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Case Report

Obstetrics and Gynaecology Section

Middle Interhemispheric Variant of Holoprosencephaly – Presenting as Non-Visualized Cavum Septum Pellucidum and An Interhemispheric Cyst in A 19-Weeks Fetus

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ABSTRACT

Middle Interhemispheric variant (MIH) is a rare subtype of holoprosencephaly (HPE), also known as syntelencephaly. We present a case of MIH, which was diagnosed as an interhemispheric cyst on antenatal sonography at 19 weeks, but later diagnosed as MIH variant of holoprosencephaly after a postabortal MRI and perinatal autopsy.

Keywords: Arachnoid cyst, Interhemispheric fissure, Ventriculomegaly

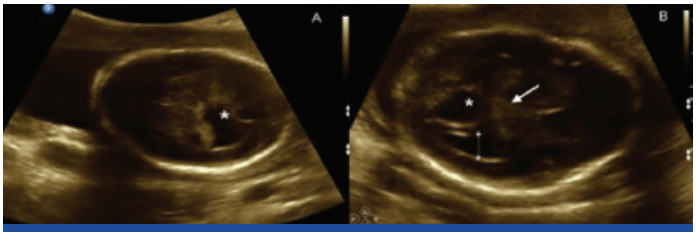
CASE REPORT

A 27-year-old primigravida in a non-consanguineous marriage was referred to us at 18 weeks of gestation, with the mid trimester anomaly scan showing mild unilateral ventriculomegaly [Table/Fig-1a] and a suspected neural tube defect. Detailed neurosonogram showed mild unilateral ventriculomegaly (atrium of right lateral ventricle measuring 10-11 mm), and non visualization of Cavum Septum Pellucidum. Body of Corpus callosum was not seen clearly. There was an anechoic area measuring 2 cm, seen replacing the central part of interhemispheric fissure, which was thought as an interhemispheric cyst, probably an arachnoid cyst [Table/Fig-1b]. Interhemispheric fissure was thought to be seen in the anterior and posterior parts. There was an echogenic area in the middle of brain causing slight midline shift to left [Table/Fig-1b]. This was suspected to be a choroid plexus tumour like papilloma.

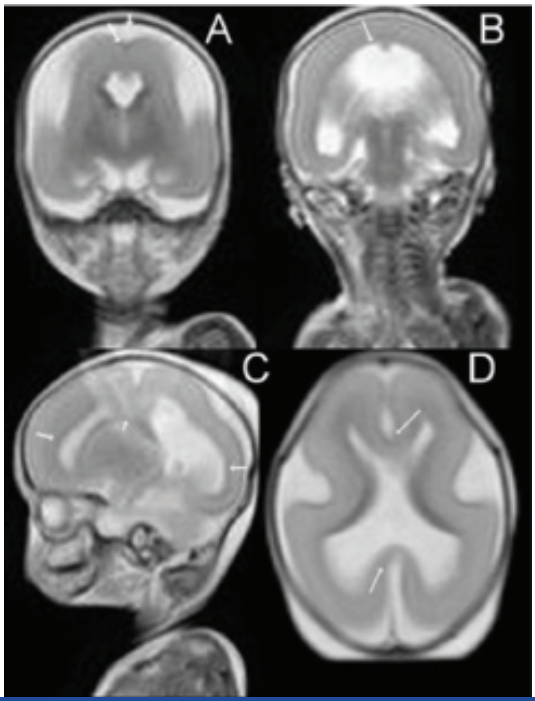
Considering the uncertainty of neurological prognosis, couple opted for termination of pregnancy and consented for postmortem examination of the fetus. The study has the approval of institutional ethics committee. Post mortem MRI [Table/Fig-2a-d] showed abnormal midline fusion of cerebral hemispheres in the posterior frontal and anterior parietal regions, with normal separation of rest of the brain. The falx cerebri was not visualized. Body and rostrum of corpus callosum were found to be deficient. Genu and splenium were seen. Cavum septum pellucidum was not visualized. Prominent lateral ventricles, quadrigeminal cistern and cisterna magna were noted. Third and fourth ventricles were normal. What was thought of as an interhemispheric cyst in prenatal ultrasound, was the prominent supracerebellar cistern. The echogenic area in the center was the choroid plexus in the fused central part (body) of the lateral ventricles.

Perinatal autopsy [Table/Fig-3a-c] confirmed non separation of posterior frontal and anterior parietal lobes of cerebral hemisphere. Falx cerebri and body of corpus callosum were absent. Hypoplastic olfactory bulbs were noted. Monoventricle was noted (fusion of body of lateral ventricles). Thalami and third ventricles were normal. No other structural anomalies were noted. Amniocentesis showed normal karyotype.

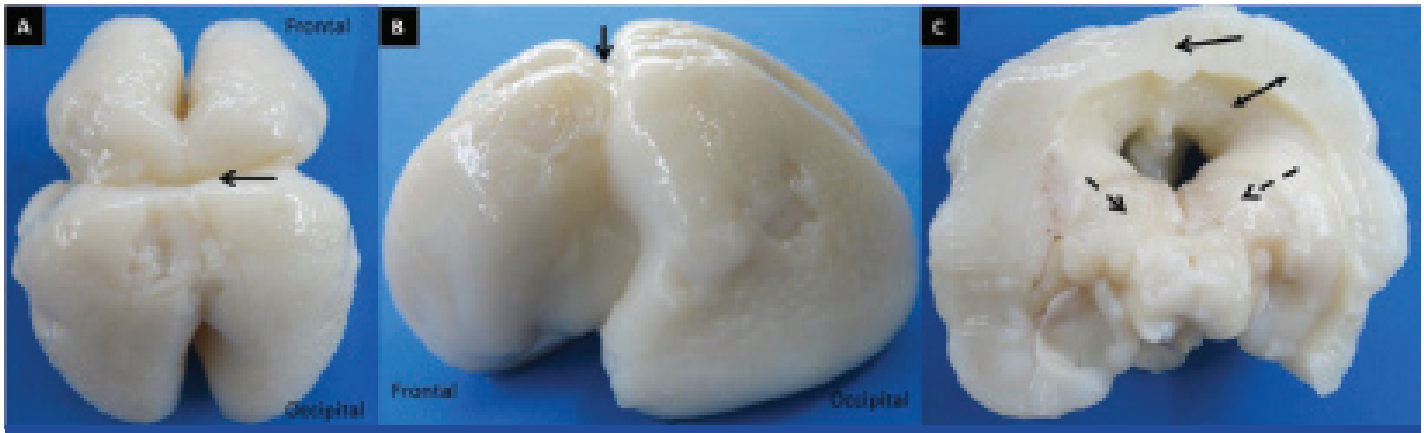
Couple were counseled that fetus had nonsyndromic holoprosencephaly, which is a genetically heterogenous condition with empiric risk of recurrence in subsequent pregnancies being 6-10%. They were offered further genetic testing in the form of genomic microarray and Next Generation Sequencing panel testing, in order



[Table/Fig-1a&b]: Antenatal Ultrasound pictures
1a. Initial ultrasound picture, suspicious of ventriculomegaly (*at the midline anechoic area, thought of as dilated lateral ventricles at referral)
1b. Subsequent image showing normal posterior horn of ventricle (calipers), an interhemispheric anechoic area (*) and an echogenic area near the midline, probably fused choroid plexus (arrow). Cavum septum pellucidum is not seen



[Table/Fig-2a-d]: MRI of the fetus, after induced abortion
Coronal T2WI (2a) shows midline fusion of cerebral hemispheres (long arrow) and sylvian fissures is passing almost coronally over the vertex of the fused brain to join with the fissure from the other side (short arrow). Note the fusion of the lateral ventricles (2b); Sagittal T2WI (2c) and axial MR; (2d) shows normal development of genu and splenium of corpus callosum. Axial T2W; (2d) showing separated interhemispheric fissure anteriorly and posteriorly. MR features are suggestive of syntelencephaly



[Table/Fig-3a-c]: Autopsy pictures suggestive of syntelencephaly
Superior (a), lateral (b) and coronal (c) views of brain show non-separation of posterior frontal and parietal lobes of cerebrum [a,b,c (black arrow)], single cerebral ventricle [c, (double headed arrow)] and thalami [c, (dotted arrow)]

to know the aetiological associations, which they were not keen on. Prenatal diagnosis can be attempted in each of the subsequent pregnancies with a detailed neurosonogram, although minor variants could be missed.

DISCUSSION

In MIH variant of holoprosencephaly, only posterior frontal and anterior parietal lobes of the fetal brain are undivided to varying extent. This is a major brain malformation with significant neurological sequel [1-3]. However, it is a challenge to accurately diagnose this malformation in the fetus, Prior to 20 weeks. In the mid trimester anomaly scan, several midline brain malformations may present with non visualised cavum septum pellucidum [4]. A cystic area in the midline can often give rise to a confusing picture.

In countries like India, where there are strict regulations on the medical termination of pregnancy (MTP), detailed targeted prenatal ultrasound is performed prior to 20 weeks, usually around 18 weeks. This is because legally MTP cannot be performed beyond 20 weeks. The evolving major abnormality in the fetal brain may thus be regarded as a minor variation leading onto wrong diagnosis or a delayed diagnosis. Even prenatal MRI is hard to interpret before 20 weeks. However, accurate diagnosis of fetal brain abnormality is very important for prognostication so that all options are available for the couple.

Prenatal diagnosis of MIH with neurosonogram alone, especially prior to 20 weeks, is rarely reported in the literature. It is difficult to distinguish among various midline brain anomalies in the fetus [1,2]. Often, other abnormalities like agenesis of corpus callosum and interhemispheric cysts are misinterpreted as holoprosencephaly. Ventriculomegaly is the usual reason for referral, as in our case. In the case reported by Pulitzer et al., [1], prenatal diagnosis was suspected by a neurosonogram at about 22 weeks, which was confirmed by a prenatal MRI. Posada reported a case where MIH was diagnosed with the help of prenatal MRI at around 34 weeks, along with multiple other malformations [3]. Malinger et al., presented a prenatal series of 25 cases among whom CSP was not seen [4]. Two among them were diagnosed to have MIH at 23 weeks of gestation. Neurosonograms were enhanced by a vaginal sonography. One case was referred as ventriculomegaly and the other as an interhemispheric arachnoid cyst. Picone et al., [5] published a case of MIH, who was referred with an absent cavum septum pellucidum and suspected absent corpus callosum. Detailed neurosonogram followed by prenatal MRI confirmed MIH variant of HPE at 26 weeks of gestation. This was associated with an unusual appearance of the corpus callosum and rare chromosomal abnormality: a 45X/46, XX/47, XX, +18 mosaicism.

It is important to distinguish MIH variant of HPE from other less severe midline brain anomalies of the fetus like isolated partial agenesis of corpus callosum and interhemispheric arachnoid cysts, because the neurological prognosis is better in later. However compared to other more severe forms of HPE, MIH variant leads onto fewer neurological disabilities [6], although there is a wide spectrum of manifestations. Motor and cognitive problems are less severe. Endocrinal dysfunction and choreoathetosis are much less common. However, upto 40% may have seizures and upto 86% may have spasticity. Very mild clinical phenotype has also been reported in the literature in which motor development was mildly delayed, and academic skills were near normal except for mild reading disability [7].

Whenever cavum septum pellucidum is not seen, agenesis of corpus callosum is suspected, and there is a midline cystic area mimicking an interhemispheric arachnoid cyst, or a case is referred with mild/asymmetric ventriculomegaly, it is worthwhile performing a prenatal MRI to rule out more serious anomalies including MIH variant of HPE. Considering prenatal MRI is increasingly available in developing countries, this modality should be utilized optimally to arrive at a specific neurological diagnosis, so couple has all options for management of pregnancy, and also accurate prognostication and counseling.

Prognosis of the fetus also depends on whether this is an isolated brain abnormality or whether it is associated with a chromosomal/genetic abnormality [8]. DNA microarray and Next Generation Sequencing panel testing should be done whenever possible, in order to know the aetiological associations. Brown LY et al., reported a case of syntelencephaly associated with ZIC2 gene mutation [9]. Yuichi Abe et al., published a report of a 20-month-old boy with syntelencephaly, in whom using genomic microarray, a heterozygous deletion was demonstrated involving EYA4 gene [10]. Co-existing cerebral cortical abnormalities would also lead on to poor prognosis. Recurrence risk can be as high as 13% in apparently isolated MIH [11]. Recurrence may be high if parents have balanced translocation. In future pregnancies, prenatal diagnosis is mainly by ultrasound.

CONCLUSION

MIH variant of HPE should be considered one among the differential diagnosis whenever midline brain structures are not satisfactorily visualized or when there is a suspicion of interhemispheric cyst. Prenatal MRI and perinatal autopsy should be increasingly used so as to arrive at a specific diagnosis.

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