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Holoprosencephaly – Case Reports of A Rare Neurological Malformation

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Abstract

Holoprosencephaly (HPE) is a complex structural anomaly of the developing forebrain caused by incomplete division of prosencephalon into two separate hemispheres and ventricles resulting in dysmorphism of brain and face and neurological impairment. HPE has incidence rate of 1:250 in utero and the live birth rate is 1:16,000. It is classified into three types based on the degree of cerebral involvement; lobar, semi-lobar and alobar. There are various etiological factors involved in causation of Holoprosencephaly including environmental, chromosomal and genetic syndromes. Ultrasound (US) is the primary mode of investigation for examination of the foetal brain. Magnetic resonance imaging (MRI) plays an important role in further diagnosis and characterization of the variant of HPE and helps in determining the degree of neurological involvement.

There are no treatment options available for HPE and the surviving children with HPE have developmental disabilities correlating with the degree of cerebral involvement. Recent advances in diagnostic methods and improved patient management have increased the survival rate in patients with HPE.

Keywords: Holoprosencephaly(HPE), Magnetic resonance imaging(MRI), Ultrasound (US), alobar, semi-lobar, lobar, malformation.

Introduction

Holoprosencephaly (HPE) is a malformation resulting from failure of bifurcation of foetal forebrain into two separate hemispheres occurring between 18th and 28th day of gestation and affecting both the forebrain and face. It is estimated to occur in 1/16000 live births and it is often accompanied by early embryonic loss [1],[7]. It can be caused by genetic and environmental factors. Approximately 25-50% of patients of HPE have a recognised syndrome (e.g., Pallister-Hall) or a single gene defect. Non-syndromic HPE are associated with number of environmental teratogens (e.g., retinoic acid and alcohol) and maternal factors like pre-pregnancy

diabetes, smoking and substance abuse. Four main alleles have been identified SHH, ZIC2, SIX3, TGIF, however in 70% of cases molecular basis remains unknown [1],[2].

Phenotypically, HPE presents with dysmorphism of brain and face. It is divided into three classic variants depending on the degree of cerebral involvement; alobar, semi-lobar, lobar. Presentation and prognosis of HPE vary widely depending on these variants.

Ultrasound (US) remains the first investigation in examination of foetal brain in suspected cases of HPE. Magnetic resonance imaging(MRI) plays an important role in further characterization of the variants of HPE due to its multi-planar acquisition of images and better visualisation neurological anatomy. We describe 3 cases of HPE studied retrospectively after receiving permission from concerned authorities (Head of the Department of Radiodiagnosis and Hospital Director) of MGM Hospital, Navi Mumbai and review the salient features of its different variants and their MR appearances.

Case 1:

An 8-year-old male child presented to OPD with complaints of Shortening of neck, short stature, and developmental delay.

Antenatally it was a twin pregnancy. Twin B was completely healthy term neonate but twin A (patient) showed moderate dilatation and fullness of bilateral lateral ventricles in anomaly scan done at 21 weeks, growth scan done at 29weeks and 35 weeks. Patient was followed up with MRI when he started having symptoms.

Figure 1:

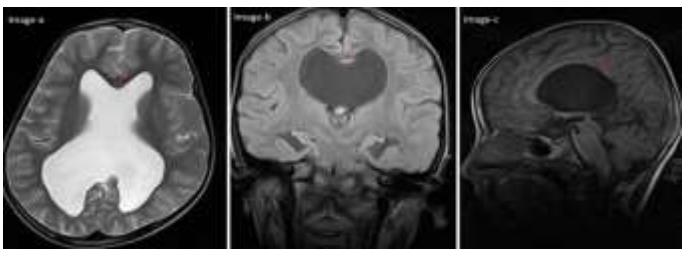


Image-a: T2 Axial section of MRI brain showing fusion of frontal horns of bilateral lateral ventricles.

Image-b: Coronal image of MRI brain showing fused frontal horns of bilateral lateral ventricles with absent septum pellucidum. While the inter hemispheric fissure appears normal

Image-c: T1 sagittal image of MRI brain showing partial agenesis of posterior body and splenium of corpus callosum.

Case 2:

A 20-year-old phenotypically normal male patient with normal development and motor functions came with complaint of headache for which MRI was done and incidental findings were noted.

Figure 2:

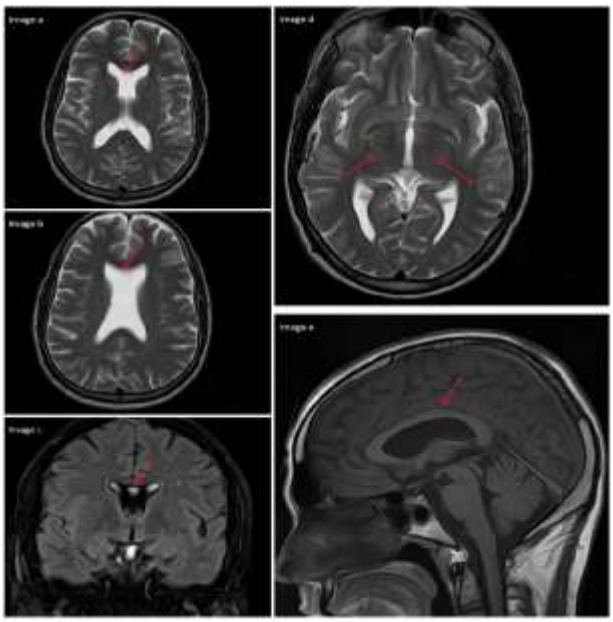


Image-a and Image-b: T2 Axial images of MRI brain showing fusion of frontal horns of bilateral lateral ventricles.

Image-c: Coronal image of MRI brain showing fused frontal horns of bilateral lateral ventricles with absent septum pellucidum. While the inter hemispheric fissure appears normal

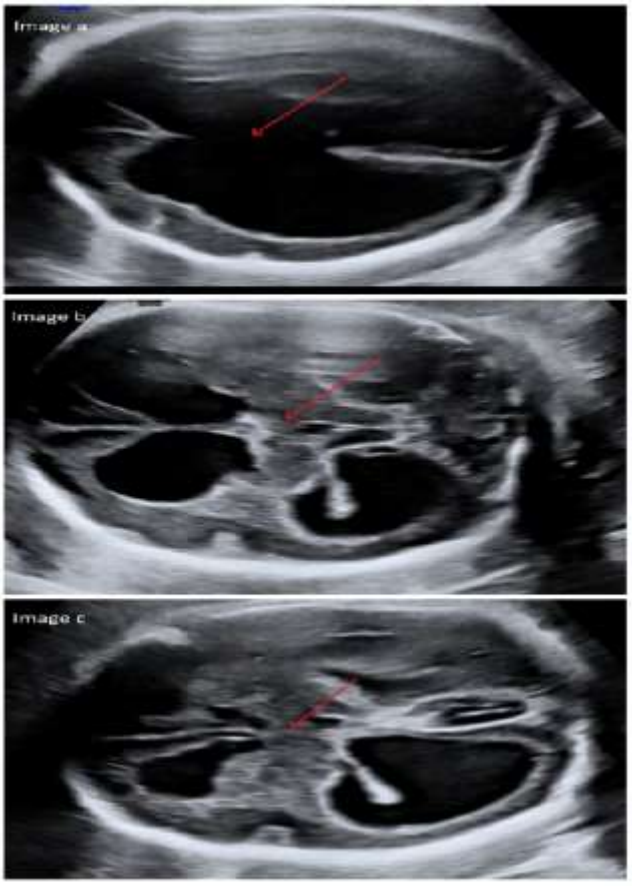
Image-d: T2 axial image showing normal and completely separated bilateral thalami with a normal third ventricle.

Image-e: T1 sagittal image showing normal corpus callosum.

Case 3:

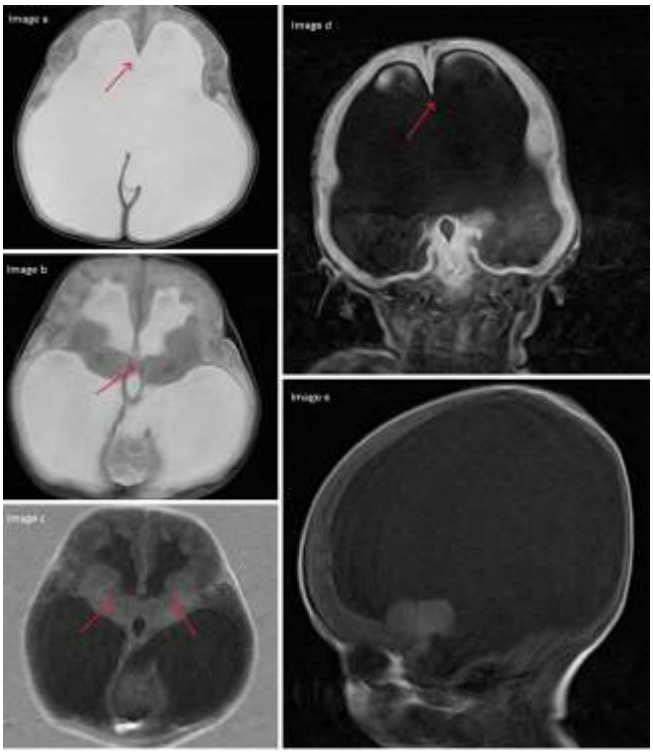
A 1-day-old neonate with hydrocephalus. On antenatal ultrasound done at 28 weeks, there was gross dilatation of bilateral lateral ventricles which were inter-communicating with each other septum pellucidum was absent (Fig 1,2), with thin corpus callosum and both thalami were partially fused (Fig 3,4). A diagnosis of semi-lobar holoprosencephaly was made.

Figure 3:



On antenatal ultrasound done at 28 weeks, there was gross dilatation of bilateral lateral ventricles which were inter-communicating with each other, septum pellucidum was absent (image –a), with thin corpus callosum and both thalami were partially fused (image-b and Image-c). A diagnosis of semi-lobar holoprosencephaly was made. Patient was followed-up with MRI after birth.

Figure 4:



There was gross dilatation of bilateral lateral ventricles with gross compression of adjacent neuro-parenchyma.

Image-a: T2 Axial images of MRI brain showing fusion of frontal horns of bilateral lateral ventricles with absent septum pellucidum.

Image-b and Image-c: Axial T2W and IR images showing partially fused thalami with dysmorphic bilateral basal ganglia.

Image-d: Coronal image of MRI brain showing fused frontal horns of bilateral lateral ventricles with absent septum pellucidum. While the inter hemispheric fissure and midline falx were normal.

Image-e: T1W sagittal image showing non-visualization of corpus callosum.

Discussion

Holoprosencephaly is a spectrum of malformations having common embryologic origin. It can be divided on

the basis of severity of malformations into alobar variant (most severe form), semi-lobar variant (intermediate form) and lobar variant (least severe form)[3], [4], [5], [6], [7], [8], [9], [13], [14], [15].

Alobar variant: It is the most severe form and most of the times it is not compatible with life. It is found in 1/250 terminated pregnancies and 1/15000 live births[1],[6]. Foetuses with severe alobar HPE are often spontaneously aborted, in-utero demise and still births are common. Surviving individuals present with severe mental retardation and have a poor quality of life. Alobar variant shows presence of a single crescent shaped mono-ventricle which communicates with a large dorsal cyst. Cerebral mantle is fused anteriorly across the midline with absent septum pellucidum, falx cerebri and inter-hemispheric fissure. Basal ganglia and thalami are fused across the midline with absent third ventricle. The brain appears thin and has an agyric surface or few shallow sulci may be present.

The most severe facial malformations are associated with alobar variant of HPE affecting the development of eyes, nose, upper lip and palate. Eyes, optic nerves, olfactory bulbs and tracts may be absent completely or fused. Ophthalmologic defects include cyclopia (single central eye), synopthalmia (two eyes fused in the midline) and hypotelorism. Nasal defects include complete absence of nose with a proboscis (ethmocephaly) or a small nose with a single nostril (cebocephaly). Nasal defects are also associated with oral anomalies such as midline cleft lip and/or cleft palate and can additionally contribute to feeding difficulties

Semi-lobar variant: It is intermediate in severity. It shows partially formed inter-hemispheric fissure and incomplete falx. Temporal horns of lateral ventricles may be partially formed but the septum pellucidum is absent. Thalami are partially fused and a rudimentary third ventricle is present. There is agenesis of corpus callosum or splenium may be present but the genu and body of corpus callosum are absent. Semi-lobar variant may be associate with vascular anomalies such as azygous anterior cerebral artery and rudimentary deep veins. The facial anomalies and developmental outcomes in semi-lobar HPE are extremely variable ranging from anopthalmia/micropthalmia, absent nasal septum, cleft lip/palate to relatively normal facial appearances. Macrocephaly is common in these patients due to hydrocephalus. Developmentally, these patients present with profound intellectual disabilities and are non-verbal. Degree of dystonia and spasticity varies depending upon the degree of cerebral involvement. In terms of motor deficit, some patients are wheel-chair dependant and some achieve independent ambulation.

Lobar variant: It is the least severe and best differentiated form.

Lobar form shows presence of interhemispheric fissure and falx, absent septum pellucidum and frontal horns of lateral ventricles communicate freely. The frontal horns are present but are dysplastic-appearing. Corpus callosum is absent, hypoplastic or normal with midline fusion of cingulate gyrus. Bilateral thalami are completely separated with normal third ventricle. Macrocephaly which is due to hydrocephalus in most of the cases is often present. Mild developmental delay, hypothalamic-pituitary dysfunctions and visual disturbances are common in these patients. These patients have relatively normal facial features, however cleft lip, hypotelorism and depressed nasal bridge may be present. Due to relatively normal phenotype, these patients are often diagnosed late after emergence of symptoms like developmental delay, epilepsy or motor disturbances.

The patients with HPE are prone to develop various disorders: endocrinopathies like diabetes insipidus,

adrenal hypoplasia, hypogonadism, growth hormone deficiency correlating with the degree of hypothalamic non-separation[7],[10],[11]; neurological problems like epilepsy, spasticity, severe developmental delays, cardiovascular and respiratory problems, temperature instabilities and malnutrition[7],[9],[12],[14]. Therefore, these patients should be followed up closely. Treatment is symptomatic and supportive and requires multidisciplinary management. Child outcome depends on severity and associated complications. Mildly affected children may exhibit few symptoms and may live a normal life[7],[10].

Conclusion

Holoprosencephaly is an extremely important diagnosis to make. The role of radiologist in making this diagnosis is key. Early antenatal diagnosis with the help of Ultrasound is important in deciding the further outcome of pregnancy. MRI in utero or postnatally, provides further information and characterization about the variant of HPE and the degree of cerebral involvement. Once the diagnosis is made, it helps clinician in anticipating further outcome of the patient in terms of degree of motor impairment, intellectual disability and complications like endocrinopathies and temperature instabilities in neonatal period and can guide them in planning of proper management and rehabilitation.

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