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## Isolated, Absent Cavum Septum Pellucidum: A Single Center's Outcomes and Review of the Literature

Renee Bardini

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Isolated, Absent Cavum Septum Pellucidum: A Single Center's Outcomes and Review  
of the Literature

by


Renee Bardini, BS

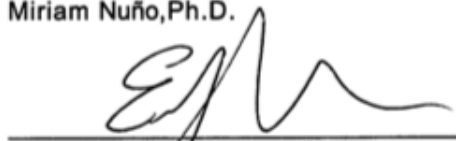
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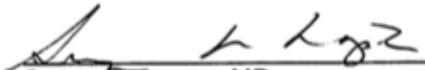
  
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Isolated, Absent Cavum Septum Pellucidum: A Single Center's Outcomes and Review  
of the Literature

A

Thesis

Presented to the Faculty of

The University of Texas

MD Anderson Cancer Center UTHealth

Graduate School of Biomedical Sciences

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Science

by

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May 2021

# Isolated, Absent Cavum Septum Pellucidum: A Single Center's Outcomes and Review of the Literature

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An absent cavum septum pellucidum (CSP) has traditionally been associated with a wide range of neuroanatomical anomalies. With recent advancements in prenatal imaging, however, an absent CSP that occurs in isolation of other anomalies is becoming a more frequent finding. Yet knowledge of clinical outcomes remain limited. Our study aims to describe ultrasound abnormalities associated with an absent CSP and the postnatal outcomes of an isolated, absent CSP. Additionally, we explore the accuracy of prenatal ultrasounds in evaluating for an absent CSP.

This is a retrospective study of all cases diagnosed with an absent CSP between January 1, 2009 and June 2, 2020 at our institution. Cases with additional structural abnormalities were included in a prenatal chart review. A postnatal chart review was only performed for cases in which the absent CSP occurred in isolation. Clinical outcomes were largely obtained from available medical records. When medical records were unavailable, outcomes were obtained directly from the child's mother via phone survey.

We identified 158 patients who were referred to our institution for a suspected absent or absent CSP. Follow-up imaging revealed that 25.9% of patients had a

present CSP, 63.9% had an absent CSP in conjunction with other abnormalities, and 10.1% (N=16) were found to have a prenatally isolated, absent CSP.

Outcome data was available for 10 of these 16 patients. Through postnatal evaluation of our isolated, absent CSP cohort, we found that two patients had discordant postnatal imaging and one patient received a diagnosis of SOD. Most patients who retained a diagnosis of an isolated, absent CSP postnatally had developmental delay ranging from mild motor and speech delay to global developmental delay (n=5/6).

Our study found that fetal MRIs may be more sensitive in diagnosing a prenatally suspected isolated, absent CSP, but are not accurate predictors of who may ultimately receive a SOD diagnosis.

In conclusion, an absent CSP is often associated with additional abnormalities. When isolated, the risk for SOD and developmental delays is increased.

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# Isolated, Absent Cavum Septum Pellucidum: A Single Center's Outcomes and Review of the Literature

## **Introduction**

The cavum septum pellucidum (CSP) is a translucent, vertical membrane that forms along the midline separating the lateral ventricles of the brain during fetal development. The CSP is fully formed by 17 weeks' gestation and is typically visible by ultrasound from the second trimester until 36-40 weeks' gestation when the CSP begins to fuse<sup>1,2</sup>. Normal development of the CSP during fetal development is an important marker of typical brain formation. When the CSP is absent or not visualized on ultrasound or MRI, it often indicates the failure of midline structures to develop or damage to normal structures<sup>2</sup>. The incidence of an absent CSP is estimated to occur in 2-3/100,000 neonates<sup>3</sup>. An absent CSP is typically associated with a wide range of neuroanatomical anomalies such as holoprosencephaly, agenesis of the corpus callosum, ventriculomegaly, schizencephaly, and hydrocephalus.

When an absent CSP is secondary to a structural brain abnormality, the prognosis is typically dependent upon the concomitant brain abnormality. The prognosis is less certain when an absent CSP is detected in isolation. This uncertainty can be partially attributed to the limitations of prenatal imaging. For example, septo-optic dysplasia (SOD) is associated with an isolated, absent CSP. SOD is characterized by permutations of midline brain abnormalities, pituitary hypoplasia and optic nerve hypoplasia.<sup>4</sup> Pituitary function and optic nerve hypoplasia cannot be adequately assessed in the prenatal setting. Therefore, a diagnosis of SOD requires postnatal evaluation by an endocrinologist and ophthalmologist, even if optic nerve hypoplasia or hypoplastic pituitary gland can be identified on fetal MRI<sup>5</sup>. The challenges

in diagnosing SOD are further complicated by the fact that it is rarely associated with a known genetic cause; therefore, prenatal genetic testing cannot rule out SOD. Waiting for a postnatal evaluation can cause anxiety and fear in expectant parents, particularly because there is limited data on the frequency, outcomes and management recommendations related to an isolated, absent CSP.

To date, there have been few studies that examine outcomes of pregnancies with an isolated, absent CSP. Furthermore, all studies have been small and limited in scope. Two of the studies, one by Pillard et al. and another by Vawter et al., suggest that 25% of prenatally diagnosed isolated, absent CSP cases receive a diagnosis of SOD upon postnatal evaluation. Those who did not have SOD and retained a diagnosis of an isolated, absent CSP postnatally had either normal neurological outcomes or mild delays<sup>1,6</sup>. In addition, Pillard et al. indicates that the accuracy of MRI and ultrasound are comparable when evaluating for the absence of the CSP prenatally.<sup>1</sup> A more recent study by Shinar et al. determined that of those with a seemingly isolated, absent CSP diagnosed prenatally, 27% received a diagnosis of SOD. Those who retained a diagnosis of an isolated, absent CSP had normal development.<sup>4</sup>

This study aims to further explore the implications of an isolated, absent CSP in order to provide better prenatal counseling to expectant parents. Determining the outcomes associated with this cohort will help patients and guide clinicians' perinatal management. We also aim to describe associated anomalies in the non-isolated cases and assess the accuracy of confirmed absent CSP cases using MRI when evaluating on prenatal ultrasound.

## **Methods**

A retrospective study of all cases diagnosed with an absent CSP was performed between January 1<sup>st</sup>, 2009 and June 2<sup>nd</sup>, 2020 at our institution. This study was

approved by the institutional review board at the University of Texas, Houston (HSC-MS-20-0489). Cases were identified querying our medical record system for the terms “absent CSP”, “cavum absent”, “cavum septum pellucidum absent”, “absent cavum septum pelucidum”, “absent cavum septum pellucidum”, “not visualized CSP”, “abnormal cavum septum pellucidum” “cavum septum pellucidum not visualized” and “abnormal CSP”. A prenatal chart review was performed in all cases that were referred to our center for absent CSP (suspected and confirmed), including non-isolated cases. Clinical data were gathered from available maternal medical records. Data gathered included demographic information, prenatal ultrasound and MRI findings, and genetic testing results.

Prenatal ultrasound examinations were performed using a Voluson E8 ultrasound machine. Ultrasounds were performed transabdominally or transvaginal when necessary. Prenatal and postnatal MRI examinations were performed using either Siemens Sola 1.5 T or Phillips 1.5 T.

A postnatal chart review was only performed on the cases in which the absent CSP occurred in isolation, without additional structural parenchymal abnormalities. In our review, cases with corpus callosum abnormalities, severe ventriculomegaly (>15mm), migration disorders, holoprosencephaly, posterior fossa abnormalities, schizencephaly, hemihydranencephaly, intraventricular and parenchymal hemorrhage, dolichocephaly/microcephaly and extracranial congenital anomalies were excluded from postnatal chart review. Cases of isolated, absent CSP with lateral

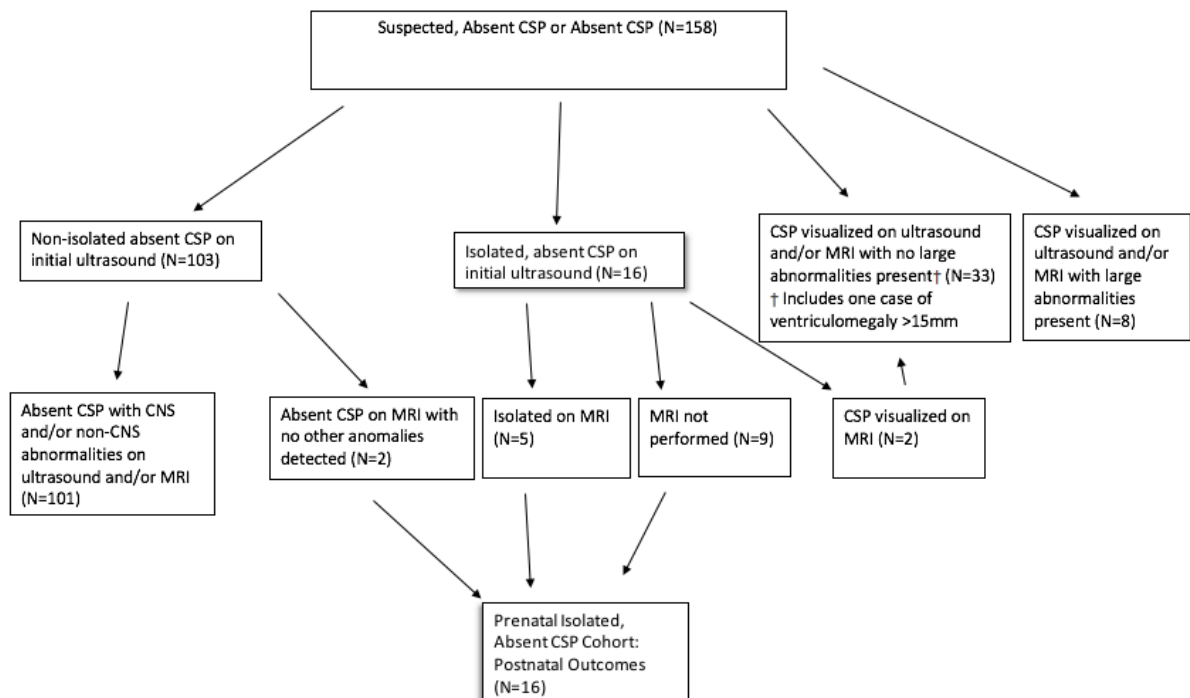
ventriculomegaly less than 15 mm were reviewed and included if there were no additional abnormalities noted.

The postnatal outcomes for our isolated, absent CSP cohort were collected from maternal and neonatal medical records. Postnatal outcomes included ophthalmologic, endocrine, and genetic evaluations. In addition, postnatal imaging and developmental outcomes were also analyzed. In many cases, clinical postnatal outcomes were not available due to lack of follow-up at our institution. In these cases, the mother of the child was contacted directly by phone up to three times and offered participation in a verbal phone survey to obtain postnatal outcomes including both imaging and developmental outcomes. Survey data were collected in Qualtrics and data was analyzed utilizing STATA software.

## **Results**

From January 1<sup>st</sup>, 2009 to June 2<sup>nd</sup>, 2020 there were 158 patients who were referred to our institution for a suspected absent CSP or an absent CSP (Figure 1).

Figure 1: Study Cohort



Approximately a quarter (25.9%) of patients were found to have a present CSP through follow-up imaging. The majority of which, 80.5%, had no other large anomalies present. Of those confirmed to have an absent CSP, the majority were detected in conjunction with other extracranial or intracranial abnormalities (63.9%). 10.1% of cases referred for an absent or possibly absent CSP were found to have an isolated, absent CSP either through subsequent ultrasound and/or MRI (Figure 1).

### *Prenatal Chart Review*

There were 101 patients found to have an absent CSP secondary to a structural brain abnormality or extracranial abnormality. The majority, 94 (93%), had intracranial abnormalities. Among the 94 patients with other structural brain abnormalities, the most common finding was a corpus callosum abnormality (27.7%), followed by a posterior fossa abnormality (24.5%) and holoprosencephaly (22.3%). (Table 1).

Table 1: Intracranial Anomalies Associated with an Absent CSP (n=94)

Variables	
Intracranial Anomalies n, (%)	
Corpus Callosum Abnormalities †	26 (27.7)
Posterior Fossa Abnormalities ‡	23 (24.5)
Holoprosencephaly	21 (22.3)
Ventriculomegaly >15mm §	7 (7.4)
Trisomy 18 Related Anomalies	7 (7.4)
Other ¶	5 (5.3)
Migration Disorder ¢	4 (4.3)
Turner Syndrome Related Anomalies	1 (1.1)

† includes colpocephaly cases, ‡ includes dandy Walker, cerebellar hypoplasia, cerebellar dysgenesis, vermian hypoplasia, rhombencephalosynapsis, mega cisterna magna § includes aqueductal stenosis

¶ schizencephaly, hemihydranencephaly, intraventricular and parenchymal hemorrhage, dolichocephaly/microcephaly, ¢ polymicrogyria

There were 43 patients who, in addition to an absent CSP, were found to have extracranial abnormalities (with and without other intracranial anomalies). In this cohort, the most common abnormalities included heart defects (41.8%), followed by skeletal defects (34.8%) and facial clefts (23.2%) (Table 2).

Table 2: Extracranial Anomalies Associated with an Absent CSP (N=43)

Variables	
Extracranial Anomalies, n (%)	
Heart Defects	18 (41.8)
Skeletal Defects†	15 (34.8)
Facial Cleft	10 (23.2)
Clubfeet/Rocker Bottom Feet	7(16.2)
Renal Anomaly‡	6 (13.9)
Congenital Diaphragmatic Hernia	3 (6.9)
Omphalocele/Gastroschisis	3 (6.9)
Ambiguous Genitalia	2 (4.6)
Lung Anomaly §	2 (4.6)
Sacroccygeal Teratoma	1(2.3)
Tracheoesophageal Fistula	1(2.3)
Encephalocele	1(2.3)
Features of Bardet Biedl Syndrome	1(2.3)

† includes short long bones, absent radii/ulnae, polydactyly, syndactyly, contractures, hypo mineralization of bones

‡ includes kidney agenesis, fusion of kidneys, large hyperechoic kidneys and duplicated collecting systems

§ includes lung agenesis and pulmonary hypoplasia

After an ultrasound and/or MRI at our institution, 16 patients (10.1%) were diagnosed with an isolated, absent CSP (Figure 1). Maternal and obstetric demographics for these patients are listed in Table 3.

Table 3: Maternal and Obstetric Demographics for Cases with a Prenatally Diagnosed Isolated, Absent CSP (n=16).

Variables	
Maternal Demographics, n (SD)	
Age	26.9 (5.7)
Height, cm	159.9(5.3)
Weight, kg †,	62.3 (13.0)
BMI †,	24.0 (4.5)
Race, n (%)	
Caucasian	8 (50.0)
African American	8 (50.0)
Ethnicity, n (%)	
Hispanic	8 (50.0)
Pregnancy Demographics, n (%)	
Male Fetus	13 (81.3)
Nulliparous	8 (50.0)
Singleton Pregnancy	16 (100.0)
Exposures to the Pregnancy, n (%) ‡	
Gestational Diabetes	0 (0)
Pregestational Diabetes	0 (0)
Chronic Hypertension	3 (23.1)
Prenatal Hypertension	1 (7.7)
Exposure to Drugs/Alcohol §	0 (0)

† among n=15, ‡ among n=13, § among n=14

Among the 16 patients in our prenatal isolated, absent cohort, six (37.5%) had bilateral or unilateral mild ventriculomegaly (< 15mm). Seven patients also underwent fetal MRI, none of which had an obvious optic nerve or pituitary abnormality, but one patient did have a pituitary gland that was not well-delineated. There were minor abnormalities identified in our prenatal isolated, absent cohort, including IUGR, oligohydramnios, oral cyst, thinned corpus callosum, enlarged cisterna magna, suprarenal cystic structure and slightly enlarged cerebral vermis (Table 4). With regard to prenatal genetic testing and screening, seven patients had negative non-invasive prenatal testing (NIPT), one patient had an amniocentesis and normal chromosome microarray (CMA), and two patients were found to have slightly elevated levels of msAFP (2.54 and 2.7 MoM).

Table 4: Prenatal Findings for Cases with a Prenatally Diagnosed Isolated, Absent CSP (N=16)

Variables		Comments
Prenatal Genetic Testing, n (%) †		
NIPT	7 (46)	Low risk
Other Prenatal Screen	4 (26.7)	msAFP (n=2), Quad (n=2)
Abnormal msAFP Screen	2 (13.3)	2.54, 2.7 MoM
Prenatal Diagnostic Testing	1 (.06)	Normal CMA
Gestational Age of Abnormal Ultrasound (weeks), mean (SD)	28.6 (4.4)	
Any Abnormalities on Initial Ultrasound, n (%) ‡	2(12.5)	
Prenatal Ventriculomegaly <15mm, n (%)	6 (37.5)	
Right Ventricle Size mm (N=4), mean (SD)	11.75 (1.87)	Range: 10-14.1
Left Ventricle Size mm(N=6), mean (SD)	11.63 (2.04)	Range: 9.4- 15
Fetal MRI, n (%)	7 (43.8)	
Obvious Optic Nerve Abnormality	0 (0)	
Pituitary Gland Ectopia	0 (0)	
Pituitary Gland Was Not Well Delineated	1 (14.3)	
Gestational Age of MRI (weeks), mean (SD)	28.4 (3.5)	
Other Minor Findings on Prenatal Imaging, n (%)		
IUGR	1 (.06)	
Echogenic Focus	1 (.06)	
Oligohydramnios	1 (.06)	
Oral Cyst	1 (.06)	
Thinned Corpus Collosum	1 (.06)	
Enlarged Cisterna Magna	1 (.06)	
Suprarenal Cystic Structure	1 (.06)	
Slightly Enlarged Cerebral Vermis	1 (.06)	

† among n=15, ‡ One patient was thought to have dolichocephaly, normal on MRI. The other patient was thought to have an abnormal pericallosal artery, normal on MRI

### Postnatal Chart Review

Postnatal clinical outcomes were available for ten patients, including developmental outcomes, imaging, endocrine and/or ophthalmological outcomes.

Prenatal and postnatal imaging data for those with a prenatally diagnosed isolated, absent CSP is described in Table 5.

Table 5: Prenatal and Postnatal Imaging Results for Cases with a Prenatally Diagnosed Isolated, Absent CSP (N=16)								
Case	Ultrasound Gestational Age (weeks+days)	Prenatal Ultrasound, Absent CSP	MRI Gestational Age (weeks+days)	Fetal MRI, Absent CSP	Slight Abnormalities on Prenatal Ultrasound or MRI	Postnatal MRI, Absent CSP	Concordant Postnatal Imaging	Comments
1	26+0	Yes	33+3	Yes	N/A	N/A	N/A	Agenesis of corpus callosum and absent CSP noted on postnatal MRI
2	33+3	Yes	N/A	N/A	N/A	Yes	No	
3	33+2	Yes	N/A	N/A	N/A	Yes†	Yes	† Postnatal imaging was collected verbally from the mother; type of postnatal imaging is unknown. Small PDA noted at delivery
4	23+3	Yes	25+4	Yes	Cerebral Vermis Slightly Enlarged	Yes	Yes	
5	25+3	Yes	26+1	Yes	N/A	N/A	N/A	
6	25+2	Yes	31+0	Yes	Thinned corpus callosum and Suprarenal Cystic Structure	Yes	Yes	
7	19+2	Yes	23+3	Yes	Oligohydramnios, Echogenic focus	N/A	N/A	
8	27+6	Yes	29+0	Yes	Oral Cyst	N/A	N/A	
9	26+3	Yes	N/A	N/A	N/A	N/A	N/A	
10	30+0	Yes	N/A	N/A	N/A	No	No	CSP visualized on postnatal



								MRI. Diminutive optic nerves noted on postnatal MRI. No endocrine abnormalities
11	28+2	Yes	N/A	N/A	N/A	N/A	N/A	
12	28+2	Yes	N/A	N/A	N/A	N/A	N/A	
13	28+5	Yes	30+3	Yes	N/A	Yes	Yes	
14	33+0	Yes	N/A	N/A	IUGR	Yes	Yes	
15	35+1	Yes	N/A	N/A	Enlarged Cisterna Magna	N/A	N/A	
16	34+1	Yes‡	N/A	N/A	N/A	N/A	N/A	‡suspected absent

Five of the patients were lost due to lack of follow-up at our institution and one was lost to fetal death unrelated to the absent CSP. Of the ten patients in which clinical outcomes were available, seven had a postnatal MRI/imaging after delivery. For six of the seven patients, the imaging was available for review. For one patient, postnatal imaging was reported from the mother (case 3). Five patients were confirmed to have an isolated, absent CSP via postnatal imaging. One patient, however, was found to have agenesis of the corpus callosum in conjunction with an absent CSP on postnatal MRI (case 2). Another patient was found to have a present CSP on postnatal MRI (case 10). This same patient was also found to have diminutive optic nerves (Table 5). One patient with an isolated, absent CSP confirmed through postnatal MRI was also given a diagnosis of SOD, meeting two of the three diagnostic criteria: absent CSP and optic nerve hypoplasia (case 6). Lastly, one patient was suspected to have a SOD diagnosis given the presence of hypernatremia syndrome and strabismus postnatally (case 1). However, a formal SOD evaluation was not performed (Table 6).

Development assessments were available for the eight patients with either an isolated, absent CSP or SOD diagnosis (suspected or confirmed). The mean age of follow-up was 16.8 months. Developmental outcomes are described in Table 6. Five of the six patients who retained a diagnosis of an isolated, absent CSP had some sort of

follow-up was 16.8 months. Developmental outcomes are described in Table 6. Five of the six patients who retained a diagnosis of an isolated, absent CSP had some sort of developmental delay ranging from mild delays to global development delay. Two patients had episodes concerning for seizures (case 13 and 14), however, a formal neurology work-up has not yet been performed. Lastly, one patient was reported to have behavioral issues (case 4).

Table 6: Developmental and Clinical Outcomes for Cases with a Postnatal Diagnosis of an Isolated, Absent CSP (N=14)												
Case	Outcome	Genetic Testing	GA at Birth	Birth weight, %	Eye Exam at Birth	Abnormal Endocrine Testing	NICU Admission	No. of days in NICU	Feeding Issues	Seizures	Diagnosis of SOD	Clinical Outcome
1	Live Birth	Normal CMA	38+0	44th	N/A	N/A	No	N/A	No	No	Suspected	Meeting all of his developmental milestones as of 2 months. Strabismus in right eye and hypernatremia syndrome were noted. In addition, microcephaly and spasticity were appreciated on exam. Global developmental delay. In occupational, speech, physical, and developmental therapy. Had CPAP for 2 days in NICU. †reported by mother
3	Live Birth	N/A	41+0	67th	Normal†	Normal†	Yes	4	No	No	No	
4	Live Birth	N/A	39+5	55th	Normal	Normal	Yes	7	No	No	No	
5	Live Birth	N/A	37+0	25th	N/A	N/A	No	N/A	No	No	No	Fine motor delay, speech delay, and behavioral problems like hitting. An autism spectrum diagnosis has been ruled out for this patient.
6	Live Birth	N/A	38+2	49th	Optic nerve hypoplasia, bilaterally	Normal	Yes	7	No	No	Yes	Normal development as of 12-month follow-up
7	Fetal Death	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	Live Birth	Normal prenatal CMA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No postnatal data
9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No postnatal data
11	Live Birth	N/A	42+0	30th	N/A	N/A	No	N/A	No	No	No	Normal development
12	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No postnatal data
Abnormal CMA: Mother reports a CNV in chromosome 13, report unavailable												
13	Live Birth	38+5	29th	Normal	Normal	Normal	Yes	12	No	New possible new starting spells	No	Mild motor delays. Currently in physical therapy
Abnormal movements concerning for possible seizure activity starting at 15 months												
Normal CMA, WES, and Fragile X												
14	Live Birth	39+2	4th	Normal	Normal	Normal	Yes	5	No		No	Motor and speech delays. Patient is in ECI getting both developmental therapy and physical therapy.
15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Slight dysmorphic features present.
16	Live Birth	N/A	39+2	34th	N/A	N/A	No	N/A	No	N/A	N/A	No postnatal data

## **Discussion**

With advancements in prenatal ultrasound and fetal MRI technology, an absent CSP that occurs in isolation of other anomalies is becoming a more frequent prenatally identified finding<sup>5,7</sup>. Yet little is known about the outcomes associated with it, posing significant challenges for clinicians and patients.

We present a single institutional experience of 158 pregnancies who were referred for a suspected absent or absent CSP, 16 of which were isolated.

### *Septo-Optic Dysplasia*

Our study found that of those with concordant postnatal imaging or no postnatal imaging, 12.5% (1/8) received a diagnosis of SOD. This patient had an absent CSP and optic nerve hypoplasia but did not have endocrine abnormalities by 12 months of age (case 6). However, another patient in our cohort has a suspected diagnosis of SOD as strabismus and hypernatremia syndrome were noted postnatally (case 1). This patient had a fetal MRI but received no postnatal imaging at our institution or an ophthalmology / endocrinology evaluation. This patient was lost to follow-up at 2 months. Therefore, those that receive a postnatal SOD diagnosis may be as high as 25% in our cohort (2/8). Similar to other studies, we found that a majority of those with a prenatally diagnosed isolated, absent CSP retained a diagnosis postnatally (Table 7).

<b>Table 7: Summary of Outcomes from Studies of an Isolated, Absent CSP</b>			
Studies	SOD diagnosis, % (n/N)	Normal Development in Isolated Cases without a SOD diagnosis, % (n/N)	Type of Delays Seen
Lepinard et al. <sup>8</sup>	50 (1/2)	100 (1/1)	N/A
Malinger et al. <sup>9</sup>	0 (0/16)	93.75 (15/16)	Motor and language delay
Damaj et al. <sup>7</sup>	17.6 (3/17)	64.7(11/14)	Behavioral problems, language delay, and visuo-spatial dyspraxia

Pilliod et al. <sup>1</sup>	25 (2/8)	83.3 (5/6)	Mild gross motor delays
Vawter-Lee et al. <sup>6</sup>	25(2/8)	83.3 (5/6)	Mild speech and gross motor delay
Shinar et al. <sup>4</sup>	27.8 (5/12)	100 (4/4)	N/A
Present	12.5 (1/8)	16.7(1/6)	Delays ranging from global developmental delay to mild language and motor delay

Our cohort had seven patients with a fetal MRI that confirmed a prenatal diagnosis of an isolated, absent CSP. For all seven, there was no clinical suspicion of a SOD diagnosis prenatally, beyond an absent CSP. One patient had a pituitary gland that was not well-delineated, though postnatal outcomes regarding this patient are unknown (case 7). For our one patient with a clinical diagnosis of SOD, optic nerve hypoplasia was not appreciated on fetal MRI. In line with previous studies, our study suggests that a postnatal evaluation is needed to confirm a diagnosis of SOD and visualization of the optic nerve and/or pituitary gland on fetal MRI is not predictive of a SOD diagnosis.

Similar to recommendations proposed by Vawter et al., the delivery of a child with a prenatally diagnosed isolated, absent CSP should take place at an institution where a postnatal SOD evaluation can be promptly conducted, whether after delivery or in the newborn setting.<sup>6</sup> A postnatal SOD evaluation should include a brain MRI to assess for midline brain defects, optic nerve hypoplasia, and pituitary size. In addition, an evaluation by ophthalmology and endocrinology is needed for the assessment of clinical features associated with SOD. This evaluation is critical in order for patients to receive the correct diagnosis and medical management.

### *Developmental Outcomes*

Unlike other studies that demonstrated reassuring developmental outcomes in their isolated cohorts, developmental delay was associated with our patients who retained a diagnosis of an isolated, absent CSP postnatally. Excluding those with a SOD or suspected SOD diagnosis, five out of six (83.3%) of our patients with an isolated, absent CSP exhibited some level of delay, ranging from global developmental delay to mild motor and language delay (Table 7). One patient also exhibited behavioral problems (case 4). This discrepancy may be due to several factors including limited sample sizes, selection bias for those who received follow-up care, lack of long-term follow-up for this patient population, and the use of non-validated measures for the assessment of development. It may also be attributable to the fact that not all of our patients had a postnatal brain MRI or standardized postnatal SOD evaluation.

Similar to this study, Pillard et al. also experienced a lack of follow-up for their cohort, having postnatal data for eight of fifteen patients. Comparably, postnatal developmental outcomes were collected in a non-standardized fashion and the mean age of follow-up was 16.9 months. However, their study found that most patients who retained a diagnosis of an isolated, absent CSP postnatally had normal outcomes with only a minority of patients exhibiting mild delays<sup>1</sup>. Studies by Vawter et al., Shinar et al., and Damaj et al., conversely, had postnatal outcomes for a majority, if not all, of their cohort with a prenatally diagnosed isolated, absent CSP<sup>4,6,7</sup>. However, their ability to obtain postnatal outcomes can be partially attributed to differences in inclusion criteria. For example, Vawter et al. only included patients in which postnatal outcomes were available<sup>6</sup>. These studies also had a more standardized approach to obtain postnatal outcomes. Vawter et al. used Ages and Stages Questionnaire (ASQ) and Parents' Evaluation of Developmental Status (PEDS) when assessing development and Shinar et al. reports using standardized developmental tests<sup>4,6</sup>. Furthermore,

Damaj et al. collected developmental outcomes with a questionnaire sent to the physician monitoring the child<sup>7</sup>. Again, these studies showed reassuring neurodevelopmental outcomes for a majority of patients.

Though there are some discrepancies in this study when compared to others, both this study and others observed children with an isolated, absent CSP having developmental delays. Because an isolated, absent CSP may increase the risk for developmental delay, primary care providers and parents should monitor development for these children and refer to therapies when appropriate.

#### *Discordant Imaging and Imaging Recommendations*

Of the ten patients for which postnatal outcomes were available, seven had postnatal brain imaging performed. In contrast to other studies, we found that 28.6% of patients (2/7) with a prenatally diagnosed isolated, absent CSP had discordant postnatal imaging. One was found to have agenesis of the corpus callosum in conjunction with an absent CSP. The other patient's CSP was visualized. Neither patient had fetal MRI. This discordance differs from Vawter-Lee et al. and Damaj et al., who did not report any cases of discordant prenatal and postnatal imaging within their cohort.<sup>6,7</sup> Pillard et al. found that during postnatal imaging, 12.5% (n=1) of their cohort had discordant imaging. For their discordant case, postnatal imaging by ultrasound suggested an intact CSP with cavum et vergae, though this case was complicated by prematurity. The number of cases with discordant postnatal imaging may be higher in our cohort since not all cases had a fetal MRI (n=9). This differs from previous studies, where most, if not all, patients underwent a fetal MRI. The lack of fetal MRIs in our cohort can be partially attributed to insufficient insurance coverage. Because fetal MRIs may be more sensitive than ultrasounds in diagnosing an absent CSP, they should be

considered by providers if available. Similarly, insurance companies may want to consider expanding coverage for the use of fetal MRIs for this indication. If only a prenatal ultrasound is used to confirm an isolated, absent CSP, there may be a greater chance for discordant postnatal imaging.

In addition, approximately one quarter of patients referred to our institution for evaluation of an absent CSP or suspected absent CSP identified on ultrasound were found to have a present CSP. If an absent CSP is identified, many patients will be found to have a present CSP on follow-up imaging if referred to a specialized center for evaluation. Patients should thus be counseled on the likelihood of this outcome.

Lastly, while a postnatal MRI is recommended when an isolated, absent CSP is observed prenatally, both insufficient insurance coverage and limited institutional resources may be prohibitive. In this case, despite its limitations, a postnatal head ultrasound may be considered in the newborn period to confirm the presence of an isolated, absent CSP.

### *Prenatal Counseling*

Prenatal counseling for pregnancies with an isolated, absent CSP remains challenging due to the variability and uncertainty in postnatal outcomes that surround this diagnosis. Pregnancies identified to have an isolated, absent CSP are at an increased risk for SOD and developmental delays. Developmental delays may vary in both severity and the type of delay exhibited. This study did not identify any prenatal findings that would predict likely postnatal outcomes when a pregnancy is observed to have an isolated, absent CSP. Therefore, patients should be counseled on all possible clinical outcomes that may arise in the postnatal setting. This includes the phenotypic variability observed in those diagnosed with SOD, the possibility and scope of



developmental delay for those with an isolated, absent CSP, and the chance for normal development. Given the uncertainty and variability surrounding postnatal outcomes for this cohort, patients may experience a wide range of psychosocial issues ranging from hopelessness, guilt, and frustration<sup>10</sup>. Clinicians may want to focus on managing uncertainty for these patients by having discussions that form a strong patient-clinician relationship which can foster shared-decision making<sup>11</sup>. Furthermore, providing written information regarding the scope of postnatal outcomes may be a useful resource for patients. Focusing on managing patient's uncertainty may ultimately help patients better understand the wide range of possible postnatal results and cope with the associated psychosocial effects.

### *Limitations and Future Directions*

While this study adds to limited information available on outcomes associated with a prenatally diagnosed isolated, absent CSP, it does have some limitations to consider. First, incomplete medical records and lack of follow-up at our institution precluded the reporting of outcomes for all patients in our cohort. Second, not all patients in our study had postnatal imaging. Lastly, short term developmental outcomes for these patients were assessed using medical records and parental reports, which are not validated measures.

Future prospective studies looking at the long-term developmental outcomes of this patient population are needed. In addition, a more robust study looking at the utility of fetal MRI in predicting SOD diagnoses could potentially improve the ability of clinicians to counsel patients more effectively. Lastly, a paper by Falco et al. suggests using a transvaginal ultrasound for evaluation of an abnormal CSP<sup>12</sup>. Further prospective studies analyzing the detection rate of an isolated, absent CSP using both

sonography methods should be considered given that insurance issues may limit access to a fetal MRI.

### **Conclusion**

An isolated, absent CSP is a rare prenatal finding. Counseling and management for these patients remains difficult due to limited outcome data on these pregnancies. Our study found that a prenatally identified isolated, absent CSP is clinically significant as it is associated with an increased risk for SOD and developmental delays. Furthermore, our data suggests that fetal MRIs may be more sensitive in diagnosing a prenatally suspected isolated, absent CSP. However, fetal MRIs are not fully accurate in predicting who may receive a SOD diagnosis, underscoring the importance of a postnatal SOD evaluation. A SOD evaluation should include a brain MRI and evaluation by both endocrinology and ophthalmology. Postnatally, a majority of patients with a prenatally diagnosed isolated, absent CSP will retain a diagnosis. Those who do may be at risk for developmental delay, emphasizing developmental monitoring for these patients.

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## Vita

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