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REVIEW ARTICLE

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Obliterated cavum septi pellucidi: is it always a benign finding? A case report and narrative review of the literature

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ABSTRACT

Objective: The septum pellucidum is a virtual cavity located at the anterior part of the brain midline, which only in fetal life has a certain amount of fluid inside. The presence of an obliterated cavum septi pellucidi (oCSP) in the prenatal period is poorly described in the literature but, nevertheless, it constitutes an important clinical dilemma for the fetal medicine specialist in terms of significance and prognosis. Moreover, its occurrence is increasing maybe because of the widespread of high-resolution ultrasound machine. The aim of this work is to review the available literature regarding the oCSP along with the description of a case-report of oCSP with an unexpected outcome.

Methods: A search of the literature through Pubmed was performed up to December 2022 with the aim to identify all cases of oCSP previously described, using as keywords "cavum septi pellucidi," "abnormal cavum septi pellucidi," "fetus," and "septum pellucidum." Along with the narrative review, we describe a case-report of oCSP.

Results: A 39 years old woman was diagnosed with a nuchal translucency between the 95° and 99° centile in the first trimester and an oCSP and "hookshaped" gallbladder at 20 weeks. Left polymicrogyria was found at fetal magnetic resonance imaging (MRI). Standard karyotype and chromosomal microarray analysis (CMA) were normal. After birth, the newborn presented signs of severe acidosis, untreatable seizures and multiorgan failure leading to death. A targeted gene analysis of the epilepsy panel revealed the presence of a *de novo* pathogenic variant involving the *PTEN* gene. The literature review identified four articles reporting on the oCSP of which three were case report and one was a case-series. The reported rate of associated cerebral findings is around 20% and the rate of adverse neurological outcome is around 6%, which is higher than the background risk of the general population.

Conclusions: This case-report and review of the literature shows that oCSP is a clinical entity poorly described so far and that, despite the generally good prognosis, it requires caution in counseling. The diagnostic work-up should include neurosonography while fetal MRI may be always indicated for non-isolated cases only, depending on local facilities. Targeted gene analysis or whole exome sequencing may be indicated for non-isolated cases.

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Cavum septi pellucidi; neurosonography; fetal MRI; targeted next generation sequencing; PTEN gene

Introduction

The cavum septi pellucidi (CSP) is an important landmark of the evaluation of the fetal brain anatomy and its normal appearance reassures the clinician about the regular brain development. Failure to visualize the CSP indicates a detailed evaluation of brain anatomy by neurosonography (NSG) to look for specific malformations like holoprosencephaly, agenesis of the corpus callosum and septo-optic dysplasia [1]. The management of an obliterated and hyperechoic CSP, defined as the absence of fluid inside it with consequent overlapping of the lamina and hyperechoic appearance, is still controversial if fetal brain anatomy looks otherwise normal. Recent published guidelines

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on fetal neurosonography and fetal MRI do not mention if the presence of oCSP is an indication to perform more in-depth examinations [1,2]. However, referrals of cases with an abnormal appearance of the CSP are increasing probably because of the spread of high-resolution ultrasound machines. Abnormalities of the anterior complex always alert the clinicians performing ultrasound as they can be a sign for more complex malformations, involving the cortex, the limbic system, or being the expression of subtle intraventricular hemorrhage [3]. However, because of the relatively recent description of this anatomical variant, there is a lack of guidance in the management and counseling.

Herein, we report a case-report of oCSP along with a narrative literature review with the aim of reporting an updated summary of the previously published evidence and exploring new insights on the clinical and prognostic significance of oSCP.

Materials and methods

Description of a case-report of oCSP with an unexpected postnatal outcome and literature search performed from inception until December 2022 in PubMed (Medline). For the purpose of the search, a combination of key terms was used which included "abnormal fetal cavum septi pellucidi", "non-visualization of fetal cavum septi pellucidi," "septum pellucidum," and "fetus." Full-text article only were included in the study.

Results

Case report

A 39-year-old woman was seen at 12 weeks of gestation for the routine first trimester chromosomal screening. She was at her fourth spontaneous pregnancy with a history of two miscarriages and one uneventful pregnancy. The family history was silent, and a possible consanguinity was denied. The nuchal translucency (NT) measured between the 95° and 99° centile with a resulting high risk for trisomy 21 (1:157). A chorionic villus sampling was performed showing a normal male karyotype (46, XY).

Due to the presence of a NT between the 95° and 99° centile, a detailed anomaly scan was performed at 20 weeks that highlighted an obliterated and hyperechoic CSP and a "hook-shaped" gallbladder (Figure 1). A fetal MRI was performed showing multiple small folds on the surface of the left frontal cortex and an abnormal thickening of the left parietal lobe, suggestive for left polymicrogyria (Figure 2(a)). An array Comparative Genomic Hybridization (a-CGH) on the preserved fetal DNA was performed and was normal. After counseling, the couple decided to continue with the pregnancy and declined further diagnostic evaluations. At the follow-up scan at 30^{+6} weeks the corpus callosum appeared shorter in length as per corpus callosum hypoplasia. A second fetal MRI was offered and declined by the couple. The baby was born at 36 weeks with an uncomplicated cesarean section for labor dystocia after a spontaneous onset of labor. The computerized cardiotocography was normal throughout labor and the birthweight was appropriate for gestational age. The Apgar score was low with a score of 1 and 6 at the first and fifth minute, respectively. The umbilical cord pH was 6.7 with −23 base excess. Since signs of perinatal asphyxia were present, therapeutic hypothermia was started and the newborn was transferred to the neonatal intensive care unit with continuous positive pressure respiratory support.

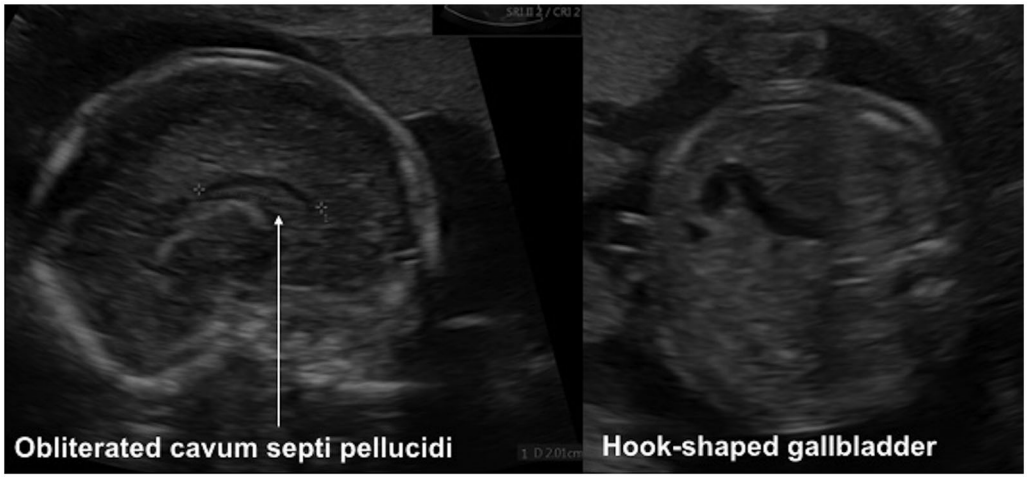

Figure 1. Prenatal ultrasound pictures showing the presence of a sagittal view of the fetal brain showing a normal corpus callosum and obliterated cavum septi pellucidi and a transverse view of the fetal abdomen with a hook-shaped gallbladder.

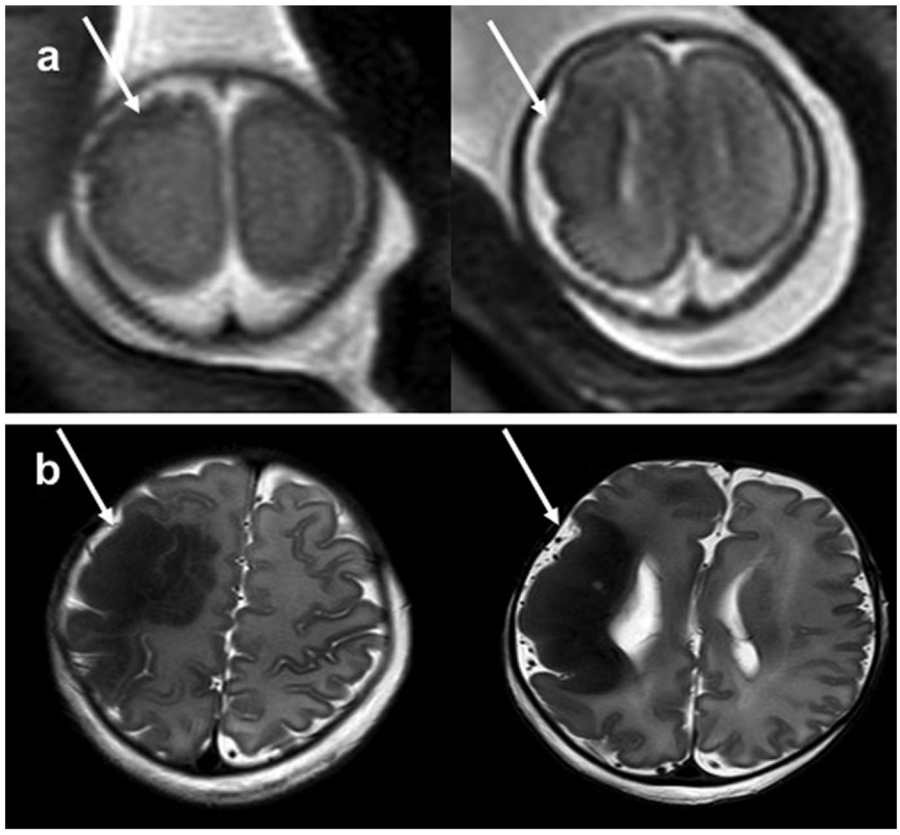

Figure 2. Prenatal and postnatal magnetic resonance pictures: (a) irregular surface of left frontal lobe with multiple small folds suggestive for polymicrogyria and abnormal thickening of cortex in the left parietal lobe at prenatal MRI (white arrow); (b) gyral cortical thickening and gyri separated by shallow sulci with hypointense signal and massive thickening of cortex in the left parietal lobe without intervening sulci at postnatal MRI (white arrow).

After 12 h, an endotracheal intubation was required due to seizures and muscular stiffness. Despite the administration of three combined antiepileptic drugs, an epileptic status refractory to pharmacological treatment developed.

The postnatal MRI performed at 72 h of life showed signs of severe damage at the level of the left cerebral hemisphere and basal ganglia with abnormal cortical thickness and configuration, abnormal white matter signal and an enlarged left ventricle (Figure 2(b)). The baby developed acute kidney failure and died at four days of life.

Autopsy showed severe brain parenchyma dysmorphism in the left frontal and parietal hemisphere with abnormal cortex stereometry due to disarrangement and abnormal neuronal organization (Figure S1). There were also multicentric malacic areolas, countless microcalcifications, arteriolar walls calcinosis, irregular microcirculation, heavy venous stasis, necrobiosis of the basal nuclei and calcification of the medial cerebral artery with colliquation and absence of gyri of the left cortex. Multiple visceral peritoneal adhesions with synechiae were noted in the abdominal cavity resulting in displacement of the internal organ and misalignment of the left kidney, left testicle and intestinal tracts, gastric verticalization and traction on the gallbladder wall that explained the "hook-shaped" appearance at ultrasound. Due to the presence of multiple visceral adhesions a screening panel for congenital infections was performed and resulted negative.

Because of the presence of untreatable seizures, the geneticists performed a targeted next generation sequencing (NGS) analysis for epilepsy that revealed the presence of a *PTEN* pathogenic variant [c.697C > T (p.Arg233Ter)]. The segregation analysis in the parents demonstrated a *de novo* origin of the variant.

Literature review

The presence of an oCSP is reported in four full-length articles summarized in Table 1 [4–7]. The largest series is by the group of Malinger et al. that include 23 fetuses with a prenatal diagnosis of oCSP. They found that the rate of associated brain abnormalities was around 20% and, in isolated cases, the neurodevelopmental outcome was abnormal in 1 out of 16 cases (6%). Among the three case-report, two were

Table 1. Articles reporting on the prenatal diagnosis of obliterated cavum septi pellucidi.

Reference	Number of cases	Gestational age at diagnosis	Associated findings at ultrasound	Associated findings at fetal or postnatal MRI	Genetic anomalies	Adverse perinatal outcome
Current case	1	20 weeks	Hook-shaped gallbladder; first trimester NT between 95° and 99° centile	Polymicrogyria	*De novo* PTEN gene mutation	Neonatal death
Malinger et al. [4]	23	22–34 weeks	*6 cases (26%)*[a]*:* - Mild ventriculomegaly ($n = 2$) - Short CC ($n = 1$) - Aberrant callosal artery ($n = 1$) - Abnormal frontal horns ($n = 2$) - Bilateral choroid plexus cysts ($n = 1$) - Periventricular pseudocysts ($n = 1$)	*Performed in seven cases:* - Confirmed US anomalies in 3 - CC dysplasia in 3 - Suspicion of abnormal CSP and CC at 24 weeks but normal findings at 29 weeks	Karyotype available for 10 fetuses and normal	– 1 TOP –1 motor and language delay
Pugash et al. [5]	1	19 + 4 weeks	Possible subtle dysmorphic appearance of the splenium	-Optic chiasm hypoplasia - Agenesis of pituitary gland - Posterior callosal dysgenesis[b]	Normal karyotype	Global neurodevelopmental delay and panhypopituitarism
Zorila et al. [6]	1	NA	None	None	Normal karyotype	Normal
Stanislavsky and Goergen [7]	1	20 weeks	None	- Abnormal appearance of the rostrum (26 weeks) - Hypoplastic genu and absent rostrum (postnatal)	Normal karyotype and micro-array	Normal (long term follow-up not available)

MRI: magnetic resonance imaging; NT: nuchal translucency; PTEN: Phospathase and TENsin Homolog; CC: corpus callosum; US: ultrasound; TOP: termination of pregnancy.
[a]Some fetuses presented multiple findings.
[b]Performed at 10 months of age.

associated to abnormal findings at ultrasound and/or fetal or postnatal fetal MRI, while in one the presence of oCSP was isolated. Genetic analysis was normal in all cases reported.

Discussion

Literature review

The first description of the CSP date back to the 80s when the advent of static and real-time ultrasound allowed the identification of intracranial fetal structures and the ventricular system [8,9]. The CSP has been defined as a rectangular-shaped structure identified by two hyperechoic lines interrupting the midline in its anterior third, that can be visualized in the axial plane of the fetal head at the screening anomaly scan [1]. It is a peculiar structure of the fetal brain since close to term the amount of fluid within it diminishes, and it becomes a virtual cavity in most two-month-old infants [10]. The reason why the *septum pellucidum* present fluid inside its leaves in the prenatal period only, while it shrinks postnatally, is not clear.

Nomograms has been reported for its evaluation and previous studies report that the CSP should always been visible between 17–20 and 37 weeks and for biparietal diameter of 44–88 mm, but it's becoming increasingly evident that in some cases the appearance of fluid may happens later or not at all [1,11,12]. The anatomical landmarks of the CSP are anteriorly, the genu of the corpus callosum; superiorly, the body of the corpus callosum; inferiorly, the pillars of the fornix and posteriorly the rostrum of the corpus callosum [1]. Given its anatomical contiguity with the corpus callosum, the CSP has become the most important marker for corpus callosum abnormalities at the screening anomaly scan [1]. Alongside these, other anomalies of the anterior complex have been added such as holoprosencephaly and septal optic dysplasia. Figure 3 summarizes the main aspects of the CSP depicting the presence of a normal CSP (a), an oCSP (b), an agenesis of CSP (c), an holoprosencephaly (d), and an agenesis of the corpus callosum. While abnormalities of CSP associated to other fetal brain malformation have been widely described in the literature, the presence of an oCSP has been poorly reported and little explored in terms of clinical and prognostic significance.

The CSP is generally considered as an inert structure whose main function is of anatomical barrier. However, its development is closely linked to that of the corpus callosum so that the CSP is not visualized

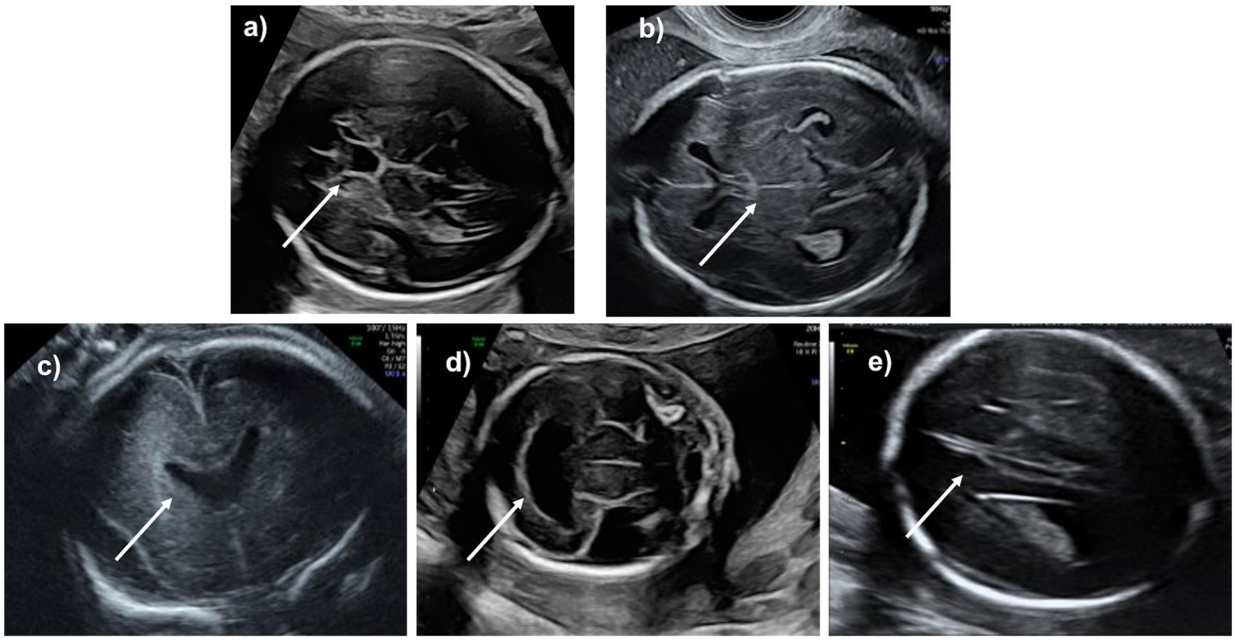

Figure 3. Pictorial essay showing different appearance of the cavum septi pelluci: normal in (a); obliterated in (b); agenesis of the CSP in (c); holoprosencephaly in (d); agenesis of the corpus callosum in (e).

in complete forms of agenesis of the corpus callosum or partially altered in its morphology in cases of partial agenesis of the corpus callosum [3,13]. At the same time, the CSP is completely absent in cases of septo-optic dysplasia, characterized by severe alterations of the optic nerve and pituitary gland [14]. Therefore, the CSP could have the function of relay station involved in the function of the limbic system as well as of the corpus callosum. However, the impact of "minor" alteration of the CSP, such as the absence of fluid within it, is still not known. In the largest case-series by Malinger et al. the authors conclude that, in most cases, an isolated oCSP can be considered a normal variant. However, there are some considerations to make about this article: the first, is that being one of the main centers for neurosonography, their classification of an oCSP as "isolated" implies the execution of a detailed ultrasound evaluation performed by expert operators. In fact, they report a rate of associated brain abnormalities of about 20%, after a detailed neurosonography was performed. The second is that being a retrospective study, fetal MRI was not performed in all cases and follow-up is not always available. Despite this, they report a risk of adverse perinatal outcome of 6%, which is higher than for the general population [4]. In the three case-report, only one report a normal outcome while the other two report associated fetal brain anomaly in both, plus neurodevelopmental delay in one [5–7].

Case-report

The main finding of this study is that oCSP may be related to poor postnatal outcome and that its sonographic finding on second trimester ultrasound indicates the performance of a fetal neurosonography to rule out the presence of associated abnormalities. In our case, the presence of two findings, such as the oCSP and the hook-shaped gallbladder, drove the decision to perform a fetal MRI, with the finding of severe left polymicrogyria (PMG). The prenatal diagnosis of PMG is not easy neither very common and it is mainly possible if a third trimester, or occasionally second trimester, fetal MRI is performed [15]. Usually, it follows secondary diagnostic investigations related to the presence of other brain malformations, like ventriculomegaly or absent cavum septum pellucidum [16]. The prenatal association between an oCSP and PMG has never been reported before. In postnatal series, Squier et al. found that the presence of PMG may cause adhesions of the frontal lobe and abnormal development of the midline falx [17]. In our case, autopsy described a complete disarrangement of the cerebral cortex suggesting the presence of a damage occurred at early gestational ages that could explain why PMG was clearly evident at the 20 weeks fetal MRI. We hypothesize that the early cerebral insult, that caused a severe and early form of PMG, may have affected the formation of the midline falx causing the obliterated appearance of the CSP. The association of

PMG and a PTEN mutation has been reported in postnatal series only [18]. The *PTEN* gene works as a tumor suppressor involved in the pathogenesis of multiple types of familiar cancers but also as an important regulator of the brain development. Postnatal evaluation of patients with a *PTEN* mutation showed that in 54% of cases there was PMG associated to macrocephaly but, despite the high rate of cognitive disability, only 17% had epilepsy and usually of a less severe degree compared to other forms of PMG [18]. Moreover, *PTEN* mutation is associated to vascular anomalies characterized by a systemic pattern of arterial calcifications and dilatation of the draining venous segment [17,19]. In our case, there was a systemic involvement of internal organs with multiple visceral adhesions associated to vascular anomalies, like diffuse microcalcifications and heavy venous stasis of the vessel. It can be, therefore, argued that the presence of a PTEN mutation caused an early and severe multisystemic organ involvement secondary to a diffuse vascular damage, as shown by the presence of an "hook-shaped" gallbladder and severe PMG in the early second trimester.

If initially the PTEN gene was mainly related to overgrowth syndromes and familiar cancer predisposition, its role as an important regulator of the brain development has been explored only recently such that in 2018 it has been included in the last "Gene Reviews Polymicrogyria Overview" among 50 other genes causative for PMG [10].

PTEN mutations can be found at whole exome sequencing (WES) analysis which is a fairly established practice in the postnatal work up of critically ill children, but its use in the prenatal setting is still under debate. Recently, the American College of Medical Genetics and Genomics (ACMG) has introduced the indication to perform WES in fetuses with one or more malformations if karyotype and CMA are both negative as it improves the diagnostic rate of 8–10% [20]. However, its use in the setting of prenatal diagnosis is not as widespread due to the costs, time required to obtain the results and difficulties in interpreting unexpected results.

This case highlights that counseling in the presence of oCSP remains uncertain and further research is needed. However, even when associated with mild extra cerebral signs, a fetal MRI should be considered. In case PMG is detected prenatally, karyotype and CMA analysis remain the first-line approach, but WES or targeted gene analysis should be taken into consideration if both are negative.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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