

Spectrum of *corpus callosum* agenesis – two different clinical patterns

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Abstract

Agenesis of the corpus callosum (ACC) is a malformation which may occur either isolated or in association with other CNS or systemic abnormalities. ACC occurs sporadically, although the incidence is increased in chromosomal disorders such as trisomy 8, 13, or 18. Familial cases have also been reported. Apart from the CNS, the musculoskeletal and genitourinary systems may be affected as well. We report two clinical cases of infants diagnosed with ACC, associating different clinical presentations. A clinical presentation of hypothalamic-pituitary dysfunction, optic nerve atrophy, recurrent seizures, mycrocephalus, and failure to thrive, led to a septo-optic dysplasia - DeMorsier’s syndrome diagnosis in the first case; in the second case, an association of macrocrania, hydrocephalus and interemispheric cyst were found in an asymptomatic infant, who was diagnosed with ACC and type 1a interemispheric cyst at the age of 8 months.

Key words: callosal agenesis, *diabetes insipidus*, macrocrania, *hydrocephalus*, infant, TF ultrasound.

Introduction

The corpus callosum is the main transverse tract of fibres that connects the two cerebral hemispheres. It is classically separated into four segments: the rostrum, genu, body, and splenium. The development of the corpus callosum begins in the 8th week of fetal life anteriorly at the genu and continues posteriorly. The rostrum develops last, usually folding back under the genu. The mature *corpus callosum* is developed by the 20th week of gestation [1, 2]. Once formed, the callosum thickens with increasing myelination, except during a period of axonal elimina-

tion near birth. Antenatal ultrasound diagnosis of ACC is possible from about 20 weeks’ gestation [3]. ACC has been estimated to occur in 1 to 3 per 1,000 and is more common among developmentally disabled populations [4]. Anomalies of the *corpus callosum*, including agenesis and hypogenesis, may be associated with a wide variety of other brain malformations [5, 6].

Transfontanellar (TF) ultrasound represents the most appropriate screening tool for ACC suspected cases. The following ultrasound features are present in ACC:

On coronal sections (fig.1, fig.2)

- absent *corpus callosum*
- widely separated frontal horns and bodies of the lateral ventricles
- angled lateral peaks of the frontal horns and bodies of the lateral ventricles
- enlarged atria and occipital horns (colpocephaly)

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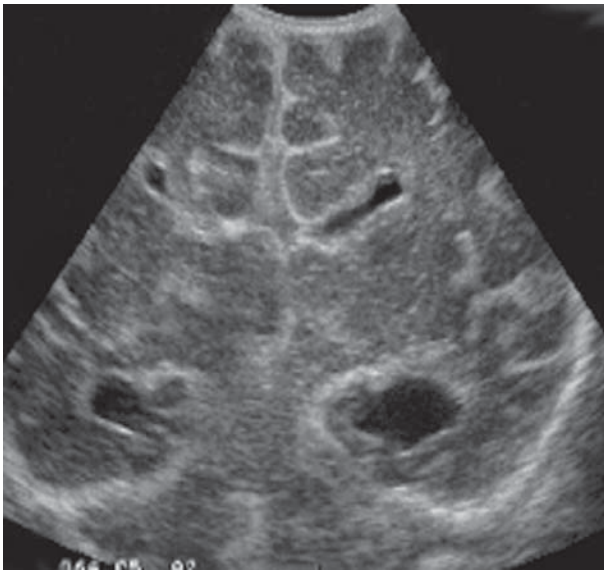


Fig.1. Anterior coronal view: absent *corpus callosum*, absent *septum pellucidum*, laterally angled peaks of the frontal horns, widely separated frontal horns and bodies of the lateral ventricles.

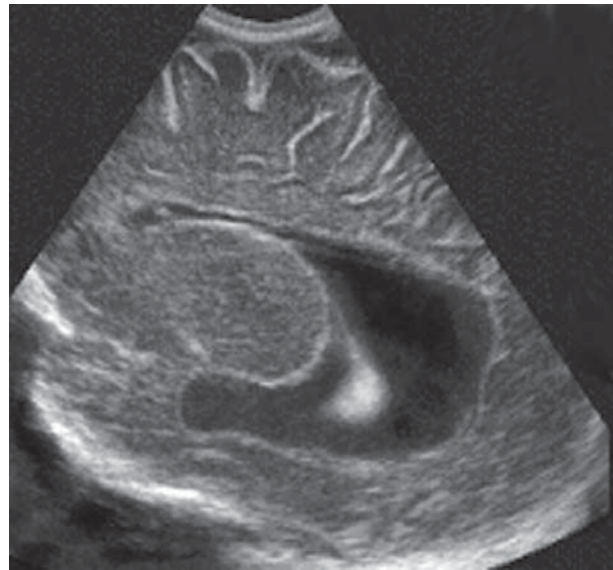


Fig.3. Sagittal view at lateral ventricle level: absent *corpus callosum*, difference between frontal and occipital horn dimensions, absent pericallosal sulcus, absent cingulated gyrus and sulcus.



Fig.2. Posterior coronal view: dilated atria and occipital horns (colpocephaly), laterally angled peaks of the frontal horns and bodies of the lateral ventricles.

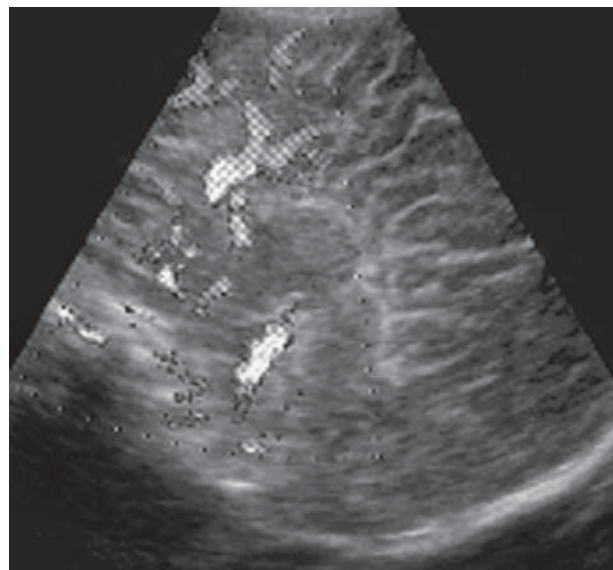


Fig.4. Midline sagittal view: medial cerebral gyri and sulci with a radial pattern extending to the roof of the elevated third ventricle (sunburst sign). Color Doppler: absence of the pericallosal artery.

- absent *septum pellucidum*
- variable dilatation and upward displacement of the third ventricle

On sagittal sections (fig. 3, 4)

- absent *corpus callosum*
- discrepancy between frontal and occipital horn sizes

- absent pericallosal sulcus
- absent cingulated gyrus and sulcus
- medial cerebral gyri and sulci with a radial pattern extending to the roof of the elevated third ventricle (sunburst sign)
- on color Doppler: absence of the pericallosal artery

An associated midline interhemispheric cystic lesion, a separate arachnoid cyst, or a communicating porencephalic cyst may be seen with US

Once the ultrasound diagnosis of ACC is established by TF ultrasound, other associated abnormalities should be ruled-out by CT or MRI scans.

Case. 1: DM, 2 month-aged female infant is admitted in the Mother and Child Care Institute (IOMC) Bucharest for generalized hypertonia, clonic-type seizures, opisthotonic posture and intermittent fever. Summarizing data from the infant's medical history: severe intrauterine growth restriction (term birth weight 1990g), Apgar score 7 (1min), 8 (5 min), early neonatal sepsis successfully managed in the maternity. On admission, the infant is microcephalic with a head circumference at the 25th percentile, (fig.5) malnourished and apparently dehydrated, with intermittent fever spikes and recurrent subtle-type seizures. Following the **TF ultrasound** examination the absent *septum pellucidum*, with a squared appearance of the frontal horns (fig. 6 and 7) and callosal agenesis revealed on sagittal scans (fig.8 and 9) raise the suspicion of **septo-optic dysplasia - DeMorsier's syndrome** diagnosis.

Optic nerve atrophy is diagnosed following the ophthalmologic examination. Cerebral CT scan confirms the ultrasound diagnosis (fig.10-12). Sustained polyuria (6-9 ml/kg/1h), along with constant low urine osmolarity and serum electrolyte changes (persistent hypernatremia) are highly suggestive for secondary *diabetes insipidus*. With a 20 mg/kg/day antidiuretic hormone treatment both polyuria and hypernatremia are successfully managed.

Case 2: AN, 8-month male infant is referred to the Institute for Mother and Child Care Bucharest for routine head ultrasound and clinical evaluation. The main reason for referral



Fig.5. The particular aspect of the cranium – microcephaly.

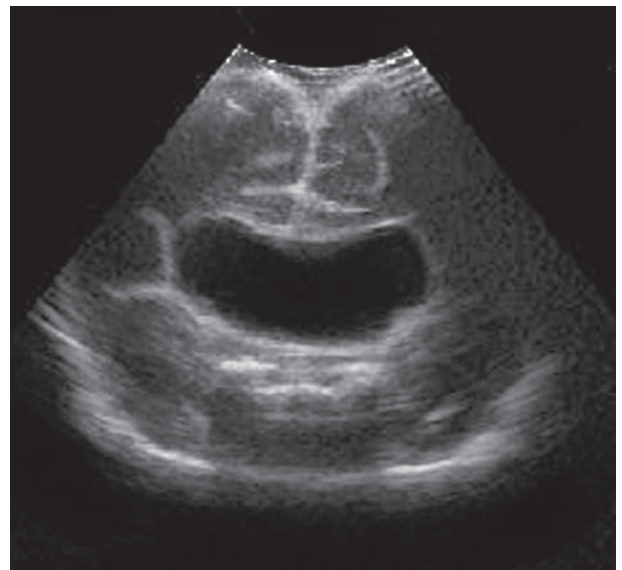


Fig.6. Anterior coronal view: absent *septum pellucidum*, with squared appearance of the frontal horns and ACC.

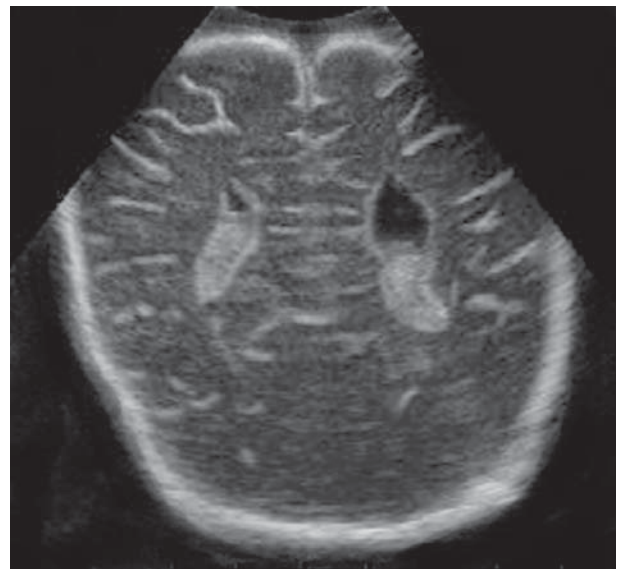


Fig.7. Coronal view: widely separated frontal horns and bodies of the lateral ventricles.

is an abnormal head circumference. Summarising his medical history: the baby boy is the first child of an apparently young and healthy couple, born at term by caesarean section after an uneventful pregnancy with 3300 g weight, 50 cm length and a head circumference of 39 cm (on the 95th percentile). From birth until his referral to the Institute for Mother and Child Care his weight and height growth rate is on the 50th percentile, but his head circumference is constantly above the 97th percentile. The baby's neuro-developmental status at the age of 8 month is considered to be in the normal range: at the age of 3 months, he

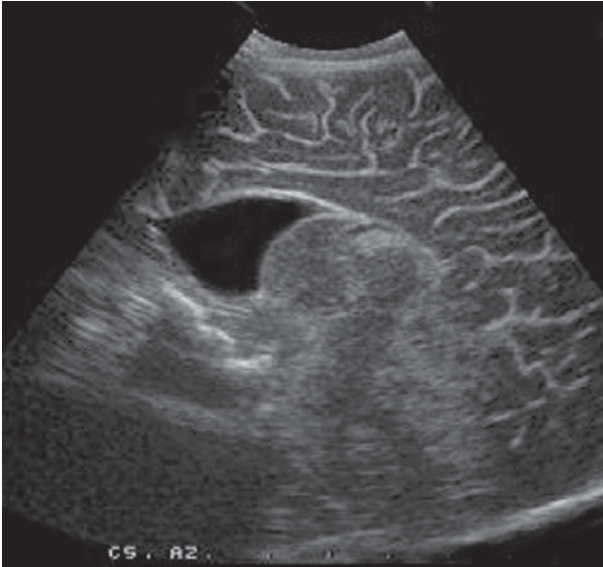


Fig.8. Sagittal view: enlarged anterior horns, sulci with a particular radial pattern.

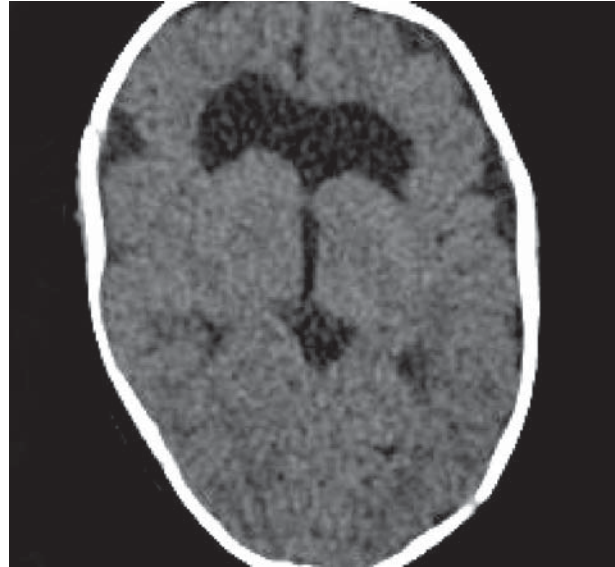


Fig.10. CT scan: ACC and septum pellucidum agenesis with anteriorly fused lateral ventricles.

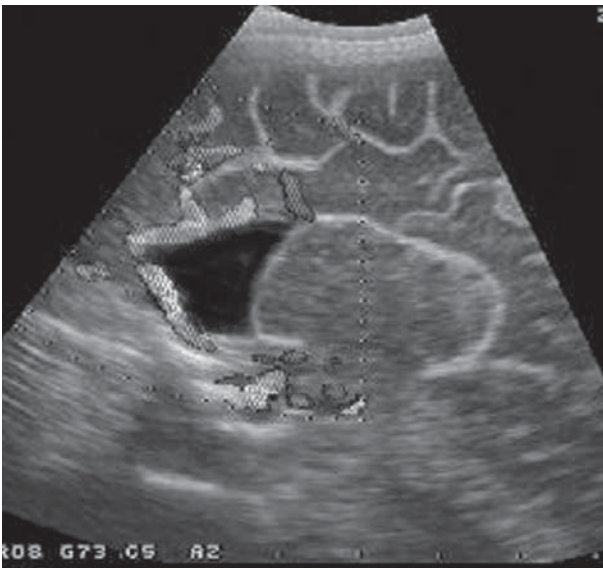


Fig.9. Sagittal view: enlarged anterior horns, sulci with a particular radial pattern, color Doppler examination.



Fig.11. CT scan: ACC and septum pellucidum agenesis with anteriorly fused lateral ventricles. Bilateral schizencephaly (arrows).

is controlling his cervical axial muscle tone (head support) and at 7 months, he is able to sit unsupported. Social smile, visual fixation and pursuit were present by the age of 3 months. Transfer of objects is noted by the age of 6 months.

TF ultrasound, first performed at 8 months, reveals the absence of *corpum callosum* and *septum pellucidum*, with moderately dilated and midline fused lateral ventricles (fig.13-15).

A large interemisferic cyst is also noted. The cyst extends to the cranial surface of frontal and parietal lobes.

On sagittal views, the cyst is separated anteriorly from the ventricular system by a thin echogenic membrane, but it communicates posteriorly with the ventricular system (fig.16). The normal posterior fossa appearance on TF ultrasound rules out the association with a Dandy Walker malformation.

The MRI confirms the ultrasound data: corpus callosum and septum pellucidum agenesis, hydrocephalus involving lateral and third ventricles. The large inter-

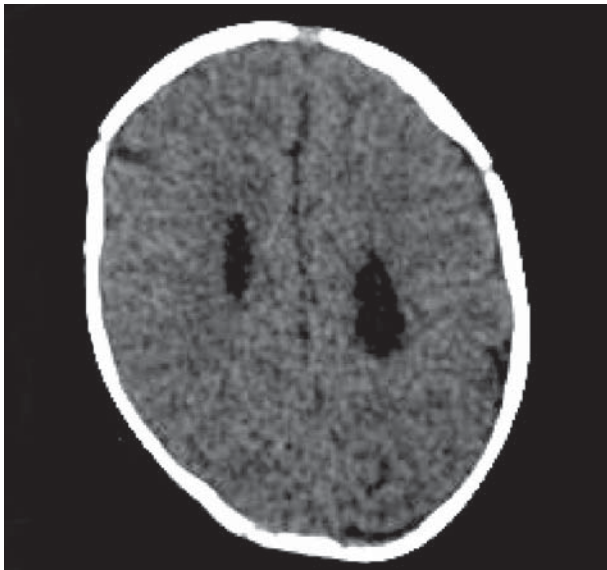


Fig.12. CT scan: posterior view at the occipital horns level.

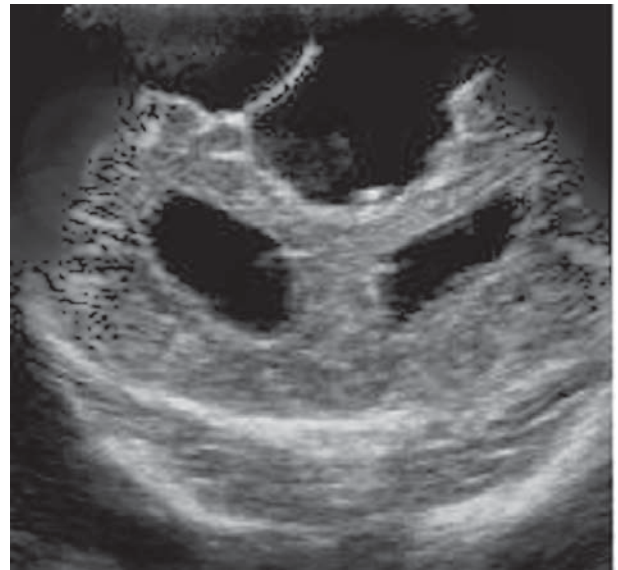


Fig.14. Coronal view: the anterior horns of the lateral ventricles are moderately dilated. The interhemispheric cyst is apparently not communicating with the ventricles.

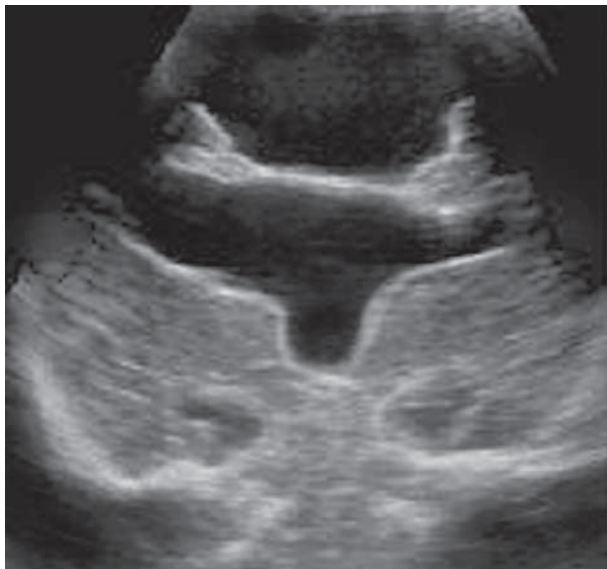


Fig.13. Anterior coronal view: midline fused lateral ventricles, lateral and third ventricle dilatation, absent *septum pellucidum* and ACC. Large cyst located superior to the lateral ventricles.



Fig.15. Coronal view: the dilated bodies of lateral ventricles. The interhemispheric cyst is apparently not communicating with the ventricles.

hemispheric cyst is also visualised and the posterior located communication with the lateral ventricles is noticed (fig.17, 18). Except for the compressed frontal and parietal cerebral structures by the interhemispheric cyst, no other cerebral abnormalities are noticed (e.g. polymicrogyria, gray matter heterotopia, schizencephaly). The structures of the posterior fossa are observed to be normal.

According to both ultrasound and cranial MRI imaging data and relying on Barkovich's classification (table 1) a diagnosis of callosal agenesis with type 1a interhemispheric cyst is established.

The baby is referred to the specialised Neurosurgery Department for an appropriate therapeutical approach.

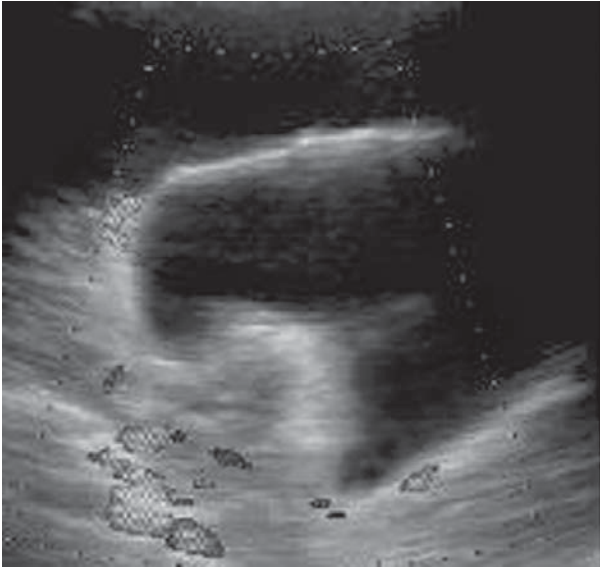


Fig.16. Sagittal view: the dilated bodies of the lateral ventricles. Posterior communication with the interhemispheric cyst.

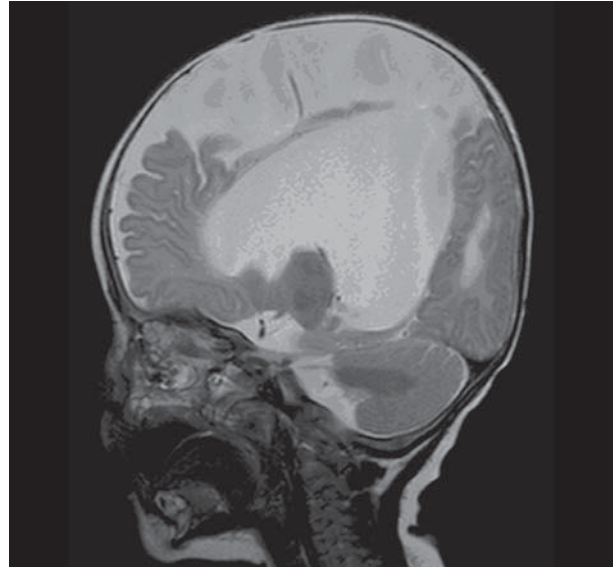


Fig.18. MRI examination: the sagittal view reveals a posterior communication between the cyst and the ventricular system.

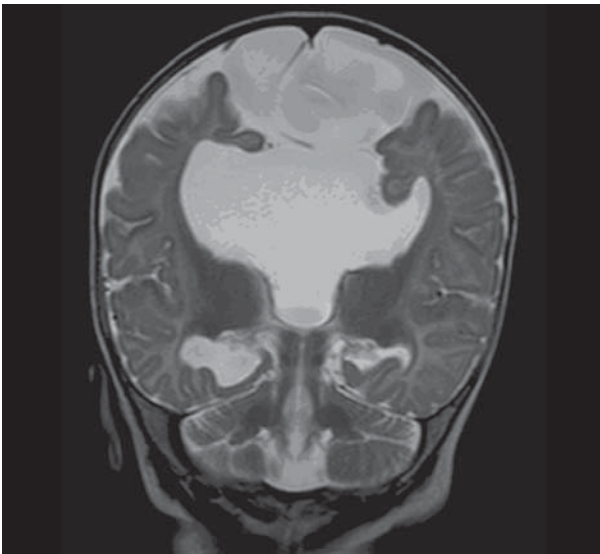


Fig.17. MRI examination, coronal view: dilated and midline fused lateral ventricles, moderately dilated third ventricle. Interhemispheric cyst extending to the inner cranial surface.

Discussion

ACC is one of the most commonly encountered and probably one of the most genetically diverse brain malformations. It is associated with many chromosomal abnormalities and malformative syndromes as well as to several inherited metabolic diseases. When isolated, ACC is commonly asymptomatic and represents an accidental imaging discovery.

Septo-optic dysplasia (SOD) also referred as de Morsier syndrome, is a rare, and heterogeneous condition first described by Reeves [7] in a 7-month-old baby with absent *septum pellucidum* and optic nerve abnormalities. SOD is an anterior midline congenital anomaly defined by any combination of: optic nerve hypoplasia, midline brain abnormalities (e.g. ACC and absence of the *septum pellucidum*) and pituitary hypoplasia with secondary hypopituitarism [8, 9]. The reported incidence of SOD is 1/10.000 live births [10] and it is thought to be equally prevalent in males and females. Although the condition is generally sporadic, familial cases have been described.

The absent *septum pellucidum* in SOD causes a box-like or squared off appearance of the frontal horns of the lateral ventricles on coronal TF images or on CT and MR sequences. Because of the associated agenesis or hypoplasia of the *septum pellucidum*, SOD is usually classified as the mildest form of holoprosencephaly. The dysplastic optic pathways lead to a range of visual dysfunctions, from mild forms to complete blindness. In addition to visual impairment, patients with SOD often present with seizures, as in case 1. The association of hypothalamic-pituitary dysfunction is observed in more than 50% of cases [11, 12]. As observed in case 1, this may manifest as *diabetes insipidus* or as growth retardation due to diminished growth hormone secretion.

Callosal agenesis associated with interhemispheric cysts is relatively rare; the association has been subject to a varied and confusing terminology. The origin of interhemispheric cysts in ACC is controversial. Arachnoid

cyst, neuroepithelial cyst and ependymal cysts have all been suggested as a possible cause.

The most recent system for classifying morphologically distinct cases of interhemispheric cysts that occur in the presence of ACC was established by Barkovich et al in 2001 [13]. Based on ventricular, cystic, and gross morphologic abnormalities, the classification divides cases of interhemispheric cysts associated with ACC into type 1 cysts, which are diverticula of the lateral or third ventricles, and type 2 cysts, which do not appear to communicate with the ventricular system and have a loculated appearance (table 1).

In case 2 the diagnosis of callosal agenesis with type 1a interhemispheric cyst is based on both clinical and imaging data. A normally developed baby with macrocra-

nia, in which the TF ultrasound diagnosed ACC, *septum pellucidum* agenesis and a unilocular, not septated large interhemispheric chist communicating posteriorly with the lateral ventricles is consistent with the ACC and type 1a interhemispheric cyst diagnosis. The ultrasound examination also ruled out the Dandy-Walker malformation by the observation of a normal posterior fossa. The association is possible, but not mandatory for diagnosis. The ultrasound observations were confirmed by the MRI scan, which revealed the unilocular cyst with an isotense to CSF content. The MRI also ruled-out subcortical heterotopia, schizencephaly, polymicrogyria, cerebral dysplasia or hypoplasia, thalamic fusion or other possible associated abnormalities.

In current ultrasound practice, the most important condition to be differentiated from interhemispheric cysts is the alobar holoprosencephaly because in this case, early diagnosis and treatment are mandatory in order to prevent severe developmental deficit.

Conclusion

In both reported cases the TF ultrasound examination established a diagnosis of ACC. Different clinical patterns are observed in each case, leading to the conclusion that ACC represents an associated anomaly in various syndromes with different degrees of severity and organ implications. The article’s aim is to raise paediatric ultrasound specialists’ awareness on the complexity of ACC presentation patterns.

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Table 1. Classification of ACC with interhemispheric cyst - Barkovich et al [13]

Type 1 - Extension or diverticulation of third or lateral ventricles			
Subtype	Cyst Characteristics	Communication	Possible associated abnormalities
Type 1a: Presumed communicating hydrocephalus	Isointense to CSF (MR), unilocular	with LV only	Macrocephaly, hydrocephalus, Dandy-Walker malformation
Type 1b: Hydrocephalus secondary to diencephalic anomaly	Isointense to CSF (MR), unilocular	with LV and obstruction of III rd V	Macrocephaly, diencephalic malformation (eg, thalamic fusion without subcortical heterotopia)
Type 1c: Small head size and cerebral hypoplasia	Isointense to CSF (MR), unilocular	with LV and III rd V	Microcephaly, cerebral dysplasia or hypoplasia
Type 2 Loculated, lack of communication with ventricular system			
Type 2a: No abnormality except ACC	Isointense to CSF (MR), multilocular	No communication	Macrocephaly, hydrocephalus
Type 2b: Aicardi syndrome	Hyperattenuation (CT), hyperintense (T1W MR), multilocular	No communication	Female predominance, subependymal heterotopia, polymicrogyria, seizures, hypoplastic falx cerebri, uni- or bilateral ventriculomegaly, developmental delay
Type 2c: Subcortical heterotopia	Isointense to CSF(MR), multilocular	No communication	Subcortical heterotopia, developmental delay

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