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ORIGINAL ARTICLE

Choroid plexus cysts do not affect fetal neurodevelopment

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Objective: To determine whether an isolated finding of a choroid plexus cyst (CPC) during routine ultrasound is associated with altered fetal growth or development.

Study design: Prospective, case–control study comparing 35 CPC cases to 67 controls. Neurobehavioral development assessment included 50 min long serial recordings of heart rate, motor activity and their interrelation at 24, 28, 32 and 36 weeks gestation. Growth measurement was based on three ultrasound evaluations of femur length, biparietal diameter, head circumference and abdominal circumference at initial exam, 28 and 36 weeks.

Results: Longitudinal analyses revealed no differences in fetal heart rate, variability or accelerations; the number or duration of fetal movements or total motor activity; nor fetal movement-fetal heart rate coupling. CPC cases had slightly smaller head and abdominal circumferences at 28 weeks, but these differences had disappeared by 36 weeks. CPC detection was more common when routine exams were conducted earlier (18.8 versus 19.5 weeks; $P<0.01$).

Conclusion: Despite the presumption that CPCs with normal karyotypes are benign variants, little empirical support exists. These results indicate that CPCs detected by prenatal ultrasound do not pose or reveal a threat to fetal development.

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Introduction

Choroid plexus cysts (CPCs) are among the most common incidental findings in routine mid-gestation comprehensive ultrasounds, with reported detection rates ranging from less than 1 to 3.6%.[1–4] Significant controversy exists in the degree to which CPCs, in the absence of other abnormal ultrasound findings, are harbingers of chromosomal anomalies. CPCs are more prevalent in fetuses with trisomies 18 and 21, but the degree to which an isolated finding elevates risk for aneuploidy and whether parents should be informed of the finding remains the topic of vigorous debate.[1,5–8] However, neither side of this debate disputes the tenet that isolated CPCs, when not associated with abnormal karyotypes, are benign variants of periventricular development without implications for subsequent pregnancy or child outcomes.

This prevalent view, which was expressed in the original report of five prenatal CPC cases by Chudleigh in 1984[9] is based largely on clinical perception without broad empirical support. We could find that only two studies have investigated developmental outcomes of children with prenatal CPC detection. The first relied on telephone surveys of parents regarding their child's developmental proficiency at a follow-up point that ranged from 12 to 82 months. Responses indicated unremarkable developmental outcome.[10] However, this report is of limited utility because it lacked a control group and the methodology is best suited to detect only dramatic deviations from normal development. The second and only study to systematically measure developmental outcomes compared 37 children with prenatal CPC detection to 48 control children with normal ultrasound findings tested between 3 and 8 years of age.[11] Assessments administered were age-dependent and no differences were detected on measures of general IQ, mental development, motor development or adaptive functioning. However, small but significant differences were detected in several measures of language functioning. The wide age range of the children (3 to 8 years old) and a significant difference in age at testing between cases and controls makes this finding difficult to fully evaluate.

Given the paucity of developmental data, the current report is generated by a longitudinal, prospective case–control investigation designed to systematically examine whether CPCs are associated with altered development, commencing with measurement during the prenatal period. We focus on both fetal growth and functional development as assessed through neurobehaviors. Neurobehavioral

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development includes those parameters that have a strong maturational component and are presumed to reflect the development of the underlying neurosubstrate. Measurement of these subtle aspects of functioning, including how fetuses move, the nature and magnitude of fluctuations in heart rate patterns and the linkage between motor and cardiac activity, has served to detect differences in development between fetuses affected by a variety of conditions, including congenital malformations,[12] growth restriction,[13] maternal diabetes[14] and substance exposure.[15] Further consensus that fetal neurobehaviors provide opportunities to assess indirectly the nervous system, with implications for development after birth, has come from numerous sources focused on normally developing fetuses.[16–18]

The assumption that isolated CPCs with normal karyotyping are benign variants is predicated on the position that this variation in choroid plexus histology neither indicates persistent central pathology nor is a marker for dysgenesis in other portions of the nervous system. Given their transient and principally vascular nature,[8,19,20] we hypothesized that it is unlikely that their detection would connote atypical neural development with implications for functional development. As such, we did not expect to find differences between groups.

Materials and methods

Participants

Cases comprised women in whom an isolated CPC was detected in mid-pregnancy (mean gestational age = 19.3 weeks, s.d. = 1.3) during a comprehensive ultrasound exam at an urban, university-based hospital and affiliated satellite center, or were referred for further evaluation from a local provider. Of the 3254 women receiving anatomy scans from 1 December 2001 to 16 March 2004, CPCs were identified in 118 (3.6%) cases. To eliminate other potential confounds to fetal neurobehavioral and growth variables, eligibility was limited to low risk, non-smoking women with singleton pregnancies that were progressing normally. Thirteen potential participants were excluded based on the following exclusion criteria at intake: abnormal ultrasound findings in addition to CPC ($n = 5$), two of which were later diagnosed with trisomy 18; other existing conditions of pregnancy ($n = 3$); cigarette smoking ($n = 3$); or adolescent pregnancy ($n = 2$). Seventy-seven (73.3%) of the remaining eligible women were offered study participation by a sonographer or attending physician participating in recruitment. A total of 52 women contacted the research coordinator; enrollment was declined owing to scheduling problems ($n = 3$), living too far from the study site ($n = 6$) or lack of interest ($n = 8$), resulting in 35 CPC cases for study participation. Data regarding the prevalence of aneuploidy linked to CPC detection in participants who did not contact us and did not have any other suspect findings on ultrasound were not collected.

Approximately two controls were recruited for each case. Potential controls were recruited serially by identifying eligible women who received a normal ultrasound at the same location, met the inclusion criteria and were matched to the prior case by both race/ethnicity and insurance category (public versus private) to provide some degree of control for socio-economic status. A total of 67 controls was recruited. Women were informed about the nature of the study and interested participants contacted the research coordinator.

Ethics

The study was approved by the university's Institutional Review Board and women provided written, informed consent.

Procedure

The choroid and ventricles were imaged by scanning through the fetal head in the axial plane. The distal choroid and ventricle were imaged at the level of the occipital horn of lateral ventricle. The proximal choroid and ventricle were imaged on an inferior to superior para axial plane. In addition, the choroid was scanned in axial or coronal planes from anterior to posterior or posterior to anterior projection in order to ascertain symmetry and further evaluate texture. The choroid was visualized again at 28 weeks to determine status of the cyst(s). Four standard parameters were used to measure fetal growth at the initial scan and again at 28 and 36 weeks gestation: biparietal diameter, head circumference, abdominal circumference and femur length.

Fetal monitoring commenced at 24 weeks gestation and was repeated at 28, 32 and 36 weeks gestation. Monitoring occurred at the same time of day during each visit (either 1300 or 1500) for 50 min, with the mother resting comfortably in a semirecumbent, left-lateral position. Fetal data were collected using a Toitu (Model MT320) fetal actocardiograph (Toitu Co. Ltd, Tokyo, Japan). This monitor detects fetal movement and fetal heart rate through the use of a single, wide-array transabdominal Doppler transducer and processes this signal through a series of filtering techniques. The actograph detects fetal movements by preserving the remaining signal after band-passing frequency components of the Doppler signal that are associated with fetal heart rate and maternal somatic activity. Reliability studies comparing actograph-based versus ultrasound-visualized fetal movements have found the performance of this monitor to be highly accurate in detecting both fetal motor activity and quiescence.[21,22]

Fetal data were collected from the output port of the monitor and digitized through an A/D board using streaming software. Data were analyzed off-line using software developed in our laboratory. Digitized heart rate data underwent error rejection procedures based on moving averages of acceptable values as needed. Fetal variables included three cardiac measures: fetal heart rate, variability (s.d. of each 1-min epoch aggregated over time) and accelerations, defined as occurring when heart rate values attained 10 beats per minute (b.p.m.) above baseline for greater than or equal to 15 s.

Fetal movement measures were based on the actograph signal, which ranges from 0 to 100 in a.u. A movement bout was considered to begin when the first spike of the actograph attained amplitude of 15 U and end when there was a cessation of 15 Unit signals for at least 10 s. The number of movements and duration of each was quantified. Total motor activity was computed as the number of movement bouts multiplied by the mean movement duration, yielding a measure of the total time spent moving during the 50 min recording in seconds.

A measure of the synchronous association between fetal movement and heart rate was calculated as an indicator of the strength of the neural association between somatic and cardiac processes. Fetal movement–fetal heart rate (FM–FHR) coupling was defined as the proportion of fetal movements associated with excursions in heart rate $\geqslant$5 b.p.m. over baseline within 5 s before the start of a movement or within 15 s after the start of a movement, consistent with previously developed criteria.[23]

Statistics

Examination of group (CPC versus control) differences in fetal characteristics, pregnancy outcome and maternal socio-demographic variables were analyzed using *t*-tests and χ^2 statistics as appropriate. Between-group and gestational age effects for growth parameters, assessed at three time points, were analyzed using repeated measures analysis of variance. Weighted least-squares analysis was used to model the developmental trends of fetal neurodevelopment measures over time and examine potential group differences during the total observation period. This method estimates the correlation structure generated by the repeated measurements on the same fetus and uses the estimate to weight the observations in the regression analysis. Robustness of the estimated unstructured correlation matrix was assessed using generalized estimating equations methodology.[24] Results are generated as *Z*-scores (coefficient estimate/s.e.); values $\geqslant$1.96 are significant at the $P<0.05$ level.

Because results were expected to support the null hypothesis, sample size computations were based on the ability to detect even a trend (i.e., $P<0.10$) level of difference. Estimated parameters from a previous two sample project[16] unrelated to the current topic but using similar fetal neurobehavioral measures indicated sufficient sample size to detect differences where $\alpha = 0.10$ with statistical power ranging from 0.70 to 0.80, depending on variable domain.

Results

Maternal socio-demographic and infant characteristics are presented in Table 1. In general, participants in both groups were college educated, non-minority, married, employed and had planned pregnancies. There were no significant differences between cases and controls in any maternal characteristic. Fetal sex was equally distributed between groups: 51.6% of cases and 53.2% of controls were female.

Table 1 Mean (s.d.) maternal characteristics at study entry

	CPC cases (n = *35*)	*Controls* (n = *67*)
Maternal characteristic		
Age (years)	32.3 (5.2)	31.1 (5.4)
Education (years)	16.5 (2.6)	16.5 (2.1)
Occupational status[a]	7.1 (1.5)	7.2 (1.5)
Height (inches)	64.7 (3.4)	64.5 (2.7)
Body mass index (BMI)	22.7 (3.4)	23.9 (3.8)
First prenatal visit (weeks)	8.5 (2.5)	7.9 (2.0)
Nulliparous	60.0%	64.2%
Race/ethnicity		
African-American	5.7%	8.9%
Asian	5.7%	3.0%
Non-Hispanic white	88.6%	88.1%

Abbreviations: CPC, choroid plexus cyst; s.d., standard deviation.
[a]Occupational status based on Hollingshead two-factor index.

Cysts were categorized on the basis of laterality and number. At the initial ultrasound, bilateral cysts were detected in 63.6% of cases and most (66%) displayed multiple cysts per side. With the exception of three instances (8.6%), all cysts had resolved by the 28-week ultrasound. The initial ultrasound scan was conducted slightly earlier for fetuses in which a CPC was detected than in those where it was not (18.8 versus 19.5 weeks; $t\ (100) = 2.59$, $P<0.01$).

A number of exclusionary conditions developed in both groups following enrollment. These include: preterm delivery in five (14.3%) cases and three (4.5%) controls; prescribed bed rest owing to preterm labor or partial abruption without preterm delivery (one per group); undetected congenital malformation (cleft palate; one case, with preterm delivery); maternal gestational diabetes (two controls); and significant maternal illness (one control). These were excluded from analysis to control for conditions that may independently affect growth and neurodevelopment. Two cases and one control discontinued participation owing to scheduling problems. Although there were nearly three times as many cases than controls that delivered prematurely, the study is insufficiently powered to detect significant differences based on their low incidence. Most (75%) instances of prematurity were mild (i.e., 35 to 36 weeks). Of the remaining participants, there were no differences in either gestational age at delivery between cases and controls (38.9 versus 39.1 weeks), birth weight (3356 versus 3544 g) or length (50.8 versus 51.5 cm). Analyses of fetal growth and neurodevelopment data were limited to the remaining 27 cases and 59 controls.

Neurobehavioral measures

There were few instances of missing data owing to either non-compliance or technical problems at any visit (four recordings at 24 and 36 weeks, none at 28 weeks and three at 32 weeks). Longitudinal modeling does not exclude cases with missing values, thus all participants were included in these analyses. As expected, fetal heart rate decreased over gestation, whereas variability in heart rate and the number of accelerations increased (all three P's <0.0001). No differences were found in fetal heart rate ($Z=1.59$; NS), variability ($Z=0.30$, NS) or accelerations ($Z=-0.14$, NS) between CPC cases and controls over time, nor were there significant differences in the trajectory of gestational changes between these groups. Figure 1a presents the data for fetal heart rate; individual data points, distinguished by case versus control designation, are presented along with a line fitted to reflect averages. Although the overall longitudinal results were not significant, cross-sectional analyses by gestational age revealed slightly, but significantly, faster heart rates at 24, 28 and 32 weeks for CPC cases. However, mean differences were small, ranging from 2 to 4 b.p.m. and had equalized to the control mean by 36 weeks. Variability in heart rate (Figure 1b) showed virtually overlapping mean values between groups, as did the number of accelerations (not shown).

Fetal motor activity showed a moderate decline in terms of the amount of time spent moving ($Z=-1.96$, $P=0.05$) and in the number of individual movements ($Z=-5.07$, $P<0.0001$), but

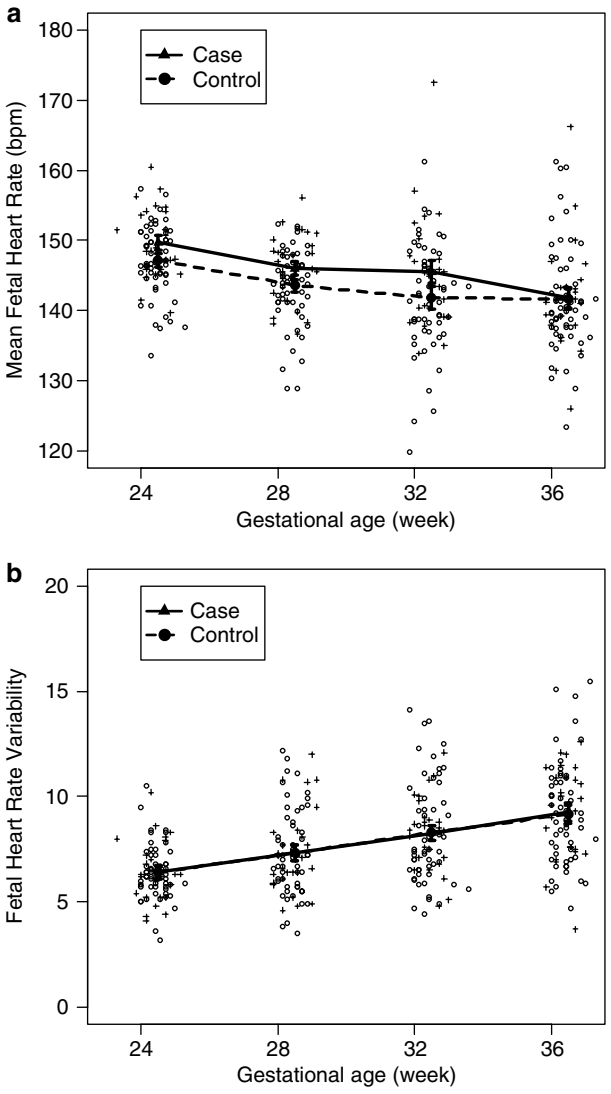

Figure 1 Mean and s.e. at each gestational age for (**a**) fetal heart rate and (**b**) fetal heart rate variability. '+' indicates individual CPC case values; '○' indicates control values.

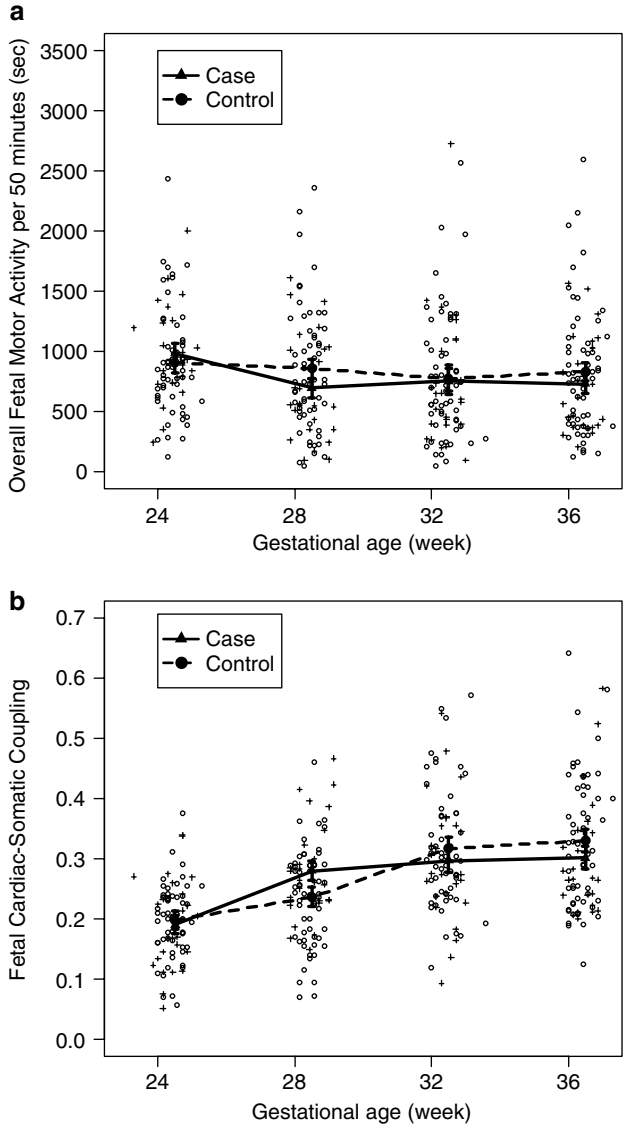

Figure 2 Mean and s.e. at each gestational age for (**a**) fetal motor activity and (**b**) fetal cardiac–somatic (FM–FHR) coupling. '+' indicates individual CPC case values; '○' indicates control values.

Table 2 Means (s.d.) for growth measures for CPC cases and controls

	Initial scan[a]		*28 weeks*		*36 weeks*	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Femur length (mm)	29.2	31.1	53.9	53.9	68.7	68.7
	(0.4)	(0.4)	(2.8)	(2.6)	(2.8)	(2.8)
Abdominal circumference (mm)	137.9	145.7	244.9	252.9**	333.2	330.9
	(1.7)	(1.8)	(16.0)	(14.2)	(20.2)	(21.5)
Head circumference (mm)	161.2	168.9	268.8	273.3*	327.0	329.5
	(1.7)	(1.8)	(13.7)	(9.3)	(13.0)	(11.9)
Biparietal diameter (mm)	43.4	45.4	72.7	73.4	89.3	89.9
	(0.4)	(0.5)	(3.6)	(3.4)	(3.8)	(3.2)

Abbreviations: CPC, choroid plexus cyst; s.d., standard deviation.
[a]*Note*: Growth measures for the initial scan were adjusted for the gestational age, based on the 5-day difference in age at scan. s.d. for these values reflect unadjusted results.
*$P<0.10$; **$P<0.05$.

there was no change in duration of individual movements. CPC cases did not differ from controls in the total time spent moving ($Z=-0.70$, NS), the number of movements made ($Z=0.15$, NS) or the duration of individual movements ($Z=-0.84$, NS), nor were there significant differences in developmental trajectory of any movement measure between groups. Figure 2a presents the data for total motor activity; plots for both number and duration of movement (not shown) show similar levels of correspondence.

As expected, FM−FHR coupling significantly increased as gestation advanced ($Z=10.28$, $P<0.0001$). However, there was no difference between CPC cases and controls (Figure 2b).

Growth measures

Growth results are presented in Table 2. There were significant or near significant differences in all four growth parameters between cases and controls at intake. However, statistical adjustment for the difference in gestational age at the initial ultrasound eliminated these differences. Longitudinal analyses revealed several significant or near significant gestational age by CPC interactions, raising the potential of different growth trajectories in each group. Cross-sectional analyses (*t*-tests) found that abdominal circumference was smaller in the CPC group than the control (t (81) $=2.33$, $P<0.05$) and there was a trend towards a similar difference in head circumference (t (81) $=1.76$, $P<0.10$) at 28 weeks. By 36 weeks, no significant differences in any growth parameter were detected; in fact, CPC cases showed slightly higher abdominal circumference means. There were no differences in gestational age at testing between groups beyond the initial scan.

Discussion

CPC detection can generate a cascade of events, not the least of which involves conferral of significant levels of parental anxiety that are often centered on nervous system concerns.[6,25] Assurances that the variant is benign are consistent with the findings of this study, in which we were unable to detect differences in a broad spectrum of neurobehavioral development measures during the second half of gestation. To our knowledge, this study is the first to examine potential antenatal consequences of mid-gestation CPCs in the developing fetus. Neurobehavioral development during the fetal period lays the foundation for behavior after birth and its measurement has been demonstrated to be sensitive enough to detect alterations caused by a number of adverse fetal conditions and malformations. Failure to detect differences in cases versus controls based on fetal sex, maternal demographic variables and pregnancy outcomes is consistent with reports based on population-based studies.[26]

With respect to somatic growth, two small differences in size (head and abdominal circumference) emerged at 28 weeks only. Examination of Table 2 reveals that, with the exception of femur length, most values for CPC cases were consistently lower than those of controls. This raises the question as to whether the study was sufficiently powered to detect additional growth differences should they exist given that sample size power analyses were based on neurobehavioral measures. Power analysis based on study results indicates comparable (0.70 to 0.80) power to detect differences of approximately 0.5 to 0.6 s.d. for growth parameters; observed differences ranged from approximately 0.2 to 0.5 s.d. at 28 and 36 weeks. Power for detecting smaller mean differences is considerably lower and would require a large sample; however, the issue of clinical meaningfulness of small differences observed in large samples becomes paramount to interpretation.

The finding that pregnancies in which a CPC was detected had ultrasound exams nearly 1 week earlier suggests that earlier scans may be more likely to detect CPCs owing to closer proximity to the period of maximal villi infiltration. If true, this raises the possibility that fetuses in our control group, and in other studies of similar nature, may have had CPCs that resolved before the second trimester exam. A population-based approach is necessary to determine whether this was an idiosyncratic finding or more pervasive. Similarly, our observation that CPC detection was associated with a tripled incidence of mildly preterm delivery, which was statistically not significant in this study, requires a population-based approach to confirm or disconfirm.

The debate as to whether to inform parents when an isolated CPC is detected prenatally hinges on the psychological disturbance this information can confer, which can be intense. Complicating the matter for parents is the notion that CPCs may elevate the chance of bearing a child that is significantly cognitively impaired but that the CPC itself serves only as a marker for this possibility. Ultrasound findings that are not linked to development of the nervous system, such as nuchal thickening, likely generate less persistent anxiety as there is no ambiguity regarding a link to subsequent development in a chromosomally normal offspring.

Findings from this study should provide some degree of reassurance that fetuses with and without CPCs grow and develop in a parallel manner *in utero*. Examination of longer-term postnatal developmental outcomes in this sample is currently underway.

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