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Semi-Lobar Holoprosencephaly Diagnosed at Term: The Critical Role of Prenatal Diagnosis

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Abstract | **Case Report**

***Objective*:** To report a case of semi-lobar holoprosencephaly (HPE) diagnosed at term in the context of an unmonitored diabetic pregnancy, emphasizing the importance of early prenatal screening**.** ***Case Report*:** A primigravida with poorly controlled type 1 diabetes and no structured prenatal care was admitted in preterm labor at 36 weeks. An emergency ultrasound revealed intrauterine growth restriction, microcephaly, and semi-lobar HPE with major facial dysmorphism (hypotelorism, single nostril). The infant was delivered vaginally. At birth, the newborn exhibited profound clinical signs of life-threatening instability and died within 12 hours. Karyotype was normal. ***Conclusion*:** Semi-lobar HPE is a severe congenital brain malformation often associated with craniofacial anomalies and poor prognosis. This case highlights the critical role of prenatal ultrasound in early detection, especially in high-risk pregnancies, allowing timely counseling, multidisciplinary management, and the consideration of medical termination in severe cases.

Keywords: Holoprosencephaly, Diabetic Pregnancy, Prenatal Ultrasound Diagnosis, Perinatal Mortality.

INTRODUCTION

Holoprosencephaly (HPE) is a rare congenital brain abnormality resulting from incomplete division of the prosencephalon into two hemispheres, typically occurring during the fourth week of gestation [1]. It is the most frequent brain malformation during embryogenesis, with an incidence of 1/250, but only 1/16,000 at birth due to the high rate of associated spontaneous abortions [2].

Three main forms are recognized: alobar, semi-lobar, and lobar, depending on the degree of hemispheric separation. Alobar and semi-lobar forms are associated with a very poor prognosis, often justifying medical termination of pregnancy [3].

We report a case of semi-lobar HPE with major facial malformations, diagnosed late, illustrating the need for structured prenatal care.

CASE PRESENTATION

The patient was a primigravida, with no known consanguinity, who had been treated for insulin-dependent type 1 diabetes since childhood, without any other significant pathological history or known exposure to teratogens. No structured prenatal care was performed.

Due to limited resources, the patient had only a first-trimester ultrasound at 11 weeks, performed by a midwife in a private practice. The limited-quality ultrasound revealed a single brain ventricle (Fig. 1). She had no subsequent prenatal follow-up consultations.

She presented to our facility for the first time on the day of preterm labor at 36 weeks of gestation, in the obstetrical emergency department. The full infectious workup performed upon admission was negative for HIV, syphilis, toxoplasmosis, cytomegalovirus, hepatitis B and C, and group B streptococcus.

An emergency ultrasound showed severe intrauterine growth restriction (estimated weight 1900 g), microcephaly, with semilobar HPE, characterized by incomplete hemispheric division, partial fusion of the thalamus, rudimentary cerebral lobes, and a monoventricle (Fig. 2). Major facial dysmorphia suggestive of cebocephaly was present: marked hypotelorism and a single nostril (Fig. 3).

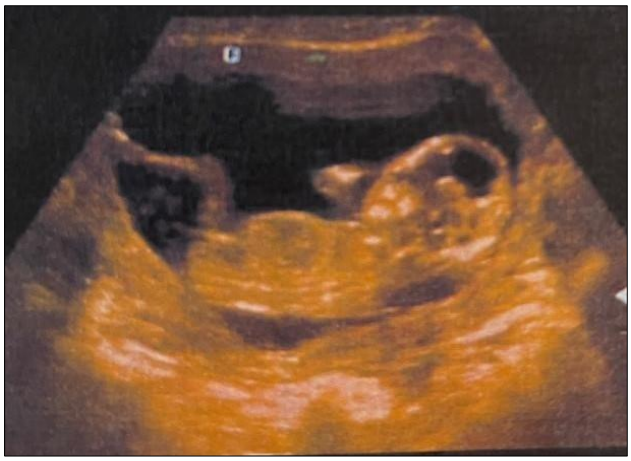

Fig. 1: Ultrasound sagittal view at 11 WA showing a single cerebral ventricle, suggestive of early brain malformation

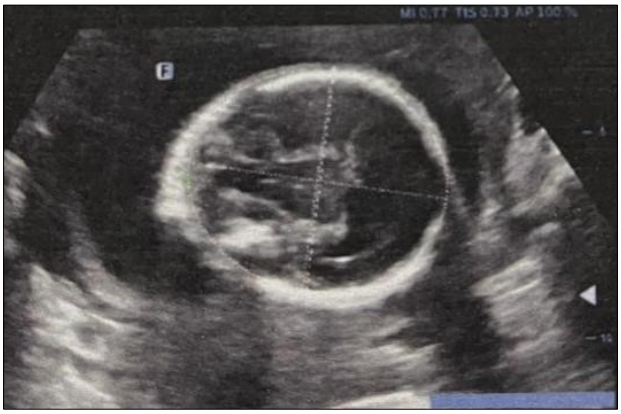

Fig. 2: Ultrasound demonstrated microcephaly, a monoventricular brain, partial fusion of the thalami, an incomplete interhemispheric fissure, findings consistent with a diagnosis of semi-lobar holoprosencephaly

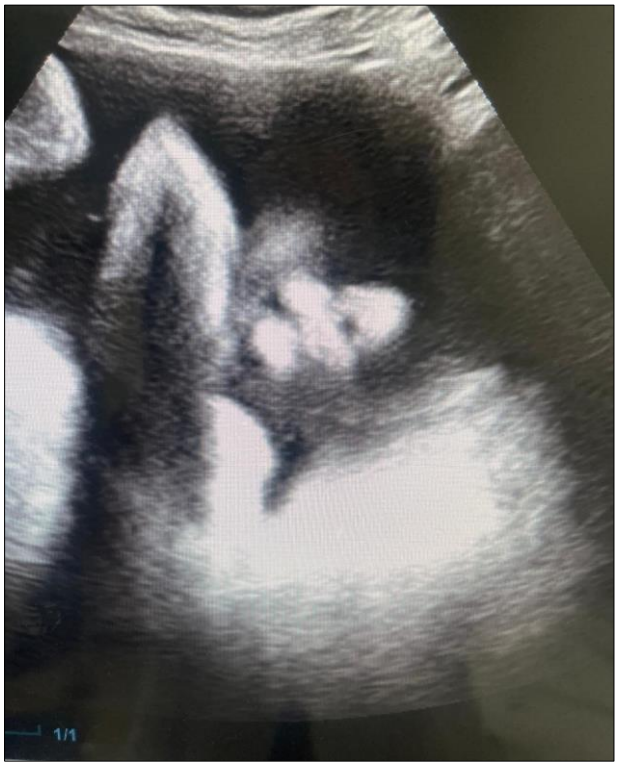

Fig. 3: The coronal nose-lip view on ultrasound demonstrated a single nostril

The delivery was vaginal, with instrumental extraction using a vacuum due to abnormal fetal heart rhythm. The male newborn weighed 1950 g, with an Apgar score of 2 at 1 minute and 4 at 5 minutes. He presented severe respiratory distress, generalized hypotonia, and absence of primitive reflexes. Despite active neonatal resuscitation, the infant's condition rapidly deteriorated, with death occurring within 12 hours of birth. Phenotypically, craniosynostosis, a triangular face, low-set ears, hypotelorism, and a single nostril were observed (Fig4). The postnatal karyotype was normal.

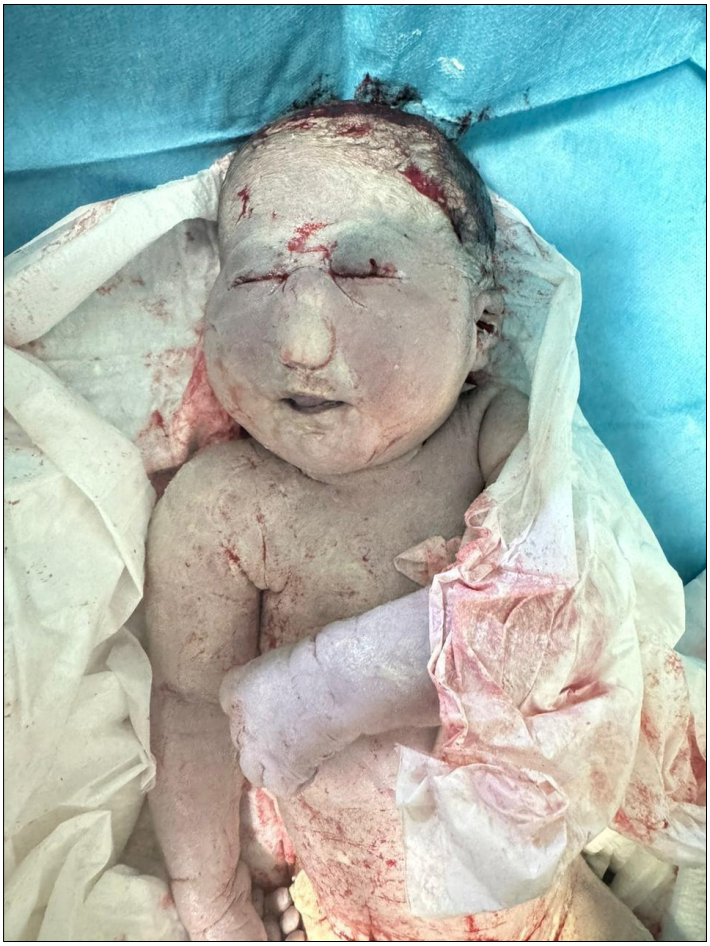

Fig. 4: The image shows a triangular facial shape, a triangular face, low-set ears, hypotelorism, and a single nostril

DISCUSSION

Holoprosencephaly is classified into four types based on the degree of hemispheric separation:

- Alobar form: the most common and severe, with complete absence of interhemispheric separation, a single ventricular cavity, and absence of midline structures.
- Semilobar form: intermediate in severity, with partial posterior hemispheric separation, frontal fusion, and a single ventricular cavity.
- Lobar form: the least severe, with almost complete hemispheric separation and continuity of the medial frontal cortex.
- Median interhemispheric variant or syntelencephaly: characterized by dorsal fusion of the posterior frontal and parietal areas [4].

The pathogenesis is multifactorial, including both genetic and environmental causes [5]. Approximately 25-45% of cases are associated with chromosomal abnormalities, notably trisomy 13 [6]. The four main genes involved in HPE are SHH, SIX3, ZIC2, and TGIF [7]. Sporadic forms with a normal karyotype represent approximately 6% of cases [8]. In our case, the karyotype was normal, with no consanguinity or family history, suggesting a sporadic form. Among environmental factors, maternal diabetes is clearly associated with a significant risk (~1%) (5). Barr *et al*., reported a 200-fold increased risk in diabetic mothers [9]. In this case, the insulin-dependent diabetes was poorly controlled. Infections can also lead to HPE, but this hypothesis was ruled out here.

Prenatal diagnosis relies on ultrasound, which can show a single ventricular cavity, thalamic fusion, and absence of median structures as early as the first trimester. The diagnosis of alobar HPE can be made as early as 9 weeks, semi-lobar at 11 weeks, and lobar at 21 weeks. Fetal MRI improves the detection of milder forms, such as lobar HPE or median interhemispheric fusion [10]. Our patient had only a poor-quality

ultrasound at 11 weeks showing a single ventricle, but the full diagnosis was not made until 36 weeks, with microcephaly, a single ventricle, partial thalamic fusion, corpus callosum agenesis, and an incomplete interhemispheric fissure, indicating semilobar HPE.

Facial abnormalities are common and reflect the embryological connections between the neuroectoderm and facial structures. Their severity is often proportional to the severity of brain abnormalities. Demyer and Zeman stated that "the face predicts the brain" in 80% of cases. Severe forms (cyclopia, ethmocephaly, proboscis) are typical of alobar HPE; less severe forms exhibit various dysmorphias. Median cleft lip-palate is common and requires a full morphological assessment [11]. In our case, hypotelorism and proboscis with a blind single nostril were present.

Management depends on the type of HPE and associated malformations. It is multidisciplinary, combining pediatrics, neurosurgery, genetics, imaging, and psychology. It may include nutritional support, anticonvulsant therapy, hormonal treatment, reconstructive surgery for clefts, and a ventriculoperitoneal shunt [12]. The prognosis is poor and depends on the degree and type of HPE, as well as the extent of facial dysmorphic features. A Dublin study showed a mortality rate of 95% in alobar forms, compared to 22% for semi-lobar and 21% for lobar forms [13].

Conclusion

Holoprosencephaly is a rare cerebral malformation due to incomplete division of the forebrain. Its etiology is complex and multifactorial. Due to financial constraints, the patient did not receive prenatal care, leading to a late diagnosis of semilobar HPE with severe craniofacial anomalies and early neonatal death within the first 12 hours of life. Earlier diagnosis would have allowed for better parental support, psychological support, and the possibility of medical termination of pregnancy. In less severe forms, multidisciplinary care is essential to support families.

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