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Research Paper

Isolated Absent Septum Pellucidum: A Retrospective Study of Fetal Diagnosis and Postnatal Outcomes

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ABSTRACT

Background: Absent septum pellucidum (ASP) is a brain abnormality often associated with neuroanatomic abnormalities including septo-optic dysplasia (SOD). We aimed to determine how frequently prenatally diagnosed isolated ASP is confirmed by postnatal imaging and to examine clinical outcomes for ASP.

Methods: This was a retrospective study of maternal-fetal dyads referred to Children's National Hospital from January 1, 2012, to June 30, 2019. We included cases with fetal diagnosis of isolated or complex ASP. Diagnosis was based on ASP and the presence or absence of additional neuroanatomic findings. Data included obstetric and birth history, genetic testing, imaging, and neurodevelopmental outcomes.

Results: ASP was diagnosed in 35 fetuses. Of 17 fetuses with isolated ASP, 10 had postnatal evaluation. In five (50%) isolated ASP cases, postnatal imaging revealed additional brain abnormalities. The five children with postnatally confirmed isolated ASP had lower rates of hydrocephalus (0% vs 54%) and abnormal feeding (0% vs 20%), hearing (0% vs 14%), and vision (0% vs 14%) than those with complex ASP (n = 17). Children with isolated ASP had lower rates of developmental delay (33% vs 50%) and seizures (11% vs 30%) than children with complex ASP. One child with prenatal isolated ASP was diagnosed with SOD (10%).

Conclusions: Few children with prenatally diagnosed isolated ASP had SOD diagnosed postnatally. Overall, children with isolated ASP demonstrate better outcomes than children with complex ASP. Fetal magnetic resonance imaging is a useful tool to evaluate the septum pellucidum and may reveal additional abnormalities that can impact prognosis and affect prenatal counseling.

Introduction

Absent septum pellucidum (ASP) is a midline brain abnormality that can be detected on prenatal ultrasound (US). ASP occurs in two to three per 100,000 children postnatally.[1] The septum pellucidum begins to form at 10 to 12 weeks gestational age (GA) and is fully developed by 17 weeks GA, around the same time as the corpus callosum is completing development.[2] The septum pellucidum is composed of white matter along the medial walls of the lateral ventricle and is lined by ependyma along the ventricular surface[1] and contains glial cells, scattered neurons, fiber bundles, and veins that connect to the choroid plexus.[2] The septum pellucidum likely serves as a relay station with the hippocampus and the hypothalamus,[2] thus serving an important function of the limbic system.

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Evaluation of the septum pellucidum at the second trimester fetal anatomy US is recommended by the American College of Obstetricians and Gynecologists, the American College of Radiology, and the American Institute of Ultrasound in Medicine.[3] According to the American College of Obstetricians and Gynecologists, detection of a septum pellucidum abnormality warrants further evaluation[3] and is a common reason for referral to a maternal-fetal medicine (MFM) specialist. When the septum pellucidum is absent on prenatal US, parents are counseled on the risk of septo-optic dysplasia (SOD), a condition consisting of some combination of optic nerve hypoplasia, pituitary dysfunction, and midline brain malformations.[4] ASP can be associated with other abnormalities, including schizencephaly, Chiari II malformation, holoprosencephaly, encephalocele, agenesis of the corpus callosum (ACC), porencephaly, and hydranencephaly, and can occur in isolation.[5] Recent studies have suggested that absence or abnormality of the septum pellucidum may be associated with psychiatric illnesses including schizophrenia and bipolar disorder.[6,7] Given the risk of other central nervous system (CNS) abnormalities with ASP, evaluation by fetal magnetic resonance imaging (feMRI) can help prognostication and prenatal counseling. However, the actual rate of isolated ASP without concomitant brain malformation is not well described in the literature and the neurodevelopmental outcomes are largely extrapolated from small sample sizes. Studies have indicated that isolated ASP carries a low risk of developmental delay ranging from 0% to 20%.[5,8-11] However, few studies have investigated the rate of neurological abnormalities including seizures or abnormal tone in cases of postnatally confirmed isolated ASP.

The Prenatal Pediatrics Institute (PPI) at Children's National Hospital (CNH) is an established tertiary referral center in Washington, DC, for feMRI and pediatric subspecialty consultations including fetal neurology consultation. In this study, we aimed to (1) describe the spectrum of fetal brain MRI abnormalities for patients prenatally referred for suspected ASP, (2) determine the frequency of postnatal confirmation of fetally diagnosed isolated ASP, and (3) expand knowledge of prenatal and postnatal outcomes associated with isolated and complex ASP to improve prenatal neurology counseling to families.

Methods

We performed a retrospective chart review of maternal-fetal dyads who were referred to the PPI at CNH in Washington, DC, from January 1, 2012, to June 30, 2019, with a referral diagnosis of corpus callosum or septum pellucidum abnormality, completed feMRI at CNH, and a prenatal neurological consultation. Referral diagnoses were based on outside fetal US findings by the referring providers (MFM specialist or obstetrician); fetal cases included had maternal prenatal referral diagnoses of ASP or abnormal septum pellucidum or suspected abnormality of the corpus callosum (i.e., agenesis, dysplasia, or hypoplasia). Suspected abnormalities of the corpus callosum may be seen by prenatal US in cases of ASP and other midline abnormalities. Patients were excluded from the study if they did not have a confirmed septum pellucidum abnormality on prenatal imaging at CNH. Fetal cases with the finding of ACC were excluded. In the case of a multiparous pregnancy, only the fetus with an ASP was included. Postnatally, the infants were included. The study was approved by the CNH Institutional Review Board. The study received a waiver of informed consent.

Medical record data were collected from the electronic medical record system (Cerner) and the PPI patient database (MADAMS). Maternal data included past and present medical history; obstetric, social, and relevant family history; results of prenatal tests; feMRI and US reports; and pregnancy outcome. According to an internal clinical protocol, pregnant patients referred for an feMRI undergo an obstetric US on the same day as feMRI and fetal neurology consultation. Diagnosis of the septum pellucidum abnormality was based on feMRI findings in combination with US. feMRI brain findings were reported by one of four experienced pediatric neuroradiologists. Infant data included brain imaging results, results of genetic testing, details from postnatal evaluations, and placental pathology. Pre- and postnatal imaging studies were reviewed when needed to compare with imaging reports. Deidentified data were entered into a REDCap database.[12]

The maternal-fetal dyads were divided into two groups (Fig) based on feMRI findings. The *prenatal isolated ASP* group included fetuses found to have ASP or abnormality of the septum pellucidum without any other CNS abnormalities on feMRI, with the exception of mild to moderate ventriculomegaly; isolated ASP can be associated with squaring off of the frontal horns of the lateral ventricles and caudal displacement of the fornix, which can lead to the appearance of ventriculomegaly.[13] The *prenatal complex ASP* group included fetuses found to have one or more CNS abnormalities in addition to absence or abnormality of the septum pellucidum on feMRI. Postnatally, infants were grouped by postnatal brain MRI findings. The *postnatal isolated ASP* group included infants with ASP without other CNS abnormalities. The *postnatal complex ASP* group included infants found to have one or more CNS abnormalities in addition to ASP on brain MRI.

Statistical analysis was performed using Microsoft Excel to evaluate correlations between obstetric risk factors, imaging findings, and neonatal outcomes. Continuous data were calculated as mean and S.D.; two-tailed t test was used to calculate P values. Categorical data were calculated as count and percent; χ^2 test was used to calculate P values. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Between January 1, 2012, and June 30, 2019, 35 maternal-fetal dyads were evaluated at the PPI at a mean ± S.D. of 26.7 ± 4.7 weeks' gestation with feMRI and fetal neurology consultation and were included in this study (Table 1, Figure). The mean maternal age was 27.0 ± 6.4 years. In 16 cases (46%), the mother was a primigravida. There were two twin pregnancies in the cohort, each with one affected fetus. One (3%) pregnancy was conceived with reproductive assistance.

Prenatal evaluations

Seventeen maternal-fetal dyads (49%) were classified as *prenatal isolated ASP* and 18 (51%) were classified as *prenatal complex ASP* after evaluation by feMRI. In the prenatal complex ASP group, a variety of additional brain findings were identified on feMRI including microcephaly, Dandy-Walker malformation, polymicrogyria, schizencephaly, cerebellar hypoplasia, gray matter heterotopias, and moderate to severe ventriculomegaly. There was no difference in maternal age or GA at feMRI between the groups with isolated ASP and complex ASP. Twenty-one (60%) pregnancies were evaluated with prenatal screening or genetic testing (Table 2). Of the five fetal cases with abnormal prenatal genetic testing, one case was lost to follow-up and one pregnancy resulted in an intrauterine demise. The remaining three cases had prenatal genetic screening concerning for possible trisomy 21; none of the infants had confirmatory postnatal testing due to low postnatal concern for trisomy 21. The prenatal complex ASP group had a higher rate of abnormal prenatal screening or testing (40%) compared with the

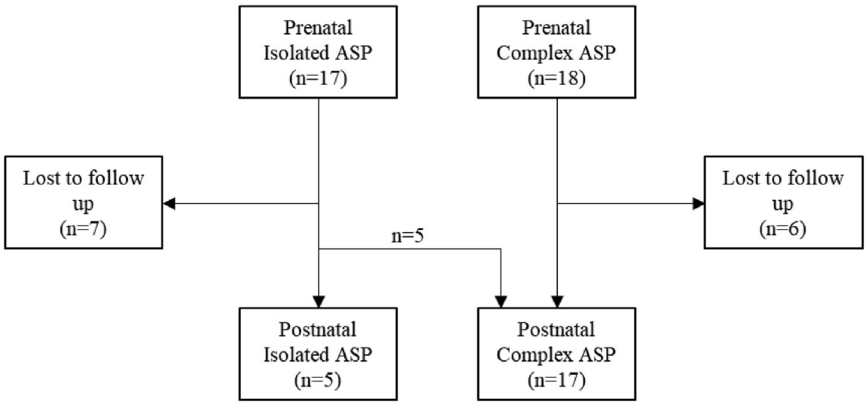

FIGURE. Classification of isolated versus complex ASP by pre- and postnatal imaging. ASP, absent septum pellucidum.

prenatal isolated ASP group (9%) ($P = 0.10$) (Table 2). Both prenatal groups had similar pregnancy outcomes with one termination and one intrauterine demise in each group.

Postnatal evaluations

Twenty-two of 33 (67%) live-born infants had some form of follow-up at CNH (Table 3). The mean duration of postnatal follow-up from the first to the most recent visit was 520 ± 515 days, with a follow-up range of age 0 to 1907 days. Many infants (70%, 14 of 20) had three or more postnatal assessments by any pediatric specialty at CNH, including neurology, developmental pediatrics, endocrinology, ophthalmology, and genetics. The mean age at first postnatal imaging was 45.6 ± 87.4 days. Twenty infants had at least one postnatal brain MRI; two infants only a head US.

Of the 17 maternal-fetal dyads with prenatal isolated ASP, birth data were reported for 10 infants (59%); of the 18 maternal-fetal dyads with prenatal complex ASP, birth data were reported for 12 infants (67%) (Table 4). There was no difference in GA at birth, APGAR scores, delivery complications, or rates of admission to the neonatal intensive care unit (NICU) between the two groups. Ten infants in each group were evaluated at CNH at least once after delivery. Two infants had only postnatal imaging, but no neurological or developmental evaluations. The first postnatal brain imaging was earlier in the prenatal complex ASP group compared with the isolated ASP group (20 ± 12 days vs 80 ± 125 days, $P = 0.21$). When comparing neurological examination findings between groups, the prenatal complex ASP group had higher rates of dysmorphism, altered mental status, abnormal extraocular movements, abnormal facial movements, and abnormal tone at any postnatal assessment; however, only increased rate of dysmorphism in the prenatal complex ASP group (10% vs 50%) was found to be significantly different. Infants diagnosed prenatally with complex ASP had higher rates of developmental delay, fine motor delay, abnormal feeding, abnormal hearing, and seizures.

Postnatally, five of 10 (50%) infants with prenatal isolated ASP were confirmed to have isolated ASP on brain MRI. The other five infants suspected to have an isolated ASP prenatally were found to have an additional brain abnormality on postnatal brain MRI and were reclassified to the postnatal complex ASP group (Fig, n = 17). Additional brain findings identified on postnatal brain MRI, not seen on feMRI included hippocampal dysplasia, infundibular/optic chiasm cyst, optic pathway hypoplasia, pontine and cerebellar hypoplasia, and moderate ventriculomegaly. Only one infant with prenatal isolated ASP was found to have SOD (10%).

All five infants with postnatal isolated ASP had at least one assessment at CNH after delivery. Infants with complex ASP were more likely to have an abnormal neurological examination at any visit (73% vs 20%, $P = 0.04$) (Table 5). Eight of the 20 (40%) infants followed, including those with isolated and complex ASP, had developmental delay (Table 6). Only infants with postnatal complex ASP developed hydrocephalus. A genetic diagnosis was found after delivery in two infants (14%) in the postnatal complex ASP group (Table 6); diagnoses included FOXG1 syndrome and 7p22.20-p21.3 deletion, both diagnosed by chromosomal microarray. Both infants

TABLE 1.
Prenatal Data Classified by ASP Type

Prenatal Data	Prenatal Isolated ASP (n = 17)	Prenatal Complex ASP (n = 18)	*P* Value	Postnatal Isolated ASP (n = 5)	Postnatal Complex ASP (n = 17)	*P* Value	Total (n = 35)
Maternal age at first visit, years (mean ± S.D.)	27 ± 6	27 ± 7	0.80	25 ± 5	27 ± 5	0.18	27 ± 6
Gravida, % (n)							
G = 1	41 (7)	50 (9)	0.60	20 (1)	41 (7)	0.39	46 (16)
G ≥ 2	59 (10)	50 (9)		80 (4)	59 (10)		54 (19)
Para, % (n)							
P = 0	71 (12)	56 (10)	0.36	80 (4)	53 (9)	0.83	63 (22)
P ≥ 1	29 (5)	44 (8)		20 (1)	47 (8)		37 (13)
Gestational age at first visit, weeks (mean ± S.D.)	25 ± 4	28 ± 5	0.07	25 ± 4	27 ± 5	0.34	27 ± 5
Multiple gestation, % (n)	6 (1)	6 (1)	0.97	0 (0)	12 (2)	0.42	6 (2)
Reproductive assistance, % (n)	6 (1)	0 (0)	0.30	0 (0)	6 (1)	0.58	3 (1)

Abbreviation:
ASP = Absent septum pellucidum
P values calculated by two-tailed *t* test for continuous variables. *P* values calculated by χ^2 test for categorical variables.

TABLE 2.
Prenatal Testing Data Classified by ASP Type

Prenatal Testing	Prenatal Isolated ASP (n = 17)	Prenatal Complex ASP (n = 18)	*P* Value	Postnatal Isolated ASP (n = 5)	Postnatal Complex ASP (n = 17)	*P* Value	Total (n = 35)
Prenatal genetic testing, % yes, (n)	65 (11)	56 (10)	0.58	80 (4)	59 (10)	0.39	60 (21)
Abnormal testing, % (n)	9 (1)	40 (4)	0.10	25 (1)	20 (2)	0.84	24 (5)
By first trimester screening,* % (n)	9 (1)	10 (1)	0.94	25 (1)	10 (1)	0.47	10 (2)
By second trimester screening,† % (n)	0 (0)	20 (2)	0.12	0 (0)	10 (1)	0.51	10 (2)
By NIPT/cfDNA,‡ % (n)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	0 (0)
By amniocentesis or microarray, % (n)	0 (0)	10 (1)	0.28	0 (0)	0 (0)	-	5 (1)

Abbreviations:
AFP = Alpha-fetoprotein
ASP = Absent septum pellucidum
cfDNA = Cell-free DNA
DIA = Dimeric inhibin A
hCG = Human chorionic gonadotropin
NIPT = Noninvasive prenatal testing
PAPP-A = Pregnancy-associated plasma protein-A
uE3 = Unconjugated estriol
P values calculated by χ^2 test for categorical variables.
* First-trimester screening: measurement of PAPP-A and hCG in maternal serum in combination with an ultrasound to measure nuchal translucency; assesses for the risk of trisomy 18 and 21.[14]
† Second-trimester screening (also known as quadruple test or quad screen): measurement of AFP, uE3, hCG, and DIA in maternal serum; assesses for the risk of trisomy 18 and 21, spina bifida, and abdominal wall defects.[14]
‡ cfDNA: examines DNA released from the placenta into the maternal bloodstream and assesses for the risk of trisomy 13, 18, and 21 and sex chromosome aneuploidies.[14]

had additional medical comorbidities apparent on prenatal imaging and after delivery.

Discussion

In this single-center retrospective study, we found differences in neurodevelopment between infants with isolated and complex forms of ASP. Notably, there was a low rate of postnatal diagnosis of SOD in our cohort of infants with prenatal isolated ASP, which is important given that this outcome is often discussed as a major risk for this finding in prenatal counseling. However, we found that SOD is actually fairly uncommon compared with developmental delay and other neurological abnormalities that infants with isolated or complex ASP may have.

Although our study has an overall small number of cases with ASP, it is one of the largest to compare prenatally diagnosed isolated ASP with complex ASP and correlate with postnatal imaging confirmation and infant follow-up. Other studies have focused on SOD as the main postnatal diagnosis; our study broadens the spectrum of neuroanatomic and neurodevelopmental abnormalities that are associated with ASP, beginning with findings from the prenatal period.

ASP occurs either from agenesis associated with abnormal midline development or is acquired because of hydrocephalus or other *in utero* cerebral injury. As a result, many cases of ASP are associated with other underlying brain malformations, including schizencephaly, holoprosencephaly, ACC, and ventriculomegaly.[13] Nevertheless, ASP can be seen on US or on feMRI as an isolated finding. However, it is difficult to accurately evaluate the optic nerves on US or feMRI,[15,16] so the primary differential for isolated ASP on prenatal imaging includes SOD, a syndrome characterized by optic nerve hypoplasia, pituitary gland dysfunction, and ASP.[1,17] Two of the three classic features are needed to make a definitive diagnosis of SOD.[4] Current literature suggests that the rate of postnatal diagnosis of SOD ranges from 18% to 67%.[8-11,18,19] Postnatal brain MRI is therefore a helpful tool to distinguish isolated ASP from ASP with SOD.

We report a lower rate of postnatal diagnosis of SOD in our cohort compared with similar studies.[8-11,18,19] Given SOD is a main concern when isolated ASP is seen on prenatal imaging, our

TABLE 3.
Postnatal Follow-Up Classified by ASP Type

Follow-up Data	Prenatal Isolated ASP (n = 10)	Prenatal Complex ASP (n = 12)	*P* Value	Postnatal Isolated ASP (n = 5)	Postnatal Complex ASP (n = 17)	*P* Value	Total (n = 22)
# of fetal cases with postnatal assessment, n	10	10		5	15		20
1 Assessment, % (n)	20 (2)	0 (0)		20 (1)	7 (1)		10 (2)
2 Assessments, % (n)	20 (2)	20 (2)		40 (2)	13 (2)		20 (4)
3+ Assessments, % (n)	60 (6)	80 (8)		40 (2)	80 (12)		70 (14)
Age at first postnatal imaging, days (mean ± S.D.)	80 ± 125	20 ± 12	0.21	105 ± 144	32 ± 60	0.45	46 ± 87
Age at first postnatal assessment, days (mean ± S.D.)	440 ± 426	686 ± 563	0.31	581 ± 518	557 ± 513	0.94	563 ± 514
Days of follow-up from first visit to most recent, days (mean ± S.D.)	387 ± 418	653 ± 566	0.27	547 ± 514	511 ± 515	0.91	520 ± 515
Median	267	468		250	414		362
Range	[0, 1171]	[29, 1907]		[0, 1171]	[12, 1907]		[0, 1907]

Abbreviation:
ASP = Absent septum pellucidum
P values calculated by two-tailed *t* test for continuous variables.

TABLE 4.
Newborn Data Classified by ASP Type

Outcome	Prenatal Isolated ASP (n = 10)	Prenatal Complex ASP (n = 12)	*P* Value	Postnatal Isolated ASP (n = 5)	Postnatal Complex ASP (n = 17)	*P* Value	Total (n = 22)
Gender							
Male, % (n)	30 (3)	50 (6)	0.34	20 (1)	47 (8)	0.19	41 (9)
Female, % (n)	70 (7)	50 (6)		80 (4)	53 (9)		59 (13)
Gestational age at birth, weeks (mean ± S.D.)	38 ± 2	38 ± 3	0.98	39 ± 1	38 ± 2	0.15	38 ± 2
Birth weight, g (mean ± S.D.)	2951 ± 776	3329 ± 747	0.32	3269 ± 684	3108 ± 812	0.70	3150 ± 784
Birth head circumference (mean ± S.D.)	33 ± 3	37 ± 4	0.06	34 ± 2	35 ± 5	0.87	35 ± 4
Birth length (mean ± S.D.)	48 ± 4	51 ± 4	0.14	49 ± 3	49 ± 4	0.86	49 ± 4
APGAR score							
1 minute (mean ± S.D.)	8 ± 2	7 ± 2	0.45	8 ± 2	8 ± 1	0.97	8 ± 2
5 minute (mean ± S.D.)	9 ± 1	8 ± 1	0.67	8 ± 1	8 ± 1	0.93	8 ± 1
Delivery complications, % (n)	30 (3)	18 (2)	0.53	20 (1)	25 (4)	0.82	24 (5)
NICU stay, % (n)	30 (3)	36 (4)	0.76	20 (1)	38 (6)	0.47	33 (7)
Length of stay, days (mean ± S.D.)	16 ± 9	30 ± 39	0.57	7 ± 0	29 ± 35	-	25 ± 33

Abbreviations:
ASP = Absent septum pellucidum
NICU = Neonatal intensive care unit
P values calculated by two-tailed *t* test for continuous variables. *P* values calculated by χ^2 test for categorical variables.

findings could impact prenatal counseling given to families at MFM or prenatal pediatrics appointments. Patients may make pregnancy management decisions following discussion about concern for ASP and SOD. In most studies on isolated ASP, including ours, at least one pregnant woman elected to terminate her pregnancy. As such, accurate data on what has long been assumed to be the most serious outcome associated with prenatal isolated ASP are important for accurate prenatal counseling. feMRI can help to determine the presence of other important associated fetal brain findings that likely have a greater impact on neurological prognosis and that may indicate risk for a genetic syndrome.

Half of the infants presumed to have isolated ASP by prenatal imaging were postnatally found to have an additional CNS abnormality, highlighting the importance of postnatal brain MRI. Although feMRI has improved markedly in the last several years, some abnormalities in the fetal brain may still be too subtle to be seen prenatally or the GA of imaging may be too early to detect all relevant findings given the protracted duration of fetal brain development. In our cohort, the infants found to have an additional CNS abnormality had lower rates of developmental delay and seizures compared with their prenatally diagnosed complex ASP counterparts, although our results did not reach statistical significance likely due to the small sample size. Our findings raise the possibility that even when an additional CNS abnormality is found on postnatal MRI, prenatally diagnosed isolated ASP generally carries a good prognostic outcome. Given the differences seen in our cohort between infants with isolated and complex ASP, postnatal brain MRI is important to confirm the prenatal diagnosis, to provide more accurate prognostic information to families, and to guide further monitoring or evaluation.

Contrary to our hypothesis, infants with postnatal confirmed isolated ASP had similar rates of developmental delay, need for rehabilitative therapy, and seizures when compared with their complex ASP counterparts. Furthermore, we found a slightly higher rate of developmental delay than other studies. Previous studies found developmental delays in 0% to 20% of infants with isolated ASP,[5,8-11] whereas one-third of our cohort had speech, gross motor, or fine motor delays. These results do not seem to be impacted by prematurity—a common cause of developmental delay—as the groups were similar in mean birth GA. A 2019 study found the national rate of developmental disability in children in the United States to be approximately 17%[20]; however, the rate in our cohort was nearly double that. Only a portion of infants in our study had a documented Ages and Stages Questionnaire or other developmental screening tool. Developmental delay was either self-reported by parents or documented by a provider following physical examination. As a result, subtle developmental delays may have been missed in our data and reports may not be completely accurate. In addition, parents of children with developmental delays may have been more likely to follow-up at CNH. Our study did not control for socioeconomic factors such as family socioeconomic status, parental education, or income, all of which also contribute to child neurodevelopment.[20,21]

This study was notably limited by small sample size, but given the infrequency of this brain abnormality our study was larger than others on isolated ASP and contributes to our knowledge about this condition. Owing to the small sample size, differences were not

TABLE 5.
Physical Examination Findings Classified by ASP Type

Physical Examination Finding	Prenatal Isolated ASP (n = 10)	Prenatal Complex ASP (n = 10)	*P* Value	Postnatal Isolated ASP (n = 5)	Postnatal Complex ASP (n = 15)	*P* Value	Total (n = 20)
Dysmorphism, % (n)	10 (1)	50 (5)	0.05	0 (0)	40 (6)	0.09	30 (6)
Abnormal mental status, % (n)	0 (0)	20 (2)	0.14	0 (0)	13 (2)	0.39	15 (3)
Abnormal extraocular movements, % (n)	11 (1)	30 (3)	0.31	0 (0)	29 (4)	0.18	21 (4)
Abnormal facial movements, % (n)	0 (0)	10 (1)	0.30	0 (0)	7 (1)	0.55	5 (1)
Abnormal tone, % (n)	40 (4)	50 (5)	0.65	20 (1)	53 (8)	0.19	45 (9)

Abbreviation:
ASP = Absent septum pellucidum
Subjects classified as having a physical examination finding if identified at any postnatal assessment. *P* values calculated by χ^2 test for categorical variables.

TABLE 6.
Long-Term Outcomes Classified by ASP Type

Outcome	Prenatal Isolated ASP (n = 10)	Prenatal Complex ASP (n = 10)	*P* Value	Postnatal Isolated ASP (n = 5)	Postnatal Complex ASP (n = 15)	*P* Value	Total (n = 20)
Any delays, % (n)	33 (3)	50 (5)	0.46	40 (2)	43 (6)	0.91	40 (8)
Communication or language, % (n)	22 (2)	40 (4)	0.41	20 (1)	36 (5)	0.52	30 (6)
Gross motor, % (n)	22 (2)	40 (4)	0.41	20 (1)	36 (5)	0.52	30 (6)
Fine motor, % (n)	0 (0)	30 (3)	0.07	0 (0)	21 (3)	0.26	15 (3)
Required therapy (PT/OT/speech), % (n)	33 (3)	50 (5)	0.46	40 (2)	43 (6)	0.91	40 (8)
Abnormal feeding, % (n)	10 (1)	20 (2)	0.53	0 (0)	20 (3)	0.28	15 (3)
Abnormal hearing, % (n)	0 (1)	20 (2)	0.16	0 (0)	14 (2)	0.37	10 (2)
Abnormal vision, % (n)	11 (1)	10 (1)	0.94	0 (0)	14 (2)	0.37	10 (2)
Seizures, % (n)	11 (1)	30 (3)	0.31	20 (1)	21 (3)	0.96	20 (4)
Hydrocephalus, % (n)	30 (3)	50 (5)	0.36	0 (0)	53 (8)	0.04	40 (8)
Genetic diagnosis, % (n)	10 (1)	10 (1)	-	0 (0)	14 (2)	0.37	10 (2)

Abbreviations:
ASP = Absent septum pellucidum
OT = Occupational therapy
PT = Physical therapy
P values calculated by χ^2 test for categorical variables.

statistically significant regarding neurodevelopmental outcomes, although we did note some trends. Our data were derived from a single center and were limited by retrospective design. Multicenter registries and studies would enable a larger number of cases to be studied given the infrequency of this diagnosis, even in a large regional prenatal referral center such as the PPI at CNH. We also had a high percentage of cases that were lost to follow-up (36%); some of these infants were known to have been seen at other neurological practices in the Washington, DC, area not affiliated with CNH, but records were not available. In addition, children with normal development may be less likely to be seen after birth by pediatric specialists, which may contribute to the relatively higher rates of developmental delays among children for whom we have follow-up data. Since CNH is a free-standing children's hospital without a birthing center, we had diminished access to delivery and newborn data. Our data on outcome were limited by the wide age range of postnatal follow-up and by assessments documented by different pediatric subspecialty providers. Although certain outcomes evaluated in our study such as dysmorphism, abnormal tone, and abnormal feeding may be present in infancy, other outcomes such as developmental delay, abnormal hearing or vision, or seizures may develop and present throughout childhood. As such, incidence of these outcomes may have been underestimated in our study.

In addition to postnatal brain MRI, we recommend that all children with ASP have routine developmental screening given the increased risk of developmental delay seen in our cohort. We also recommend that children with ASP have a full developmental evaluation around age two years, when many delays may become apparent to ensure appropriate early intervention rehabilitative therapies. Given the risk of SOD, all children with isolated ASP should have a visual evaluation by an ophthalmologist after birth to rule out optic nerve abnormalities. Some infants in our cohort with isolated ASP were admitted to the NICU preemptively after birth for monitoring; however, given the low rate of immediate postnatal complications for most infants, NICU admission should be based on other factors and not solely on ASP. We do not recommend routine screening for non-neurologic comorbidities in this population unless other abnormalities are seen on US or feMRI. We offer prenatal genetic consultation and genetics follow-up after delivery to families referred to PPI for ASP; genetic testing, particularly given the increasing accessibility of exomic and genomic testing, may reveal other comorbidities in this population and illuminate directions for future research.

Our study shows that isolated ASP (whether isolated or complex postnatally) trended toward better neurodevelopmental outcomes than complex ASP. Notably, our data support a low rate of postnatal diagnosis of SOD in cases of isolated ASP than previously reported. Our study demonstrates that feMRI is important for providing prognosis in pregnancies in which ASP is suspected, especially given that fetal diagnosis can impact pregnancy decisions and find additional conditions of the fetal brain, but that postnatal brain MRI is still necessary.

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