Midline Brain Anomalies II: Holoprosencephaly

5

5.1 Embryology

During neural development, after primary neurulation, the cranial end of the neural tube forms three vesicles—the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain) [1–3]. The prosencephalon develops from the process of ventral induction, which consists of three interconnected events—formation, cleavage, and midline development. Prosencephalon further differentiates to form telencephalon that develops into cerebrum-lateral ventricles and diencephalon which forms the thalami-III ventricle. There is also cleavage and midline development occurring in prosencephalon. Abnormalities of formation result in aprosencephaly and atelencephaly. Abnormalities of cleavage lead to holoprosencephaly. Abnormalities of midline development result in agenesis of the corpus callosum, septo-optic dysplasia, and isolated septal agenesis [1].

5.2 Aprosencephaly, Atelencephaly

Aprosencephaly refers to failure to form prosencephalon.

Atelencephaly refers to failure to form telencephalon. It refers to abnormal division of prosencephalon into telencephalon/diencephalon leading to rudimentary diencephalic structures [1, 4].

Imaging features

- Is usually diagnosed by USG
- Severe microcephaly with no normal cerebral structures. Seen as amorphous mass and fluid within the cranium
- Cerebellum may be hypoplastic
- Severe craniofacial anomalies—Micrognathia, oculofacial defects including cyclopia, Cleft palate
- Urogenital anomalies—Anorectal atresia, Renal agenesis, ambiguous genitalia
- Can show associated limb and Cardiac anomalies

Prognosis

Prognosis is bad with death occurring in the prenatal or neonatal period.

5.3 Holoprosencephaly (HPE)

Rare Spectrum of disorders arising due to incomplete separation of the two cerebral hemispheres (which usually occurs during the fifth week of gestation).

Incidence 1 per 10,000–16,000 live births [5].

The main types are listed below in the order of decreasing severity: (Modified DeMyer classification) [6–8]:

1. Alobar holoprosencephaly
2. Semilobar holoprosencephaly
3. Lobar holoprosencephaly
4. Middle Interhemispheric variant
5. Septo optic dysplaia
6. Minimal HPE [9]
7. Microform HPE [1.9]

Pathogenesis and genetics

The etiology is multifactorial. Chromosomal and genetic abnormalities have been implicated including trisomy 13, trisomy 18, and Sonic hedgehog gene [10–12]. Maternal diabetes mellitus, retinoic acid, and alcohol use have also been implicated.

HPE may be associated with several syndromes such as Goldenhar syndrome, Meckel syndrome, Martin syndrome, Pallister–Hall syndrome, Fitch syndrome, Steinfeld syndrome, hypertelorism and ectrodactyly syndrome, velocardiofacial syndrome, Lambotte syndrome, acrocallosal syndrome, and Smith–Lemli–Opitz syndrome.

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Non-cleavage of the telencephalic vesicle during the fifth and sixth week of gestation results in holoprosencephaly. It has three major subtypes based on the degree of cleavage between the hemispheres (Fig. 5.1). In the most severe type, alobar HPE, there is complete noncleavage of the cerebral hemispheres, leading to a single midline ventricle often communicating with a dorsal cyst (Fig. 5.1b). In semilobar HPE, the telencephalon remains uncleaved in the cranial part, whereas the posterior interhemispheric fissure is present (Fig. 5.1c). In lobar HPE, cleavage is near complete (Fig. 5.1d). Arhinencephaly and septal agenesis also belong to the HPE spectrum, although they can also exist as isolated anomalies unrelated to HPE.

Dorsal Cyst A dorsal cyst is commonly seen in alobar HPE (92% of cases). It is less frequently seen in semilobar HPE (28% of cases) and lobar HPE (9% of cases) [9, 11]. It is postulated that outflow of cerebrospinal fluid from the third ventricle is obstructed by the fusion of thalami. This results in the third ventricle ballooning out posteriorly in the suprapineal recess, at the point of least resistance.

Association
Rhombencephalosynapsis, Subcortical heterotopias. Polyhydramnios are commonly associated with HPE. Abnormal cleavage of the vesicles also leads to a large spectrum of midline anomalies of the face. Facial anomalies range from hypotelorism with a single upper central incisor, hypoplastic nose with a single nostril (cebocephaly), median cleft lip and palate, to cyclopia (with proboscis and synophthalmia).

5.3.1 Alobar HPE

It is characterised by complete or near complete non-cleavage of the forebrain [9].

Imaging features
- Is usually diagnosed by USG by demonstrating "Absent Butterfly sign." The butterfly sign is normally seen in a transverse first-trimester brain scan. The choroid plexus is narrow in the middle but broader on the lateral aspect, and when seen side by side resembles a butterfly [13].
- Head size is reduced and shows a rounded contour.
- *The following are absent*—Olfactory bulbs and tracts, cavum septum pellucidum, corpus callosum, and interhemispheric fissure (Fig. 5.2a–f).
- The lateral and III ventricles are replaced by a monoventricle (Fig. 5.2a, b).
- A dorsal cyst is often present (Fig. 5.2d–f).
- On the sagittal views, the brain may show the following shapes: *ball, cup, or pancake* (Fig. 5.3). In the ball-type, a good volume of cerebral cortex completely encircles the monoventricle (Fig. 5.3a). In the cup type, the monoventricle is partially encircled by the cortex that gives a "cup" configuration (Fig. 5.3b). In the "pancake" form, a small volume of cortex is seen at the base of the skull and appears flattened (Fig. 5.3c).
- The basal ganglia, hypothalamus, and thalami are fused in the midline (Fig. 5.2b). The optic nerves may be absent, fused, or normal.
- The anterior and middle cerebral arteries may be absent and replaced by a network of vessels originating from the internal carotid and basilar arteries [14].
- Facial malformations are severe.
- Subcortical heterotopia [15].

Differential diagnosis
Semilobar holoprosencephaly—Partial cleavage of the cerebral hemispheres is seen.

Severe hydrocephalus—Normal ventricular configuration is maintained in hydrocephalus although dilated. Midline falx is visualized.

Hydranencephaly—Midline falx is visualized.

Prognosis Mental retardation is profound and often fatal in the neonatal period.

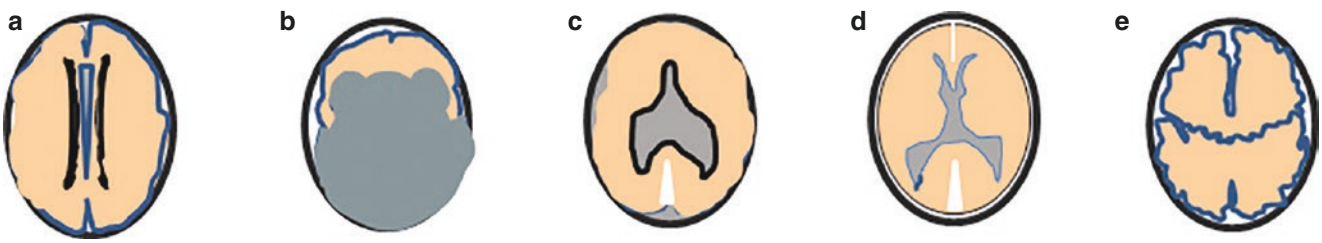

Fig. 5.1 Schematic diagram showing the types of holoprosencephaly. (**a**) Normal, (**b**) Alobar HPE (**c**) semilobar HPE, (**d**) lobar HPE, (**e**) middle hemispheric variant HPE

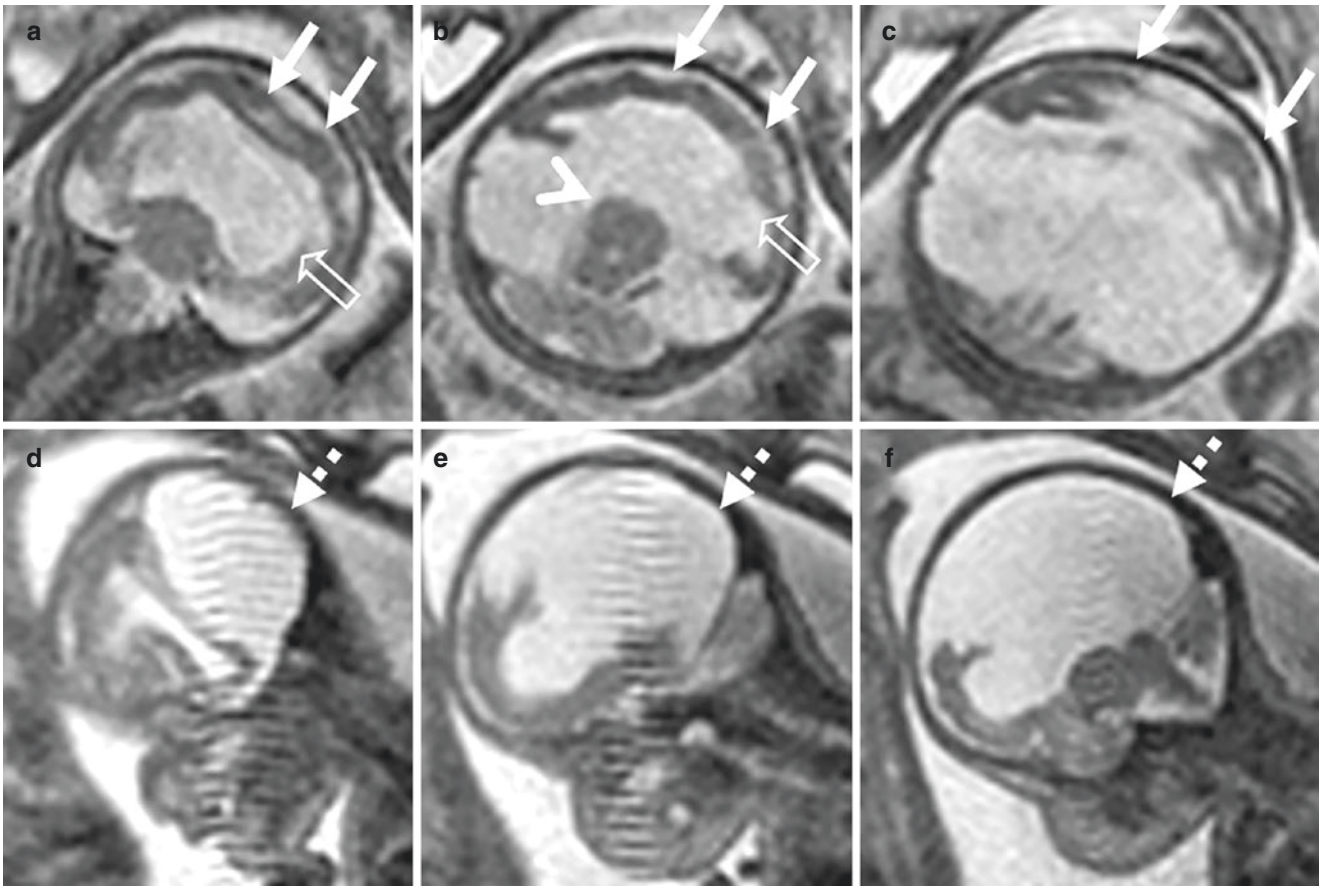

Fig. 5.2 Axial T2W images (**a**, **b**, **c**) show uncleaved cerebral hemisphere (arrows), mono ventricle (open arrows), fused thalami (arrowhead), Sagittal T2W images (**d**, **e**, **f**) show dorsal cyst (broken arrows)—features of *lobar holoprosencephaly*. The brainstem and cerebellar hemispheres are normally visualized

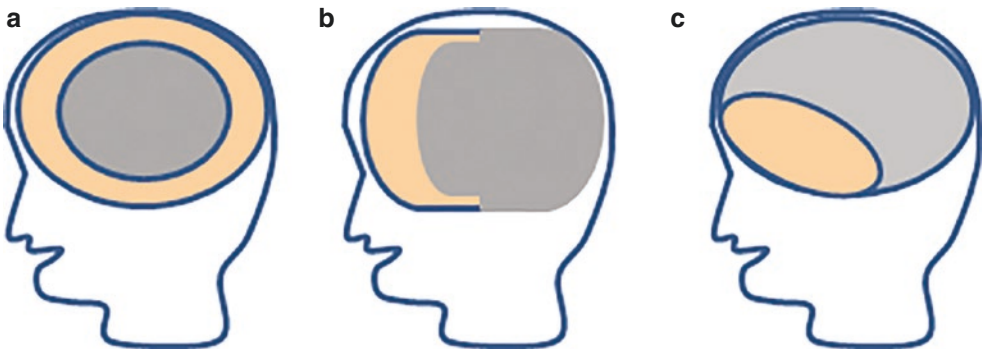

Fig. 5.3 Schematic diagram showing the shapes of the brain in alobar HPE on the sagittal view: (**a**) ball, (**b**) cup, (**c**) pancake

5.3.2 Semilobar HPE

It is characterized by incomplete cleavage of the forebrain, the frontal regions being affected [11, 16].

Imaging features

- In some cases, inability to detect the CSP may be the only obvious finding on USG at the 18–20-week anomaly scan [17] whereas it is a straightforward diagnosis on MRI
- Absent septum pellucidum, olfactory tracts, and bulbs
- Complete or partial non-cleavage of the thalami (Fig. 5.4a)
- Non-cleavage of more than 50% of frontal lobes (Fig. 5.4b, c)
- Mono-ventricle with partially formed temporal and occipital horns
- Partially formed falx cerebri and interhemispheric fissure
- Absent or hypoplastic corpus callosum
- Dorsal cyst may be present (Fig. 5.4d)
- Facial malformations are mild or absent

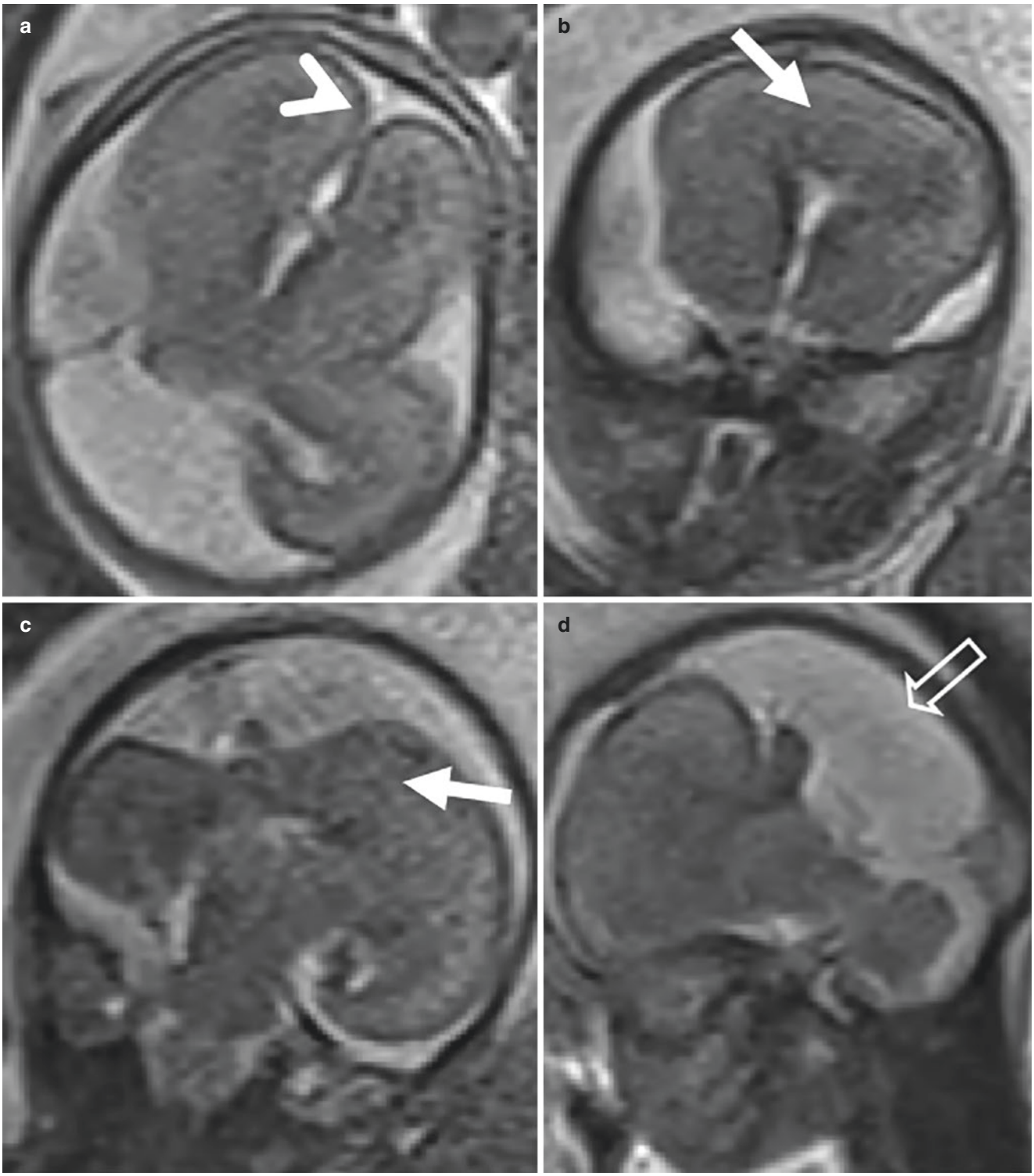

Fig. 5.4 Axial (**a**), coronal (**b**, **c**), sagittal (**d**) images of a 21-week fetus showing partial fusion of bilateral frontal and parietal lobes (arrows), the septum is not visualized, cystic area is seen in the parieto-occipital region (open arrows) with the diencephalic ventricle, the midline falx cerebri is not fully formed (arrowhead)—features of *Semilobar holoprosencephaly*

Differential diagnosis Alobar holoprosencephaly, Lobar holoprosencephaly, Arachnoid cyst.

Prognosis Mental retardation is profound and often fatal in the early childhood.

5.3.3 Lobar HPE

It is characterised by incomplete cleavage of the forebrain (but better than that of Semilobar HPE), the basi frontal regions being more affected. The interhemispheric fissure, falx are formed and the thalami are separated (Fig. 5.5a, b).

Imaging features

- Absent septum pellucidum.
- The frontal horns of bilateral lateral ventricles are fused. The fused segment is seen to communicate with the third ventricle.
- Noncleavage of the fornices [18].
- Normal or hypoplastic corpus callosum.
- The interhemispheric fissure is completely or near completely formed.
- The thalami are completely or almost completely separated.
- The inferior most portions of the frontal lobes are fused (Fig. 5.5a, b).
- Anterior cerebral artery is seen inferior to the frontal bones (snake under the skull sign) [19].

Differential diagnosis Semilobar holoprosencephaly, SOD.

Prognosis and management

Children with lobar HPE may survive into adulthood. Common causes of death include respiratory infections, intractable seizures, dehydration secondary to uncontrolled and diabetes insipidus. Death due to improper control of respiration and heart rate due to brainstem malfunction have also been described [20].

Medical management includes correction of hypothalamic and endocrinologic dysfunction, appropriate therapy for motor/developmental/visual impairment, seizures, and hydrocephalus. Genetic testing, determination of any associated syndromes, and appropriate genetic counseling may also be offered.

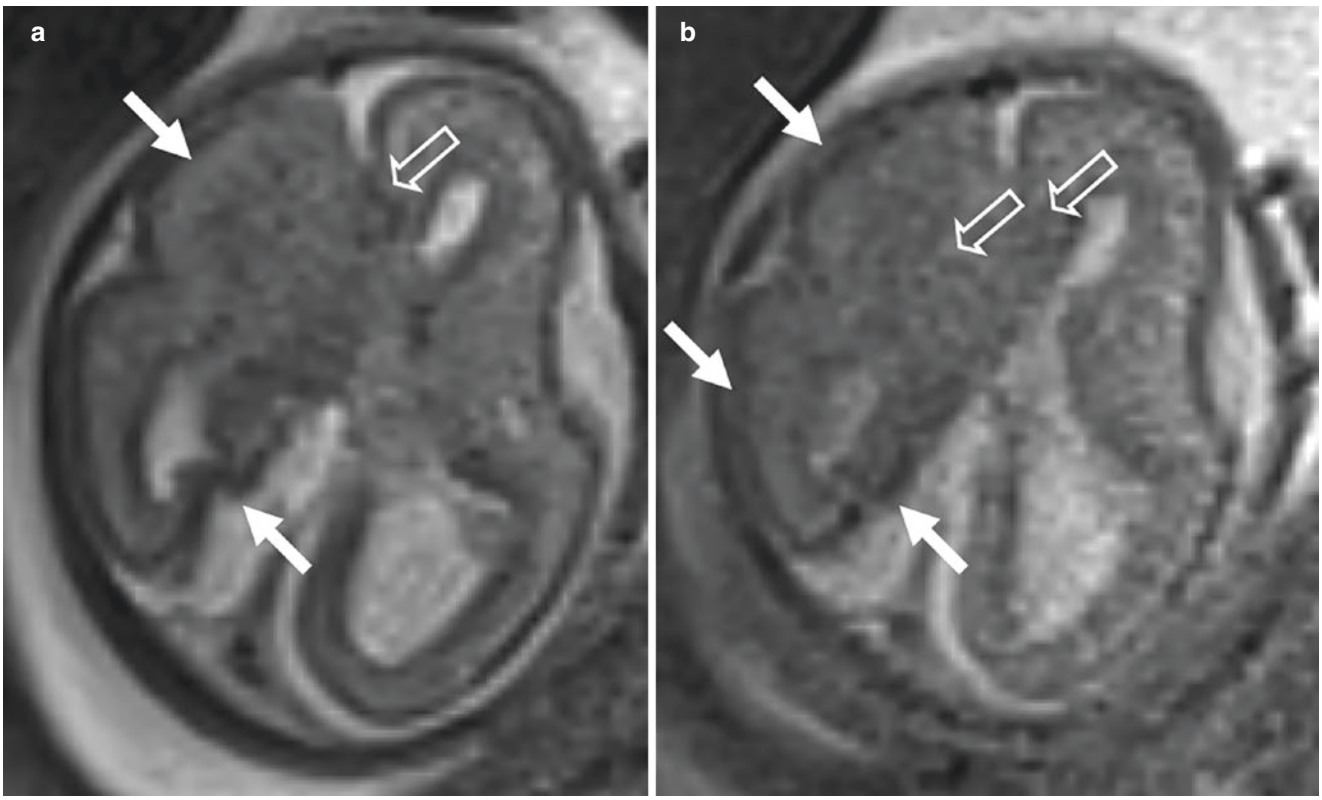

Fig. 5.5 Axial T2W images (**a**, **b**) of a 22-week fetus show a small right cerebral hemisphere with cortical abnormality (arrows). There is partial fusion of the cerebral hemispheres at the level of basal ganglia and in the frontal region (open arrows)—*lobar type of holoprosencephaly*. Mild ventriculomegaly of left lateral ventricle is also seen

5.3.4 Middle Interhemispheric Variant (MIH)

It is mild form of HPE where the cleavage has not occurred in the posterior frontal and parietal lobes (Fig. 5.1e).

Synonym—Syntelencephaly.

Imaging features [21–24]

- Absent septum pellucidum
- Agenesis or hypoplasia of the body of corpus callosum
- Dorsal cyst may be present
- Vertically oriented Sylvian fissures which are abnormally connected across midline over the vertex of the brain
- Cortical dysplasia or subcortical heterotopias may be present
- Mild craniofacial abnormalities
- There are fairly well-developed frontal and occipital lobes and the intervening interhemispheric fissure. However, the interhemispheric fissure and falx are absent in the middle interhemispheric region

Differential diagnosis

1. Lobar HPE—In lobar HPE, the most severely noncleaved part is the basal forebrain, whereas, in MIH, the non-cleaved part is in the posterior frontal and parietal lobes.
2. Schizencephaly—There is no non-cleavage abnormality.

Prognosis Developmental delay, mental retardation, seizures, and Spasticity or hypotonia may be present in postnatal life.

Children with MIH may walk with support and show mild impairment in speech and motor functions. Developmental outcome of Children with MIH is similar to that in lobar HPE [25–27].

5.3.5 Septo Optic Dysplaia

Is discussed in Chap. 4.

5.3.6 Minimal HPE

Is characterized by trivial craniofacial malformations, non-cleavage in the preoptic (suprachiasmic) area, thickened or dysplastic fornix, and absent or hypoplastic anterior part of the corpus callosum. These patients also had single unpaired anterior cerebral artery [28].

Prognosis Patients often manifested mild developmental delay in the form of language delay, learning disabilities, or behavioral disturbances, while motor function was relatively spared [11].

5.3.7 Microform HPE

Microform HPE occur in relatives of patients affected by HPE, exhibit craniofacial anomalies and do not show brain involvement [28, 29].

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