

## ■ Case report

## Alobar holoprosencephaly: A case report

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(Received: 7 May 2015; Accept: 26 Oct 2015)

### Abstract

Holoprosencephaly (HPE) is a rare congenital brain malformation associated with multiple midline facial defects. This anomaly is resulted from the failure of diverticulation and cleavage of primitive prosencephalon during weeks 4-8 of gestation. HPE is the most common forebrain developmental anomaly in human with the incidence rate of 0.49-1.2 cases per 10,000-20,000 term births. In this study, we described a case of HPE in a neonate with gestational age of 32 weeks. Antenatal ultrasonographic diagnosis was performed, and the infant was presented with macrocephaly, bilateral microphthalmia, hypotelorism, proboscis and ambiguous genitalia.

**Keywords:** Holoprosencephaly, Hypotelorism, Pregnancy, Proboscis, Outcome

### Introduction

Holoprosencephaly (HPE) is a rare congenital anomaly, which occurs due to the failure of prosencephalon to develop into two hemispheres (1). Incidence of HPE has been estimated at the maximum of 1.2 cases per 10,000-20,000 term births, and one case per 250 spontaneous abortions (2, 3). HPE has heterogeneous etiology, and some of the contributing factors are insulin-dependent diabetes mellitus (1% risk for HPE), maternal alcoholism, smoking habits and environmental factors (4).

HPE is classified into different types, including alobar, semi-lobar, lobar and middle interhemispheric HPE ranging from mild to severe. As such, alobar HPE is considered as the most serious form of the disorder, while the middle interhemispheric type is relatively mild (1, 3). According to the National Institute of Neurological Disorders and Stroke (NINDS), the majority of cases diagnosed with HPE are of the severe type, and this condition could lead to neonatal mortality and stillbirth (1).

Clinical manifestations of HPE are variable depending on the severity of the disorder. In HPE, the embryonic forebrain fails to develop into bilateral cerebral hemispheres, which leads to facial defects and brain malformations (1). Among the facial defects associated with HPE are cyclopia (i.e., birth with a single eye), missing nose and proboscis-like nose located above the eye (5). Neonates with HPE are exposed to a higher risk of seizure and mental retardation, and severe anomalies often lead to miscarriage or stillbirth (6). In mild cases of HPE, brain functions might be normal, and facial deformities of the eyes, nose and upper lip occur at the minimum (1).

In previous studies, Arnold et al. (2009), Tonni et al. (2008), Swatek et al. (2013), Niknejadi et al. (2008) and Saedi et al. (2014) have described cases with HPE (7-11). In this report, we aimed to describe a case of alobar HPE in a neonate born in Zabol, Iran.

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## Case Presentation

A neonate diagnosed with HPE was born via caesarean section to an Iranian mother with gestational age of 32 weeks and birth weight of 2,630 grams in Amiralmomenin Hospital of Zabol, Iran in 2013. The mother was a 30-year-old multiparous woman with no history of neurologic deficits in her children. She received prenatal care during pregnancy and had no history of infection. Furthermore, she had no history of smoking, alcohol consumption, antenatal complications (e.g., diabetes mellitus and infection) and use of medications (e.g., aspirin, lithium, retinoic acid and anticonvulsants). Also, family history of the mother was negative in terms of neurological disorders in her children, parents and siblings.

Serological tests were performed during the prenatal examination, and the results were negative for syphilis, human immunodeficiency virus, hepatitis B, hepatitis C and rubella. Antenatal routine ultrasonographic examination of the fetus at week 32 of gestation was indicative of a fetal anomaly, and the fetus was diagnosed with HPE using a three-dimensional ultrasound. Therefore, the mother was hospitalized immediately after diagnosis, and the neonate was delivered via caesarean section. Physical examinations were indicative of hydrocephalus leading to macrocephaly, and the neonate died immediately after birth.

Head circumference of the infant was 4 cm larger than chest circumference. In addition,

ambiguous genitalia was identified with an enlarged clitoris, a small penis and closed labia resembling a scrotum. On the other hand, facial defects such as premaxillary agenesis, ocular hypotelorism, bilateral microphthalmia and proboscis were evident. Moreover, orbits were located between the mouth and proboscis (Figures 1 and 3). However, previous antenatal ultrasonographic results were not available.

## Discussion

In this study, we presented a unique case of severe HPE diagnosed via routine ultrasound in a neonate born in Zabol, Iran. Based on the severity, HPE is classified into three major types of alobar, semi-lobar and lobar, and the alobar type is considered as the most serious type of this condition. Earliest diagnoses for alobar, semi-lobar and lobar HPE are reported during weeks 9.5, 13 and 21 of pregnancy, respectively (12, 13).

The case presented in this study was diagnosed with alobar HPE at week 32 of gestation, while the routine ultrasound performed at week 12 of gestation revealed no abnormalities in the foetus. In one study, Mircea et al. (2012) described two foetuses diagnosed with alobar HPE and lobar HPE diagnosed at week 29 of gestation (14). Therefore, it could be concluded that time of HPE diagnosis is not restricted and it may vary depending on ultrasound devices and radiologists involved in the process.

To date, the exact origin of HPE remains



**Figure 1.** Alobar holoprosencephaly, limb



**Figure 2.** Alobar holoprosencephaly, genital



**Figure 3.** Alobar holoprosencephaly, head

unknown, and no specific causes could be identified in the majority of cases. In this regard, several risk factors have been proposed, including smoking habits, alcoholism, maternal diabetes mellitus, pregnancy infections (e.g., syphilis, toxoplasmosis, rubella, herpes and cytomegalovirus) and use of medications during pregnancy (e.g., aspirin, lithium, thiorazine, anticonvulsants, birth control pills and retinoic acid). According to the literature, bleeding during the first trimester of pregnancy and history of miscarriage in women could result in the birth of neonates with HPE; however, no significant correlation has been reported between the incidence of HPE and maternal age (15, 16).

In the current study, the mother was a 30-year-old multiparous woman without any history of miscarriage or bleeding during the first trimester of pregnancy. Moreover, she had no history of smoking, alcohol consumption, diabetes mellitus, infection and other risk factors associated with HPE. In another study, Saeidi et al. (2014) reported a case of alobar HPE with no history of the related risk factors (11).

Although many children with HPE have normal karyotypes, specific chromosomal abnormalities have been identified in some patients, the most frequent of which is trisomy 13. Evidence suggests that HPE could be hereditary in some families; however, degree of severity is variable among the affected individuals in the same family. In this regard, several genes have been recognized to play a role in the development of HPE (17, 18). In their study, Niknejadi et al. (2010) reported

a case of HPE in one of the fetuses in a twin pregnancy, while the other fetus was diagnosed with Down syndrome. According to their findings, karyotyping of both fetuses would be warranted if one of the twins had major malformations. In the study by Saeidi et al. (2014), chromosomal analysis was indicative of a normal karyotype in an infant diagnosed with alobar HPE (11). One of the limitations of the current study was lack of genetic tests on the neonate diagnosed with HPE.

Clinical findings of HPE are variable depending on the severity of the condition (19). Some of the prominent clinical manifestations of HPE are absence of the eyes, cebocephaly, cyclopia, proboscis, cheilo/palatoschisis and agnathia (i.e., severe micrognathia). Among these factors, cyclopia, proboscis and cheilo/palatoschisis are associated with the incidence of severe HPE. Microcephaly or macrocephaly in some cases is indicative of the presence of hydrocephaly. On the other hand, mental retardation is known to have a direct correlation with the severity of HPE (20).

In the current report, the patient was diagnosed with severe HPE, and clinical findings were hydrocephaly, macrocephaly, proboscis (a rare finding), hypotelorism and bilateral microphthalmia; also, the orbits were located between the mouth and proboscis in the infant.

In the literature, several studies conducted by Thakur et al. (2002), Tokmak et al. (2014), Gawrych et al. (2009), Gupta et al. (2010) and Abubakar et al. (2014) and National Institutes of Health Clinical Center (2015) have reported cases of HPE accompanied by the aforementioned clinical manifestations (21-26). In the current study, ambiguous genitalia was a significant manifestation of HPE in the patient, which has not been reported by previous studies in this regard.

## Conclusion

In conclusion, patients diagnosed with HPE should receive individualized treatment despite possible complications; in general, HPE treatment is symptomatic and supportive. Prognosis of HPE depends on the severity of brain abnormalities,

facial malformations and clinical complications. Severe HPE is a fatal condition in the majority of cases (27), as the neonate in the current study died immediately after birth.

### Conflict of interest

None declared.

### Authors' contributions

M Amirshahi, A Salehi, A Kerami, and A Abdollahimohammad gathered the data. F Naroei, F Mirshekari, and L Mirshekari wrote the Persian version of the manuscript. L Mansoorifar and M Mirshekari wrote the English version. A Sanangoo edited the manuscript. The idea of the of the article was from L Mirshekari.

### Acknowledgements

The authors would like to express deep appreciation of the mother of newborn for her cooperation in the study. The authors would also appreciate the assistance from Staffs of Zabol Amirmomomin Hospital.

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