CASE REPORT

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Sonographic Diagnosis of the Middle Interhemispheric Variant of Holoprosencephaly in the Prenatal Period

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ABSTRACT Holoprosencephaly is a disorder of development and separation of prosencephalic vesicles. There are 3 main types of holoprosencephaly: alobar, semilobar, and lobar. A rare form of the disease, middle interhemispheric variant (MIHV), or syntelencephaly, is a generally milder variant characterized by the absence of the cavum septum pellucidum and a single fused ventricle. Etiology is multifactorial and most cases are sporadic. However, the disease has also been associated with teratogenic exposure, intrauterine infections, maternal metabolic diseases, genetic disorders such as chromosomal aneuploidies and single gene disorders. Our aim is to share the characteristics of our case with MIH variant, which was reported very rarely in the prenatal period, and to compare it with other cases in the literature.

Keywords: Holoprosencephaly; chorionic villus sampling; cleft palate; diagnostic imaging; ventricular septal defect

Holoprosencephaly (HPE) is a disorder of development and separation of prosencephalic vesicles. The prosencephalon cannot be divided sagittally into the cerebral hemispheres, transversely into the diencephalon and telencephalon, and horizontally into the olfactory and optic spheres on during develepment. There are 3 main types of HPE: alobar, semilobar, and lobar.[1] The incidence is higher in abortions compared to live births (1/200-250 abortions and 1/10,000 live births).[1,2] Recently, middle interhemispheric variant (MIHV) or syntelencephaly, which is a milder form of the disease compared to these 3 main types, has been defined, and 6 articles in the literature reported that there are 11 MIHV cases diagnosed during the prenatal period.[3,4] MIHV is usually a milder variant with the characteristic sonographic findings of a single fused ventricle and absence of the cavum septum pellucidum (CSP). The separation of the posterior part of the frontal lobe and the parietal lobe is impaired in MIHV. The basal forebrain, anterior frontal and occipital lobes are normally separated.[3,4] Etiology is multifactorial and most cases are sporadic. However, the disease has also been associated with teratogenic exposure, intrauterine infections, maternal metabolic diseases, genetic disorders such as chromosomal aneuploidies and single gene disorders.[5]

Our aim is to share the characteristics of our case with MIH variant, which was reported very rarely in the prenatal period, and to compare it with other cases in the literature.

CASE REPORT

A 31-year-old female gravida 2 para 1 applied to the perinatology outpatient clinic to have a combined screening test at 13 weeks of gestation. The patient had no significant past medical and surgical history, consanguineous marriage, systemic disease, smoking and alcohol use, and genetic disease in her previous pregnancies and in her family. In the ultrasound examination, the fetus was compatible with 13 weeks

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and 5 days, and the nuchal translucency was measured as 3.7 mm. While falx cerebri was observed in the frontal and occipital regions, separation defect in the middle part of the brain and fusion of the thalamus were observed. There was ascites in the chest wall and the stomach and bladder could not be observed clearly. Chorionic villus sampling (CVS) was performed on the patient at the 14th week of her pregnancy. The TORCH result was negative. In addition, cavum septum pellicidum was not observed and corpus callosum dysgenesis, right pelviectasis, cleft palate and hypertelorism, persistent right umbilical vein, 1.7 mm inlet ventricular septal defect were observed in the ultrasound follow-ups until CVS was concluded (Figure 1, Figure 2, Figure 3). Bladder was seen but stomach could not be observed. The patient's CVS result was reported as trisomy 13. Termination was performed at the 18th week of pregnancy with the decision of the patient and her husband (Figure 4). The family did not accept the autopsy.

Figure 5 was shared to clarify the distinction of our MIH variant case from semilobar HPE, with this

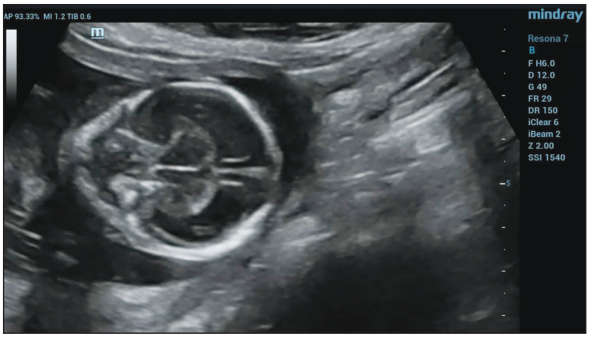

FIGURE 1: Gray-scale ultrasonography at the 16 weeks of gestation, middle interhemispheric variant of holoprosencephaly.

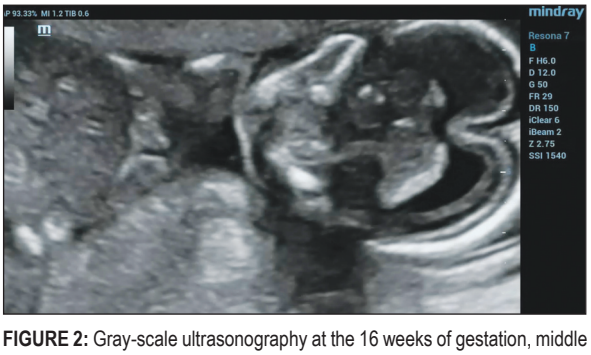

FIGURE 2: Gray-scale ultrasonography at the 16 weeks of gestation, middle interhemispheric variant of holoprosencephaly in coronal plane.

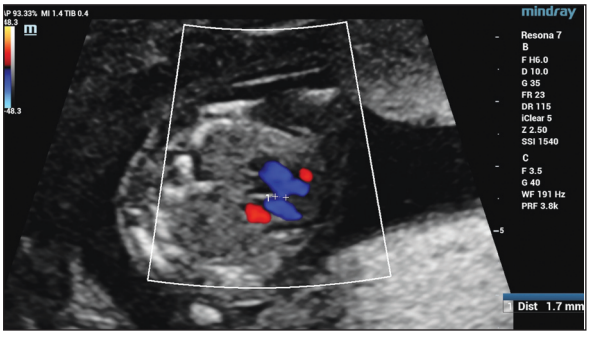

FIGURE 3: Gray-scale ultrasonography at the 16 weeks of gestation, ventricular septal defect.

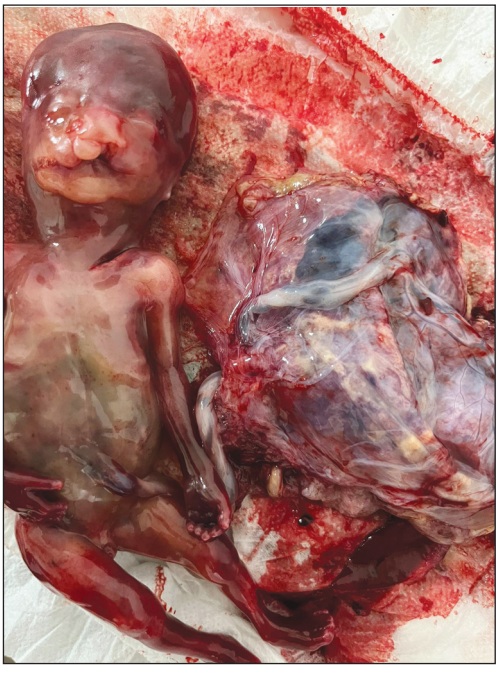

FIGURE 4: Macroscopic image of the delivered baby (cleft lip and palate, hypertelorism).

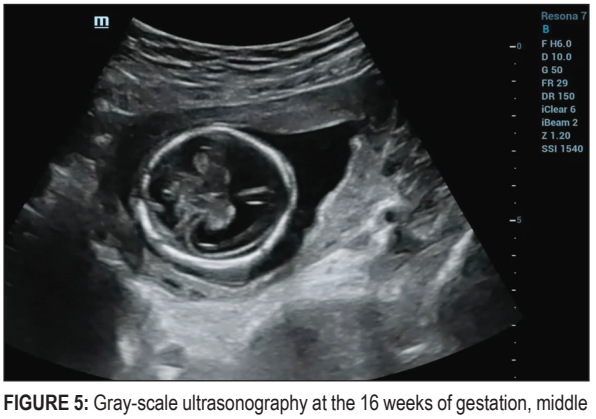

FIGURE 5: Gray-scale ultrasonography at the 16 weeks of gestation, middle interhemispheric variant of holoprosencephaly in axial plane.

sharing, the development of anterior interhemispheric fissure and anterior horns of lateral ventricles was emphasized.

Informed consent was obtained from the parents about the use of data.

DISCUSSION

HPE is the most common developmental anomaly of the forebrain. In particular, the diagnosis of alobar HPE can often be made with the first trimester ultrasound examination of pregnancy, because midline structures, including the falx cerebri, cavum septum pellicidum, corpus callosum, and third ventricle, are usually not observed.[6] In the semilobar type, there are only rudimentary posterior horns of the lateral ventricles, and there is only partial development in the interhemispheric fissure and falx cerebri in the posterior region.[1,4] In our case with MIH variant, there were interhemispheric fissures in the anterior part and anterior horns of the lateral ventricles. MIHV is more difficult to diagnose in the prenatal period because it manifests clinically with less severe lesions than the 3 main subtypes of HPE. Imaging findings in MIHV are manifested by the absence of the corpus callosum as well as failure to separate the posterior frontal and parietal lobes, but the hypothalamus and lentiform nuclei are usually separated normally.[7] It has seen that only 3 of the cases in the literature were diagnosed before the 20th week of pregnancy.[3,8] Our case was also diagnosed in the early period of the 2nd trimester. Otherwise, only 3 of the cases in the literature were diagnosed with fetal magnetic resonance imaging (MRI).[4,9,10] Although MRI is successful as a second-line imaging modality to exclude additional brain anomalies, diagnosis of the disease is possible with ultrasound depending on the operator's experience. Many serious fetal abnormalities can be recognized by an 11-14 week ultrasound examination performed according to a standard protocol. Additional screenings may be required in both the 2nd and 3rd trimesters to maximize prenatal detection of fetal abnormalities.[6,11]

While other forms of HPE may cause significant facial anomalies, according to literature, the faces of patients with MIH variant have been usually normal. Hypertelorism and ocular proptosis was reported in only one case.[3] Therefore, these patients may not be diagnosed until the first year of life, and in some asymptomatic cases, until adulthood with the desired neuroimaging methods for indications such as developmental delay.[12] In our case, cleft palate and lip, which are important facial anomalies, and hypertelorism were observed. Also, the presence of accompanying additional structural anomalies may contribute to a more detailed examination of the fetus and an earlier diagnosis of the disease.

Chromosomal abnormalities and abnormalities in other organ systems may accompany approximately 25-50% of HPE cases. The most common chromosomal anomalies are trisomy 13, trisomy 18 and triploidy, respectively.[1,13] In the genetic analysis of MIH variant cases, *ZIC2* gene mutation (13q32del) was observed in 5 of 11 patients, and this penetrance reaching almost 50% indicates that this transcription factor is one of the most common mutations in HPE probands.[13,14] The *ZIC2* gene is involved in the Sonic Hedgehog (SHH) signaling pathway, and loss of function of this gene can lead to craniofacial malformations.[14] In our case, trisomy 13 was found in the karyotype analysis performed. Genetic analysis should be recommended, when a MIH variant is suspected.

In conclusion, although the MIH variant has been rarely reported in the prenatal period in the literature, the diagnosis can be made sonographically from the early 2nd trimester. This variant should be considered in the differential diagnosis when CSP is not observed, and genetic examination should be recommended to investigate these cases.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Miraç Özalp;* ***Design:*** *Miraç Özalp, Veli Mihmanlı;* ***Control/Supervision:*** *Veli Mihmanlı;* ***Data Collection and/or Processing:*** *Miraç Özalp, Tuğba Salman;* ***Analysis and/or Interpretation:*** *Miraç Özalp, Tuğba Salman;* ***Literature Review:*** *Miraç Özalp, Tuğba Salman;* ***Writing the Article:*** *Miraç Özalp, Tuğba Salman;* ***Critical Review:*** *Veli Mihmanlı;* ***Materials:*** *Tuğba Salman.*

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