Middle interhemispheric variant of holoprosencephaly in a 21-week fetus: a case report

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ABSTRACT

Highlights: Middle interhemispheric variant (MIH) is a rare subtype of holoprosencephaly (HPE). The differential diagnosis between variants of HPE may be difficult. Prenatal MRI has a fundamental role in the diagnosis. Careful attention to specific neurosonographic features can help in early diagnosis.

Holoprosencephaly (HPE) is the most common malformation of the forebrain in humans. It is a structural anomaly of the brain resulting from failed or incomplete forebrain division in the fourth week of gestation. According to De Myer's classification, three types of HPE, of increasing severity, are described: lobar, semilobar and alobar. Milder subtypes of HPE include the middle interhemispheric (MIH) variant, also known as "synthelencephaly", which is characterized by a midline connection of the two hemispheres in posterior frontal and parietal regions with separation of the anterior frontal and occipital lobes. Most severe HPE cases are diagnosed by ultrasound examination (US) and magnetic resonance imaging (MRI) during pregnancy. We present a case of MIH variant, diagnosed in a 21-week fetus by US and confirmed by MRI.

KEYWORDS

Holoprosencephaly, middle interhemispheric, syntelencephaly, prenatal ultrasound, neurosonography.

Introduction

Holoprosencephaly (HPE) is the most common malformation of the forebrain in humans. It is a structural anomaly of the brain resulting from failed or incomplete forebrain division in the fourth week of gestation [1]. The prevalence is 1/16,000 live newborns, while the incidence in conceptuses is as high as 1/250; the condition shows a worldwide distribution [2]. According to De Myer's classification, three types of HPE, of increasing severity, are described based on the degree of separation of the prosencephalon and the presence or absence of the interhemispheric fissure: the lobar, semilobar and alobar types [3]. The lobar type is characterized by inadequate anterior brain separation, a well-structured third ventricle and incomplete development of the lateral ventricles. In semilobar HPE, the posterior falx and posterior interhemispheric fissure are present, but the anterior brain is not separated. The alobar type is the most severe, and it appears as a mass of cerebral tissue with a crescent-like monoventricle. Milder subtypes of HPE include the middle interhemispheric (MIH) variant, also known as "syntelencephaly", which was first described by Barkovich and Quint in 1993 [4]. In MIH, the posterior frontal and parietal lobes fail to separate, with varying lack of cleavage of the basal ganglia and thalami and absence of the body of the corpus callosum, but presence of the genu and splenium of the corpus callosum. These forebrain malformations related with MIH are usually associated with facial anomalies (such as anophthalmia, cyclopia, hypotelorism, median labio-palatine cleft, bifid uvula, solitary median maxillary central incisor), with a broad spectrum of clinical manifestations. Furthermore, 25-50% of humans with HPE have chromosomal abnormalities or single gene disorders [5]. Most of the severe HPE cases are diagnosed by ultrasound examination (US) and magnetic resonance imaging (MRI) in pregnancy. However, MIH variant cases are often not amenable to prenatal diagnosis due to the macroscopically normal brain.

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The etiology of HPE is very heterogeneous. There are environmental factors known to cause HPE, such as alcohol intake and insulin-dependent maternal diabetes. Other environmental causes are presumptive: tobacco consumption, use of retinoic acid and intake of statins. Also, infectious agents like toxoplasmosis, cytomegalovirus, syphilis and rubella are known to cause HPE. Moreover, chromosomal anomalies are responsible for the majority of HPE cases (up to 50%), while the remaining cases (including both syndromic and non-syndromic HPE) are associated with pathogenic mutations. In non-chromosomal and non-syndromic cases, HPE is usually considered to be inherited in an autosomal dominant mode [6]. For these reasons, it is necessary to investigate even mild facial abnormalities in the parents.

Case presentation

We present the case of a 29-year-old woman, primiparous, with no history of relevant previous diseases and no history of neurological pathologies in the family.

First trimester screening was carried out and indicated a

low risk for the main chromosomal anomalies. Cell-free fetal DNA testing (NIPT) was performed and showed a low risk of trisomy 21,13,18 and sex chromosome anomalies.

The mother was not ill during the pregnancy and did not take any medication; similarly, she did not consume alcohol or other toxic substances. She was protected for rubella. Her serologies were negative for human immunodeficiency virus, hepatitis B and C viruses, toxoplasmosis and syphilis. Her partner has a mild form of cleft lip/palate.

The presumptive diagnosis of MIH was made at 21 weeks through prenatal US. During the second trimester screening US the sonographer was challenged by what he took to be an unusually enlarged cavum septum pellucidum (Figures 1, 2).

The patient was referred to our hospital to undergo level II US for a suspected corpus callosum disorder.

The US revealed: partial absence of the falx cerebri in the posterior part of the frontal lobes and anterior parietal lobes; anterior displacement of the anterior cerebral artery, with a course below the frontal bones; absence of the cavum septum pellucidum (Figure 3); absence of the intermediate portion of the corpus callosum. The diagnosis was middle interhemispheric (MIH) variant of holoprosencephaly (Figure 4, a-c).

Afterwards, the patient underwent genetic counseling, amniocentesis and fetal MRI. The latter confirmed fetal syntelencephaly. However, the karyotype examination was normal (46, XX), and the array-CGH was also negative.

The patient decided to terminate the pregnancy. Histological examination of the placenta was performed, which revealed inhomogeneous and dysmorphic maturation of the chorionic villi. In addition, the autopsy described a female fetus with cerebral malformation (MIH variant of holoprosencephaly) associated with heterotopia of cortical neurons and failure to visualize the median portion of the corpus callosum. There were no other obvious malformations affecting other systems or organs.

Figure 1 Trans-ventricular axial plane.

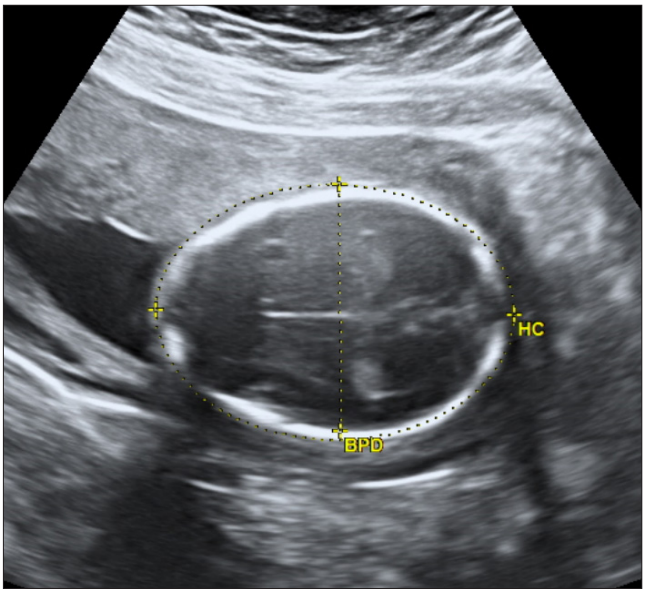


Figure 2 Trans-cerebellar axial plane.

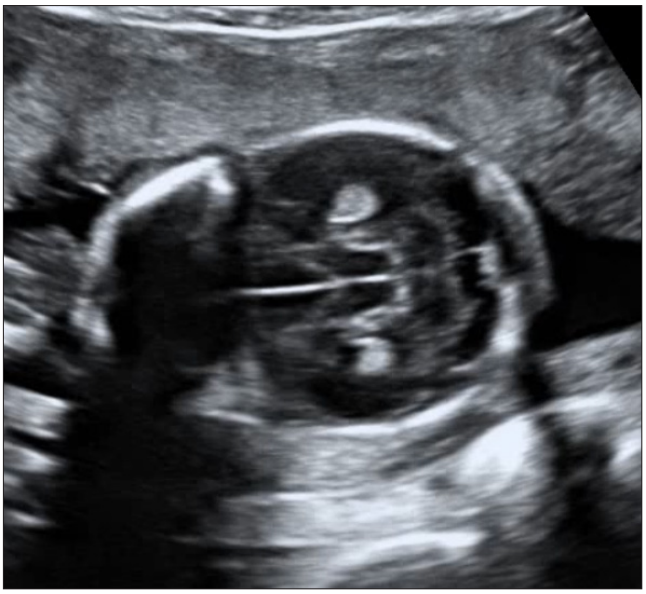


Figure 3 Sagittal plane with CD imaging. Note the absence of the intermediate portion of the corpus callosum.

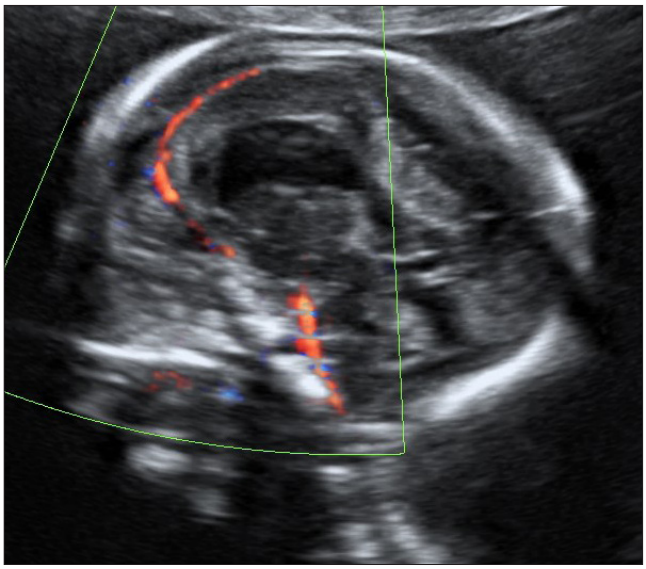


Figure 4a Coronal planes. Note the partial absence of the falx cerebri.

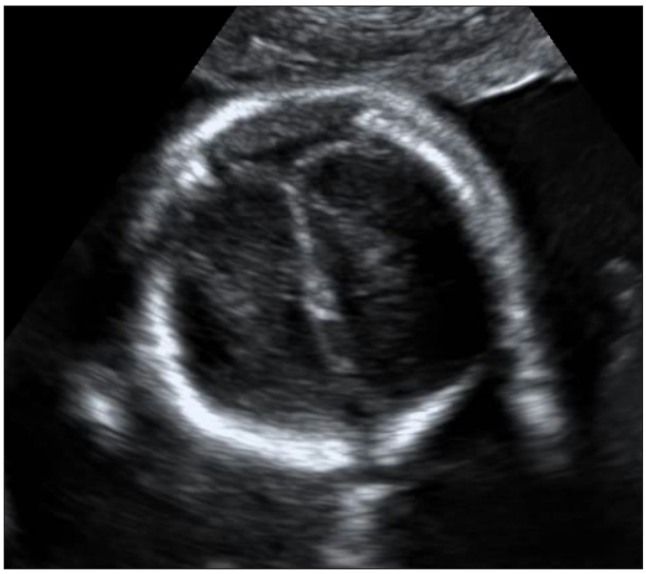


Figure 4b

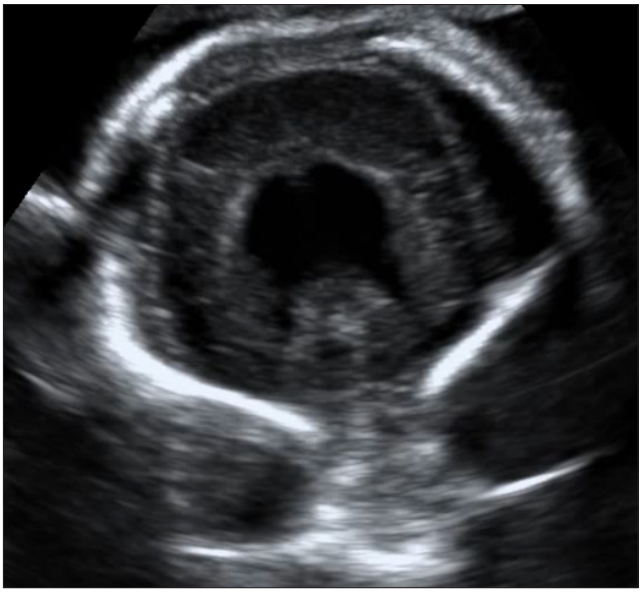
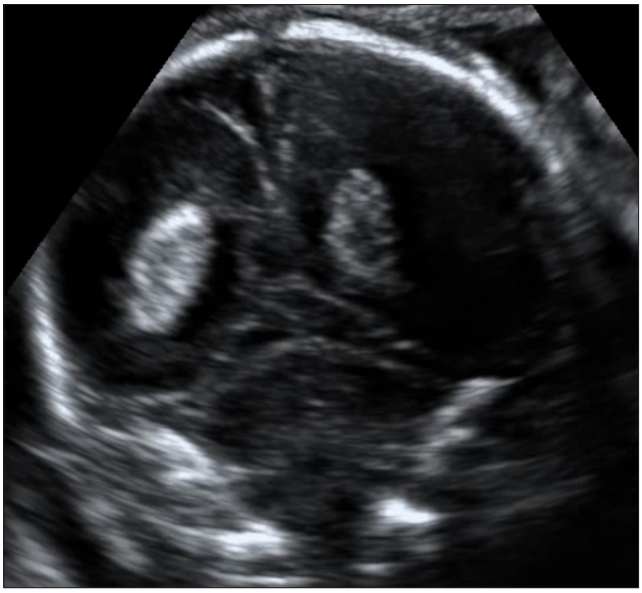


Figure 4c



Discussion

In the present work we present a rare case of the MIH variant of holoprosencephaly, diagnosed at second trimester prenatal US and confirmed by MRI.

In MIH variant of holoprosencephaly, only the posterior frontal and anterior parietal lobes of the fetal brain are undivided to a varying extent. This is a brain malformation that can have significant neurological sequelae, even though they are the mildest within the holoprosencephaly spectrum: mild to moderate spasticity is the most common motor symptom, followed by hypotonia. Speech and oromotor development are usually delayed [7]. However, it is difficult to accurately diagnose this malformation in the fetus.

In all subtypes of holoprosencephaly absence of the septal pellucidum is associated with an incomplete interhemispheric fissure. At second-trimester US screening for fetal anomalies, this kind of disorder may appear to the examiner in the form of numerous ambiguous sonographic features: a non-visualized cavum septum pellucidum (in the majority of the cases) [8], ventriculomegaly, a communication between the anterior part of the lateral ventricles, or a cystic area in the midline, sometimes referred to as a "wide cavum septum pellucidum", as in our case.

When the septum pellucidum is absent (a condition occurring in 2-3 cases in 100,000 in the general population), the examiner should consider the possibility of a holoprosencephaly spectrum disorder. Prenatal diagnosis of the MIH variant, which may present as absence of the septum pellucidum, is rare and it is usually discovered postnatally in children evaluated for developmental delay [8,9].

Literature regarding this kind of anomaly is scarce, due to the rarity of the condition. Vasudeva *et al.* [10], reported a case of mild unilateral ventriculomegaly at 19 weeks of gestation. At the referral US an interhemispheric cyst was suspected, along with a papilloma of the choroid plexus. Postmortem MRI showed that what was thought to be an interhemispheric cyst was the prominent supracerebellar cistern. The echogenic area in the center was the choroid plexus in the fused central part of the lateral ventricles. Perinatal autopsy confirmed non-separation of the posterior frontal and anterior parietal lobes of the cerebral hemisphere, and the case was diagnosed as MIH variant.

Picone *et al.* [11] published a case of MIH variant, referred with an absent cavum septum pellucidum and suspected absent corpus callosum. MRI and postmortem evaluation confirmed the diagnosis, made at 26 weeks of gestation.

In the case presented by Posada and Castillo [12], the diagnosis was also made later in pregnancy, at 34 weeks of gestation. Pulitzer *et al.* [13] suspected a case of holoprosencephaly in a fetus at 22 weeks of gestation and fetal MRI led to the correct diagnosis of MIH variant.

Gounongbé *et al.* [6] presented the first case in the literature of MIH associated with ZIC2 missense mutation diagnosed prenatally. In their case, the diagnosis was made during the third-trimester US, and was based on the absence of a septal cavity and fusion of the occipital horns of the lateral ventricles.

The available literature confirms the heterogeneity of the clinical manifestations of HPE and the MIH variant, and the diagnostic challenge these conditions pose, especially prior to 20 weeks of gestation. The role of fetal MRI appears to be fundamental in order to confirm the diagnosis and differentiate between the variants, thereby helping with parental counseling.

Conclusions

The prognosis of HPE, including the MIH variant, is generally poor, hence careful attention to the specific imaging features will improve prenatal diagnosis and will assist in the management of this developmental anomaly and in the counseling of parents. Prenatal MRI and perinatal autopsy can aid the US examination, especially in the case of neurological disorders

detected during the second trimester of pregnancy. These examinations can allow the most detailed diagnosis possible and help to further research around these rare findings.

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