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Holoprosencephaly: Prenatal Sonographic Diagnosis

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Fourteen cases of holoprosencephaly (HP), including 10 cases of alobar HP and four cases of semilobar HP, were identified by prenatal sonography. Intracranial and extracranial findings were reviewed to determine the accuracy and spectrum of the sonographic features. All 14 cases were reliably distinguished from other causes of fetal hydrocephalus (n = 58) detected during the same period by demonstrating absence of the midline echo (falx cerebri and interhemispheric fissure), fusion of the thalami, and abnormal ventricular configuration. Four cases of semilobar HP demonstrated incomplete fusion of the thalami and partial separation of the ventricles compared with alobar HP. Eight cases demonstrated a dorsal cyst including five with alobar HP and three with semilobar HP. One case demonstrated an unusual extraaxial fluid collection surrounding the brain, thought to be from rupture of a dorsal cyst. Facial features that were identified included a proboscis (three cases), midline facial cleft (three cases), and hypotelorism (five cases). Extracranial abnormalities that were identified included polydactyly (two cases), renal dysplasia (two cases), omphalocele (one case), and fetal hydrops (one case).

We conclude that fetuses with HP can exhibit a spectrum of sonographic findings and that alobar or semilobar HP is reliably distinguished from other causes of fetal hydrocephalus by distinctive intracranial findings.

Holoprosencephaly (HP) refers to a spectrum of disorders resulting from absent or incomplete cleavage of the forebrain (prosencephalon) during early embryonic development [1–3]. Compared with other causes of hydrocephalus, HP is associated with a high rate of chromosomal anomalies, concurrent malformations, and a poor fetal outcome [1–5]. Distinguishing HP from other causes of hydrocephalus is important for patient counseling and for guiding appropriate obstetric management of affected pregnancies [6].

HP is usually categorized as alobar, semilobar, or lobar depending on the degree of forebrain cleavage [1]. Alobar HP is the most severe form, resulting in a monoventricular cavity; fusion of the thalami; and absence of the corpus callosum, falx cerebri, optic tracts, and olfactory bulbs. Semilobar HP shares many of these same features but demonstrates partial segmentation of the ventricles and incomplete fusion of the thalami. The least severe type, lobar HP, results in separation of the ventricles and thalami and absence of the septum pellucidum. As lobar HP may be difficult to distinguish from other mild midline malformations such as septooptic dysplasia [7] it will not be addressed here.

The typical cranial findings of alobar HP [8, 9] and semilobar HP [10] have been identified by prenatal sonography. However, because of the paucity of previously reported cases, the spectrum of cranial and extracranial findings has not been wholly emphasized. In the present study, we report our experience with 14 cases of HP diagnosed by prenatal sonography in order to describe the spectrum of findings and determine the sonographic accuracy of this disorder.

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TABLE 1: Comparison of Sonographic Findings with Pathologic and Clinical Findings in Holoprosencephaly (HP)

Case No.	Maternal Age	Sonographic Findings	Pathologic/Clinical Findings	Chromosomes	Outcome
1	24	Alobar HP, dorsal cyst, proboscis, hypotelorism	Alobar HP, dorsal cyst, cyclopia, clubfoot, polydactyly, absent adrenals, hypoplastic lung	Normal	Termination of pregnancy
2	34	Alobar HP, dorsal cyst, facial cleft, hypotelorism, hydrops	Alobar HP, dorsal cyst, facial cleft, ethmocephaly, tetralogy of Fallot, esophageal atresia	5p+	Delivered at 35 weeks; died within minutes
3	21	Alobar HP, polydactyly, renal cysts	Alobar HP, cyclopia, polydactyly, renal cysts, malrotated gut	Trisomy 13	Termination of pregnancy
4	31	Alobar HP, dorsal cyst, proboscis, hypotelorism, polydactyly	Alobar HP, dorsal cyst, cebocephaly, polydactyly, accessory spleen, absent adrenal, atrial septal defect	Normal	Cephalocentesis at 31 weeks; stillborn delivery at 32 weeks
5	31	Alobar HP, hypotelorism, renal cysts, omphalocele	Alobar HP, hypotelorism, facial cleft, renal dysplasia, omphalocele, polydactyly	Trisomy 13	Delivered at 33 weeks; died within minutes
6	19	Alobar HP, facial cleft	Alobar HP, cebocephaly, facial cleft, dysplastic kidneys	Trisomy 13	Termination of pregnancy
7	24	Alobar HP, dorsal cyst, facial cleft	Facial cleft, meningomyelocele	Not studied	Delivered at 37 weeks; died within 20 min (no autopsy)
8	23	Alobar HP	Alobar HP, normal face	Normal	Termination of pregnancy
9	17	Alobar HP, fetal demise	Macerated fetus	Not studied	Intrauterine demise at 18 weeks
10	30	Alobar HP, dorsal cyst, fluid surrounding brain	Alobar HP, normal face	Normal	Delivered at 38 weeks; died at 5 months (no autopsy)
11	33	Semilobar HP, dorsal cyst	Semilobar HP, dorsal cyst	Not studied	Delivered at 32 weeks; alive (8 months)
12	38	Semilobar HP, dorsal cyst	Semilobar HP, dorsal cyst, normal face	13q−	Delivered at 38 weeks; alive (4½ years)
13	37	Semilobar HP, dorsal cyst	Semilobar HP, ethmocephaly, facial cleft	Normal	Delivered at 38 weeks; died at 3 months (no autopsy)
14	14	Semilobar HP, proboscis, hypotelorism	Semilobar HP, ethmocephaly, malrotated gut	Trisomy 13	Termination of pregnancy

Materials and Methods

During a 5½ year period (January 1981 to November 1986), 14 cases of HP were identified by prenatal sonography at two referral centers for high-risk obstetrics. During the same period, 58 cases of fetal hydrocephalus from other causes were identified. All cases were clinically unsuspected before the initial sonographic examination; the sonograms were obtained for routine obstetric indications. Twelve cases were referred from other institutions for further evaluation and management of abnormalities suspected after an outside sonographic examination. Seven cases were initially detected at or before 24 menstrual weeks and seven cases were seen after 24 weeks.

Prospective sonographic findings were analyzed for intracranial, facial, and extracranial abnormalities. Our sonographic interpretations were compared with actual findings determined by autopsy reports; delivery notes; clinical charts; and postnatal radiographs, sonograms, and CT scans. To determine the reliability of our intracranial findings, we also reviewed the sonograms of the 14 cases of HP and the 58 cases of fetal hydrocephalus together in a blinded and random fashion.

Of the 14 fetuses studied, 12 ultimately died from termination of pregnancy (five cases), cephalocentesis (one case), intrauterine fetal demise (one case), neonatal death from anomalies incompatible with life (three cases), or respiratory causes during infancy (two cases, at 3 and 5 months, respectively). Of these 12 fetuses, 10 had an autopsy examination performed and 9 had a satisfactory brain examination without brain autolysis. The other two infants are still alive after follow-ups of 4½ years and 8 months, respectively.

Results

The clinical, sonographic, and pathologic findings are listed in Table 1. While the intracranial findings varied, all cases of HP demonstrated absence of the midline echo (falx cerebri and interhemispheric cistern) and fusion of the thalami (Fig. 1). This appearance was readily distinguished from 58 cases of fetal hydrocephalus due to other causes, which demonstrated a midline or asymmetric falx, distinct lateral ventricles, and separated thalami (Fig. 2).

Of the 14 cases studied, 10 had alobar HP and four had semilobar HP shown by sonographic, CT, and pathologic findings of the cranium. All cases of alobar HP exhibited a featureless, monoventricular cavity and central, fused thalami. Fetuses with semilobar HP exhibited partial segmentation of the ventricles, particularly the occipital horns, and incomplete fusion of the thalami (Fig. 3). The degree of thalamic fusion was seen best on coronal scans and was often appreciated best on postnatal cranial sonograms (Fig. 3C).

Eight cases demonstrated a dorsal cyst associated with alobar HP (five cases) or semilobar HP (three cases) (Fig. 3). The dorsal cyst was partially demarcated from the ventricular cavity by a ridge of cerebral tissue. Broad communication between the dorsal cyst and ventricular cavity was demonstrated near the midline (Fig. 3). One case of a dorsal cyst was referred as a suspected Dandy-Walker malformation by an outside sonographic examination. Another case demonstrated an unusual, extraaxial fluid collection surrounding the entire brain mantle, which was thought to represent rupture of the dorsal cyst into the subarachnoid space (Fig. 4).

Facial anomalies that were identified by sonography included a proboscis (three cases) (Fig. 5), hypotelorism (five

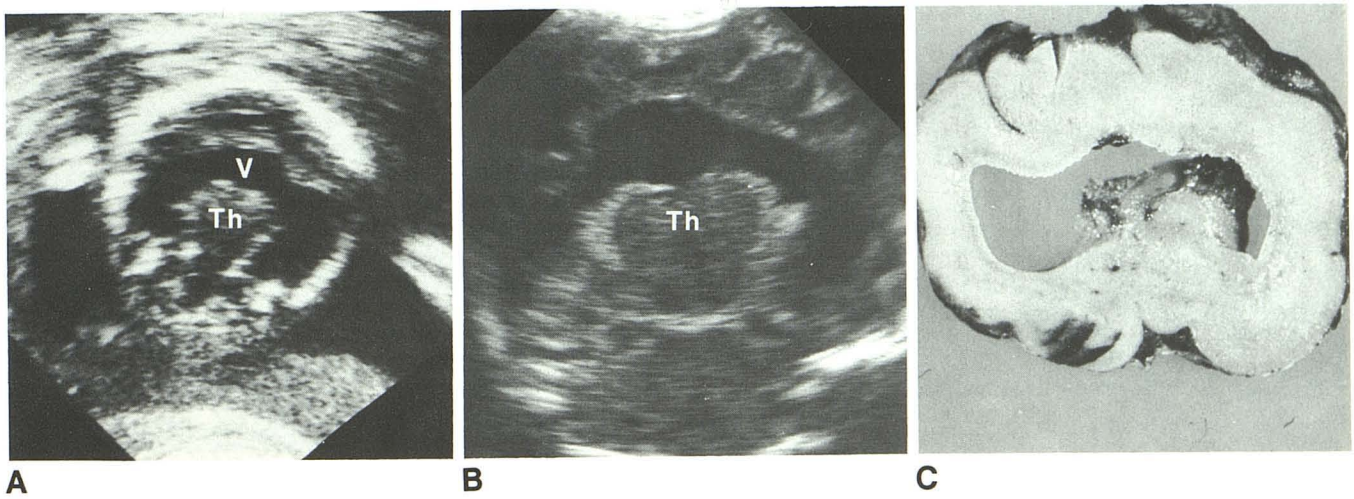

Fig. 1.—Case 6: alobar holoprosencephaly.

***A*, Coronal sonogram (upside-down) at 19 menstrual weeks shows fused thalami (Th) protruding within large monoventricle (V). Note absence of falx and interhemispheric fissure.**

***B*, Coronal sonogram immediately after delivery confirms fused, central thalami surrounded by monoventricle.**

***C*, Corresponding pathologic specimen shows fused thalami and monoventricle.**

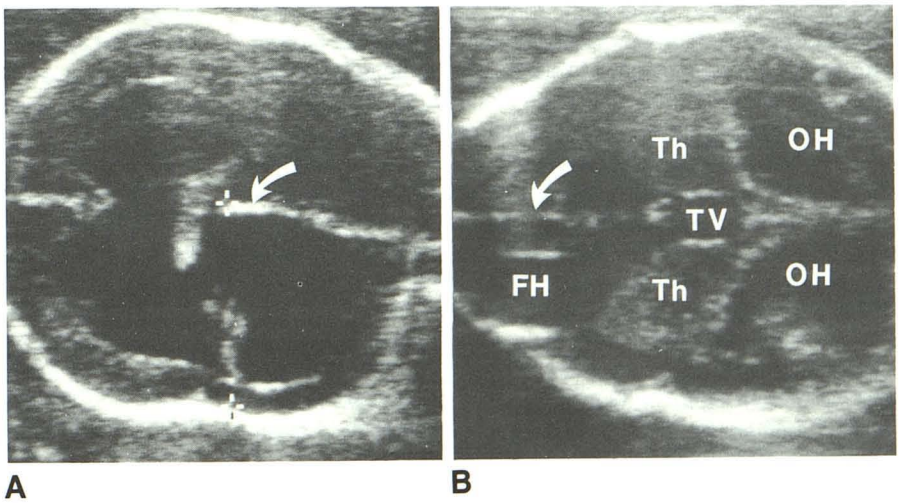

Fig. 2.—Hydrocephalus caused by Arnold-Chiari malformation.

***A*, Axial sonogram at 28 weeks shows falx cerebri (*arrow*) and distinct lateral ventricles (V).**

***B*, Axial sonogram at lower level shows separation of thalami (Th), dilated occipital horns (OH), frontal horn (FH), third ventricle (TV), and intact falx and interhemispheric fissure (*arrow*).**

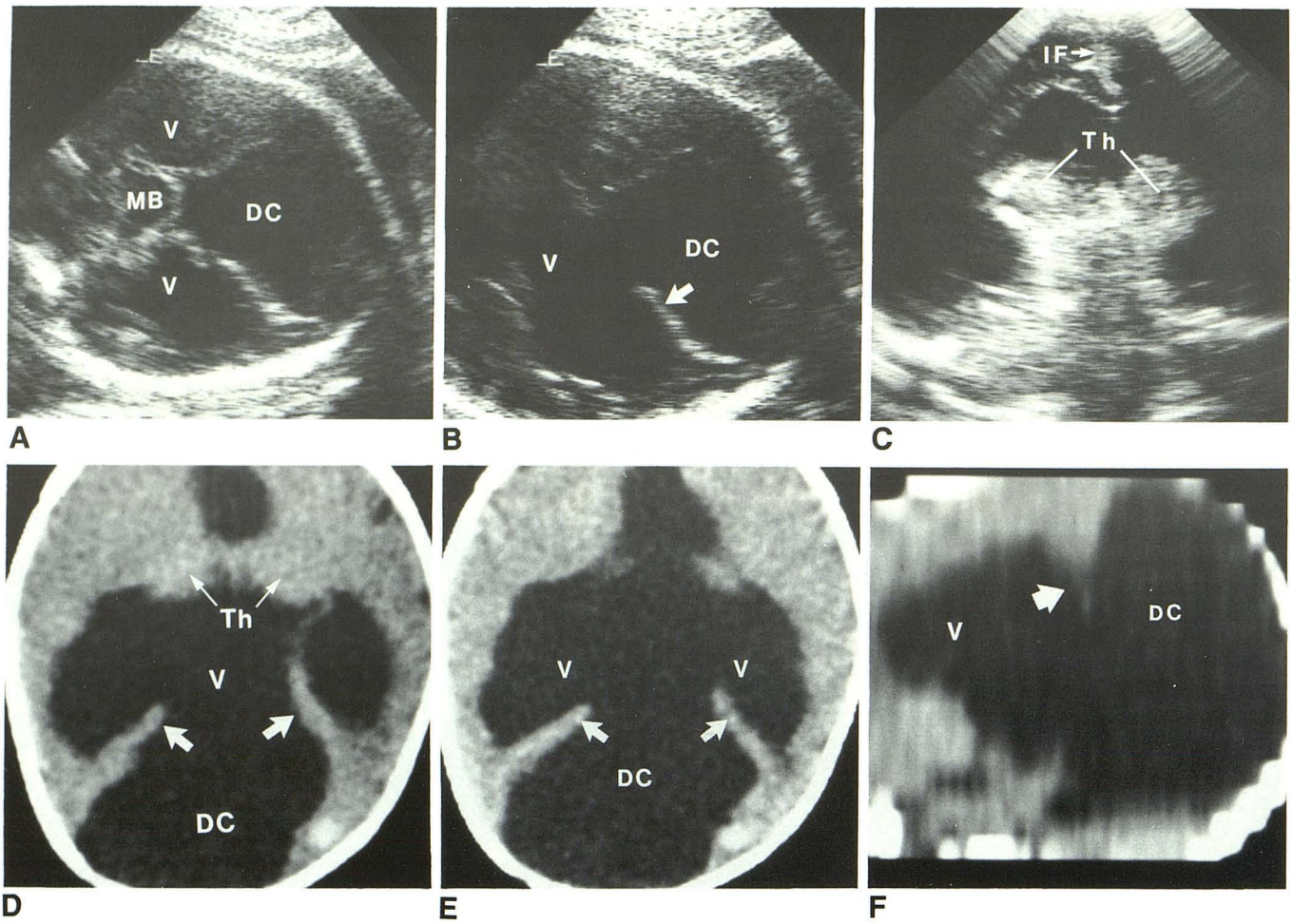

Fig. 3.—Case 11: semilobar holoprosencephaly with dorsal cyst.
***A*, Axial sonogram at 33 weeks at level of midbrain (MB) shows partial separation of dilated ventricles (V) and large dorsal cyst (DC).**
***B*, Sonogram at higher level shows absence of falx and broad communication of ventricle with dorsal cyst, partially demarcated by ridge of cerebral tissue (*arrow*).**
***C*, Coronal sonogram after birth shows incomplete fusion of thalami (Th), partial interhemispheric fissure (IF), and attempted separation of ventricles.**
***D*, CT scan shows partially fused thalami and large ventricle partially separated from dorsal cyst by cerebral tissue (*arrows*).**
***E*, CT scan at higher level better shows relationship between ventricle, dorsal cyst, and ridge of cerebral tissue (*arrows*).**
***F*, Reconstructed sagittal scan again shows ridge of cerebral tissue (*arrow*) separating ventricle from large dorsal cyst.**

cases), and midline facial cleft (three cases) (Fig. 6). Four infants failed to exhibit any facial anomaly at the time of birth and one was too macerated to examine. Extracranial anomalies, excluding the face, that were identified by sonography included polydactyly (two cases), renal dysplasia (two cases) (Fig. 7), omphalocele (one case) (Fig. 7), and fetal hydrops secondary to a complex cardiac defect (one case). In four cases, including both survivors, no extracranial abnormality was detected by clinical and/or autopsy examination. Amniotic fluid, which was increased in six cases, normal in seven cases, and decreased in one case, was not helpful for predicting extracranial abnormalities.

Chromosomal analysis was available in 11 cases. Of these, a chromosomal abnormality was identified in six cases (55%), including four cases of trisomy 13 and one case each of 13q− and 5p+. Extracranial malformations were present in five of these cases, excluding the oldest surviving infant (4½ years), who has 13q−.

Discussion

The frequency of HP has been estimated to be between 1:5200 and 1:16,000 live births [11,12]. Since many cases abort spontaneously before delivery, the frequency of HP among all pregnancies is significantly greater, and may be as high as 1:250 [13]. Assuming a frequency of at least 1:5200 for HP and 1:1000 for other causes of fetal ventricular dilatation [2, 3], HP can be expected to represent 16% or more of all cases of fetal "hydrocephalus" detected prenatally. These estimates are consistent with our own experience, as HP constituted 19% (14 of 72) of all cases of fetal hydrocephalus detected by prenatal sonography during a 5½ year

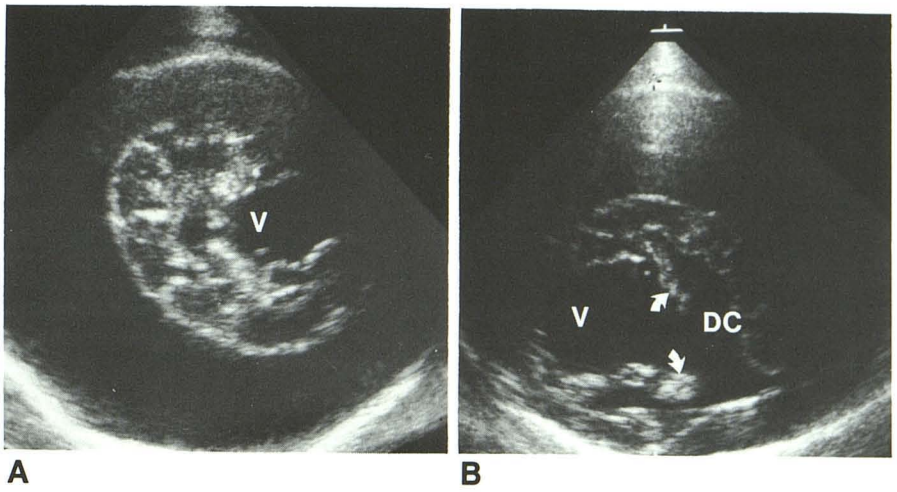

Fig. 4.—Case 10: alobar holoprosencephaly with dorsal cyst.

***A*, Axial sonogram at 30 weeks shows large amount of subarachnoid fluid surrounding brain. Note presence of central monoventricle (V) within brain.**

***B*, Repeat sonogram 2 weeks later shows interval enlargement of monoventricle, now communicating with dorsal cyst (DC) and demarcated from ventricle by ridge of cerebral tissue (*arrows*).**

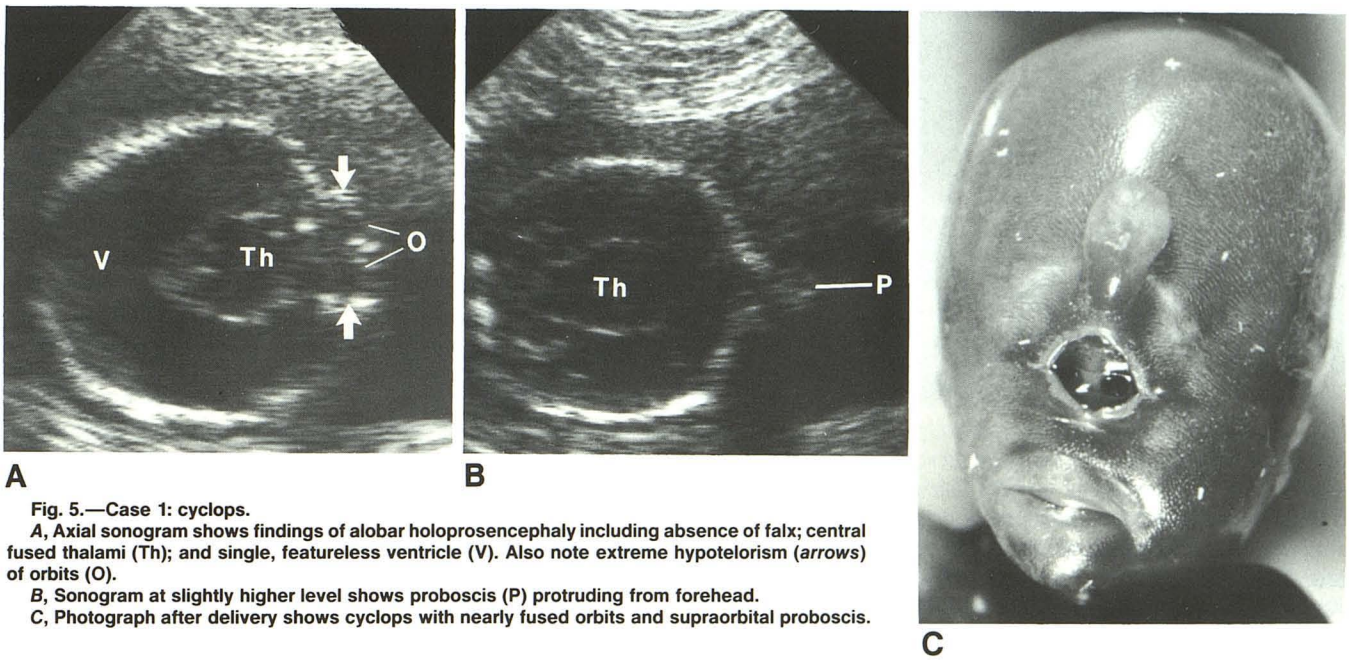

Fig. 5.—Case 1: cyclops.

***A*, Axial sonogram shows findings of alobar holoprosencephaly including absence of falx; central fused thalami (Th); and single, featureless ventricle (V). Also note extreme hypotelorism (*arrows*) of orbits (O).**

***B*, Sonogram at slightly higher level shows proboscis (P) protruding from forehead.**

***C*, Photograph after delivery shows cyclops with nearly fused orbits and supraorbital proboscis.**

period. Similarly, HP was found in 29.6% (eight of 27) of fetuses with hydrocephalus reported by Carrasco et al. [14]. Other sonography series have reported a lower frequency of HP or have not clearly distinguished HP from other causes of fetal hydrocephalus [15, 16].

As the majority of cases of HP are sporadic and clinically unsuspected [9], routine obstetric sonography is a potentially important means of prenatal diagnosis. As HP is often associated with chromosomal abnormalities, most commonly trisomy 13 [17], sonographic findings may stimulate subsequent chromosomal analysis. Six (55%) of 11 fetuses in our study were found to have chromosomal abnormalities, which is similar to the 57% reported by Chervenak et al. [9]. While karyotyping is not necessary for diagnosing HP, knowledge of a chromosomal anomaly may influence patient counseling and obstetric management. Identification of chromosomal translocation is also important for further genetic evaluation of the patients.

In addition to chromosomal anomalies, fetuses with HP have a high rate of concurrent malformations and fetal mortality compared with other causes of hydrocephalus [18]. Infants with HP who survive the newborn period have a uniformly poor outcome. The oldest survivor in our series is 4½ years old, although his intellectual development corresponds to that of a 4-month-old. The dismal prognosis of HP has led to conservative management of cases identified in utero. When detected before 24 menstrual weeks, most women will elect to terminate the pregnancy; when identified after 24 weeks, cephalocentesis may be a justifiable option [19, 20].

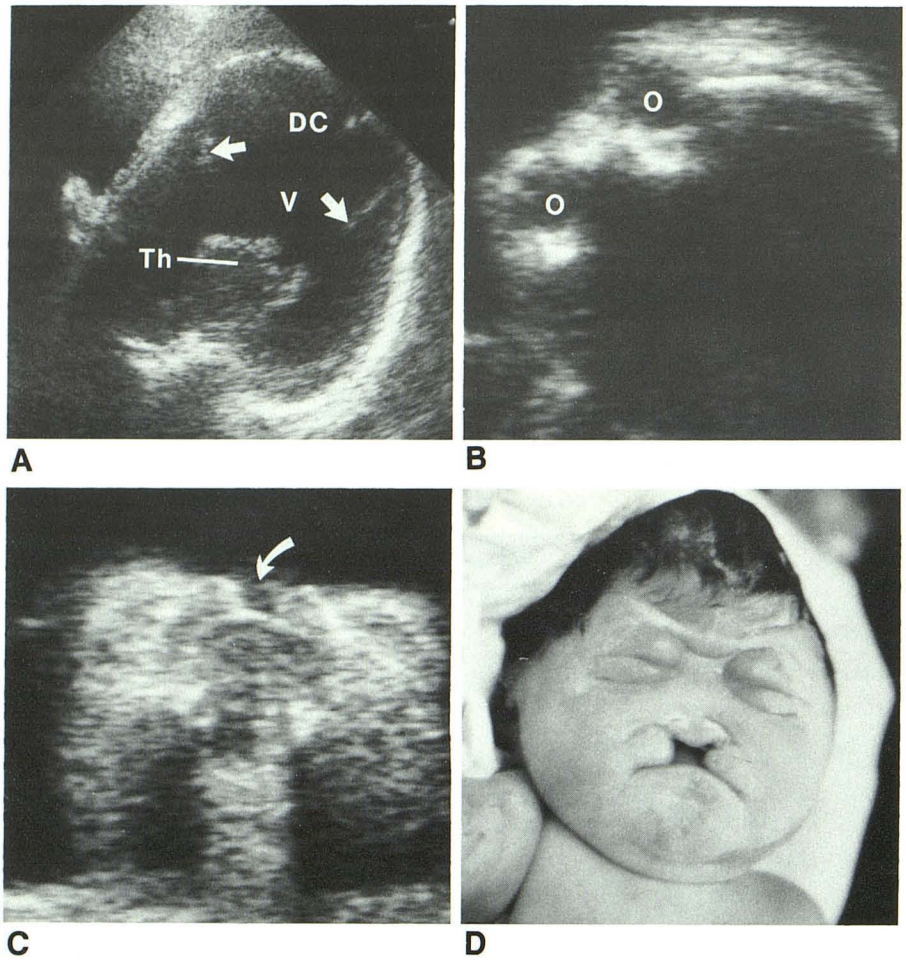

Fig. 6.—Case 3: alobar holoprosencephaly with facial cleft.

***A*, Semicoronal sonogram at 34 weeks shows central, fused thalami (Th) surrounded by monoventricle (V). Large dorsal cyst (DC) is also seen, demarcated from ventricle by ridge of cerebral tissue (*arrows*).**

***B*, Sonogram through orbits (O) shows hypotelorism and flattened midface.**

***C*, Axial sonogram of face shows midline facial cleft (*arrow*).**

***D*, Photograph of face at delivery confirms midline facial cleft, hypotelorism, and flattened midface.**

On the basis of our experience and that of others [8, 14], we believe that absence of the falx and fusion of the thalami are diagnostic features of alobar and semilobar HP (Fig. 1). Although Chervenak et al. [6, 9] have emphasized hypotelorism in association with an absent falx for diagnosing HP, we believe the intracranial findings are specific in and of themselves. A concomitant feature of alobar HP is the characteristic featureless configuration of the monoventricle, which lacks occipital, temporal, and frontal horns (Fig. 1). In cases of semilobar HP, occipital horns may be seen, but other ventricular landmarks are usually absent. An additional feature of semilobar HP compared with alobar HP is incomplete fusion of the thalami, best seen on coronal sonogram after delivery. However, distinguishing semilobar from alobar HP is somewhat subjective and is not clinically important, since the prognosis and outcome is similar for both groups.

We found that prenatal sonography can reliably distinguish HP from other causes of fetal hydrocephalus. Compared with HP, other causes of fetal hydrocephalus (Fig. 2) such as aqueductal stenosis or the Arnold-Chiari malformation demonstrate an intact falx, distinct and separate ventricles, and "splayed" thalami. Hydranencephaly or porencephalic cysts may demonstrate an absent or deviated falx, although the thalami are not fused in this situation. Furthermore, although no case of hydranencephaly was encountered in our series, reported cases demonstrate a markedly diminished or absent cerebral cortex compared with HP [21].

A dorsal cyst was observed in eight of 14 cases of HP in our series (Fig. 3) and in all five cases of alobar HP reported by Filly et al. [8]. The dorsal cyst occupies the dorsal caudal aspect of the diencephalon and, due to tentorial dysplasia, lies directly on the cerebellum [22]. It is partially demarcated from the ventricular cavity by a ridge of cerebral tissue thought to represent the hippocampal fornix [8]. The origin of the dorsal cyst is uncertain, but possibilities that have been proposed include (1) the third ventricle, (2) the velum interpositum, and (3) a remnant of the prosencephalic vesicle [5, 22]. The prosencephalic vesicle is the rostral end of the central nervous system during early embryologic development.

Unless correctly recognized, a dorsal cyst may be mistaken for other cystic masses including a Dandy-Walker malformation [7], as occurred in one case referred to us. Unlike HP, however, a Dandy-Walker malformation demonstrates a normal falx and supratentorial structures and unfused thalami. In addition, a dorsal cyst has a distinctive "boomerang" shape compared with the angulated margin of a Dandy-Walker cyst [8]. One unusual case of HP, which probably resulted from rupture of a dorsal cyst, demonstrated a large fluid collection surrounding the entire brain (Fig. 4).

As a variety of intracranial findings may be seen, so too is

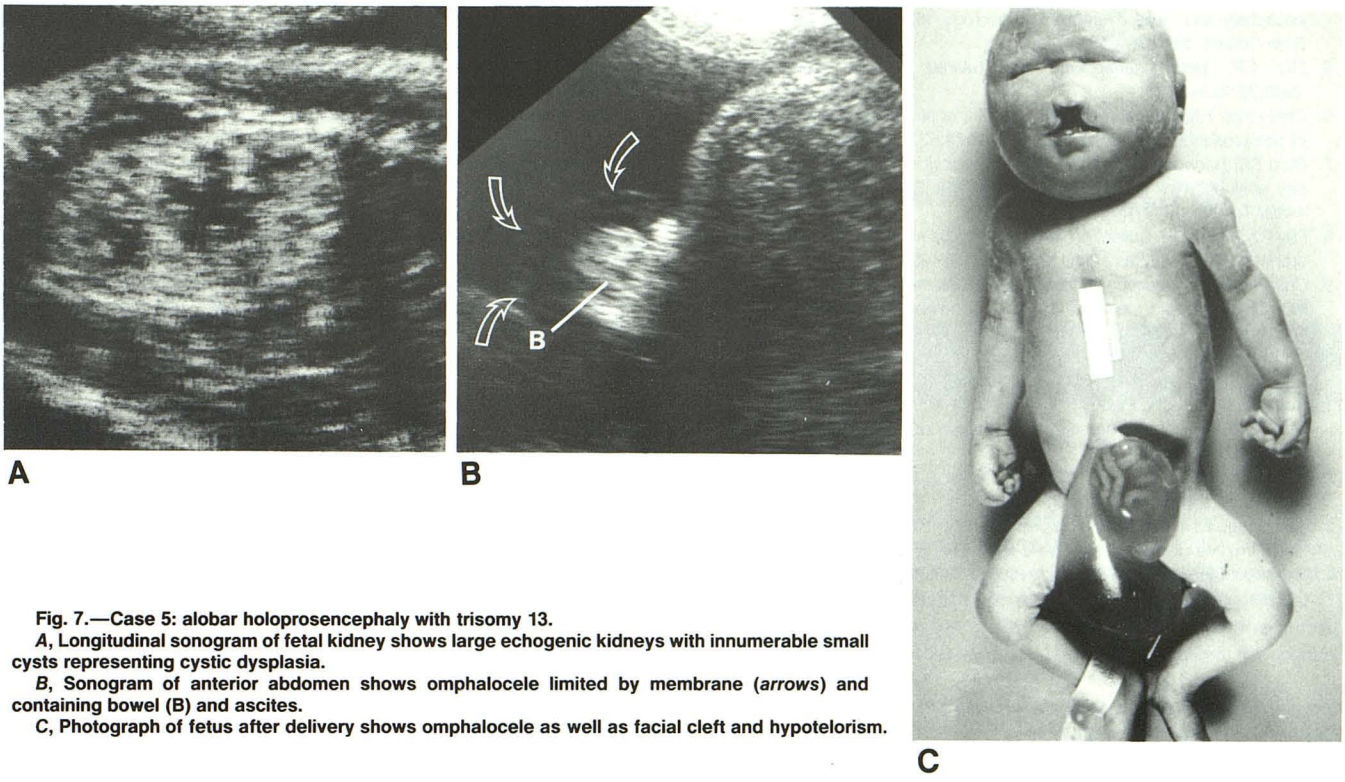

Fig. 7.—Case 5: alobar holoprosencephaly with trisomy 13.
***A*, Longitudinal sonogram of fetal kidney shows large echogenic kidneys with innumerable small cysts representing cystic dysplasia.**
***B*, Sonogram of anterior abdomen shows omphalocele limited by membrane (*arrows*) and containing bowel (B) and ascites.**
***C*, Photograph of fetus after delivery shows omphalocele as well as facial cleft and hypotelorism.**

there a spectrum of facial anomalies associated with HP [1]. Characteristic facial abnormalities, in decreasing order of severity, include cyclopia (fused or nearly fused orbits with supraorbital proboscis) (Fig. 5); ethmocephaly (hypotelorism with high, midline proboscis); cebocephaly (hypotelorism, single nostril in nose); and a median facial cleft, also called premaxillary agenesis (Fig. 6) [1]. Isolated hypotelorism or even a normal face can also occur. Facial anomalies are thought to have a common origin with the intracranial abnormalities and are caused by incomplete cleavage during embryologic development. The association between facial anomalies and HP has led to the well-known phrase, "the face predicts the brain" [23]. While this statement is generally true, identical facial features are occasionally recognized in the absence of HP [16]. Also, facial abnormalities are not invariably present, so that reliance on them will result in false-negative diagnoses of HP [8]. About 17% of fetuses with alobar HP reported by DeMyer [1] had a nondiagnostic face, and 29% (four of 14) of the cases in our series had normal facial features at delivery.

While recognition of facial or orbital abnormalities is not necessary for diagnosing HP, their presence can help predict fetal outcome. Fetuses with cyclopia or ethmocephaly rarely survive the neonatal period, and fetuses with cebocephaly or premaxillary agenesis rarely live more than 1 year [1]. Identification of facial anomalies may also predict extracranial anomalies, as eight of nine fetuses with facial anomalies had concurrent extracranial malformations in this series.

A variety of extracranial malformations can also be seen with HP and are often found in association with a chromosomal abnormality [1]. Three of four fetuses with a detectable extracranial malformation in our series had a chromosomal anomaly, including two with trisomy 13. Extracranial anomalies that were detected in association with trisomy 13 included polydactyly, renal dysplasia, and an omphalocele (Fig. 7). However, similar findings may be associated with a normal karyotype in the Meckel-Gruber syndrome (pseudotrisomy 13), an autosomal recessive disorder characterized by a triad of an encephalocele or holoprosencephaly, postaxial polydactyly, and renal cysts [24]. Recognition of these extracranial findings should initiate chromosomal analysis, since the recurrence risk for the Meckel-Gruber syndrome is 25%, compared with only 1% for sporadic cases of trisomy 13 [1].

In summary, HP is a major malformation of the central nervous system that should be distinguished from other causes of fetal hydrocephalus. Awareness of the spectrum of sonographic findings seen with HP should improve the accuracy of prenatal diagnosis. Identification of concurrent facial and extracranial malformations can help predict chromosomal anomalies and subsequent fetal outcome.

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