

# How to understand Holoprosencephaly

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## ABSTRACT

Holoprosencephaly (HPE) is a group of complex structural malformations of the forebrain that results from complete or incomplete nonseparation of the prosencephalon that yields an incomplete division of the cerebral hemispheres and of the telencephalon from the diencephalon. According to the severity of the malformation, HPE is categorized into four subtypes: Alobar HPE, semilobar HPE, lobar HPE, and a middle inter-hemispheric fusion variant (syntelencephaly). The incidence of HPE is 1 in 10,000 to 15,000 births. The etiology of HPE is very heterogeneous, and the identified causes until now are: Chromosomal (most commonly trisomy 13), monogenic, and teratogenic. The first step of the diagnostics is based on the ultrasound visualization of cerebral ventricular abnormalities, on the axial plane of the fetal brain, and on the facial anomalies.

**Keywords:** Anomaly of the brain, Cebocephaly, Corpus callosal agenesis, Facial abnormalities, Failure of midline cleavage, Holoprosencephaly, Hypotelorism, Microcephaly, Single nostril nose.

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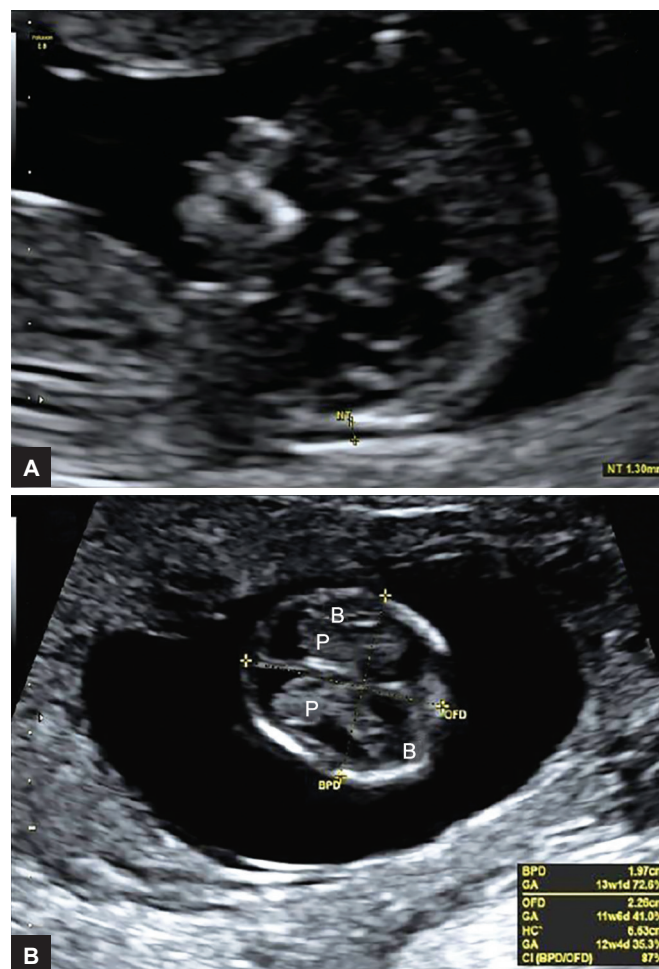
## INTRODUCTION

A large group of major congenital malformations are detectable using ultrasonography in the first trimester. It would appear that some severe structural anomalies are not as hard to detect as formerly believed, and can be diagnosed at 12 to 14 gestational weeks, if practitioners are aware of their early sonographic appearance and

structural- or functional-associated abnormalities. Views of the brain and head are among the most important images the sonographer can obtain for exclusion of a wide variety of anomalies (Figs 1 to 3).

Holoprosencephaly is a rare structural abnormality of the brain, a genetically and phenotypically heterogeneous disorder, involving the development of the forebrain and midface, and is associated with neurologic impairment and dysmorphism of the face.<sup>1,2</sup> This condition is probably associated with a high intrauterine mortality rate because it is rarely found at birth.

A widely accepted classification recognizes three major varieties of HPE: The alobar, semilobar, and lobar types.<sup>3</sup> The HPE represents a continuous spectrum of malformations based on the severity of lack of cleavage and this leads to the attempt of some researchers to incorporate



**Figs 1A and B:** Fetal brain at 13 weeks. An axial scan with the prominent echogenic choroid plexus (P) filling the lateral ventricles. The thin hypoechoic cerebral cortex (B) should not be mistaken for fluid within the ventricular system

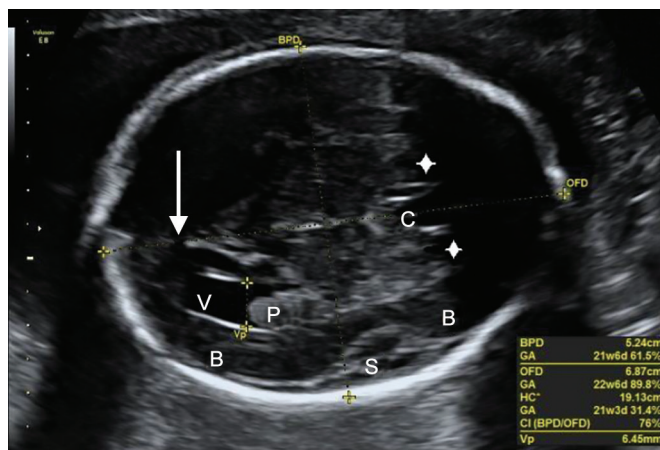
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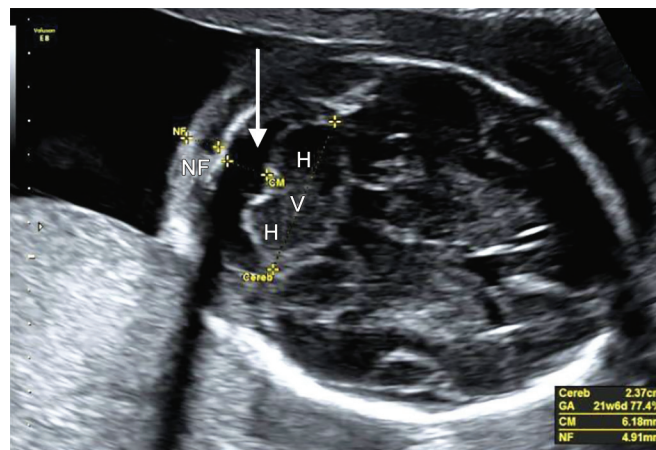
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**Fig. 2:** Lateral ventricle, cavum septum pellucidum, and subarachnoid spaces at 20 weeks. An axial image with the cerebrospinal fluid-filled occipital horn (V) surrounded by the hypoechoic cerebral hemisphere (B). Echogenic choroid plexus (P) is seen within the ventricular atrium bilaterally. The choroid plexus does not extend into the frontal horns (asterisks), which are well seen anterolateral to the midline cavum septum pellucidum (C). Arrowhead indicates cortical margins of the occipital lobe. Subarachnoid space (S)—lateral to the brain



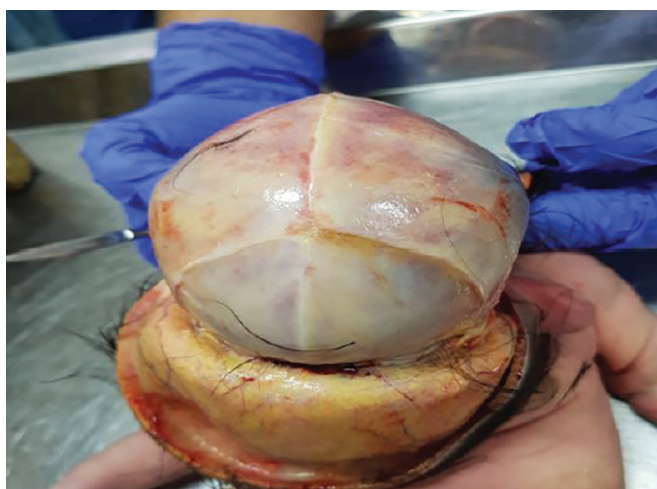
**Fig. 3:** Normal posterior fossa. Schematic diagram shows oblique views through posterior fossa; normal landmarks include the cistern magna (arrow), cerebellar hemispheres (H), midcerebellar vermis (V), and the nuchal fold (NF)

degrees of nonseparation of subcortical structures into the classification system. A recent fourth subtype of HPE, namely, middle hemispheric variant was added. In this condition, the interhemispheric fissure is formed in frontal and occipital regions, but absent in parietal regions along with fusion of the hemispheres.<sup>4</sup> Therefore, the term septopreoptic HPE has been used to describe a mild subtype of lobar HPE with nonseparation restricted to the septal or preoptic regions. Early diagnosis of HPE is possible because at this early age, the falx is already present and evident on ultrasound at 12 weeks of gestation, and, therefore, its absence (typical feature of alobar and semilobar) can be detected by the absence of the “butterfly” sign (Fig. 1). In the first trimester, the choroids are side by side, and this creates an image of a butterfly. If sonographers are unable to demonstrate this butterfly image, HPE is highly suggestive.

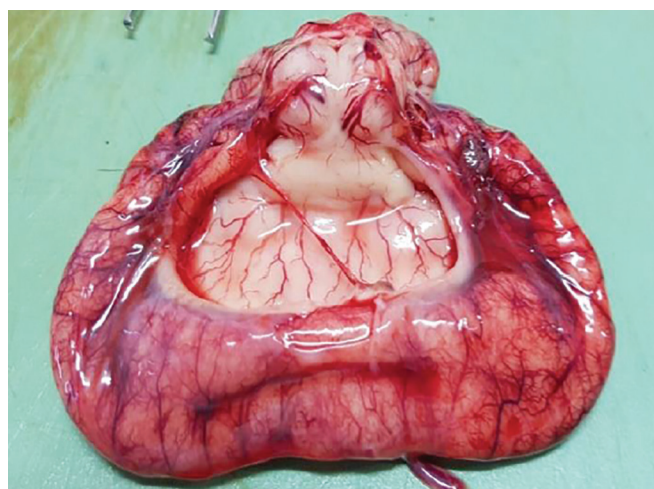
In the alobar form of HPE, the interhemispheric fissure and the falx cerebri are totally absent with a single primitive ventricle. The thalami are fused on the midline and there is absence of the third ventricle, neurohypophysis, olfactory bulbs, and tracts (Figs 4 and 5). Most cases of HPE are characterized by various craniofacial malformations, the most severe craniofacial deformity remaining cyclopia with a single or partially divided eye in a single orbit with a proboscis above the eye and absent nose (Fig. 6). Other malformations may include a single central maxillary incisor, midline cleft lip and palate, bilateral cleft lip and palate with intermaxillary rudiment, flat nose, absent nasal bridge, microphthalmia, absence of lateral philtral ridges, and absence of the superior lingual frenulum (Fig. 7).

In the semilobar variety, the two cerebral hemispheres are partially separated posteriorly, but there is still a single ventricular cavity (Fig. 8).

With lobar HPE, the anatomic damage is much more subtle. In pathologic studies, this condition is usually

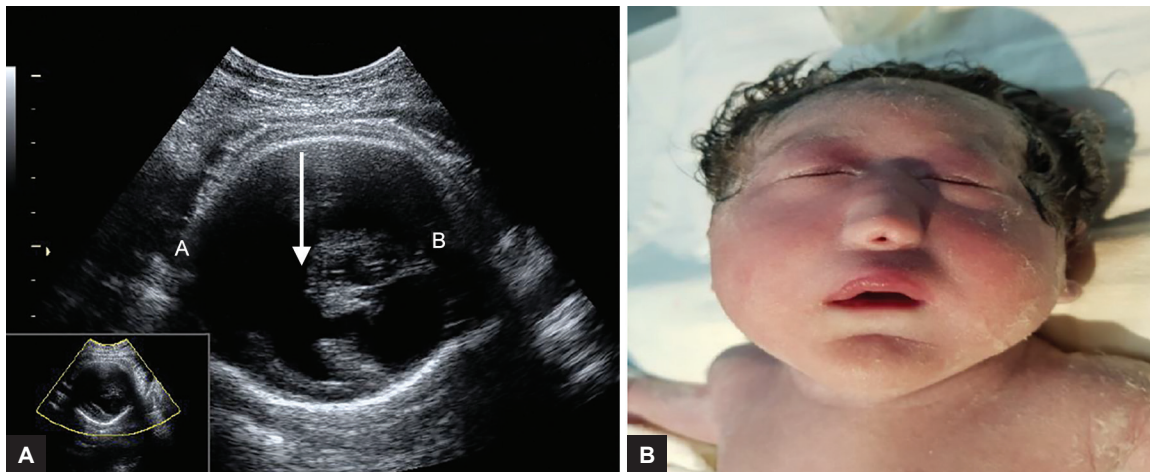


**Fig. 4:** Closed cranial sutures without fontanelles

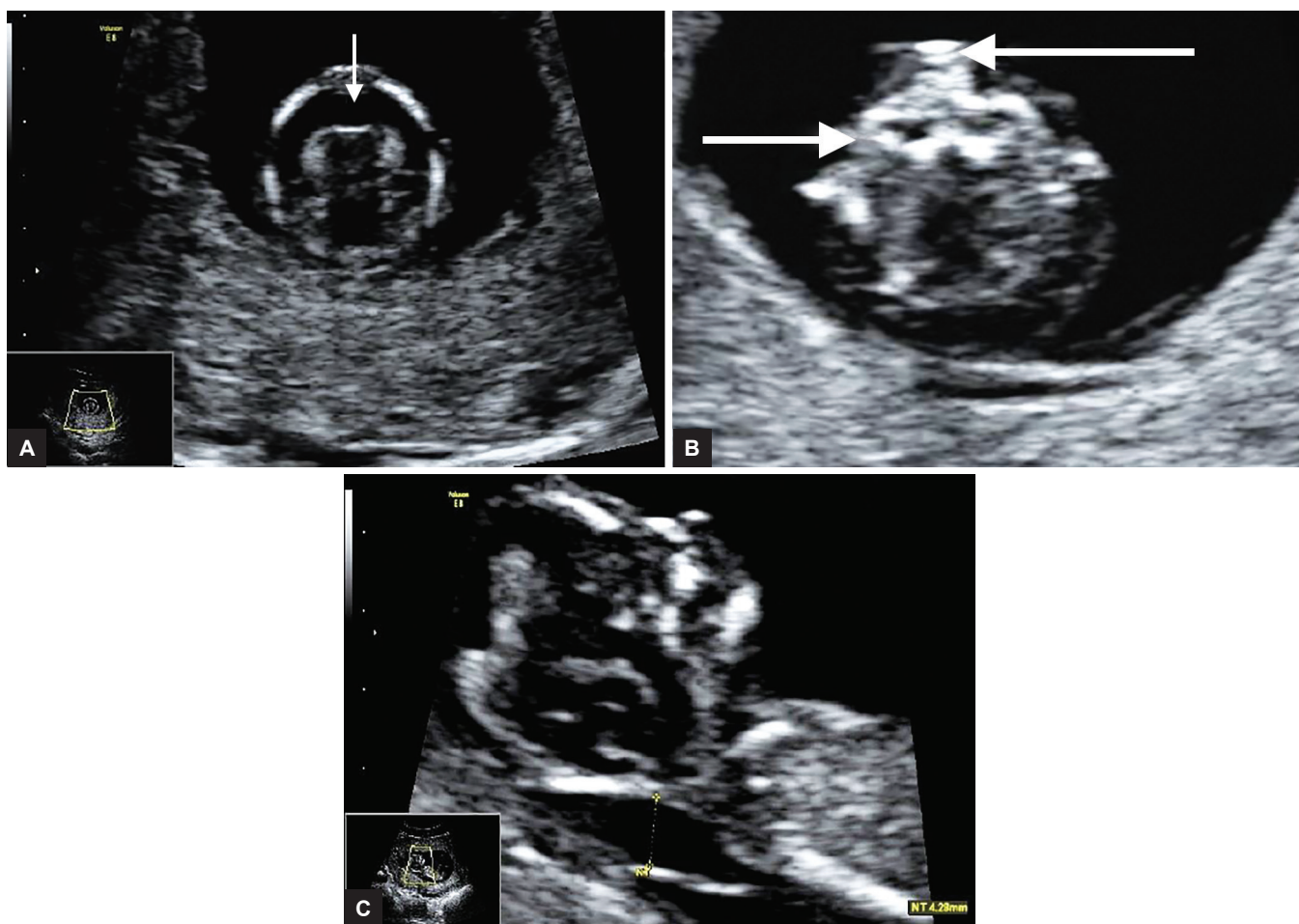


**Fig. 5:** Pathologic correlation shows single cerebral ventricle and absence of separate brain hemispheres—alobar HPE





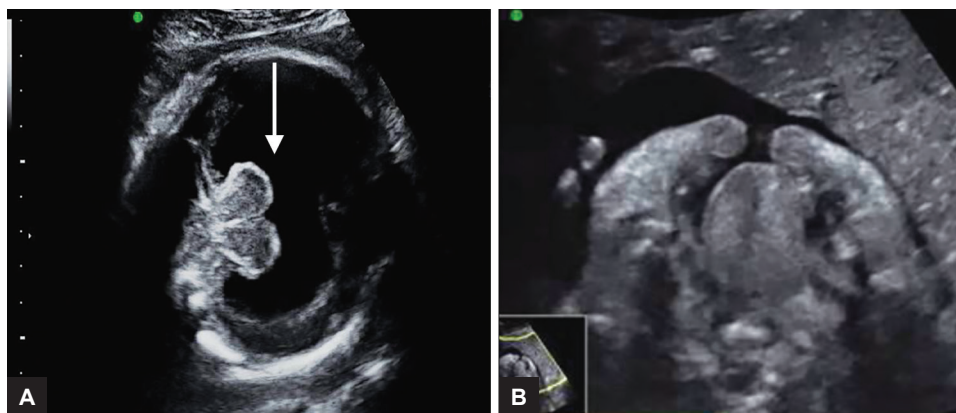
**Figs 6A and B:** Alobar HPE and fetal facial morphology



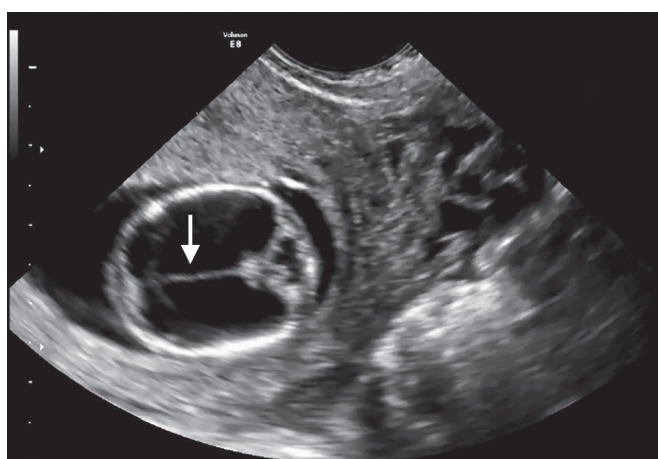
**Figs 7A to C:** Alobar HPE. (A) Transverse view of head at 14 weeks. Normal lateral ventricles were not demonstrated; (B) view slightly inferior shows hypotelorism (arrow) and proboscis; and (C) fetal karyotype was trisomy 13

described as a brain almost completely divided into two distinct hemispheres, with the only exception of a variable degree of fusion at the level of the cingulate gyrus and frontal horns of lateral ventricles. The septum pellucidum is always absent. The olfactory bulbs and tracts and the corpus callosum may be absent, hypoplastic, or normal. An interesting aspect of lobar HPE that has been recently

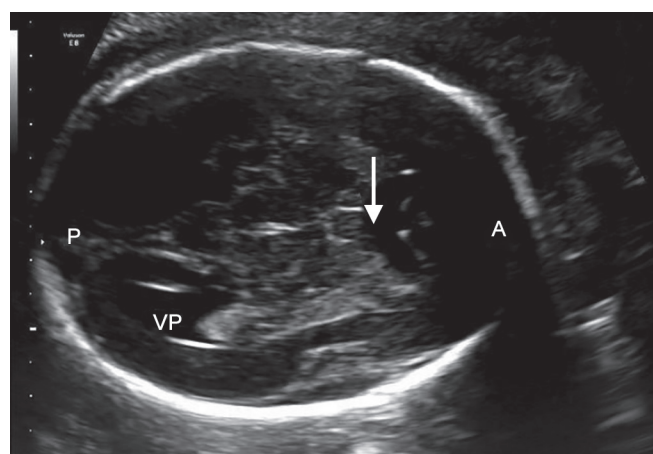
described in studies using magnetic resonance is the fusion of the fornices, which are seen as a solid fascicle running in the midline in the upper portion of the third ventricle.<sup>5</sup> Prenatal ultrasonography is not a reliable method of diagnosing mild forms of HPE, such as lobar HPE, because of its high false-negative rate; so, an Magnetic resonance imaging should be performed to confirm such forms of HPE.



**Figs 8A and B:** Semilobar HPE. Transverse image with partial separation of monoventricle. Cleft lip and palate were also identified



**Fig. 9:** A 14 weeks pregnancy with hydranencephaly. The arrow marks the presence of the interhemispheric fissure



**Fig. 10:** Coronal views with absence of the septum pellucidum and fused frontal horns (arrow). A: anterior; P: posterior; VP: posterior horn of the lateral ventricle

## DIFFERENTIAL DIAGNOSIS

Alobar HPE could be confused for hydranencephaly with cerebral tissue absence, but should be distinguished by the absence of cerebral cortex and fusion of midline thalami seen with HPE (Fig. 9). Hydranencephaly should also show absence of facial and other anomalies.

It may be very difficult to distinguish lobar HPE from agenesis of septum pellucidum with or without septo-optic dysplasia. With this condition, the cavum septi pellucidi is also absent, and the frontal horns are fused on the midline and have a typical squared roof (Fig. 10). The colorfully named “snake under the skull” sign describes the route of the anterior cerebral artery directly beneath the frontal bones as it is displaced forward by the abnormal cortical tissue of the “fused” frontal lobes. It may be seen in all forms of HPE and may be used to help with the prenatal diagnosis of lobar HPE *vs* septo-optic dysplasia.<sup>6</sup>

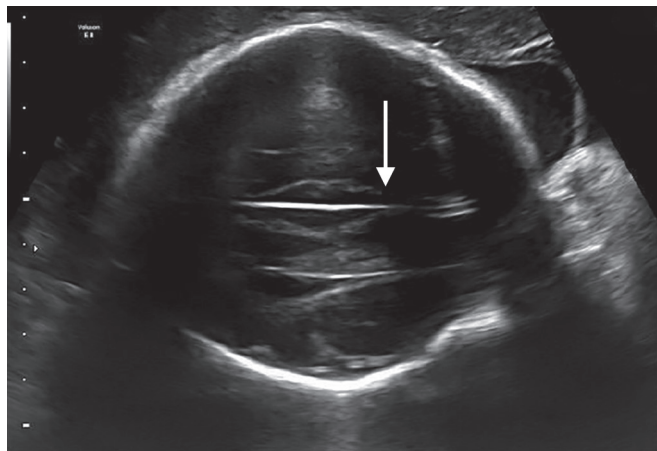
Another midline abnormality of the brain that represents a challenge to differentiate from lobar HPE is the agenesis of corpus callosum (Figs 11 and 12). The

development of the corpus callosum occurs between the 12th and 16 to 20th weeks of gestation.<sup>7,8</sup> It begins with the genu and then continues posteriorly along the body to the splenium. The rostrum is the last part to be formed. In secondary dysgenesis, parts of the corpus callosum which form before the insult will be present, whereas later parts will be absent. The presence of the rostrum essentially excludes primary agenesis. One apparent exception to this rule is HPE in which it is the anterior parts of the corpus callosum which are absent.<sup>9</sup> This has been termed atypical callosal dysgenesis.

## DISCUSSION

From an etiological standpoint, chromosomal anomalies are responsible for 24 to 45% of HPE cases, most frequently not only numeric anomalies of chromosomes 13 and 18, and triploidy, but also structural anomalies, responsible for 10 to 20% and most commonly involving 13q, 18p, 7q36, 3p24-pter, 2p21, and 21q22.3 (in decreasing order of frequency).<sup>10,11</sup>



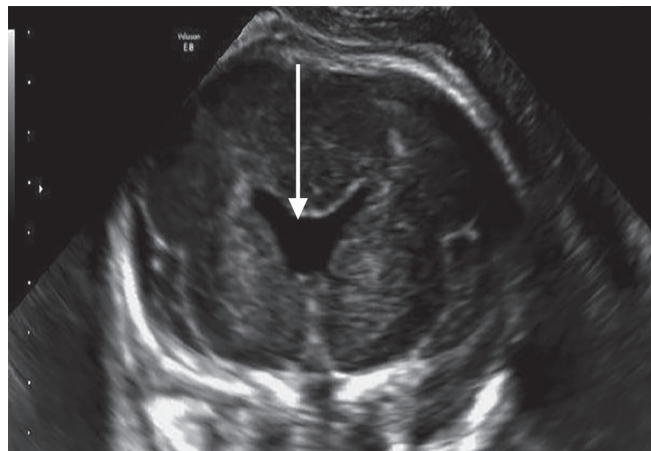


**Fig. 11:** Characteristical configuration of the lateral ventricles. Both walls of the lateral ventricles are identified where only periventricular lines are normally present: Also note characteristic dilatation of the occipital horns (colpocephaly)

According to multiple studies, the male-to-female ratio for HPE is 1:1.56. Maternal diabetes mellitus is a known risk factor; maternal use of alcohol, retinoic acid, diphenylhydantoin, aspirin, misoprostol, methotrexate, and cholesterol-lowering agents has been implicated, but not proven to be causative.

The most frequently associated anomalies include the central nervous system, the heart, the skeleton, and the gastrointestinal tract, an association that increases the risk of chromosomal and genetic anomalies. That is why karyotyping should always be performed. The empiric recurrence risk is 5 to 6%. If HPE occurs in the context of a syndrome, the recurrence risk is that of the syndrome.

The antenatal management regards looking for additional anomalies, considering fetal magnetic resonance imaging, offering karyotype with microarray analysis, and discussing management options, including pregnancy termination and timing and mode of delivery to avoid the maternal morbidity, and providing comfort care *vs* aggressive resuscitation. Mortality and morbidity associated with HPE depend on the severity of the malformations; most of the affected pregnancies result in miscarriage. Among live births, those with the severe type often die within days of birth; meanwhile, most persons with milder malformations survive beyond infancy. Life expectancy is poorest among those with syndromal and alobar HPE. In lobar HPE, patient's mental impairment and visual and olfactory abnormalities are often present, but they can lead a normal life.<sup>12</sup> About 50% are able to walk (some require assistance), have normal-to-mildly impaired hand function, and can speak single words (some speak in multiword sentences).<sup>13</sup> Children with middle hemispheric variant may ambulate with assistance, and speak and function with mild impairment,<sup>14</sup> but the developmental outcome is similar to that in lobar HPE.<sup>15</sup>



**Fig. 12:** Arrow represents absent corpus callosum and communication between the anterior horns of the lateral ventricles

## CONCLUSION

The advances of modern medicine allow patients with severe brain malformations to survive infancy, often into late childhood and adulthood. Therefore, it is useful to be able to diagnose brain malformations and prognosticate developmental potential of affected infants. Early and accurate diagnosis are essential for appropriate counseling of families with regard to pregnancy management, the options for which are subject to legal restrictions that vary from nation to nation. It is also important that affected families understand the ongoing needs of surviving children and future recurrence risks.<sup>16</sup> Future investigations are planned to correlate these morphologic abnormalities with specific clinical features and generate more accurate prognostic information.

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