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Isolated prenatal choroid plexus cysts do not affect child development

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Abstract

Objective—To examine the effect of isolated prenatal choroid plexus cysts (CPCs) on child cognitive, behavioral, motor, and autonomic development at 18 months of age.

Methods—A prospective design was implemented to identify CPC cases and controls in mid-pregnancy. Cases ($n = 25$) and controls ($n = 45$) participated in a follow-up visit when children were 18 months of age. Child mental and motor development was assessed using standard developmental assessments, socioemotional and behavioral functioning during testing was rated by examiners, and accelerometers provided measures of motor activity and energy expenditure. Cardiac patterns were collected using a three-lead electrocardiogram (ECG) and quantified as indicators of autonomic control of the heart, including vagal tone.

Results—No significant differences were found in any outcome measure between children with prenatal CPC detection and those without.

Conclusion—Findings should provide reassurance to practitioners and parents that isolated CPCs in fetuses with normal karyotypes do not affect child development after birth.

Keywords

prenatal ultrasound; prenatal diagnosis; choroid plexus cyst; child development

INTRODUCTION

Detection of choroid plexus cysts (CPCs) occurs in an estimated 0.5–3.6% of routine mid-gestation ultrasound exams (Chinn *et al.*, 1991; Kupfermink *et al.*, 1994; Demasio *et al.*, 2002; DiPietro *et al.*, 2006). While isolated CPCs are generally considered to be soft markers and a minor variation from normal anatomy without functional significance, parents are often informed of their detection due to the increased incidence in fetuses with

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aneuploidy, although this practice has been the subject of substantial debate (Filly *et al.*, 2004).

Consequently, parents who present for a routine ultrasound exam are often startled to learn of this finding and tend to interpret it as an anomaly in the fetal brain, generating significant anxiety (Cristofalo *et al.*, 2006; Larsson *et al.*, 2009). Reactions can be intense, including feelings of shock, fear, and decreased attachment that can persist into the remainder of the pregnancy, despite counseling by most (82%) providers that isolated CPCs are benign (Cristofalo *et al.*, 2006). In addition, most (79%) women reported seeking information beyond that provided by their physician, typically on the internet. An internet search on 'choroid plexus cyst' reveals a CPC parent support group website as the fourth hit (Choroid Plexus Cyst Parent Support Group, 2010), further revealing the extent of parental concern.

Although providers are nearly uniform in their view that isolated CPCs in the presence of normal karyotyping are benign findings, this position is largely based on clinical and anecdotal experience; empirical data supporting this conclusion are meager. This void may contribute to the persistent parental anxiety since there is limited information regarding developmental outcome. Previously, we have reported reassuring results of a prospective study showing no differences in indicators of fetal growth (i.e. femur length, biparietal diameter, abdominal circumference, and head circumference) or aspects of fetal neurobehavioral functioning (i.e. fetal heart rate patterning, motor activity, and their interrelation) measured from 24 to 36 weeks of gestation (DiPietro *et al.*, 2006). However, only two studies have extended investigation into the post-neonatal time period; both are limited by sample size and methodological considerations. The first relied only on parental report via telephone survey of their child's development between 1 and 7 years after birth; responses indicated unremarkable developmental outcomes (Digiovanni *et al.*, 1997). However, in the absence of a control group, only fairly gross deviations from normal development would be detectable. The other compared developmental outcomes in children with prenatal CPC detection to that of control children without CPC findings (Bernier *et al.*, 2005). No differences were detected in overall child IQ or measures of motor performance, but significant differences were detected on verbal IQ and on one of seven measures specific to language function when children were between 3 and 8 years old. Interpretation of the latter results is compromised by the fact that CPC children were tested when they were nearly a year younger than control children and it is not clear whether this was controlled for in the analysis.

The purpose of the current study was to further examine the hypothesis that isolated prenatal CPCs are not associated with variation in developmental outcomes using participants enrolled in a prospective study of cases and controls recruited shortly after the CPC was detected in pregnancy. Follow-up testing was conducted when children were 18 months old and included measures of both developmental and autonomic functioning. Developmental assessment relied on standard measures of developmental status (i.e. Bayley Scales of Infant Development), examiner ratings of socioemotional and attentional capacity, and measurement of motor activity and energy expenditure using an accelerometer. Autonomic functioning was indirectly assessed via measures of patterns of child heart rate. Measurement of phasic and non-phasic variability in heart rate has a long-standing history as

an indicator of neural control of the heart in developmental sciences and as such provides information regarding neural input (Bernston *et al.*, 1997). In particular, measurement of the magnitude of the respiratory sinus arrhythmia isolates the degree of innervation provided by the parasympathetic nervous system (i.e. the vagus) (Porges, 2007) thereby providing a more subtle and direct indicator of childhood neural functioning than afforded by measures of behavior. The study methods reflect a multidimensional approach to the evaluation of child developmental outcomes.

METHODS

Participants

The original cohort included fetuses with one or more isolated CPCs detected in mid-pregnancy during ultrasound anatomy scans. Recruitment spanned approximately 2 years during which time CPCs were identified in 118 (3.6%) pregnancies. Five were excluded due to abnormal ultrasound findings in addition to CPC, two of which were later diagnosed with trisomy 18. Eligibility was restricted to low risk, non-smoking women with singleton pregnancies that were progressing normally to control for other factors that might impinge on normal growth and development, resulting in an additional eight exclusions. Of the remainder, 77 were offered study participation by a sonographer or attending physician participating in recruitment. A total of 52 women contacted the research coordinator; of these 35 began the prenatal protocol with 31 completing it without developing exclusion criteria (e.g. gestational diabetes). Controls were recruited serially by identifying the next two eligible women who had normal findings on an anatomy ultrasound scan at the same location, met the inclusion criteria, and were matched to the prior case by both race/ethnicity and insurance category (public vs private). A total of 67 participants began the protocol; of these 7 developed exclusion criteria resulting in 60 eligible control participants. Further detail on recruitment procedures and enrollment eligibility criteria is available in DiPietro *et al.* (2006). The study was approved by the university's Institutional Review Board and women provided written consent for their child's participation.

Of the 31 cases and 60 controls eligible for postnatal follow-up, the current report is based on 25 cases (81% of eligible cases) and 45 controls (75% of eligible controls) who participated in a visit when their child was 18 months of age. Reasons for loss to follow-up included families that moved out of the area ($n = 10$; 3 cases, 7 controls) and those that were unable to be contacted or scheduled ($n = 11$; 3 cases, 8 controls). Approximately half of the children who participated in the 18 month visit were female (51%) and the sample was near exclusively non-Hispanic White (97%). Child age at the time of the visit ranged from 16.2 to 21.2 months ($M = 18.7$ months). Seven children with mild prematurity (3 cases, 4 controls; M gestational age = 36.1 weeks; range, 35.7–36.7 weeks) including one child (case) with a cleft palate were retained in the current sample. Table 1 reports sample characteristics separately for cases and controls; there were no significant differences on these measures.

Procedure

Children's development was assessed with the Bayley Scales of Infant Development II (BSID), the most widely used and validated assessment of child development (Pearson, San

Antonio, TX, USA). The BSID generates two standardized scores: a mental development index (MDI) and a psychomotor development index (PDI). Testing was done by an examiner who was blind to CPC status. The Bayley infant behavior record (IBR) was also scored at the conclusion of testing. For this age group, the scale consists of 26 items that are reduced to three factors that describe child behavior during the test situation. These include the degree to which children exhibit the following: (1) positive affect, initiative toward materials, lack of fearfulness, and social engagement with the tester (IBR-orientation/engagement); (2) attention and persistence toward tasks, cooperation, and good adaptation to new materials (IBR-emotional regulation); and (3) mature quality of motor behavior characterized by normal tone, fine and gross motor proficiency during tasks, and appropriate motor speed (IBR-motor quality).

Activity level of children during an unstructured 10-min free play and the administration of the Bayley Scales was measured using an Actical accelerometer (Mini-Mitter, Bend, OR, USA) placed on the child's ankle. Actical data during free play reflect a child's general exploratory activity level, while data during developmental testing reflect inhibitory control during attention-demanding situations. Movement data were summarized using Actical software (v. 2.02). Total energy expenditure, calculated separately for both episodes, is the total number of kilocalories expended per minute per kilogram of subject weight, as a function of total activity counts across the task and the child's current weight. Average activity count was calculated by dividing the total movement counts by the number of intervals.

Prior to developmental testing, children were instrumented with a three-lead electrocardiogram (ECG) and the signal was amplified (PhysioControl, Model Lifepak 5, Plainview, NY, USA), digitized, and recorded on a computer. Data were collected while the child was sitting quietly on the mother's lap and looking at a book or toy. R-wave detection, editing for artifact, and timing of sequential heart periods proceeded offline using MXedit software (Delta-Biometrics, Inc., Bethesda, MD, USA) and yielded measures of heart period (ms) and heart period variability (SD). Vagal tone (V) was computed using the analytic method developed by Porges (1985). Briefly, this procedure uses a 21-point polynomial to detrend sequential heart period data and a band-pass filter to extract the variance within the frequency band consistent with respiration within this age group (i.e. 0.24–1.04 Hz), which corresponds to the respiratory sinus arrhythmia. The average duration of the ECG recording was 5.0 min.

Statistical comparisons by group (CPC vs control) for demographic variables were analyzed using *t*-tests and chi-square statistics as appropriate. General linear models, controlling for age at testing, were used to evaluate group differences in developmental, activity level, and cardiac measures. Results were expected to support the null hypothesis of no differences; therefore if group differences at even a trend level (i.e. $p < 0.10$) were detected, this would be important to identify in a small sample. As a result, α increased from the more commonly used $\alpha = 0.05$ to $\alpha = 0.10$. This decreases the chance of a Type II error (i.e. detecting no difference when one exists). Given that the sample size was fixed based on the number of women carrying fetuses with CPC detection, the study yielded sufficient statistical power of 0.76 in the detection of a medium effect size difference.

RESULTS

Preliminary analyses were conducted to determine whether participants who took part in the follow-up study were different than those who did not. Mothers of toddlers who did not participate ($n = 21$) were younger in age ($t = -3.03, p < 0.01$), more likely to be single ($\chi^2 = 12.64, p < 0.01$), and more likely to be African-American or Asian ($\chi^2 = 13.51, p < 0.01$). However, there was no difference in birth outcomes between children who participated in the follow-up versus those that did not: birth weight ($t = -1.52, p = 0.13$), gestational age ($t = 0.30, p = 0.77$), length ($t = -1.23, p = 0.22$), 1- and 5-min Apgar scores ($t = -1.24, p = 0.22$; $t = 0.19, p = 0.85$), or the proportion of cases versus controls ($\chi^2 = 0.37, p = 0.54$). Child weight and height at the time of testing did not differ between CPC cases and controls ($M = 25.6$ and 26.1 lbs and $M = 25.6$ and 26.1 inches, respectively). There was a trend level difference in age at testing with CPC cases being approximately 12 days older than controls ($M = 18.9$ and 18.5 months; $t(68) = 1.97, p = 0.053$). Consequently, subsequent analyses were adjusted for age.

Means and standard deviations for developmental variables for cases and controls are presented in Table 2. Unadjusted mean values are presented for ease of interpretation, but statistical results include adjustment for age. Both groups performed equally well on both mental (MDI) and motor (PDI) development, and there were no differences in behavior during testing as reflected on the three IBR scales. The CPC case with cleft palate scored above the national and sample norms on the developmental assessments (MDI = 107; PDI = 103), so was not excluded from the analyses. There were no group differences in activity level or energy expenditure during either free play or developmental testing. No significant differences were found between CPC cases and controls for any of the three cardiac measures.

In the prenatal period, CPCs in all but three cases had resolved by 28 weeks of gestation. Two of these non-resolved cases were included in the follow-up sample and received normal developmental scores (MDI = 97 for both; PDI = 94 and 107). In addition, mothers of CPC cases reported similar, low levels of concern about their child's health ($t = 1.34, p = 0.19$) and development ($t = 1.58, p = 0.12$), relative to mothers of control children.

COMMENTS

A multidimensional assessment of developmental status, emotional regulation and social engagement, motor control and activity level under conditions of activation and inhibition, and autonomic regulation failed to reveal significant differences between children with a CPC detected prenatally as compared to those without CPC detection. While these measures do not represent the universe of child functioning, they reflect a breadth of important domains that have been related to subsequent child outcomes. In addition, they confirm the null results from the fetal data collected on this sample, which included similar measures of motor and autonomic function. The measures of variation in heart rate are perhaps the most neurally linked aspects of the outcomes included in this study (Porges, 2007) implying that prenatally detected CPCs are of little consequence to ensuing central development and the processes that underlie physiological regulation of behaviors, including attention.

Unfortunately, because data collection was ongoing at the time of publication, this study did not specifically include indicators of language performance that were highlighted in Bernier *et al.* (2005). However, it is worth noting that the lower verbal scores found in the CPC cases in the earlier report were in the upper ranges of normal functioning and as such do not reflect a deficit.

The study sample is more educated, of higher socioeconomic advantage, and less racially diverse than the general population. While this is not uncommon in studies that rely on volunteers, it raises concerns regarding generalizability. However, while socioeconomic status has clear impact on developmental assessments, there is little reason to suspect that the presence of a CPC would differentially affect child development by virtue of either socioeconomic or racial group status. It is also worth noting that while the follow-up rates for recruited and eligible participants were quite good (81%), the tested sample reflects only 22% of the total number of isolated CPC findings detected during the recruitment period, since some women were not referred, some referred women declined participation, and some were ineligible due to other pregnancy factors that were unrelated to the CPC. A related concern regards the power to detect significant differences given the sample size; this is always an important issue in studies that support the null hypothesis. This study was sufficiently powered to detect an effect size of 0.5 (i.e. a medium difference), which corresponds to a difference of equal to or greater than half a standard deviation per outcome. Inspection of Table 2 indicates that the case and control scores are substantially closer than this. A larger sample would provide increased sensitivity to detect differences between groups, but the issue of clinical meaningfulness of small differences observed in large samples would then become paramount to interpretation.

Despite these limitations, this study provides the most comprehensive examination of child development in children with prenatal choroid cyst detection conducted to date. There is no indication that isolated CPCs either pose or reveal a threat to child development. Until a study with a larger and more representative sample is undertaken, the negative results should provide reassurance to both parents and providers following detection of an isolated CPC on ultrasound in fetuses with normal karyotypes.

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REFERENCES

- Bernier F, Crawford S, Dewey D. Developmental outcome of children who had choroid plexus cysts detected prenatally. *Prenat Diagn.* 2005; 25:322–326. [PubMed: 15849792]
- Bernston G, Bigger J, Eckberg D, et al. Heart rate variability: origins, methods, and interpretative caveats. *Psychophysiology.* 1997; 34:623–648. [PubMed: 9401419]
- Chinn D, Miller E, Worthy L, Towers C. Sonographically detected fetal choroid plexus cysts. Frequency and association with aneuploidy. *J Ultrasound Med.* 1991; 10:255–258. [PubMed: 2051545]
- Choroid Plexus Cyst Parent Support Group. 2010 Available at <http://www.choroidplexuscyst.org>.

- Cristofalo E, DiPietro J, Costigan K, Nelson P, Crino J. Women's response to fetal choroid plexus cysts detected by prenatal ultrasound. *J Perinatol.* 2006; 26:215–223. [PubMed: 16554849]
- Demasio K, Canterino J, Anath C, Fernandez C, Smulian J, Vintzileos A. Isolated choroid plexus cyst in low-risk women less than 35 years old. *Am J Obstet Gynecol.* 2002; 187:1246–1249. [PubMed: 12439513]
- Digiovanni L, Quinlan M, Verp M. Choroid plexus cysts: infant and early childhood developmental outcome. *Obstet Gynecol.* 1997; 90:191–194. [PubMed: 9241291]
- DiPietro J, Costigan K, Cristafalo E, et al. Choroid plexus cysts do not affect fetal neurodevelopment. *J Perinatol.* 2006; 26:622–627. [PubMed: 16885987]
- Filly R, Benacerraf B, Nyberg D, Hobbins J. Choroid plexus cyst and echogenic intracardiac focus in women at low risk for chromosomal anomalies. *J Ultrasound Med.* 2004; 23:447–449. [PubMed: 15098860]
- Kupferminc M, Tamura R, Sabbagha R, Parilla B, Cohen L, Pergament E. Isolated choroid plexus cyst(s): an indication for amniocentesis. *Am J Obstet Gynecol.* 1994; 171:1068–1071. [PubMed: 7943072]
- Larsson A, Svalenius E, Marsal K, Dykes A. Parental level of anxiety, sense of coherence and state of mind when choroid plexus cysts have been identified in a routine ultrasound examination in the second trimester of pregnancy: a case control study. *J Psychosom Obstet Gynaecol.* 2009; 30:95–100. [PubMed: 19533488]
- Porges, SW. *Method and Apparatus for Evaluating Rhythmic Oscillations in a Periodic Physiological Response Systems.* Washington, DC: US Patent Office; 1985.
- Porges SW. The polyvagal perspective. *Biol Psychol.* 2007; 74:116–143. [PubMed: 17049418]

Table 1

Sample characteristics

	CPC cases (<i>n</i> = 25)	Controls (<i>n</i> = 45)	<i>p</i> [*]
Birth weight (g)	3337.9 (563.8)	3532.0 (482.9)	0.13
Gestational age (weeks)	38.6 (1.6)	38.9 (4.0)	0.67
Child sex (female)	52.0%	51.1%	0.94
Race/ethnicity			
African-American	0.0%	2.2%	—
Asian	0.0%	2.2%	—
Caucasian	100.0%	95.6%	0.56
Maternal characteristics			
Age (years)	32.7 (5.1)	32.3 (4.8)	0.74
Education (years)	16.9 (2.5)	16.7 (1.7)	0.71
Occupational status ^a	7.2 (1.5)	7.3 (1.3)	0.70
Marital status (married)	88.0%	95.6%	0.24

CPC, choroid plexus cysts.

^aBased on Hollingshead scoring system.*
p values based on chi-square or *t*-tests as appropriate.

Table 2

Means for 18-month development in CPC cases and controls

	CPC cases (<i>n</i> = 25) ^a	Controls (<i>n</i> = 45) ^a	<i>p</i>
Bayley Scales of Infant Development	(<i>n</i> = 23)	(<i>n</i> = 43)	
Mental development index	100.0 (11.2)	101.1 (12.4)	0.69
Psychomotor development index	93.1 (9.4)	95.9 (9.7)	0.46
IBR engagement/orientation	37.6 (5.1)	38.7 (4.3)	0.23
IBR emotional regulation	40.6 (5.6)	41.1 (6.0)	0.55
IBR motor quality	39.2 (1.2)	38.0 (2.9)	0.15
Actical measures	(<i>n</i> = 15–17)	(<i>n</i> = 33–38)	
Free play total energy expenditure	5.7 (1.5)	5.6 (1.5)	0.98
Free play average activity counts	789.6 (228.7)	846.1 (379.6)	0.55
Bayley Scales total energy expenditure	12.6 (6.6)	12.1 (5.2)	0.82
Bayley Scales average activity counts	632.2 (323.5)	645.3 (323.7)	0.59
Cardiac measures	(<i>n</i> = 24)	(<i>n</i> = 44)	
Mean heart period (ms)	483.6 (32.7)	472.5 (31.0)	0.23
Heart period variability	6.1 (0.5)	6.0 (0.6)	0.22
Vagal tone (V)	3.9 (0.7)	3.9 (0.9)	0.87

CPC, choroid plexus cysts; IBR, infant behavior record; ECG, electrocardiogram.

^aThere is variation in the *n* per analysis for each type of measure due to test-specific child compliance (Bayley Scales); technical difficulties, including child removal or accidental dislodgement of device or other technical difficulty (Actical); and inadequate signal (ECG measures).