European Journal of Obstetrics & Gynecology and Reproductive Biology 237 (2019) 85–88

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Dilated cavum septi pellucidi as sole prenatal ultrasound defect: Case-base analysis of fetal outcomes☆

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ARTICLE INFO

Article history:
Received 2 December 2018
Received in revised form 28 March 2019
Accepted 16 April 2019

Keywords:
Cavum septi pellucidi
Prenatal ultrasound
MRI
Chromosomal analysis
Prognosis

ABSTRACT

Objectives: This retrospective study was undertaken to examine fetuses with dilated cavum septi pellucidi (CSP) as an isolated finding and to identify factors impacting postnatal outcomes.
Study Design: Fully documented cases of dilated CSP as a sole prenatal defect were selected for study. Recorded data included serial sonographic examinations, fetal MRI studies, chromosomal testing, screening for infection, and postnatal follow-up. Fetal subjects were further stratified by gender, gestational age at diagnosis (<28 w or ≥28 w), CSP width at diagnosis (<10 mm or ≥10 mm), evolution at term (persistent vs non-persistent CSP), and postnatal MRI diagnosis (presence/absence of CSP cyst). Chi-square or Fisher's exact test (as appropriate) was used to compare categorical variables and patient groups.
Results: A total of 48 fetuses met our inclusion criteria, none exhibiting chromosomal abnormalities. Six (12.5%) of these 48 were subsequently diagnosed with neurodevelopmental delays. However, such delays were unrelated to any categorical variable listed above ($p > 0.05$).
Conclusions: Dilated CSP as an isolated prenatal finding by ultrasound or MRI carries a low risk of chromosomal abnormalities but a high risk of neurodevelopmental delay. These perils should be adequately conveyed to the parents of such infants.

Introduction

Ultrasound is the preferred method for screening the fetal central nervous system (CNS). It is a safe, cost-effective, and repeatable real-time modality. The cavum septi pellucidi (CSP) is a key structure in fetal brains, serving as an anatomic landmark in standard axial planes of cranial imaging. A CSP that is absent or aberrant may be indicative of fetal abnormalities. For example, absence of CSP is associated with agenesis of corpus callosum, holoprosencephaly, and sept-optic dysplasia [1,2]; and dilated CSPs may accompany congenital anomalies, such as lissencephaly, congenital heart disease, duodenal stenosis or atresia, and other conditions [3,4]. Furthermore, chromosomal defects are likely in this setting. Ho et al [3] have reported a 26.67% rate of trisomy 21 in fetuses with dilated CSPs, and a number of related chromosomal defects have been implicated by Abele et al [4]. Compared with euploid fetuses, they determined that CSP width is excessive (>95th percentile) in sizeable percentages of various fetal trisomies (trisomy 18, 92%; trisomy 21, 42%; trisomy 13, 37.5%). A postnatal study has likewise documented dilated CSPs in children with 22q11 microdeletions [5], the most common deletion in humans and the second most frequent aberration (after trisomy 21) tied to cardiac defects. In addition, the validity of dilated CSP as a prospective sonographic marker for 22q11 microdeletion has been underscored by a prenatal case-controlled study [6].

Above chromosomal findings are nevertheless typically accompanied by other structural abnormalities. Whether these stated risks apply in isolated ultrasound-detected instances of dilated CSP have yet to be determined. One of our two major goals was to retrospectively assess chromosomal defects in fetuses with dilated CSPs occurring in isolation and detected during prenatal screening. Even if unrelated, there is still much debate over the clinical significance of isolated dilated CSP and the perhaps dire consequences for parents [7,8]. Thus, we also monitored postnatal outcomes to identify prognosticators of potential use in parental counseling.

Materials and methods

This retrospective study included cases of dilated CSP reported at our institution between January 2007 and December 2017.

☆ The study was conducted in Shenyang, Liaoning, China

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https://doi.org/10.1016/j.ejogrb.2019.04.014
0301-2115/

According to prior investigations, CSP is considered dilated when the measurement exceeds the gestation age and ranges by two standard deviations [9].

Qualified subjects were singleton babies with fully documented dilated CSPs through serial sonographic examinations, fetal magnetic resonance imaging (MRI), chromosomal testing, screening for infection, and postnatal follow-up. Once detected on prenatal ultrasound, detailed ultrasound and fetal MRI studies were conducted to screen for other structural abnormalities, thereafter performing chromosomal analysis and screening for fetal infection. Premature fetuses were excluded to prevent skewing of prognostic results.

Fetal images were re-evaluated by experienced sonographers and radiologists using the Picture Archiving and Communication System (PACS; Neusoft Corp, Shenyang, Liaoning, China). A single observer measured all CSP widths, each obtained in transthalamic plane, positioning calipers at the broadest distance between internal aspects of CSP walls (perpendicular to long axis). Each measurement was performed three times, using mean values for analysis. Fetal chromosome testing was achieved through amnio- or cordocentesis. Routine diagnostics at our institution included G-banding karyotyping at 320–400, with short tandem repeat (STR). Postnatal chromosomal profiles were also obtained. Next Generation DNA Sequencing (NGS) should be performed to detect microdeletions (including 1p36 deletion syndrome, 2q33.1 deletion syndrome, 22q11 deletion syndrome, Angelman syndrome, Cri-Du-Chat syndrome, Langer-Giedion syndrome and Prader-Willi syndrome) on cases with suspected chromosomal abnormalities.

Postnatal follow-up included developmental monitoring, any symptoms, and postnatal MRI evaluations. Our pediatricians performed the postnatal developmental evaluation by asking the parents about their gross or fine motor skills, speech and language skills, cognitive or thinking skills, social and emotional skills, as well as activities of daily living (ADL) if available. ADL is the ability to handle everyday tasks. For children, that includes eating, dressing and bowel and bladder management.

Data handling and statistical analysis

Fetal subjects were further stratified by gender, gestational age at diagnosis (<28 w or ≥28 w), CSP width at diagnosis (<10 mm or ≥10 mm), evolution at term (persistent vs non-persistent CSP), and postnatal MRI diagnosis (presence/absence of CSP cyst). Incidences of chromosomal defects, neurodevelopmental delay, or other pertinent postnatal symptoms were analyzed as feasible.

Quantitative variables were expressed as means ± standard deviations (SD), reporting qualitative variables as frequencies (percentages). Chi-square or Fisher's exact test was used accordingly to compare categorical variables and groups. Standard software (SPSS Statistics v23 for Windows; IBM Corp, Armonk, NY, USA) was engaged, setting significance at $p \leq 0.05$.

Ethical approval

This study was approved by our local ethics committee (20170201, 2017PS024 K), acquiring written informed consent from maternal participants.

Results

Overall, 65,215 cases were examined by ultrasound at our institution between January 2007 and December 2017 (Each pregnancy was included only once), and 267 cases (0.41%, 267/65,215) of dilated CSP were detected. Twin pregnancies (n = 21) were excluded, and there were additional prenatal anomalies in 116 (47.2%, 116/267). Finally, 130 cases (0.20%, 130/65,215) were confirmed to have isolated dilated CSP. In 75 of the remaining 130 cases, documentation was insufficient, or the subjects were lost to follow-up. Seven premature fetuses were also excluded. Ultimately, 48 cases met our inclusion criteria. Mean maternal age was 28.80 ± 6.18 years (range, 18–41 years), and the mean gestational age at time of detection was 28.83 ± 3.26 weeks (range, 24–35 weeks). Mean CSP width was 10.28 ± 0.80 mm (range, 8.90–12.3 mm).

Fetal chromosome analysis was obtained via amniocentesis (n = 13, 27.1%) or cordocentesis (n = 35, 72.9%). No chromosomal abnormalities were identified in routine analysis. NGS was performed in 10 cases after birth and no positive result was identified, including the 6 cases with developmental delay which would be mentioned below. Screening for fetal infection was routinely performed and consistently proved negative. On follow-up ultrasound, dilated CSPs persisted in 41 (85.42%) term births. Fetal MRI reports cited possible CSP cysts in 13 cases.

In monitoring fetal outcomes (N = 48), the median age at neurologic assessment was 4.12 ± 2.88 years (range, 0.46–10 years). Postnatal MRI studies documented seven infants (14.58%) with CSP cysts, none of them undergoing surgery. Six of the 48 subjects (12.5%, 95% CI: 2.8–22.2%) were diagnosed with neurodevelopmental delays, and 12 (25%) had some nervous system symptoms on occasion. Table 1 shows the distribution of isolated dilated CSPs relative to various categorical variables, for which there were no statistical relations (all $p > 0.05$). In Table 2, instances of developmental delay are detailed. Among the 12 infants with episodic nervous system symptoms, four experienced headaches, two complained of dizziness, four had convulsions (without fever), and two displayed involuntary movements.

Comment

Early studies, including the work of Falco et al [9] (2000), have recorded a mean CSP width of 5.3 ± 1.7 mm (range, 2–9 mm), confirming that CSPs widen as gestational age and biparietal diameter (BPD) increase and diminish slightly around term. In 1998, Jou et al [10] showed that between 19 and 42 weeks of gestation, CSP width ranges from 2.0 to 10.0 mm, with a mean of 5.50 ± 1.48 mm. CSP appears to gradually widen between 19 and 27 weeks and tends to plateau between 28 weeks and term. In our analysis, we deferred to values cited by Falco et al [9] for CSP dilation (i.e., measurements beyond two standard deviations of established ranges). However, a wide (>1.0 cm) CSP or one persisting past infancy is clearly a true subtle marker of cerebral dysgenesis [11].

Table 1
The distribution of isolated dilated CSPs relative to various categorical variables.

categorical variables	n	neurodevelopmental delay	*p*-value
fetal gender			
male	26	4(15.38)	0.51
female	22	2(9.09)	
gestational age			
≥ 28 w	27	4(14.81)	0.58
< 28 w	21	2(9.52)	
CSP width			
< 10mm	15	1(6.67)	0.41
≥ 10mm	33	5(5.15)	
evolution at term			
persistence	40	6(15.00)	0.24
non-persistent	8	0(0.00)	
postnatal MRI			
CSP cyst	7	2(28.57)	0.27
absence of CSP cyst	33	4(12.12)	

Note. — data in parentheses are percentages.

Table 2
Details of the cases with developmental delay.

	GA (weeks)	Gender	CSP width (mm)	Present at term	Fetal MRI	Delivery mode	Postnatal MRI	Age at assessment	Domain of developmental delay	Performance of ADL
case 1	33	M	11.7	Y	dilated CSP	SVD (39 W)	CSP cyst	4y	Fine motor delay	Well
case 2	28	F	12.3	Y	possible CSP cyst	LSCS (37 W)	CSP cyst	2y	Fine motor delay	NA
case 3	25	M	9.9	Y	dilated CSP	SVD (39 W)	CSP persistence	6y	Gross and fine motor delay	Well
case 4	30	M	11.6	Y	dilated CSP	SVD (38 W)	CSP persistence, intracranial multiple hypomyelination	3y	Speech and language delay	Well
case 5	27	M	10.8	Y	dilated CSP	SVD (37 W)	CSP persistence, slightly external hydrocephalus	8m	Gross and fine motor delay	NA
case 6	30	F	11.2	Y	dilated CSP	LSCS (38 W)	CSP persistence, slightly external hydrocephalus	9m	Gross and fine motor delay	NA

GA: gestation age at diagnosis; M: male; F: female; CSP width: CSP width at diagnosis in ultrasound; Y: yes; Delivery mode: data in parentheses are delivery weeks; SVD: spontaneous vaginal delivery; LSCS: low segment cesarean section; y: year; m: month; ADL: activities of daily life; NA: not available.

Chromosomal abnormalities

Chromosomal abnormalities may certainly be associated with dilated CSPs. Early studies have shown that CSP widths typically are larger in fetuses with autosomal trisomies (i.e., 13, 18, or 21), as opposed to euploid fetuses [3,4]. Still, dilated CSPs in aneuploid pregnancies are regularly present alongside other structural abnormalities. Chaoui et al [6] discovered that among fetuses with 22q11 microdeletions and related cardiac abnormalities, 60–70% also demonstrated dilated CSPs.

In this regard, the present investigation diverged entirely from the known body of evidence. No chromosomal abnormalities were identified in any of our study subjects. This discrepancy is perhaps related to differing inclusion criteria. Our analysis was confined to dilated CSPs as purely isolated findings. However, there is still much debate on the need for chromosomal testing in each instance of dilated CSP. Such testing is often recommended clinically if prenatal ultrasound also reveals fetal structural abnormalities. An abundance of earlier research has shown that major structural abnormalities do correlate with chromosomal defects [1–6]. We have likewise duly observed that chromosomal abnormalities generally do not result in nominal structural abnormalities, although each case may be different. Based on our data, dilated CSPs in isolation did not heighten the risk of chromosomal abnormalities. However, there are other risk factors, such as maternal age, infections in early pregnancy, or environmental factors in this setting that may prompt chromosomal analysis.

CSP cysts

If dilation of the CSP is sufficient to cause bowed or bulging side walls, the resultant contours or any related mass effect may mimic a CSP cyst in MRI studies [11–14]. True CSP cysts are rarely detected, one study reporting an incidence of 0.04% (22/54,000) by computed tomography or MRI [15]. In the course of our study, there were pre- and postnatal diagnostic inconsistencies. Prenatal MRI studies indicated possible CSP cysts in 13 fetuses, whereas only seven cysts were identified by postnatal MRI. Thus, we believe that some suspected CSP cysts in fetal neuroimages are in fact merely overblown CSPs, which is why any CSP cyst identified by fetal MRI should be properly followed.

A CSP cyst may directly compress adjacent cerebral tissue or possibly lead to obstructive hydrocephalus, producing a variety of neurologic signs and symptoms [10,11,16,17]. In our subjects, two instances of CSP cyst presented clinically as developmental delays. However, our data do not indicate that CSP cysts adversely impact infant development. Only two patients displayed neurologic symptoms, namely headache and convulsions (without fever). These symptoms occur episodically and do not affect the children's daily lives. The other three patients with CSP cysts have shown normal development. Hence, despite some tendency for developmental delay or neurologic symptoms, a CSP cyst is not an independent risk factor.

In prenatal counseling, parents may have treatment concerns if a midline CSP cyst is encountered. Previous studies [18–20] suggest that in most patients with nonspecific symptoms, clinical observation and eventually intracranial pressure monitoring may be adequate, although the onset of specific clinical symptoms or objective intracranial pressure fluctuations will usually require prompt surgical intervention. At present, none of the patients in our study required surgery. We intend to continue surveillance, checking for any significant future abnormalities that may call for surgery. Techniques for surgically treating CSP cysts are fairly well established at present, and the risk entailed is low.

Neurodevelopmental delay

In documenting postnatal outcomes of dilated CSPs, Bronshtein and Weiner [7] reported that 50% (1 of 2 patients) survived and showed normal development during the first months of life. Vergani et al [16] have also reported that during a median postnatal follow-up period of 22 months (range, 9–84 months), all children with cyst-like lesions involving midline anatomic structures at fetal neuroimaging proved to be healthy during postnatal neuropsychologic evaluations. On the other hand, among five patients with isolated dilated CSPs investigated by Ho et al [3], all of whom survived, only 20% (1/5) displayed entirely normal development. Unlike previous studies, all neonates of our cohort survived, and the rate of normal neurodevelopment was 87.5% (42/48). Still, some subjects were not symptom-free, experiencing headaches, dizziness, or occasional convulsions. Our analysis seemed to indicate better postnatal outcomes, but again, dilated CSPs were isolated findings herein.

Ultimately, our data still reflect a 12.5% of risk of neurodevelopmental delay, defined as a significant delay in one or more of the following domains: daily activities, motor, speech/language, and social or personal development [21–23]. The patients we followed were confirmed by pediatricians as having motor delay (n = 5) or speech delay (n = 1) problems. From our perspective, dilated CSPs or CSP cysts are more likely to inflict motor impairment. Although we did examine potential relations between neurodevelopmental delay and various categorical variables (fetal sex, gestational age at diagnosis, CSP width, evolution at term, and postnatal MRI diagnosis), no independent risk factors emerged.

Limitations

This study was retrospective in nature and therefore has some limitations. Firstly, the patient population was relatively small, producing limited numbers in certain groups that may have reached statistical significance in a larger sampling. Secondly, we have a certain number of cases either lost to follow-up or had insufficient documentation. We admitted that the missing cases could great significance in the statistical analysis. Thirdly, the youngest neonate was <6 months old at the time of writing, so neurodevelopmental assessment was prohibitive. Finally, we did not test for intelligence quotient, due to the array of potential influences. We simply sought to address survival and self-care capabilities in affected fetuses, because a child with a major disability may impose a heavy parental burden. We hope that our results are of value for future prenatal counseling.

Conclusions

From the perspective of prenatal screening, we hope to find out how to deal with the problem of dilated CSP, especially for the isolated cases. Dilated CSP as an isolated prenatal finding by ultrasound or MRI carries a low risk of chromosomal abnormalities but a high risk of neurodevelopmental delay. These perils should be adequately conveyed to the parents of such infants.

Conflict of interest statement

The authors or authors' institutions have no conflict of interest.

Acknowledgment

Our funding source is Outstanding Scientific Fund of Shengjing Hospital of China Medical University. There are no study sponsors in our study.

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