are able to be reliably assessed – typically, between 3 and 5 years of age – and therefore early developmental data are rare. We provide the first prospective investigation of prenatal and early postnatal head circumference (HC), a measure that is known to correlate highly with brain size in children up to 2 years of age,⁴ using a case–control design of participants from the Western Australian Pregnancy Cohort (Raine) study.

METHODS

Participants

The Raine study is an ongoing prospective study in Western Australia, established to investigate how events during pregnancy and at the time of birth subsequently influence health. In 1989–1991, 2900 women were enrolled at 18 weeks pregnancy, and their offspring have been closely followed throughout childhood. Participant recruitment and all follow-ups of the study families were approved by the Human Ethics Committee at the University of Western Australia. Children who were from a preterm birth or multiple pregnancy, who spoke a language other than English at home, or who had been diagnosed with Down syndrome, autism or intellectual disability with a known cause were not considered for inclusion in this study.

At the 10-year follow-up, children were administered a range of psychometric assessments able to identify children with the SLI phenotype. Criteria for SLI were a standardised score >1 SD below the mean on the peabody picture vocabulary test-revised (PPVT-R)⁵ and the Recalling Sentences subtest of the clinical evaluation of language fundamentals-III (CELF-III),⁶ but within normal limits on Ravens coloured progressive matrices (RCPM).⁷ Among the participants in the broader Raine cohort who had complete data at 18 weeks gestation, and at the birth, 1-year and 10-year follow-ups (males=517; females=462), 30 (3.1%) met criteria for SLI at age 10 years.

Case–control matching

Each SLI case was individually matched with a typically developing child from the broader Raine cohort on maternal race (all Caucasian), sex, gestational age (weeks), maternal age at conception (within 3 years) and maternal smoking and alcohol intake during pregnancy, and non-verbal ability (RCPM score within 20 percentile points). All control participants performed within normal limits on the PPVT-R, the recalling sentences subtest of the CELF-III and RCPM. Matching criteria could be met for all but three SLI cases, who were matched

with their respective control participant on all conditions except for RCPM scores (match 6: SLI=40, control=75; match 16: SLI=25, control=63; match 18: SLI=30, control=75). The two groups were well matched on all variables except for scores on the PPVT-R and recalling sentences task (table 1). χ^2 analyses found no between-groups difference on a number of other sociodemographic variables recorded during pregnancy, including level of maternal education (did not complete secondary school: SLI group=26, 86.7%; control group=23, 76.7%; $\chi^2=1$, df=1, $p=0.317$), family income (below the poverty line of \$AU24 000/year: SLI group=11, 36.7%; control group=13, 43.3%; $\chi^2=0.28$, df=1, $p=0.598$), absence of the biological father in the home (SLI group=3, 10%; control group=3, 10%; $\chi^2=0$, df=1, $p=1$) and parity (parity=0: SLI group=12, 40%; control group=14, 46.7%; parity=1: SLI group=13, 43.3%; control group=9, 30%; parity >1: SLI group=5, 16.7%; control group=7, 23.3%; $\chi^2=1.21$, df=2, $p=0.55$). Furthermore, independent-samples t tests identified no statistically significant group difference in (pre-pregnancy) maternal height (SLI group: mean=164.2 cm, SD=6.16, range=150–176; control group: mean=166.2 cm, SD=5.95, range=156–178; $p=0.206$) and weight (SLI group: mean=58.6 kg, SD=10, range=45–90; control group: mean=62.7 kg, SD=17.8, range=40–120; $p=0.268$).

Biostatistical methods

All women enrolled in the Raine study received a fetal ultrasound imaging study at or close to 18 weeks gestation conducted by a qualified sonographer using one of two General Electric 3600 machines with 3.5 MHz linear array and 5 MHz sector transducers. Fetal brain size was estimated by measuring occipitofrontal HC, while overall fetal length was indexed by femur length. Infant head size was measured shortly after birth (within 3 days) by a trained research midwife and at the 1-year follow-up by a research nurse. Crown-heel length, measured immediately after birth by hospital midwives and again at the 1-year follow-up by a research nurse, provided an index of overall body length. All measurements were to the nearest mm.

Raw measurements at each time point were converted to standardised z-scores using conventional methods: (participant's measurement – reference data mean at participant's gestational age)/reference data SD at participant's gestational age. Z-scores for fetal HC and femur length were calculated using the most widely used reference data for fetal growth.⁸ Raw measurements at birth were converted to z-scores using Australian norms,⁹ while growth charts from the US Centers for Disease Control and Prevention¹⁰ were used for infant biometry in the absence of Australian norms. Each set of reference norms are stratified by gender. Norms are given to the nearest half-week for measurements during the second trimester, to the nearest week for birth measurements and to the nearest month for infant measurements. The criterion for a large HC was a z-score greater than +1 and for macrocephaly, a z-score greater than +2. The criteria for small HC and microcephaly, were a z-score less than –1 and –2, respectively.

RESULTS

We first investigated group differences in the indices of body length across the three time points. A two-way repeated measures analysis of variance revealed a main effect of time point, $F(2,116)=11.08$, $p=0.001$, but, critically, no main effect of group, $F(1,58)=0.67$, $p=0.42$, nor an interaction between time point and group, $F(2,116)=0.6$, $p=0.548$. Independent-samples t tests identified no significant difference between the case and control groups for fetal femur length (SLI: $M=-0.08$, $SD=0.14$; controls: $M=-0.06$, $SD=0.18$ [AU: Please check SD value 0.18.]), nor crown-heel length at birth (SLI: $M=-0.43$, $SD=0.85$; controls: $M=-0.4$, $SD=0.93$) or at the 1-year follow-up (SLI: $M=-0.01$, $SD=0.75$; controls: $M=0.22$, $SD=0.76$); for all comparisons, $p>0.05$.

We then used this same analysis to examine between-group differences in HC z-scores. While there was no main effect of time point, $F(2,116)=1.46$, $p=0.237$, nor group, $F(1,58)=1.7$, $p=0.197$, there was a quadratic interaction between these two factors, $F(2,116)=3.3$, $p=0.029$. The linear term for the interaction did not reach significance, $F(1,58)=0.02$, $p=0.893$. Independent-samples t test revealed a significant group difference at birth (SLI: $M=-0.52$, $SD=1.11$; controls: $M=0.07$, $SD=0.76$), $t(58)=2.44$, $p=0.018$, but not at 18 weeks gestation (SLI: $M=-0.15$, $SD=0.56$; controls: $M=0.01$, $SD=0.98$), $t(58)=0.76$, $p=0.451$, or the 1-year follow-up (SLI: $M=-0.05$, $SD=0.7$; controls: $M=0.07$, $SD=0.81$), $t(58)=0.62$, $p=0.538$.

Figure 1 shows individual head circumference (HC) z-scores at birth for the two groups. Twelve individuals in the specific language impairment (SLI) group (40%) had a small HC at birth, with three of these cases meeting the criterion for microcephaly. In comparison, one typically developing comparison participant had a small (but not microcephalic) HC at birth (z-score=-1.67). The difference between the two groups in the proportion of individuals with a small or microcephalic HC at birth was statistically significant using Fisher's exact test, $p=0.001$. There were three SLI children (10%) and five typically developing individuals (16.7%) who had a large HC at birth, a difference that did not reach statistical significance on Fisher's exact test, $p=0.71$.

DISCUSSION

Significantly more children with SLI than control participants had a small HC at birth. In contrast, there was no group difference in HC z-scores at the second trimester assessment or the 1-year postnatal follow-up, and no group difference in the indices of body length at any time point. Given that HC in early life is known to be a good indicator of brain size,⁴ these findings appear to reflect abnormal late gestation brain growth in a significant proportion of children with SLI.

Three issues concerning the participant sample require discussion. First, Raine study records show that only five of the 30 SLI participants had ever received speech and language therapy intervention. Although children not in receipt of clinical services are likely to be those with milder language difficulties, the assessments and criteria used to define the current SLI sample are widely used within this research field. Second, the SLI sample included more females than males, which contrasts with the widely held view that language difficulties are more common in males.¹¹ However, it has been suggested that the male predominance observed in many SLI studies may reflect an ascertainment bias of samples recruited from clinical or educational settings.¹¹ Third, the SLI group had a slightly lower non-verbal IQ than the comparison group, raising the possibility that a smaller HC at birth may relate to more global cognitive difficulties. However, it is important to note that all children in the SLI group had a non-verbal IQ within the normal range.

The current study is the first to link small HC at birth to a population with poor language development and in which there has been no obvious compromise in fetal development. Interestingly, there was no group difference in HC z-scores at 18 weeks gestation or at the 1-year follow-up, suggesting that abnormal neurodevelopment in SLI may be restricted to the second half of pregnancy, followed by postnatal catchup growth. Studies of SLI have identified reduced or reversed volumetric asymmetry of a number of perisylvian structures and also a reduction in white matter structures, though findings in this area have not always been replicated.² In humans, cerebral asymmetries and white matter tracts mature substantially during the latter stages of fetal development, and the current findings are consistent with the notion that development of these cerebral structures may be disrupted in SLI. This notwithstanding, we cannot rule out the possibility that the observed differences

between time points reflects a chance finding, perhaps due to the relatively small sample size. Replication of the current findings in other pregnancy cohort studies, as well as obtaining a more detailed understanding of the language characteristics of those children with reduced HC at birth, should be a priority for future research.

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Figure 1.
Distribution of head circumference z-scores at birth for the SLI cases and typically developing comparison children.

Table 1

Characteristics of the SLI cases and individually matched typically developing control participants

	SLI (n=30)	Controls (n=30)
Sex	18 F, 12 M	18 F, 12 M
Maternal age at conception	24.63 (6.01)	25 (5.14)
Range	16.03–34.35	17.16–34.71
Gestational age at second trimester scan (weeks)	18.17 (1.09)	18.63 (0.96)
Range	15.86–20.71	17.29–21.14
Gestational age at birth (weeks)	39.47 (0.9)	39.47 (0.9)
Range	38–41	38–41
Age at year 1 follow-up assessment (months)	13.1 (1)	13.43 (1.41)
Range	12–15	12–15
Age at year 10 follow-up assessment (years)	10.61 (0.23)	10.56 (0.11)
Range	10.37–11.56	10.42–10.86
PPVT-R *	78.97 (5.99)	103.97 (8.77)
Range	64–84	87–121
Recalling sentences from CELF-III †	4.8 (1.32)	10.53 (1.66)
Range	3–7	8–13
RCPM ‡	40.77 (18.14)	46.07 (19.42)
Range	18–75	21–90

* Scores are based around a standardised mean of 100 and SD of 15.

† Scores are based around a standardised mean of 10 and SD of 2.

‡ Percentiles according to RCPM norms.

CELF-III, clinical evaluation of language fundamentals-III; PPVT-R, peabody picture vocabulary test-revised; RCPM, Ravens coloured progressive matrices; SLI, specific language impairment.