Early Prenatal Diagnosis of Semilobar Holoprosencephaly Combined with a Dorsal Cyst and No Facial Defect

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Holoprosencephaly (HPE) is a complex human brain abnormality caused by incomplete cleavage of the prosencephalon into the right and left hemispheres, occurring between the 18th and 28th day of gestation. Different levels of increasing severity are defined: (1) lobar HPE, where the right and left ventricles are separated, but with some continuity across the frontal cortex; (2) semilobar HPE with a partial separation; and (3) alobar HPE, the most severe form, with a single brain ventricle and no interhemispheric fissure.

Mettler [1] described the dorsal cyst of HPE as a structure that "occupies the area of the calvarium above the dorsocaudal aspect of the diencephalons" and indicated that the "walls of this cyst are always directly continuous with the most caudal parts of the walls of the telencephalon medium and its cavity communicates directly with the common ventricle of the telencephalon". Furthermore, he added that a variable amount of the anterior wall of the dorsal cyst is "fused with the dorsal surface of the thalamus, sealing over the third ventricle". Other authors have suggested that aqueduct stenosis or atresia results in dorsal cyst formation [2,3]. There have been many reports on the nature of dorsal cyst in HPE, but it was always noted after birth. HPE is the most common but lethal defect in the congenital cerebral abnormalities. It is a heterogeneous etiologic disease that can be caused by both a teratogenic and/or a genetic basis. Alobar or semilobar HPE is usually combined with a facial defect due to the missed embryogenesis, but early prenatal diagnosis of semilobar HPE with a dorsal cyst and no facial defect is rare. Herein, we report a case of early detection of HPE with a dorsal cyst and no facial defect in a low-risk mother, to present the distinctive features of semilobar HPE and the hypotheses involving a dorsal cyst.

A 27-year-old, gravida 1, para 0, woman first visited our prenatal clinic at 9 weeks of gestation. Previous obstetric history and family history were unremarkable. An ultrasound (US) scan confirmed an intrauterine pregnancy with a fetus of crown–rump length of 2.5 cm without abnormal findings. During the second visit at 12 weeks' gestation, a second US scan illustrated a nuchal translucency measuring 1.8 mm and a clear nasal bone structure. However, a dorsal cyst over the magnum cisterna in the transverse view (Figure A) was noted. The follow-up scans showed abnormalities of the forebrain, including partial absence of the midline echo, partial fusion of the thalami and abnormal ventricular configuration (Figures B and C), but facial structure was normal. Semilobar type of HPE with a dorsal cyst was diagnosed at that time. The other organs and systems, including cardiovascular, gastrointestinal and urinary systems, were unremarkable under the sonographic examination. Examinations for the presence of toxoplasmosis, rubella, cytomegalovirus, herpes (TORCH) were performed but without positive findings. Consequently, amniocentesis was scheduled for the next visit.

At 15 weeks of gestation, another US scan was performed to confirm the last echo findings, and genetic amniocentesis was performed. The karyotype turned out to be a normal 46,XX (female). After genetic counseling, the parents chose to terminate the pregnancy. The fetus was aborted 48 hours after misoprostol 200 μg combined with Laminaria applied to internal cervical os. The abortus was sent for autopsy and demonstrated results compatible with the aforementioned US findings and diagnosis.

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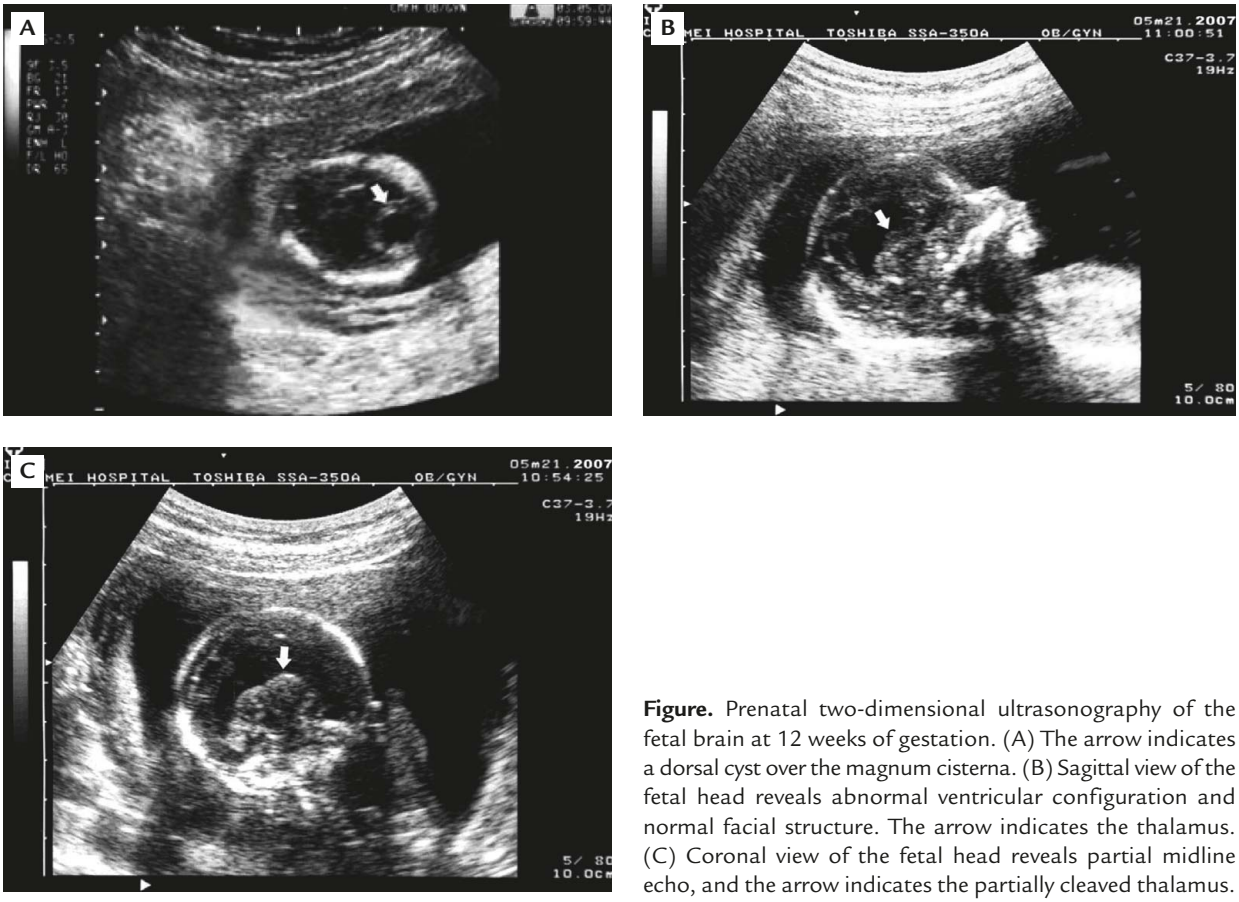

Figure. Prenatal two-dimensional ultrasonography of the fetal brain at 12 weeks of gestation. (A) The arrow indicates a dorsal cyst over the magnum cisterna. (B) Sagittal view of the fetal head reveals abnormal ventricular configuration and normal facial structure. The arrow indicates the thalamus. (C) Coronal view of the fetal head reveals partial midline echo, and the arrow indicates the partially cleaved thalamus.

HPE has an incidence rate as high as 1:250 during the process of fetal development; however, because of intrauterine death, the live born incidence rate is 1:16,000 [4]. It has been suggested that there is a high rate of spontaneous abortion [5].

HPE is usually divided into three subcategories: alobar, semilobar, and lobar [6]. In alobar HPE, the most severe form, there is entire failure of cleavage of the forebrain into the right and left hemispheres as a result of a single ventricular cavity, fusion of the thalami and agenesis of the corpus callosum, falx cerebri, optic tracts, and olfactory bulbs. Partial cleavage causes semilobar HPE, with posterior separation of the cerebral hemispheres, variable degrees of fusion of the thalami, and absence of olfactory bulbs and corpus callosum. In lobar HPE, the mildest form, the abnormality may be confined to absence of the corpus callosum, and fusion of the lateral ventricles and cingulate gyrus. The two hemispheres are separated anteriorly and posteriorly. Given their distinctions, differentiation of the alobar from semilobar forms may still be difficult prenatally, and physicians must rely on the presence of a posterior midline echo in the latter. The ultrasonographic markers of lobar HPE are subtle and may be easily missed on prenatal US. The markers include the absence of the cavum septum pellucidum, together with variable enlargements of the lateral ventricles. Our case exhibited the partial midline echo near the thalamus, partial cleavage of the thalamus and abnormal ventricular configuration, so the fetus was categorized as having the semilobar type. HPE can occur as a single finding or in combination with other abnormalities in a recognized syndrome, such as Dandy-Walker syndrome (DWS) or Smith-Lemli-Opitz syndrome. In our case, there was a dorsal cyst noted over the magnum cisterna. At the initial impression, HPE combined with DWS was suggested. Although these two major malformations rarely coexist, it has been reported [7]. However, DWS was excluded immediately owing to the intact vermis and cerebellum found in the follow-up scans. The etiology of the dorsal cyst is rarely understood, although it is usually encountered in HPE [8]. Simon and his colleagues [9] indicated the presence of a dorsal cyst correlated closely with the presence of noncleavage of the thalamus. Our case had a partial fusion of the thalamus visualized using a two-dimensional (2D) US scan. Thus, we speculated that the partially cleaved thalamus physically obstructed the entry of the cerebrospinal fluid from the third ventricle to form the cyst.

HPE is usually associated with a facial defect (i.e. cyclopia, ethmocephaly, cebocephaly, etc.), so the use of three-dimensional (3D) US makes additional diagnostic US tomograms possible. Some investigators have presented an alobar HPE with cyclopia at 9 weeks of gestation visualized using 2D and 3D US [10]. Since there was no facial defect in our case, HPE was not diagnosed until 12 weeks of gestation. During embryogenesis, the fetal ventricle of the prosencephalon does not develop into two ventricles until after 10 weeks of gestation, and it is very difficult to make a prenatal diagnosis of HPE without facial defect using 2D or 3D US before 10 weeks of gestation. In fact, 2D US is more accurate in the diagnosis of fetal craniofacial malformation than 3D US [11].

Karyotypic abnormalities were reported in approximately 55% of HPE cases, the most common of which is trisomy 13 [12]. In addition, a study showed that 39% of fetuses with trisomy 13 had HPE [13]. Other chromosomal abnormalities include trisomy 18, del(13q), del(18p), dup(3p), and del(7) [5]. However, the karyotype in our case was normal and there was no history of genetic abnormalities in their families.

Barr and his colleagues indicated that there was a 200-fold increase in the incidence of HPE in children born to mothers with insulin-dependent diabetes [14]. In addition, Chen et al reported a case of concomitant alobar HPE and caudal regression syndrome associated with maternal diabetes [15], which was likely due to the teratogenic effect of hyperglycemia, resulting from poor diabetic control, during early pregnancy. However, the mother and her family in our case had no history of diabetes.

TORCH infection may affect cerebral embryogenesis early in the pregnancy. Kilic and Yazici [16] reported a case of Cytomegalovirus, rubella virus and herpes simplex virus infection at the early stage of gestation, resulting in HPE with ocular defect. However, no TORCH infection found in our case.

In conclusion, HPE has extremely heterogeneous etiologies that can include both a teratogenic and/or a genetic basis [4], Taking personal and family medical histories (such as diabetes) and recording drug abuse or environmental factors (such as TORCH infection) are crucial. In our case, the above-mentioned risk factors were not found, so it was more difficult to diagnose accurately due to the low-risk status. Nevertheless, semilobar HPE with a dorsal cyst and no facial defect poses a challenge when making a diagnosis, especially at a very early gestational age, unless appropriate diagnostic investigation is undertaken. The use of 2D US scan should be sufficient for the diagnosis when it is performed by well-trained and skillful operators. The above-mentioned experiences of HPE survey, including history taking, etiology caused by teratogenic or genetic basis and detailed fetal echo screening, benefit us by increasing our knowledge to help us with genetic counseling and prenatal diagnoses.

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