

Differential diagnosis in fetuses with absent septum pellucidum

G. MALINGER*†, D. LEV*‡, D. KIDRON¶, F. HEREDIA††, R. HERSHKOVITZ**
and T. LERMAN-SAGIE*§

*Fetal Neurology Unit, †Department of Obstetrics and Gynecology, ‡Genetics Institute and §Pediatric Neurology Unit, Edith Wolfson Medical Center, Holon, ¶Department of Pathology, Pinhas Sapir Medical Center; Sackler School of Medicine, Tel-Aviv University, Tel-Aviv,

**Department of Obstetrics and Gynecology, Soroka University Medical Center, Beer-Sheva, Israel and ††Department of Obstetrics and Gynecology, Faculty of Medicine, Concepción, Chile

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ABSTRACT

Objective To elucidate the characteristic morphological features that may help in the prenatal differential diagnosis of absent septum pellucidum as demonstrated by ultrasound.

Methods Twenty-six fetuses were referred to the fetal neurology clinic due to mild to severe ventriculomegaly and a connection between the lateral ventricles. The following ultrasonographic features were evaluated: place and extent of the ventricular communication, non-cleavage of the hemispheres and deep gray nuclei, callosal anomalies, position of the choroid plexus, and other central nervous system and facial or body anomalies. A flowchart was created in order to facilitate the final diagnosis.

Results The presence of non-cleavage and/or characteristic facial anomalies prompted the diagnosis of holoprosencephaly (HPE) in 14 fetuses, including two fetuses with the middle interhemispheric variant. Ten fetuses were diagnosed as having hydrocephalus based on the lack of the same features and the observation that the communication between the lateral ventricles was at the level of the third ventricle with almost normal anterior and posterior segments. In two fetuses the diagnosis of septo-optic dysplasia vs. isolated agenesis of the cavum septi pellucidi was contemplated.

Conclusions The use of the proposed flowchart enabled differentiation between hydrocephalus and HPE. The communication between the ventricles in hydrocephalic fetuses may be due to a disruption of the septum

pellucidum or to a pathological enlargement of the foramen of Monro. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Absence of the septum pellucidum is usually discovered postnatally in children evaluated for developmental delay. This radiological finding is considered rare and may be associated with various congenital brain malformations, namely holoprosencephaly (HPE), septo-optic dysplasia (SOD), schizencephaly or agenesis of the corpus callosum¹. The absence of the septum pellucidum may be due to a developmental anomaly or to secondary disruption as can be seen in aqueductal stenosis, Chiari II malformation, hydranencephaly and porencephaly¹.

The two most common conditions in which the septum pellucidum may not be demonstrated are congenital hydrocephalus and HPE. Hydrocephalus is a common anomaly of the central nervous system (CNS) (0.5–3:1000 live births) with a wide range of etiologies and variable prognoses². By contrast, HPE, a condition characterized by a defect in the development of the midline embryonic forebrain, occurs less frequently (0.48–0.88:10 000 live births) and is usually associated with moderate to severe mental retardation³.

The differential diagnosis between hydrocephalus and HPE *in utero* may be difficult since a communication between the ventricles may be present in patients with hydrocephalus, and the anatomy of the midline structures may be distorted in severe cases¹.

Correspondence to: Dr G. Malinge, Department of Obstetrics and Gynecology, The Edith Wolfson Medical Center, PO Box 5, Holon 58100, Israel (e-mail: malinge@inter.net.il)

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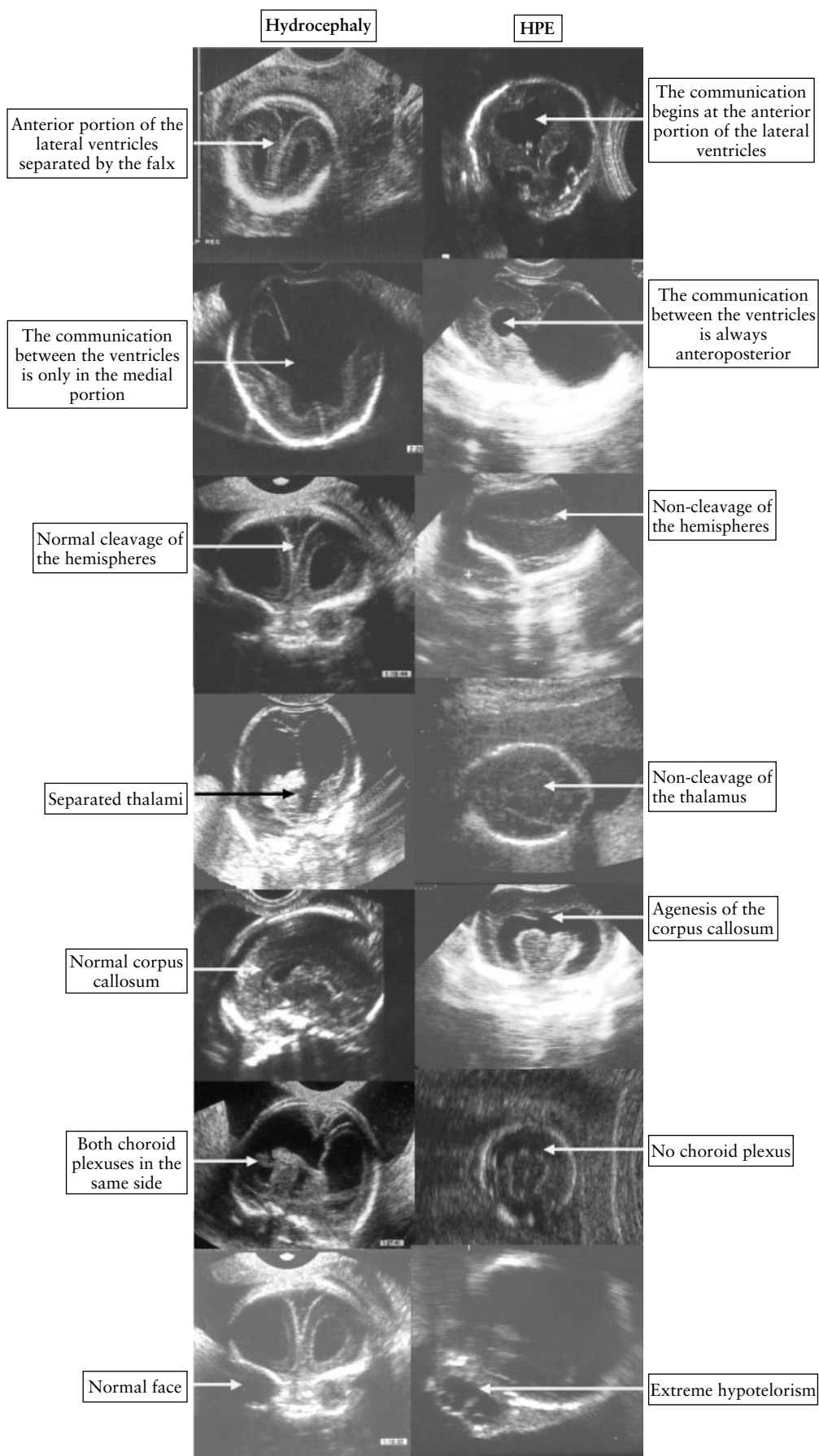


Figure 1 Ultrasonographic features used for differentiation between hydrocephalus and holoprosencephaly (HPE).

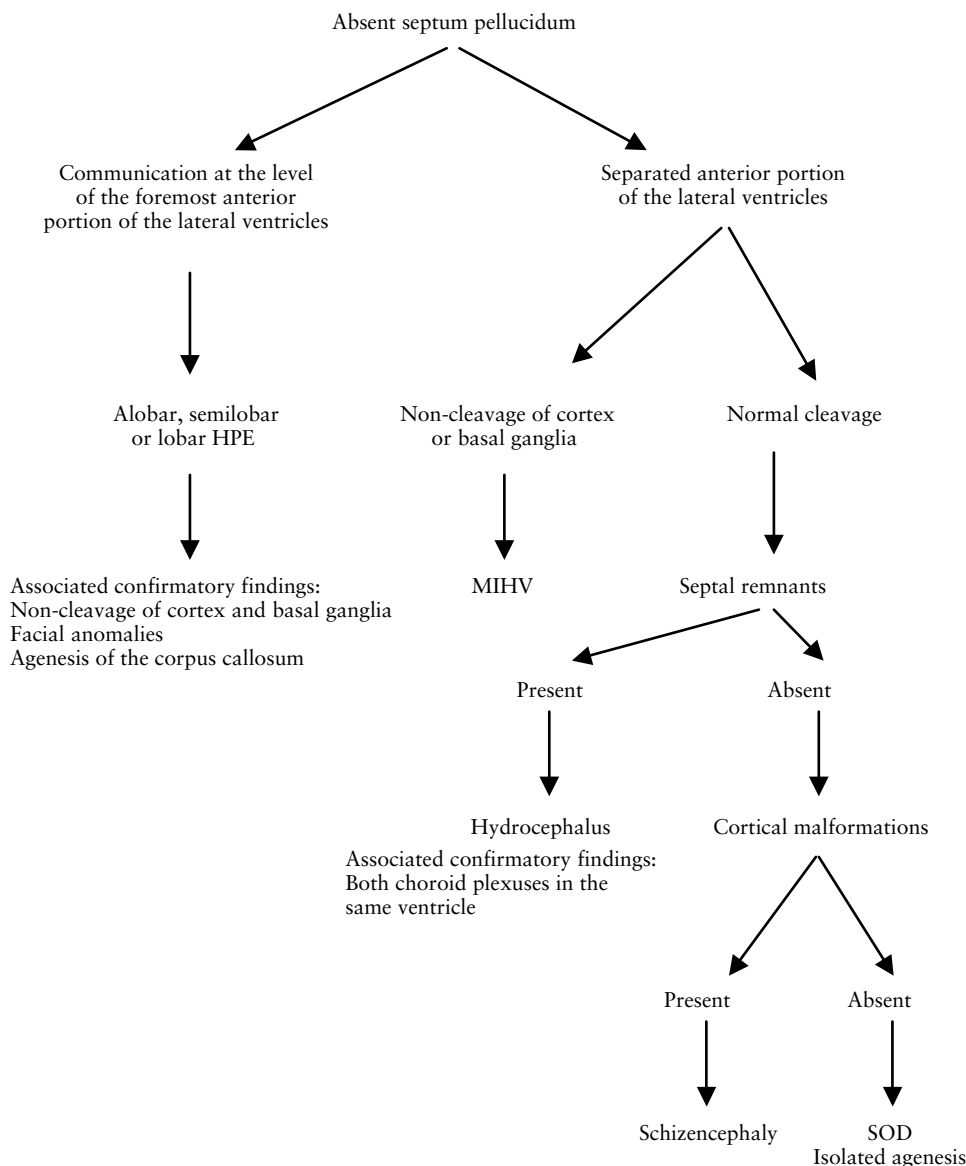


Figure 2 Flowchart used in the differential diagnosis in fetuses with absent septum pellucidum. HPE, holoprosencephaly; MIHV, middle interhemispheric variant; SOD, septo-optic dysplasia.

HPE is usually associated with mid-facial anomalies ('the face predicts the brain'⁴) but this concept is by no means axiomatic⁵ so some HPE cases with ventricular enlargement may be misdiagnosed as having hydrocephalus.

Absence of the septum pellucidum is a rarely described prenatal ultrasonographic finding and is usually attributed to HPE³. There has only been one case report demonstrating fenestration of the septum pellucidum occurring *in utero* due to aqueductal stenosis⁶.

The purpose of the present study was to describe fetuses with the ultrasonographic finding of absence of the septum pellucidum, to elucidate the characteristic morphological features that may help differentiate between primary developmental and secondary disruptive causes and to demonstrate the relative frequency of each pathology.

METHODS

The Fetal Neurology Clinic (FNC) at the Edith Wolfson Medical Center is a multidisciplinary referral center for the evaluation and counseling of pregnant women carrying fetuses with suspected CNS anomalies.

We reviewed the files of all the patients referred to the FNC during a 14-year period ending in December 2003. A total of 372 fetuses were evaluated for CNS anomalies. Of these, 25 fetuses were found to have moderate to severe ventriculomegaly and a connection between the lateral ventricles. One patient was evaluated through an e-mail consultation from the Department of Obstetrics and Gynecology, Faculty of Medicine, Concepción, Chile.

The mean gestational age at the time of referral was 24.5 (range, 14–36) weeks. All the patients were evaluated using a transabdominal approach, and when the fetuses

were in vertex presentation the study was complemented by transvaginal ultrasound as previously described⁷.

The studied ultrasonographic features included: place and extent of the ventricular communication, presence of non-cleavage of the hemispheres and of the deep gray nuclei, presence of callosal anomalies, presence and position of the choroid plexus, and presence of associated CNS, facial or body anomalies (Figure 1). The flowchart used in the differential diagnosis is presented in Figure 2. Whenever possible, the results were compared with postnatal findings at the clinical, imaging and/or pathology examinations.

RESULTS

Absent septum pellucidum was identified in 25/372 (6.7%) fetuses with suspected CNS anomalies evaluated at the FNC.

In 12 fetuses the ultrasonographic features were characteristic of classical HPE (Figure 1). Alobar HPE was diagnosed in eight patients and semilobar HPE in four. These patients all had a frontal common ventricle, and callosal and midline facial anomalies. Other features of HPE were found: non-cleavage of the hemispheres (10 patients) and non-cleavage of the thalamus (10 patients). Karyotype analysis was available in only six patients and was normal in three, trisomy 13 was found in two and triploidy in one patient. The patient with triploidy had additional malformations including an open neural tube defect, a complex cardiac anomaly and cleft lip and palate. All the parents decided on termination of pregnancy (TOP). Autopsy was performed in eight cases and postmortem magnetic resonance imaging (MRI) in one additional case. All confirmed the diagnosis of HPE. Three women underwent dilatation and extraction and therefore an autopsy was not performed.

In two patients the tentative diagnosis was middle interhemispheric variant of HPE. One patient demonstrated agenesis of the corpus callosum, communicating lateral ventricles only in their middle portion with normal-sized anterior horns and non-cleavage of the midbrain (Figure 3). Pathological verification could not be obtained by autopsy due to severe autolysis. In a second patient with asymmetric ventriculomegaly, partial agenesis of the corpus callosum and a dorsal cyst the diagnosis was suggested by ultrasound and confirmed by autopsy.

In two patients, failure of visualization of the cavum septi pellucidum with mild ventriculomegaly and a normal corpus callosum suggested SOD vs. isolated agenesis of the septum pellucidum. The shape of the lateral ventricles did not help in the differential diagnosis. After extensive discussion of the findings, the parents of one of the fetuses decided to terminate the pregnancy but refused an autopsy, and the parents of the second fetus (Figure 4) decided to continue the pregnancy. Follow-up ultrasound and MRI at 28 weeks of gestation demonstrated additional abnormal brain sulcation. However, at the time of writing the baby, aged 6 months, was developing normally.

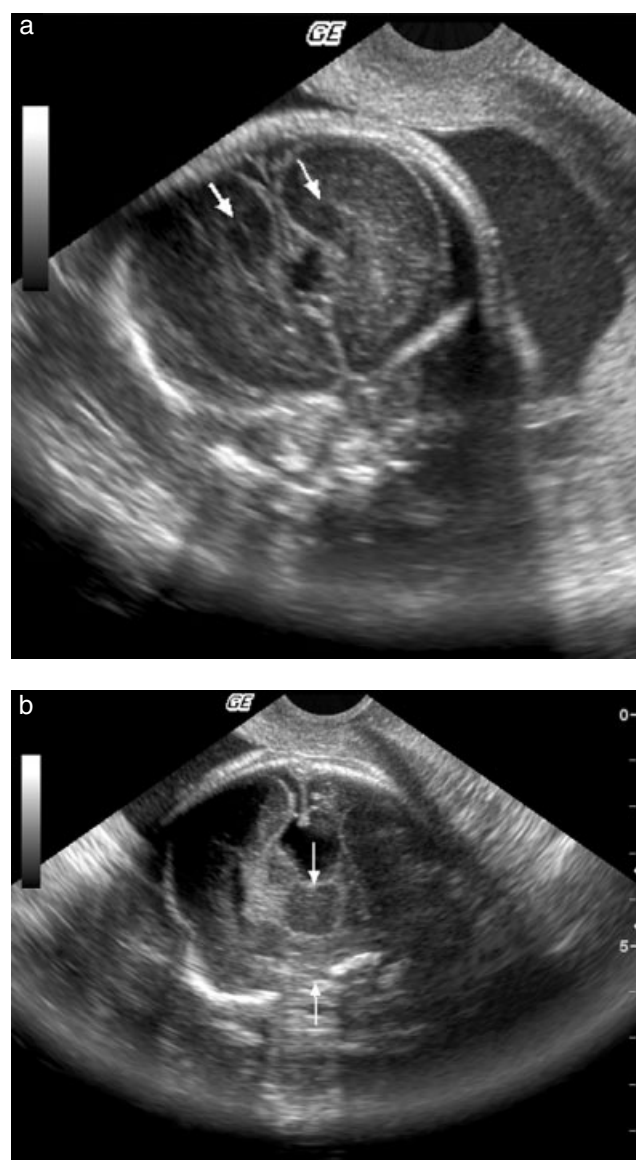


Figure 3 Transvaginal ultrasound image of a 23-week fetal brain with middle interhemispheric variant of holoprosencephaly. (a) Coronal plane at the level of the lateral ventricle frontal horns showing separated lateral ventricles (white arrows) with a complete interhemispheric fissure. (b) Coronal plane at the level of the thalamus showing a cystic cavity between the lateral ventricles and non-cleavage of the thalamus and hypothalamus (white arrows).

The common feature in the remaining 10 fetuses was the presence of a communication between both lateral ventricles in their middle portion with separated foremost portion of the anterior horns of the lateral ventricles and normal cleavage of the cortex and deep gray nuclei (Figure 5). The presence of remnants of the septum pellucidum was helpful in the diagnosis of a disruptive process. In all cases, both choroid plexuses were in the dependent lateral ventricle and there were no evident facial anomalies. Three fetuses, two of them siblings, had additional findings including arthrogryposis and severe angulation of the spine (Figure 6). Chromosomal analysis showed a normal karyotype in all these fetuses. Nine women opted for

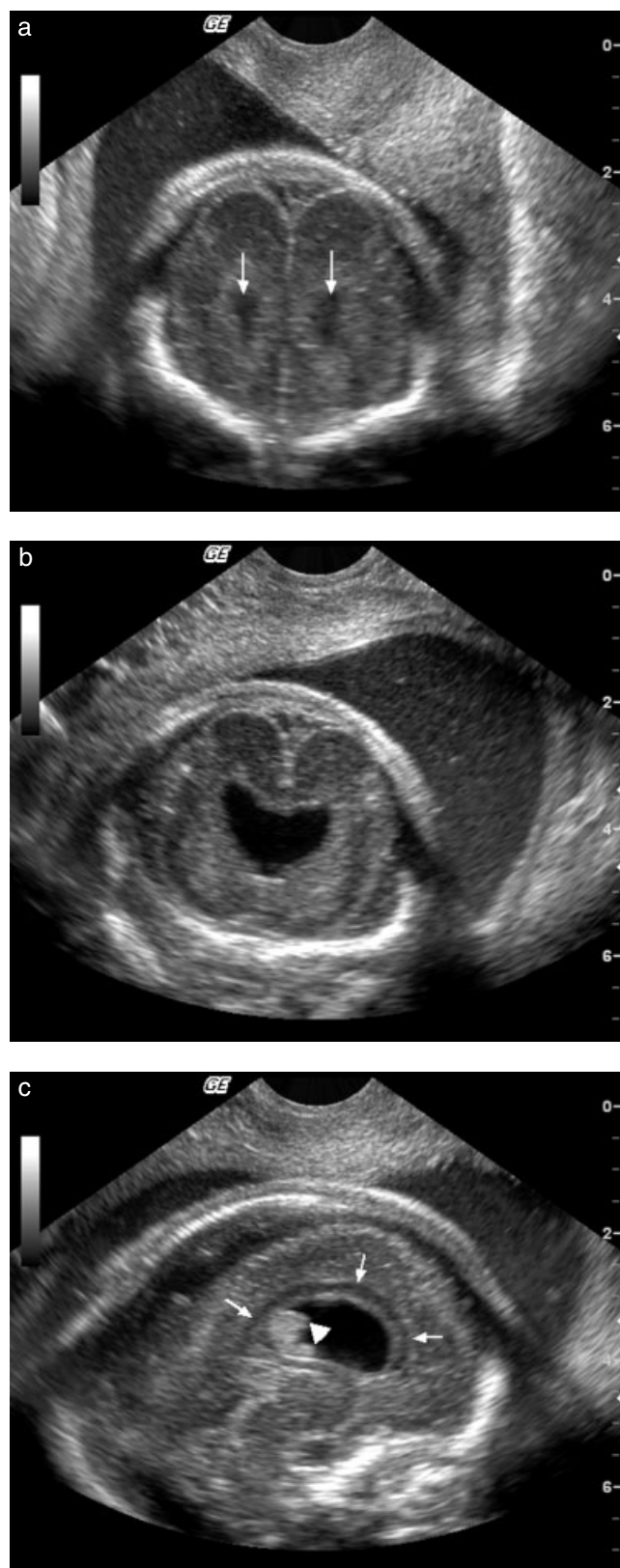


Figure 4 Transvaginal ultrasound image of a 23-week fetal brain with absent septum pellucidum and normal corpus callosum. (a) Coronal plane at the level of the lateral ventricle frontal horns showing separated lateral ventricles (white arrows). (b) Coronal plane at the level of the caudate showing absent septum pellucidum. (c) Mid-sagittal plane showing the entire corpus callosum (white arrows) with an increased curvature; note the presence of the choroid plexus inside the cavum (white arrowhead).

TOP. Hydrocephalus was confirmed by autopsy in six fetuses and was inconclusive in three due to autolysis. One child, with ventriculomegaly and septal disruption, was delivered. Postnatal MRI confirmed the prenatal diagnosis and a ventriculoperitoneal shunt was placed. Development is normal at 1 year of age at the time of writing.

DISCUSSION

Absence of the septum pellucidum is considered extremely rare and occurs in 2–3:100 000 individuals in the general population⁸. Barkovich and Norman described this finding in 1.7% of MRIs performed during a 2.5-year period¹. In their study, absence of the septum pellucidum was always associated with developmental abnormalities including: HPE, SOD, schizencephaly, hydrocephalus, encephaloceles, agenesis of the corpus callosum, porencephaly and hydranencephaly¹. They suggested an algorithm for facilitation of the diagnosis of underlying brain anomalies in these patients. The algorithm includes a stepwise visualization of the following features: the interhemispheric fissure, the corpus callosum, extracranial brain tissue, hydrocephalus, a hemispheric cleft and optic nerves. This algorithm is based on MRI and is very useful postnatally. However, it may be difficult to apply *in utero* using transabdominal ultrasound due to limitations in visualization of the interhemispheric fissure, the corpus callosum and the cortex in the axial planes. Currently, the optic nerves cannot be assessed *in utero* by ultrasound. These limitations may be potentially overcome by the use of triplanar neurosonography or fetal brain MRI, techniques that are, however, not readily available in most medical centers.

We propose a somewhat different approach using features readily demonstrated by the combination of transabdominal and transvaginal ultrasound: place and extent of the ventricular communication, cleavage or non-cleavage of the hemispheres and deep gray nuclei, callosal anomalies, position of the choroid plexus, and presence of other CNS, facial or body anomalies (Figures 1 and 2).

Using this approach we were able to diagnose *in utero* the brain anomalies associated with absence of the septum pellucidum. We identified 25 cases among 372 patients seen at the FNC and had one case referred from another center. In 12 patients the diagnosis of HPE was straightforward. In the remaining patients the differential diagnosis was made according to the proposed criteria and included two patients with suspected SOD, two patients with suspected middle interhemispheric variant of HPE and 10 patients with hydrocephalus.

A MEDLINE search, using the terms 'absent septum pellucidum' and 'communicating lateral ventricles', for reports on the prenatal diagnosis of absent septum pellucidum or communicating lateral ventricles excluding HPE yielded only two results: a case report demonstrating fenestration of the septum pellucidum in a fetus with hydrocephalus⁶ and the prenatal diagnosis of SOD⁹.

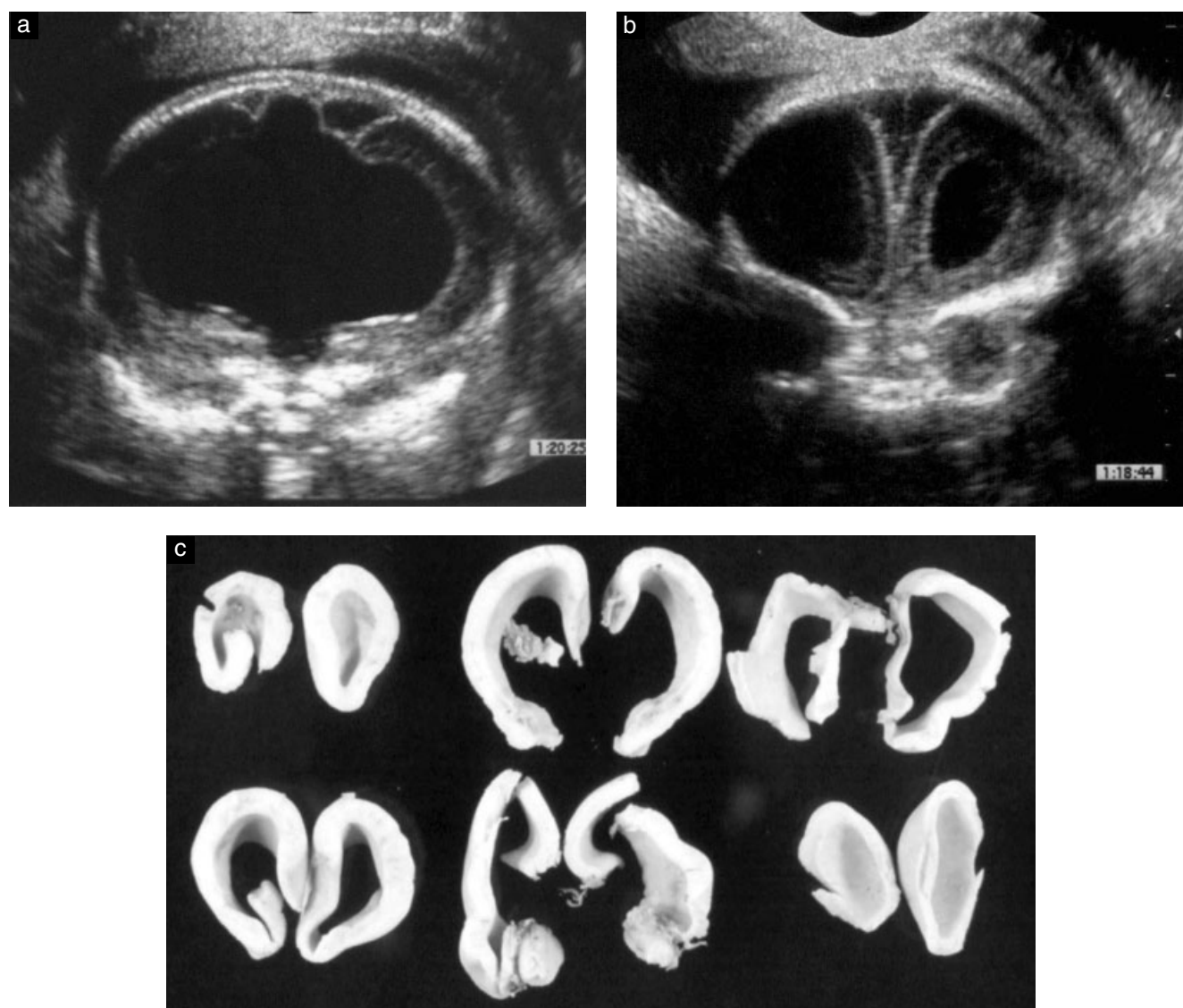


Figure 5 Ultrasound and macroscopic images of the brain of a 23-week fetus with arthrogryposis and severe angulation of the spine. (a) Transvaginal ultrasound image (coronal plane) at the level of the caudate showing the apparent presence of a large single ventricle with disruption of the cerebral mantle. (b) Transvaginal ultrasound image (coronal plane) at a more rostral level showing the presence of enlarged frontal horns with normal cleavage of the cortex. (c) Macroscopic cut of the brain showing normal cleavage of the brain.

Pooh and Pooh¹⁰ reported another case of absent septum pellucidum. This low search yield is intriguing if one considers the relatively high prevalence of this condition in our population. The possible explanations may be: an erroneous *in-utero* diagnosis of HPE due to the assumption that communicating ventricles are synonymous with HPE or non-consideration or under-reporting of absent septum pellucidum in fetuses with severe ventriculomegaly.

Although our knowledge of CNS embryology and the use of high-resolution probes makes the diagnosis of lobar and semilobar HPE possible even during the first trimester of pregnancy¹¹, the reported presence of HPE in fetuses diagnosed initially as suffering from hydrocephalus remains high and ranges from 19%³ to 29.6%¹². In the present series, 3/11 patients with HPE were referred due to severe ventriculomegaly and the fetus with the middle interhemispheric variant of HPE

was referred for a suspected interhemispheric arachnoid cyst.

Based on our study, absence of the septum pellucidum is either primary as part of a ventral induction disorder or secondary to a disruptive process. The most common ventral induction disorder is HPE, a condition characterized by a defect in the development of the midline embryonic forebrain. HPE can involve the brain, face and other midline structures to different degrees and may include craniofacial anomalies ranging from cyclopia to cleft lip and palate, or a single central incisor. The clinical presentation can include mental retardation/developmental delay, seizures, hydrocephalus, feeding problems, unstable homeostatic mechanisms and neuroendocrine abnormalities¹³.

The middle interhemispheric variant of HPE is a recently described ventral induction defect in which the posterior frontal and parietal areas lack midline



Figure 6 Whole body picture of the fetus shown in Figure 5.

separation, whereas more anterior areas of the cerebrum are fully cleaved¹⁴. The clinical prognosis is similar to lobar HPE; however, endocrine dysfunction and choreoathetosis are absent.

SOD is a midline anomaly characterized by absence of the septum pellucidum, optic nerve hypoplasia and pituitary dysfunction¹⁵. SOD has a wide range of clinical presentations including decreased visual acuity, endocrine dysfunction leading to growth delay, and mental retardation/developmental delay. Associated brain anomalies, including cortical malformations, HPE and agenesis of the corpus callosum, were present in 60% of the patients in a large series¹⁶. In these cases parental counseling is relatively easy, but in the remaining 40% of cases SOD can be difficult or impossible to differentiate from isolated absence of the septum pellucidum. In the future, new developments in molecular diagnosis may assist this task: in some patients SOD may be the result of homozygosity for an inactivating mutation in the homeobox gene *HESX1/Hesx1* or of a heterozygous mutation of this gene¹⁷. New fetal MRI sequences will also play an important role, enabling visualization of the pituitary stalk¹⁸ and abnormal optic radiation fibers in the occipital region¹⁹.

The communication between the ventricles in hydrocephalic fetuses may be due to a disruption of the falx cerebri or to an enlargement of the foramen of Monro. The presence of the choroid plexus on the same side, a

normal or bifid thalamus and the lack of common cortex and/or basal ganglia and midline facial anomalies are highly suggestive of the diagnosis of triventricular hydrocephalus.

It is important to differentiate between hydrocephalus and HPE because of the different prognosis, inheritance pattern and prenatal counseling.

The presence or absence of fused anterior horns is the most useful ultrasonographic parameter in the differential diagnosis of fetuses with absent septum pellucidum. All fetuses with fused anterior horns have HPE. In fetuses with separated anterior horns the differential diagnosis includes a disruptive process in hydrocephalus, or isolated agenesis of septum pellucidum, SOD and middle interhemispheric variant of HPE. The finding of both choroid plexuses in the dependent ventricle is diagnostic of a secondary event.

Although not used systematically in the present study, we believe that fetal brain MRI has an important role in the diagnosis of the more subtle cases associated with absence of the septum pellucidum, especially in fetuses with apparently isolated agenesis, and in the diagnosis of middle interhemispheric variant of HPE. In the remaining cases we are not of the opinion that MRI will add to the ultrasonographic evaluation regarding diagnosis or prognosis.

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