Rare disease

Prenatal ultrasound diagnosis of holoprosencephaly and associated anomalies

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Summary

Holoprosencephaly is a rare spectrum of cerebral and facial malformations resulting from incomplete division of the embryonic forebrain (prosencephalon) into distinct lateral cerebral hemisphere. Holoprosencephaly spectrum in the fetus is often associated with other anomalies, particularly of the face and extremities. Here we present three different cases of patients with holoprosencephaly who failed to attain routine sonography during 11–20 weeks owing to some unavoidable circumstances. Two of them were diagnosed during the third trimester and one in the late second trimester. Ultrasound findings of associated anomalies were confirmed after a clinical examination of the delivered fetuses.

BACKGROUND

Holoprosencephaly is estimated to occur in 1 of 10 000–20 000 live births. It is divided into alobar, semilobar and lobar forms, although there are no clear-cut defining features. A series of facial anomalies are frequently associated, owing to the common origin of the embryonic forebrain and mid-face from the prechordal mesoderm, along with some other anomalies. We report the three selected cases for their rarity and different anomalies associated with them, in addition to holoprosencephaly. This case report evaluates the importance of early ultrasound in prenatal diagnosis of holoprosencephaly and associated anomalies in a fetus and the dreaded outcome if diagnosed late.

CASE PRESENTATION

Case 1

A 27-year-old primigravida with natural conception was referred in the third trimester for fetal well-being. A previous ultrasonography was done at 6 weeks for confirmation of pregnancy and showed a single intrauterine gestational sac with fetal pole with cardiac activity. Crown rump length was 4.2 mm, consistent with a 6-week 2-day maturity. After that, she came for an ultrasonography examination directly in the third trimester.

Case 2

A 36-year-old woman, gravida 5, para 3, abortion 1, live issues 3, was admitted with labour pains and referred for sonography for the first time at 35 weeks of gestation for fetal well-being and advanced maternal age in her fifth pregnancy. She did not have any previous sonography available with her. She had three normal children and one abortion at 9 weeks in her second pregnancy, because of some unknown cause.

Case 3

A 22-year-old Indian woman, gravida 1 para 0, came for the first time in the second trimester of her pregnancy for sonographic confirmation of gestational age.

In all the above-mentioned cases, rest of the medial and family histories were unremarkable.

Physical examinations and all other laboratory investigations were within normal limits.

INVESTIGATIONS

Case 1

Ultrasonography revealed a single monoventricular cavity with partial agenesis of the corpus callosum and fused thalami suggestive of semilobar-type holoprosencephaly. A mild degree of hypotelorism was noted. In addition, the

Figure 1 Two different sections of fetal skull showing a large monoventricular cavity.

Figure 2 Semilobar type of holoprosencephaly showing fused thalami.

fetus had a cleft lip. The fetal spine did not reveal any abnormality. Fetal parameters were consistent with a 32–33-week maturity of the fetus (figures 1–4).

Figure 3 Profile view of face showing cleft lip.

Figure 4 Postnatal image of neonate showing cleft lip and limb abnormalities.

Case 2

Ultrasonography revealed a single intrauterine live fetus. Biparietal diameter, abdominal circumference and femur length were consistent with the clinically estimated gestational age of 34–35 weeks. Axial sonograms of the fetal head showed a dilated, large monoventricle with a peripheral rim of the cortex and fused thalami. Falx cerebri was present. The fetal spine showed meningocele in the lower lumbar region. Extrarenal pelvis was noted in the right kidney, an incidental finding. No facial or extremity anomalies were noted (figures 5–8).

Case 3

Case 3 Sonographic examination of the uterus revealed a single living fetus. Axial sonograms of the fetal head showed dilated cerebral ventricles and fused thalami. The spine showed meningocele in the lumbar region. Fetal biparietal diameter, abdominal circumference and femur length were consistent with the clinically estimated gestational age of 26–27 weeks. Mild polyhydramnios was noted (figures 9–11).

OUTCOME AND FOLLOW-UP

Case 1

A male child was born by vaginal delivery after induction. A clinical examination revealed the presence of a cleft lip and a mild degree of hypotelorism. The neonate also had limb abnormalities that were not documented on sonography because of the abnormal position and slightly less amount of liquor (9–10 amniotic fluid index). (However, we had informed the gynaecologist about this possibility.) The neonate died several hours after birth.

Case 2

A male child was born by vaginal delivery. A clinical examination revealed the presence of meningocele in the lower lumbar region. The neonate was admitted to the neonatal intensive care unit and died 2 days after birth.

Case 3

Subsequent sonographies at 30 and 34 weeks were done. The sonogram at 34 weeks confirmed the suspected fetal

Figure 5 Axial section of fetal skull showing a large monoventricular cavity and a peripheral thin rim of brain parenchyma.

Figure 6 Fetal skull showing fused thalami and falx cerebri.

demise. The female child showed meningocele in the lumbar region on postnatal examination.

DISCUSSION

Holoprosencephaly arises from disruption of the normal induction and patterning of the rostral neural tube during early embryogenesis.¹⁻⁶

The primary brain vesicles, the prosencephalon, mesencephalon and rhombencephalon, are formed by the third

embryonic week. Separate lateral telencephalic and diencephalic structures develop from a single prosencephalic vesicle, normally beginning by the fifth embryonic week of gestation.⁶

Holoprosencephaly results from incomplete cleavage of the prosencephalon, occurring between the 18th and the 28th day of gestation and affecting the forebrain and the face. Deficiencies in embryonic forebrain cleavage range from the most severe or alobar forms to the

Figure 7 Meningomyelocele in the lower lumbar spine.

Figure 8 Axial section of the abdomen showing extrarenal pelvis in the right kidney, an incidental finding.

Figure 9 Semilobar type of holoprosencephaly showing a large monoventricular cavity and fused thalami.

least severe or lobar forms and middle interhemispheric variant.^{1 3}

Distinctive midline facial malformations occur in most cases. These malformations are correlated with the degree of holoprosencephaly and have prognostic importance.^{7 8}

This includes:

- ▶ Cyclopia, in which a single, midline, fused eye exists in a single orbit below a proboscis.
- ▶ Ethmocephaly, in which ocular hypotelorism is present with an interorbital proboscis.

Figure 10 Meningomyelocele in the lumbar spine.

Figure 11 Postnatal image of neonate showing meningocele.

- ▶ Cebocephaly, in which ocular hypotelorism is present with a single-nostril nose.
- ▶ Ocular hypotelorism and midline clefting.
- ▶ Ocular hypotelorism and bilateral clefting.^{1 3}

Other malformations include arhinencephaly (absent olfactory bulbs and tracts), absent thalami, hydrocephalus and neural migration abnormalities. In case 1, ocular hypotelorism and midline clefting were present.

The frequency of holoprosencephaly is 1 in 10 000–20 000 live newborn. During the early embryonic period, the frequency is 1 in 250 but progressively declines because of high fetal death rates.^{4 9 10}

Researches into the aetiology of holoprosencephaly have revealed multiple teratogenic and genetic causes (chromosomal and single gene). The involvement of multiple genes has been implicated in ventral forebrain induction; their products include the Sonic Hedgehog (Shh) protein and the Hedgehog signal transduction proteins patched (Ptc),¹¹ as well as proteins in the Gli family and cholesterol biosynthesis pathways.¹²

Prenatal diagnosis of holoprosencephaly is based on transabdominal or transvaginal ultrasonography and MRI to identify most cases of alobar or semilobar holoprosencephaly.

In our cases, diagnosis was based on transabdominal ultrasonography and clinical examination.

Treatment in severe forms of holoprosencephaly is symptomatic and supportive, and requires a multidisciplinary management. The outcome of the child depends on the severity of holoprosencephaly and the associated medical and neurological complications.

Learning points

- ▶ Holoprosencephaly can be diagnosed even in the first trimester after 11–12 weeks. So, routine prenatal ultrasound should be carried out in all patients during this period.
- ▶ Ultrasound is a good modality for prenatal diagnosis of holoprosencephaly that is frequently associated with midline face deformity such as cleft lip and palate, as mentioned earlier in case 1.
- ▶ In addition to facial anomalies, anomalies of the spine and extremities are frequently associated with it and one must look for them, such as meningocele in case 2 and case 3 and limb abnormalities in case 1.
- ▶ The radiologist should remain vigilant in suspected patients who have a history of a child with holoprosencephaly, or in high-risk patients such as elderly gravida.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Cohen HL**, Sivit CJ. Holoprosencephaly. In: Cohen HL, Sivit CJ, eds. *Fetal and pediatric ultrasound: a casebook approach*. New York: McGraw-Hill, 2001:12–16.
2. **Muenke M**, Beachy PA. Holoprosencephaly. In: Scriver CR, Sly WS, Childs B, et al. eds. *The metabolic and molecular bases of inherited disease*. 8th edn. New York: McGraw-Hill Professional, 2001:6203–30.
3. **Tegay DH**, Cohen HL, Rosovsky M. Holoprosencephaly imaging. Medscape Reference. <http://emedicine.medscape.com/article/409265-overview>, 2008.
4. **Muenke M**, Beachy P. Genetics of ventral forebrain development and holoprosencephaly. *Curr Opin Genet Dev* 2000;**10**:262–9.
5. **Lewis AJ**, Simon EM, Barkovich AJ, et al. Middle interhemispheric variant of holoprosencephaly: a distinct cliniconoradiologic subtype. *Neurology* 2002;**59**:1860–5.
6. **Jones K**. *Smith's recognizable patterns of human malformations*. 6th edn. Philadelphia, PA: Saunders, 2006:701–3.
7. **DeMyer W**, Zeman W, Palmer CG. The face predicts the brain: diagnostic significance of median face anomalies for holoprosencephaly(arhinencephaly). *Pediatrics* 1964;**34**:256–63.
8. **Plawner LL**, Delgado MR, Miller VS, et al. Neuroanatomy of holoprosencephaly as predictor of function: beyond the face predicting the brain. *Neurology* 2002;**59**:1058–66.
9. **Leoncini E**, Baranello G, Orioli IM, et al. Frequency of holoprosencephaly in the International Clearinghouse Birth Defects Surveillance Systems: searching for population variations. *Birth Defects Res A Clin Mol Teratol* 2008;**82**:585–91.
10. **Dubourg C**, Bendavid C, Pasquier L, et al. Holoprosencephaly. *Orphanet J Rare Dis* 2007;**2**:8.
11. **Nanni L**, Ming JE, Bocian M, et al. The mutational spectrum of the Sonic Hedgehog gene in holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly. *Hum Mol Genet* 1999;**8**:2479–88.
12. **Roessler E**, Du YZ, Mullor JL, et al. Loss-of-function mutations in the human GLI2 gene are associated with pituitary anomalies and holoprosencephaly-like features. *Proc Natl Acad Sci USA* 2003;**100**:13424–9.

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