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Holoprosencephaly and related entities

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Summary. Holoprosencephaly is a brain anomaly of varying severity with associated extracranial, symptomatic abnormalities in only a minority of cases. The class of brain defects known as holoprosencephaly represents a continuum usually divided into three types: alobar, semilobar, and lobar. Each has both distinctive radiological characteristics and some similarities. Typical facial anomalies are found in the severe forms. Absent septum pellucidum and septo-optic dysplasia, possibly of similar embryological origin, have some resemblances to lobar holoprosencephaly, but are clinically and radiologically separate in most instances. Agenesis of the corpus callosum, which is superficially like holoprosencephaly, should not be confused with the prosencephalic defects.

Key words: Absent septum pellucidum – agenesis of the corpus callosum – arhinencephaly – brain abnormality, congenital – computed tomography, head – holoprosencephaly – septo-optic dysplasia

This condition was termed arhinencephaly by Kundrat [1] in 1882, emphasizing the absence of olfactory structures that usually occurs in this condition. Although this term is sometimes still used for this entire class of malformation even by contemporary authors, in this discussion, the term "arhinencephaly" will be used in the more limited sense to describe a defect confined to the olfactory structures. Yakovlev [2], in his extensive 1959 publication, placed the emphasis of the malformation more properly on the abnormal forebrain development, using the term "holotelencephaly", DeMyer and Zeman [3] in 1963 modified this to "holoprosencephaly", more accurately describing the fact that it is the entire prosencephalon of the embryonic brain that fails to divide properly, retaining a single or holoventricle. The anomaly is usually divided into three categories, from most severe to mildest: alobar, semilobar, and lobar. The following report is based largely on the author's personal series of 15 patients: 6 with alobar holoprosencephaly, 6 with semilobar holoprosencephaly, and 3 with lobar holoprosencephaly. Seven patients were male; eight were female.

Embryology

Holoprosencephaly is considered a defect of cleavage, rather than of closure. The most likely mechanism is that proposed by Cohen et al. [4]. They theorized that abnormal development of the notochordal plate, which greatly influences the growth of the brain and face, is the main factor in this malformation. When the notochord ends short of its normal position just behind the optic plate (Fig. 1), there is an inhibition or lack of stimulation of the optic anlagen and prosencephalon to begin their lateral movement. The adjacent olfactory placodes, whose position is determined by the rostral end of the central nervous system (prosencephalon) rather than the notochord, are also affected. These in turn influence the growth of the nasal ridges and premaxilla. Shortening of the notochord causes the olfactory placodes to be located higher than their normal location above the mouth, giving origin to the proboscis, which may be quite high on the face (even above the eye in some forms of holoprosencephaly) (Figs. 1 b and 2 a).

Ludwin and Malamud [5] believe it is specifically the prechordal mesoderm at the dorsal lip of the foregut that determines growth of the forebrain. As this is adjacent to the notochordal tip, the exact identity of the primary generator is not of practical importance. It is of interest to note that the rostral tip

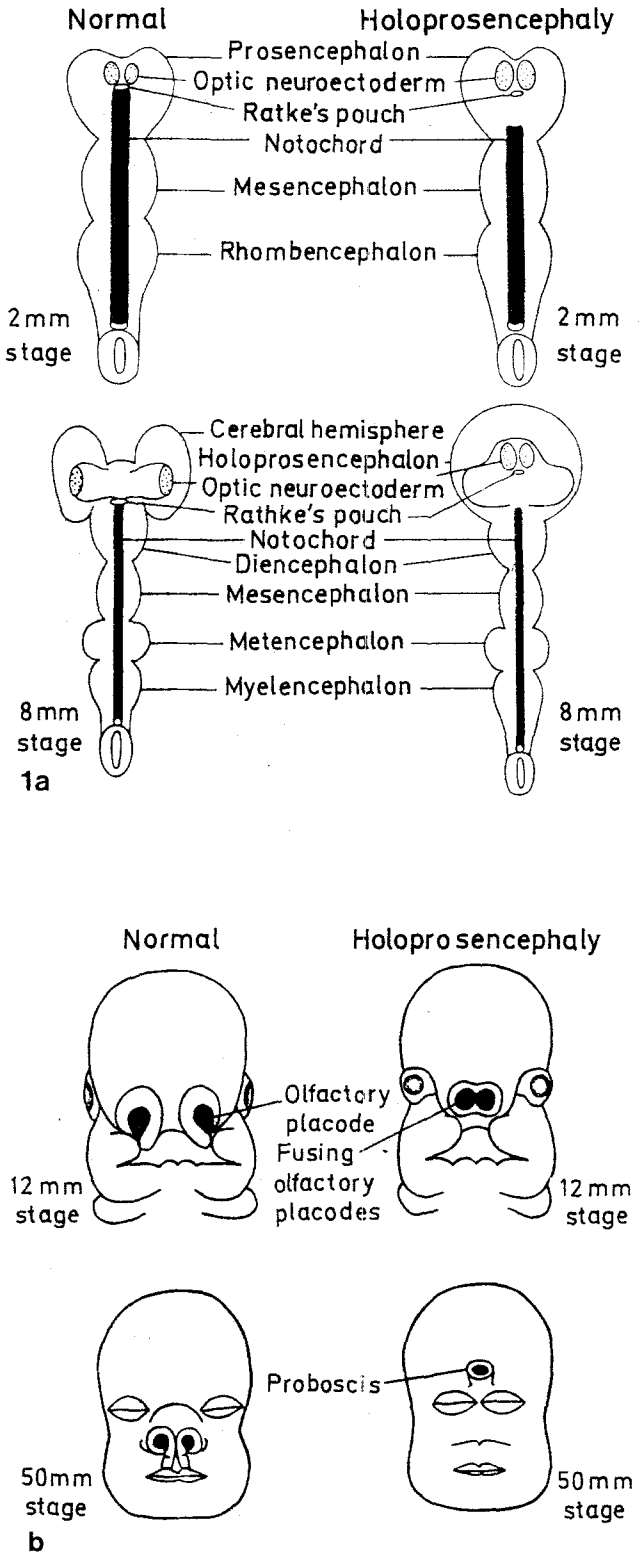


Fig. 1a. Diagrammatic sketch showing development of the notochord in the normal (left) and abnormal (right) situation (from Cohen MM et al (1971) Birth Defects 7: 125–135 [4]). **b** Diagrammatic sketch of normal facial development (left) and severe alobar holoprosencephaly (right). Fused olfactory placodes and lack of premaxilla cause development of a proboscis at or above the hypoteloric orbits from Cohen MM et al (1971) Birth Defects 7: 125–135 [4])

of neural tube closure, the anterior neuropore, is the midline site of the junction of the optic primordia [6].

Probst [6] suggests that the most severe form of holoprosencephaly with cyclopia must begin before 26 days of gestation, because the optic vesicles have already lateralized by that time and, therefore, could not "fuse" after that time. The olfactory bulbs normally appear at six weeks as paired structures. Since the olfactory bulbs are separate from their very origin, abnormalities affecting them may cause them to be absent but cannot cause them to be fused. The olfactory bulbs are usually absent in holoprosencephaly. It is not clear from the various authors whether the milder forms of holoprosencephaly reflect a lesser defect occuring at the same time, or a later growth inhibition.

Though much emphasis is placed on the lack of lateral cleavage of the brain, i.e., the optic structures and cerebral hemispheres, there is also a lack of transverse cleavage into the telencephalon and diencephalon, and a lack of horizontal separation of the optic and olfactory structures [7]. A lack of a corpus callosum is usually an accompanying anomaly, expecially in the more severe forms of holoprosencephaly. This is probably because the earlier abnormalities of holoprosencephaly prevent the callosal precursors from even forming. Though most authorities feel there is not a common origin for the two defects, not all authors agree with this [8].

Etiology and associated abnormalities

The factors causing the abnormalities of holoprosencephaly to occur in the embryo appear to be both environmental and hereditary. Experimental irradiation of fetuses has caused holoprosencephaly in mice [9], but the dose was a very high 1.78 Gy (178 rads). The eating of teratogenic plants by pregnant ewes has also induced the defect [10]. One of Probst's [6] cases was in a pregnancy that had a quinine-induced attempted abortion. Maternal diabetes has been reported [11].

A multiplicity of possible factors was noted in a fascinating study of 30 families by Roach et al. [12]. These included first-trimester bleeding in 37%, and a significantly increased incidence of dizygotic twinning in the affected generation. Mental retardation and severe mental illness were each found in about half of the families. Twenty-eight of the 30 families were very poor. Occupational exposure to metals [12] and herbicides or pesticides [4] was noted in 16 fathers.

Holoprosencephaly has also been found in a number of syndromes which have many extracranial abnormalities. Most of these are chromosomal de-

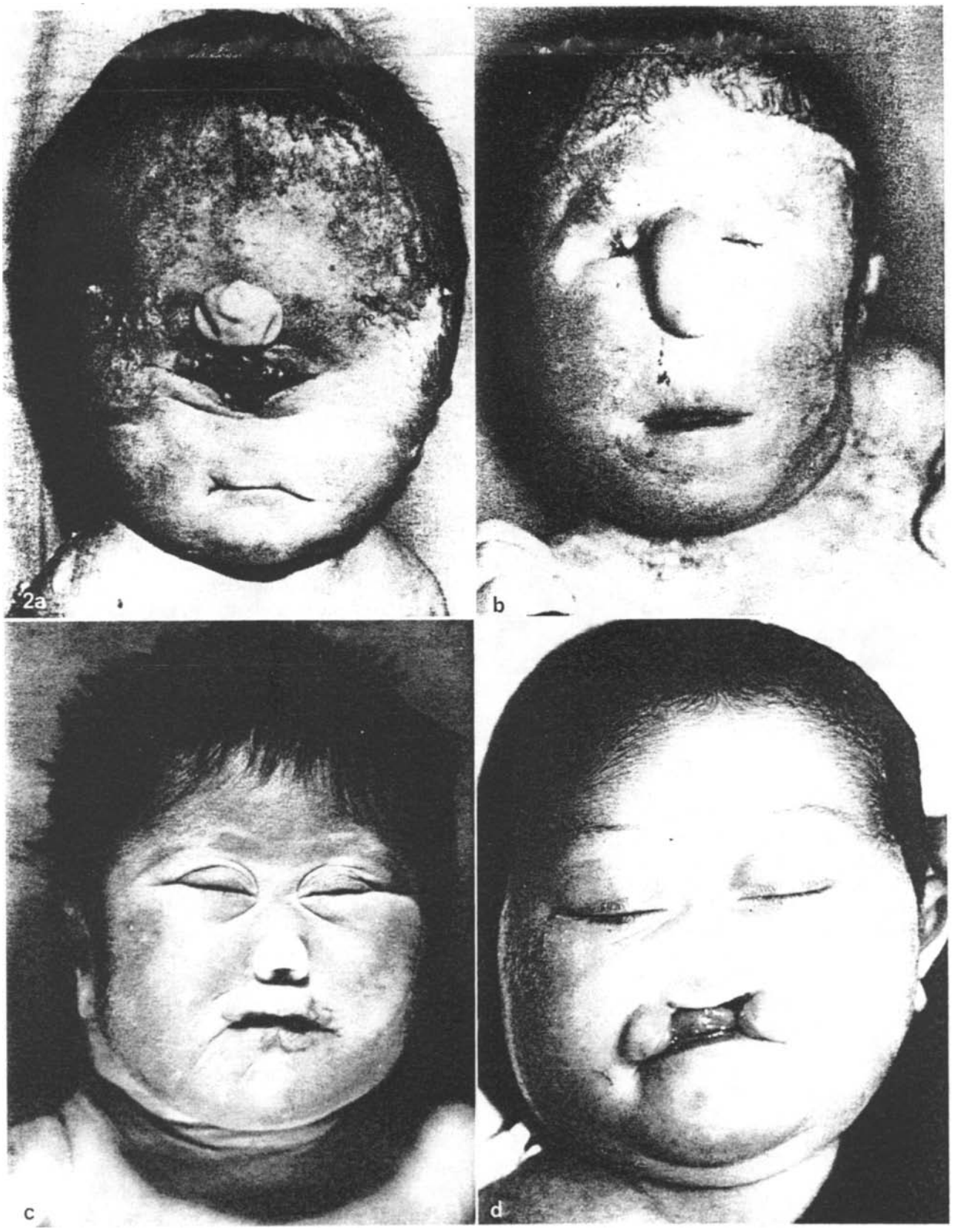
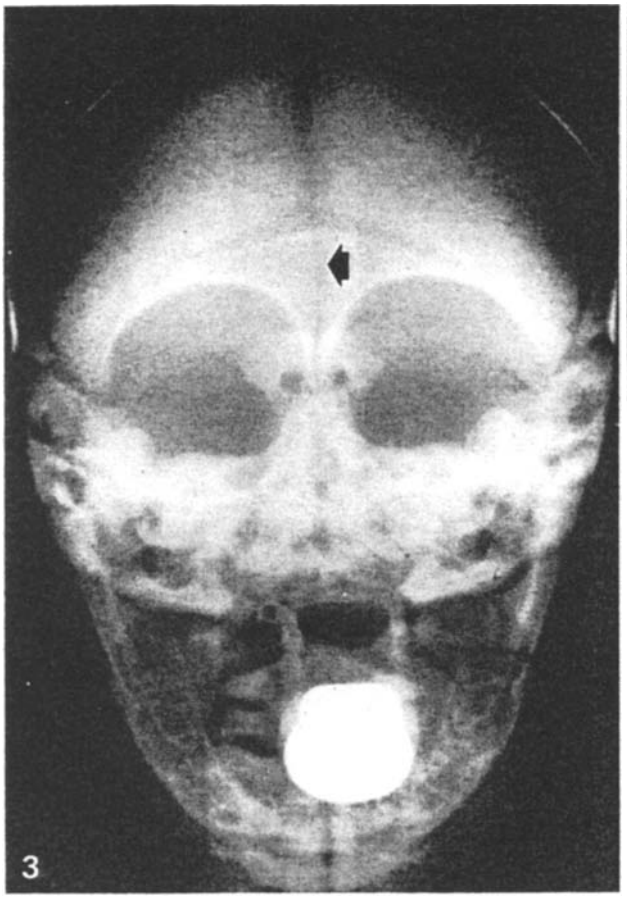


Fig. 2. a Cyclopia; **b** Ethmocephaly; **c** Cebocephaly; **d** Premaxillary agenesis (Figs. **2 a and b** are reproduced from Probst [6]; Figs. **2 c and d** are courtesy of Dr. T. P. Naidich, Chicago, IL)



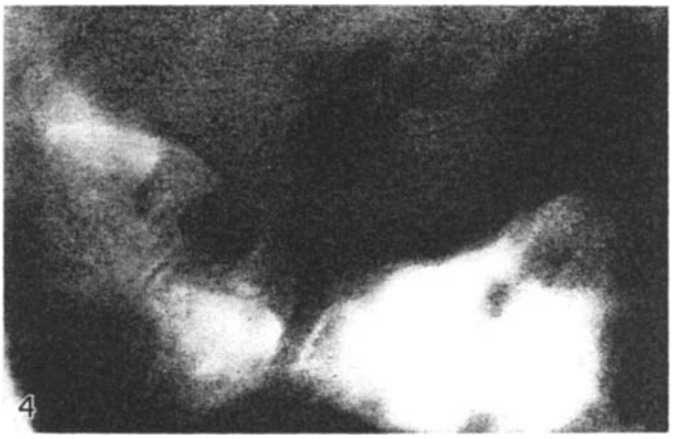


Fig. 3. Hypotelorism. AP skull radiograph shows severe hypotelorism, near fusion of the optic canals, and open metopic suture *(arrow)* in alobar holoprosencephaly (same patient as Fig. 7)

Fig. 4. Small sella turcica. Lateral projection of a pneumoencephalogram in an infant with semilobar holoprosencephaly and hypopituitarism. Large anterior clinoid processes make the sella appear somewhat larger than its actual, very small size

fects. The most common of these admittedly rare conditions include: trisomy D (13–15), trisomy E (16–18 or 17–18), trisomy 18 (18 short arm deletion) syndrome, 13q-syndrome, Meckel syndrome, Kallman syndrome, autosomal recessive form of holoprosencephaly, and the autosomal dominant form of holoprosencephaly. These and others are discussed more completely in Probst [6] and Cohen [7].

The association of holoprosencephaly with these syndromes is variable. When present, the anomaly usually manifests one of the sub-types of the alobar form, making the clinical diagnosis obvious. However, the 13q-syndrome often has lobar or semilobar holoprosencephaly. The autosomal dominant form [7] commonly is one of the milder forms. In the Kallman syndrome, hypogonadism is associated with arhinencephaly.

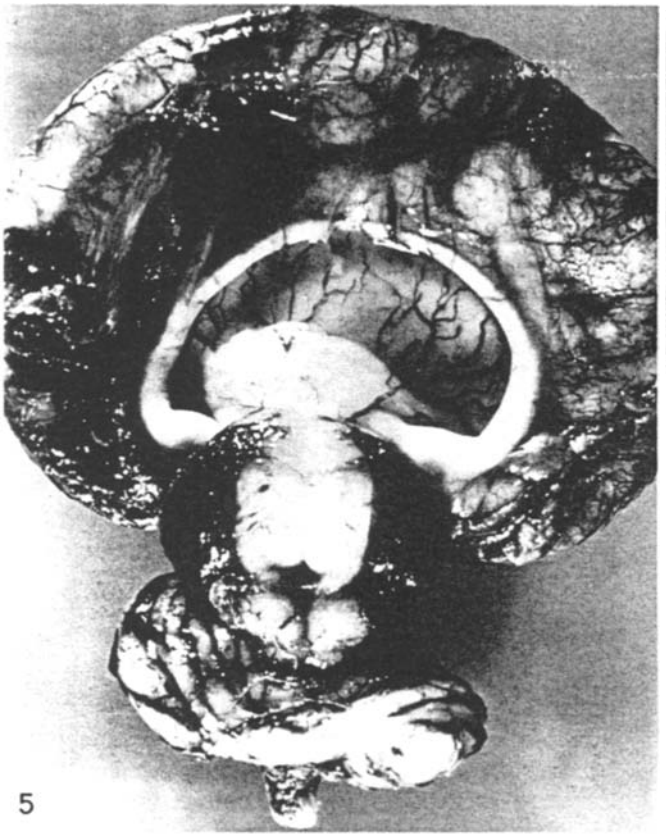
Incidence

Roach et al. [12] gave an incidence of 1 in 16,000 births, but felt the true incidence is actually higher. Trisomy 13, which has a high frequency of concurrent holoprosencephaly, has an estimated incidence of 1 in 2,000 [13]. Matsunage and Shiota [14] found a very high (0.4%) incidence of holoprosencephaly in fetuses from induced abortions, suggesting that most holoprosencephalies are fatal and would end in spontaneous abortion.

Classification

Much of the earlier literature was devoted to the most severe forms of holoprosencephaly because of the striking nature of the abnormalities and the fact that patient death in early infancy provided material for pathological analysis. The anatomic and clinical features of these severe forms have been well summarized by DeMyer et al. [15], who showed that certain severe facial anomalies were always associated with severe alobar holoprosencephaly. DeMyer and Zeman [3] first used the classification that is commonly followed today; that of alobar, semilobar, and lobar forms.

In his book, *The Prosencephalies,* Probst [6] divides the spectrum differently, using the dorsal sac (see below) to define the most severe form of the malformation. Because the dorsal sac is seen in semilobar holoprosencephaly, Probst's categories overlap those of DeMyer and Zeman [3]. A comparison between these two major classifications is provided in Table 1. In the estimation of this author, the radiology of the diseases is more easily understood by using the alobar to lobar continuum. However, any individual case may not always fit completely into one of the three categories.



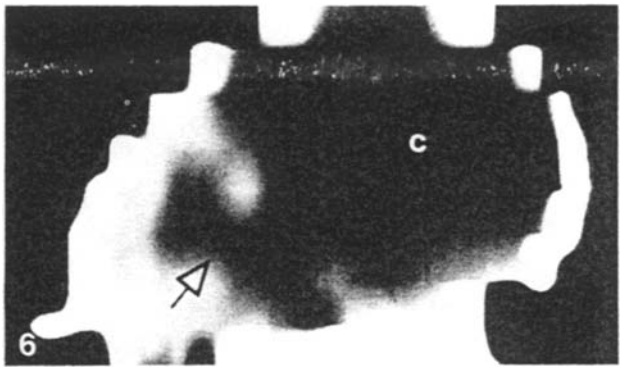


Fig. 5. "Pancake" variant of alobar holoprosencephaly. View of the dorsal aspect illustrates common ventricle and partial cerebral mantle located anteriorly. The dorsal cyst covering has been artifactually disrupted but extended from the rim of the ventricular opening to fused thalami seen immediately below it (Courtesy of Dr. R. E. Schmidt, St Louis, MO)

Fig. 6. Thalami in alobar holoprosencephaly. Parasagittal reconstruction of CT shows thalami *(arrow)* on the floor of the monoventricle. A huge dorsal cyst *(c)* is present in this infant having "pancake" holoprosencephaly

Table 1. Classifications of holoprosencephaly. (Numerical designations are in order of progression toward normal development according to each classification. They are not in complete agreement, column A has been put in sequence, and matching equivalent of column B is therefore nonsequential)

A. Modified from DeMyer and Zeman [3]	B. Probst [6]
1. Alobar with sac	1. Dorsal sac A
2. Alobar, no sac	4. Intermediate A
3. Semilobar with sac	2. Dorsal sac B
	3. Dorsal sac C
4. Semilobar, no sac	5. Intermediate B
	6. Intermediate C
5. Lobar	7. Pseudohemispheric

Facial characteristics

The facial description of the most severe forms of holoprosencephaly are given below for interest. The first three all have severe alobar holoprosencephaly and die shortly after birth or are stillborn. The descriptions are taken from DeMyer et al. [15], Probst [6], and Cohen et al. [4].

Cyclopia or cyclopy is the most severe form with eyes and orbits that are totally or nearly completely fused. There is usually a midline proboscis above the eye (Fig. 2a), though this may be absent. The nasal structures are absent. Trigonocephaly is present. The frontal bone may arise from a single ossification center [16].

Ethmocephaly (Fig. 2b) is the least common of the most severe types. It resembles cyclopia, but the orbits are separate, even though severely hypoteloric. The single or double proboscis is between the eyes, and may be bulbous. There is absence of the nasal structures and premaxilla, though as in cyclopia, there is no cleft lip. Trigonocephaly with bony fusion is present.

Cebocephaly (Fig. 2c) is characterized by a small flattened nose with a single nostril. The orbits are small, with hypotelorism. The premaxilla and nasal septum are absent.

Premaxillary agenesis or arhinencephaly with cleft lip (Fig. 2d) is compatible with life and is likely to be the most severe facial form the neuroradiologist will see. There are a small flat nose, hypotelorism, absent intermaxillary segment of the face, and usually trigonocephaly. Absence of the prolabium results in severe pseudomedian cleft lip and absent philtrum. Absence of the primary palate and the premaxilla (the portion of the intermaxillary segment of the face

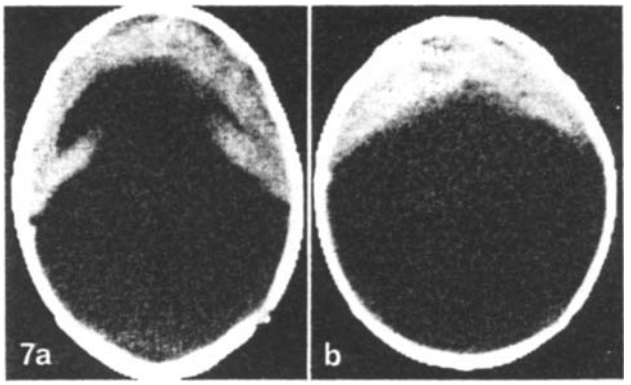


Fig. 7 a and b. Dorsal cyst. Axial CT slices through the monoventricle **(a)**, and above **(b)**. The cortex extends slightly behind the monoventricle to form the anterior border of the cyst. This patient closely resembled that of Figure 5 in the sagittal plane ("pancake" variety)

carrying the four upper incisors) results in cleft superior alveolar ridge and adjacent portion of palate [17]. The secondary palate may be intact [18] but cases seen by the present author have all had palatal clefting. This facial type has been reported to also be present in the milder semilobar form [18], and may even occur with normal brain development [19].

Milder forms. Many children with lobar and semilobar holoprosencephaly will have only mild hypotelorism and, perhaps, trigonocephaly. Microcephaly is almost always present in the severe forms, and is often seen in the milder forms. A relatively normal face does not always rule out alobar holoprosencephaly, as noted in case 18 of Probst [6]. On the other hand, infants with bilaterally cleft lip, because of the width of the defects, may look superficially worse than the child with premaxillary agenesis when, in fact, the underlying brain defect is likely to be less serious and of different type.

Hypertelorism. Many authors have referred to DeMyer and Zeman [3] as the source of the statement that semilobar holoprosencephaly may occur with hypertelorism. Those authors stated that it might occur, but had no case or reference to one where it did, in fact, occur. No case of any type of holoprosencephaly with hypertelorism has been reported in the English literature to this author's knowledge. The nature of the underlying embryological defect, in fact, should exclude this facial abnormality. It is this author's belief that hypertelorism does not occur in holoprosencephaly.

Radiology and pathology of the brain

It is somewhat paradoxical that as the radiological techniques of investigation become more accurate and more refined, allowing us to diagnose milder forms of the holoprosencephaly spectrum, the more normal brains of these less-severely affected children allow them to live into or beyond childhood, and the pathological proof so useful for correlation is no longer available. Too often CT scanning is the only radiological examination done. Other studies, especially angiography, should be undertaken on occasion to clarify the diagnosis.

Plain radiographic findings

The plain radiographic findings will reflect the clinical appearance of the child with microcephaly and hypotelorism in most cases (Fig. 3). Hydrocephalus may occur infrequently. The hypotelorism is often more striking on radiographs than it is clinically, but its presence or absence is not of clinical importance. Absence of the nasal septum, absence of the ethmoid sinuses, and a small sella turcica may also be seen (Fig. 4). Patients may evidence hypopituitarism or even have absence of the pituitary gland.

The neuroradiologist may be called on to examine the child with trigonocephaly but no other abnormalities, in order to rule out holoprosencephaly. In these cases, attention should be directed to the presence of a patent metopic suture. Except in patients with clear facial stigmata of holoprosencephaly (i.e., cyclopia, ethmocephaly, or cebocephaly), the hypotelorism seen in holoprosencephaly is *not* accompanied by the closed and thickened metopic suture of the craniosynostotic type. This observation is supported by 15 of the author's cases, and by 2 cases of semilobar holoprosencephaly with hypotelorism and patent metopic sutures reported by Kurlander et al. [17] and Currarino and Silverman [16]. Therefore, otherwise normal-appearing infants with trigonocephaly secondary to early closure of the metopic suture need not be investigated to rule out holoprosencephaly. This point has not been emphasized previously.

Specialized examinations

The first pneumoencephalographic (PEG) description of holoprosencephaly appears to be that of Goldstein and Riese in 1926 [20] (quoted by Probst [6]). The first angiographic description was in 1965 by Wisen et al. (an autopsy arteriogram) [21]. The first in vivo arteriogram was reported shortly thereafter by Zingesser et al. [22]. CT has allowed easier examination of the patients, though few have actually been reported. Byrd et al. [23] gave the earliest CT description in 1977. The following sections will combine the three examinations in dealing with the three forms of holoprosencephaly. Many of the diagnostic features demonstrated by CT and PEG are necessarily the same.

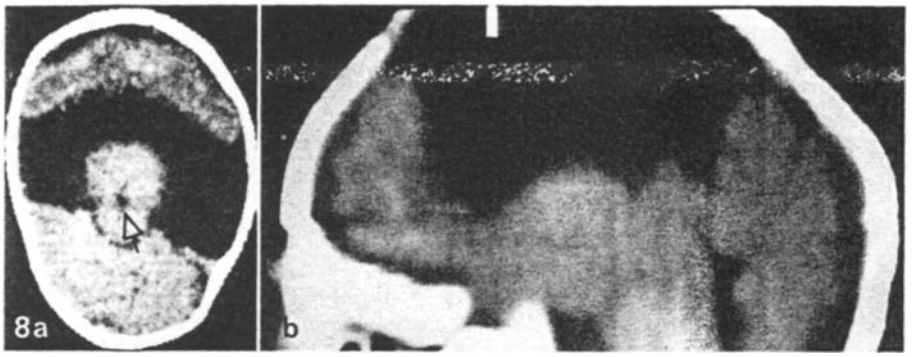


Fig. 8 a and b. "Cup" alobar holoprosencephaly. **a** Axial slice shows prominent central thalami surrounded by monoventricle and anterior cortex. Aqueduct *(arrow)* is patent in this case. **b** Sagittal reconstruction, oriented with the patient's nose to the reader's left, shows monoventricle communicating superiorly with dorsal cyst, and bordered by hypoplastic cerebrum anteriorly and posteriorly.

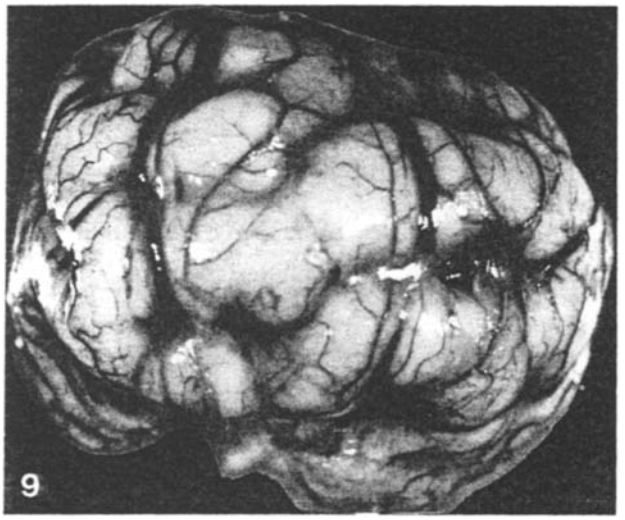


Fig. 9. "Ball" alobar holoprosencephaly. Oblique, anterolateral view of a postmortem brain. The patient's nose would be angled toward the reader's left. The interhemispheric fissure is absent, and the large gyri have a random pattern across the cortex. No cyst is visible

Alobar holoprosencephaly

DeMyer [24] subdivided this form by the shape of the holotelencephalic cortex which covers the ventricular cavity, referring to the pancake, the cup, and the ball types. These correspond to a progressively greater degree of enclosure of the common ventricle by cerebral tissue with concomitant decrease in the size of the dorsal cyst. The first two are equivalent to the dorsal sac A-type of Probst [6]. In the pancake variety, the basal ganglia and thalami remain fused in the midline at the base of the ventricular cavity (Fig. 5). The thalami are always visible on PEG or CT (Fig. 6), though the smaller and more anteriorly placed basal ganglia may not be. The cerebral canopy covers the monoventricle to the edge of the cyst (Fig. 7).

The nature of the dorsal sac or cyst is poorly understood. Probst [6] reviewed the three theories given in the literature and concluded there was not enough evidence to know which, if any, was correct. The three proposals are: (1) it arises as part of the third ventricle, (2) it is a distorted velum interpositum, and (3) it is an undeveloped portion of the wall of the prosencephalic vesicle.

In the cup variety, there is further development of the brain. The thalami are slightly more prominent, though still fused into a single mass, and there is more brain visible posteriorly (Fig. 8).

In the ball variety, there is a complete covering of the holoventricle. There is no falx present. There is no interhemispheric fissure on the brain surface (Fig. 9). Though no dorsal cyst is present, the subarachnoid space may be very large over the brain surface.

No formation of occipital or temporal horns occurs in the alobar form, though in CT sections, the midline thalami give the ventricle an "inverted-U" shape whose arms can be mistaken for temporal horn development (Fig. 10). There is no third ventricle in these forms, though there may be a slight groove in the midline of the fused thalami.

Several angiographic features are common to all types of alobar holoprosencephaly. The anterior cerebral artery (ACA) is usually a single azygous artery which wanders over the paramidline brain surface. Two anterior cerebral arteries may be present [25], each supplying one half of the holoprosencephalon (Fig. 11). The middle cerebral arteries (MCA) are often hypoplastic [26]. Since there is no sylvian fissure or operculum, the MCAs wander over the lateral cerebral surface, stopping at the edge of the dorsal cyst when one is present. The MCAs also tend to branch very early with the branches ascending quite vertically over the lateral surface of the holosphere (Fig. 11). Maki and Kunagi [27] reported one case in which a single undifferentiated artery supplied each half of the holosphere. Probst [6] noted that the posterior cerebral artery (PCA) may go anterosuperiorly to supply a very small area on the posterior edge of the open cortex. This also occurs in the semilobar form with a dorsal cyst (Fig. 12) (Probst's dorsal sac B-type).

As there is no falx, there is no inferior sagittal sinus, straight sinus, or superior sagittal sinus [25]. The internal cerebral veins are absent, and most venous drainage is on the brain surface. The olfactory bulbs

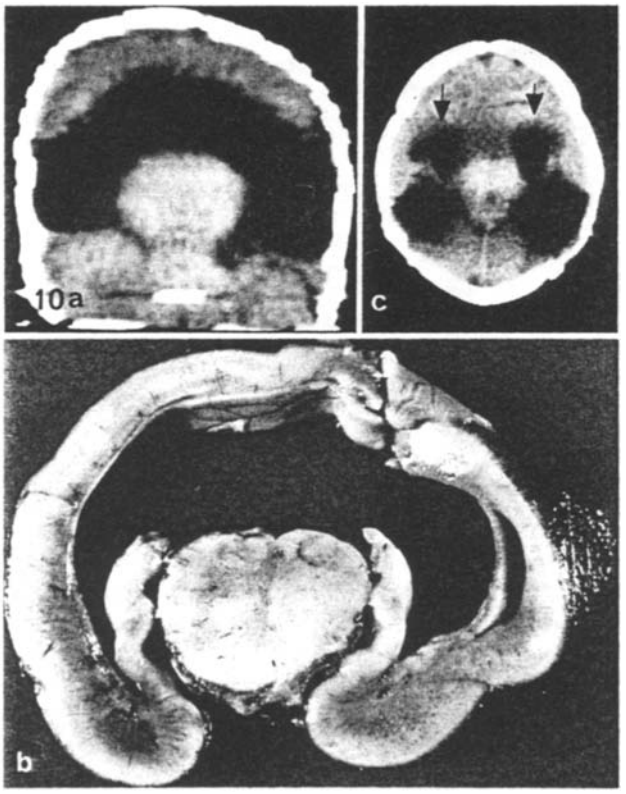


Fig. 10a–c. Alobar Holoprosencephaly. **a** Coronal reconstruction of CT of patient in Figure 7. Inferior portions of monoventricle adjacent to thalami may be mistaken for temporal horns. **b** (Different patient) Coronal anatomic section from "ball" variety of alobar holoprosencephaly demonstrates the absent interhemispheric fissure, the fused thalami centrally, absence of the third ventricle, and the encompassing holoprosencephaly (Courtesy of Dr. R. E. Schmidt, St Louis, MO). **c** Low axial CT slice of patient in Figure 6. Bottom segments of the monoventricle *(arrows)* resemble temporal horns

and tracts, not demonstrable radiographically, are missing in alobar holoprosencephaly. Heterotopic gray matter may be present on the inner ventricular surface [6]. While this should be visible on PEG or CT, this has not been definitely identified. Pachygyria and focal polymicrogyria occur, and hypoplasia of the vermis has been reported [18].

The diagnosis of the more severe forms of holoprosencephaly can also be easily made by ultrasound in infancy (Fig. 13). As the resolution of ultrasound is not yet as good as that of CT, the milder forms may well be difficult to diagnose and separate, especially as the fontanelles begin closing.

Semilobar holoprosencephaly

With the thalamic prominence causing the appearance of temporal horn formation, it may be difficult on CT and PEG to decide when temporal horn formation has truly occured (Fig. 10). Other findings are more helpful. In patients with semilobar holoprosencephaly, a rudimentary third ventricle can usually be seen on CT and PEG (Fig. 14), especially in the coronal view. On PEG, there may be a functionally patent aqueduct which is often lacking in the alobar form. The roof of the monoventricle is indented downward in the midline, a sign of beginning sagittal separation (Fig. 14b).

Separate occipital horns are visible, and on CT, a posterior interhemispheric fissure and falx can usually be seen (Fig. 15). This is variable depending on the degree of differentiation toward the lobar form. The interhemispheric fissure may be very shallow and present only between the occipital lobes, or it may extend forward into the frontal region as a well-defined structure.

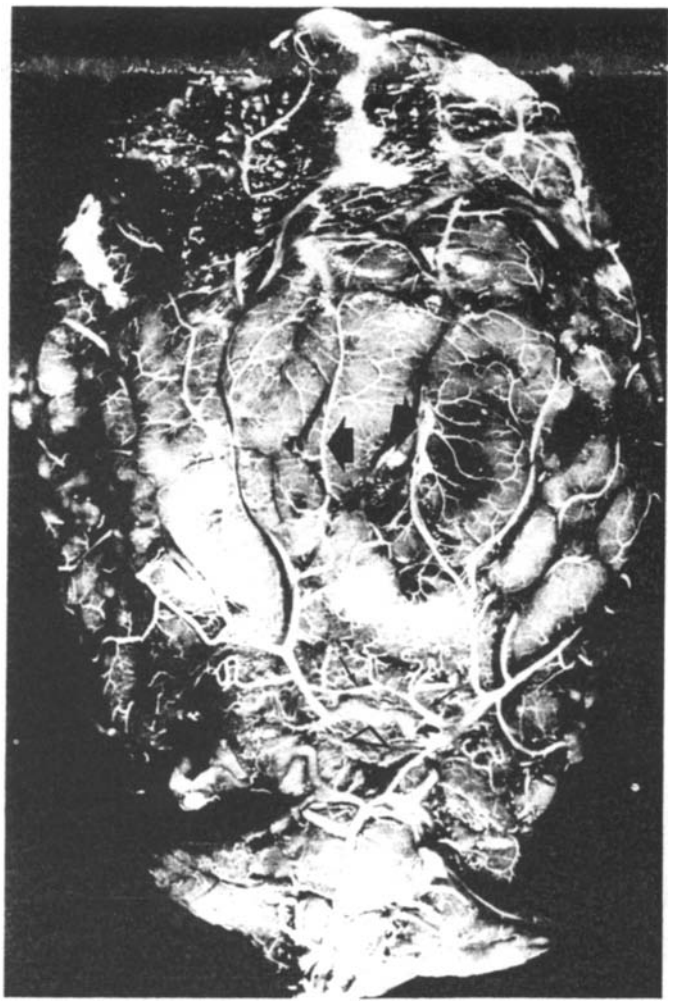
At angiography, the azygous ACA is more common, but two ACAs may be present. As there is no interhemispheric fissure anteriorly, the course of the azygous or double ACAs is aimless. No separate pericallosal and callosal marginal branches are present. The path of the MCAs is more normally defined because of some temporal lobe and sylvian fissure development (Fig. 16).

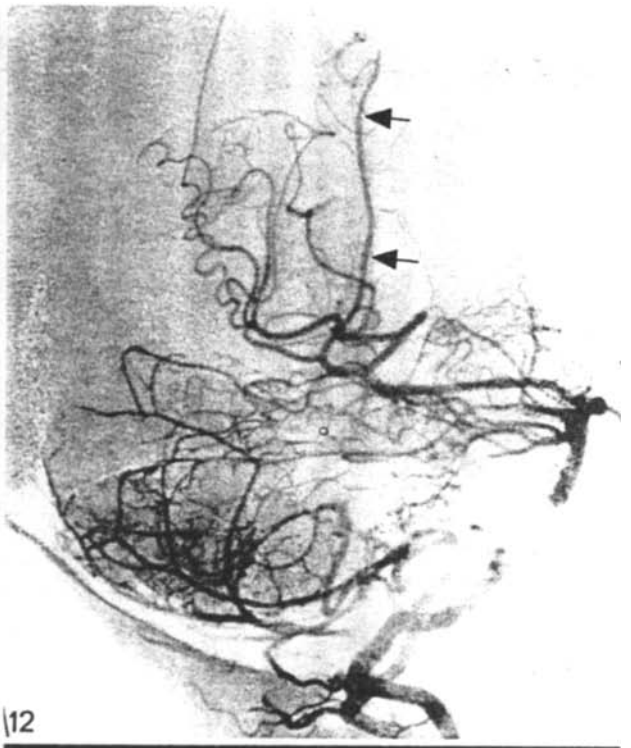
Hayashi et al [26] state that the straight sinus and internal cerebral vein are not present in semilobar holoprosencephaly. This may be true of the more primitive types which are transitional with alobar holoprosencephaly. However, in the author's experience, the internal cerebral vein, though flat and situated low along the floor of the monoventricle, is clearly seen, as is the straight sinus (Fig. 17a). The superior sagittal sinus is present in proportion to falx development, even when a dorsal sac occurs (Fig. 17b). The transverse sinuses are also developed. The inferior sagittal sinus is always absent. Zingesser et al. [22] and Khodadad and Putshar [28] have both reported cases of semilobar holoprosencephaly with persistent primitive trigeminal arteries.

Kurlander et al. [17] state the corpus callosum may be rudimentary in the semilobar form. Yakovlev [2] found callosal fibers even in alobar holoprosencephaly, but Probst [6] states that the presence of such callosal fibers should not be considered a corpus callosum, and that the corpus callosum in the usual sense is always absent. As such minimal development is not visible on radiographic studies, the exactness of such definitions is of limited use to the radiologist in establishing a diagnosis. The olfactory structures are absent or rudimentary in semilobar holoprosencephaly.

Lobar holoprosencephaly

The diagnosis of the lobar form is the most difficult because it resembles in appearance other minor





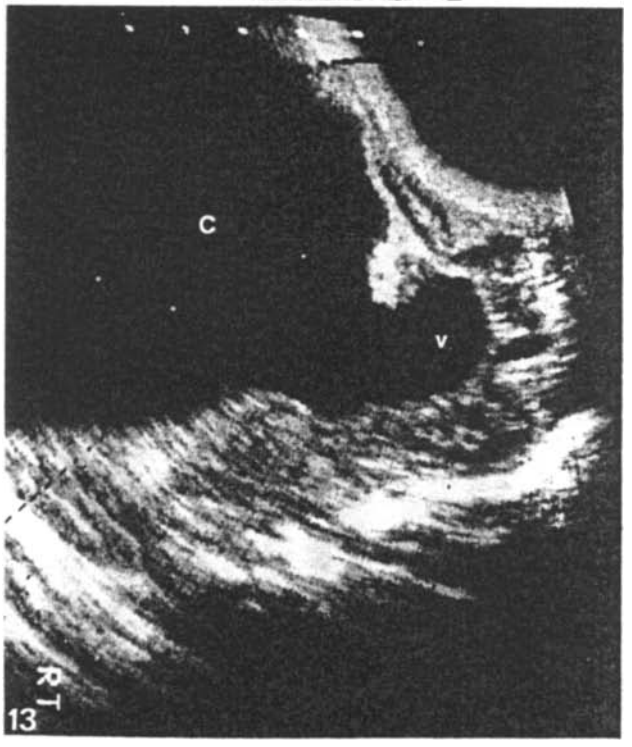


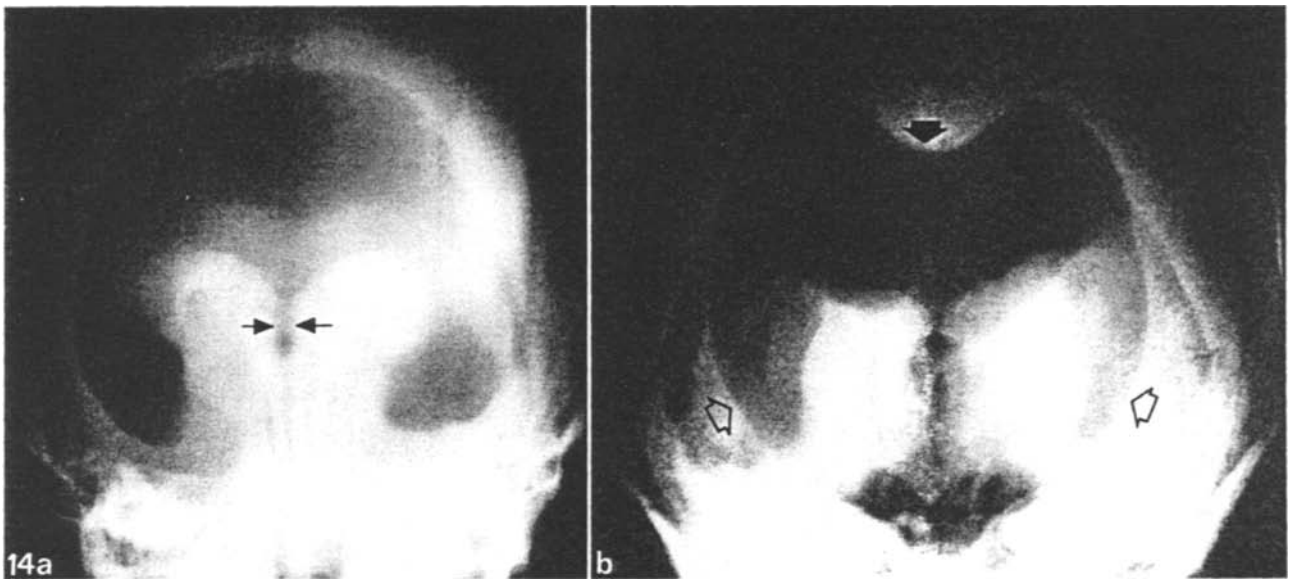
Fig. 11. Arterial pattern in alobar holoprosencephaly. Postmortem arterial injection. Ventral view shows two very small anterior cerebral arteries *(small arrows)* supplying the limited area of brain just anterior to the optic chiasm *(arrowhead)*. The middle cerebral branches can be seen rising nearly vertically to cover half of the holoprosencephalon. The most anterior branches *(large arrows)* of the middle cerebral arteries run nearly parallel to each other near to midline (Courtesy of Dr. T. P. Naidich, Chicago, IL)

Fig. 12. Posterior cerebral artery with dorsal cyst. Lateral vertebral arteriogram. Medial segment of the posterior cerebral artery, probably the parieto-occipital branch *(arrows)*, rises sharply upward in a patient with semilobar holoprosencephaly and a dorsal sac (same patient as Figs. 16 and 17)

Fig. 13. Alobar holoprosencephaly, ultrasound. Sagittal ultrasound section showing monoventricle *(v)* and huge dorsal cyst *(c)* (same patient as Fig. 7)

anomalies. On CT and PEG, the interhemispheric fissure is usually present from the occiput to the anterior portion of the frontal lobes, though it may be possible to see that it is shallow anteriorly. The interhemispheric fissure may be deep and almost complete, with only a small portion of cortex having a continued fusion in the region of or just ahead of the anterior corpus callosum. The CT and PEG findings depend primarily on the ventricular configuration.

There is good separation of the occipital horns, but the bodies of the lateral ventricles are very close, giving them a narrow appearance (Fig. 18). The continued fusion of the anterior horns tends to make their borders look somewhat square, with a flat roof



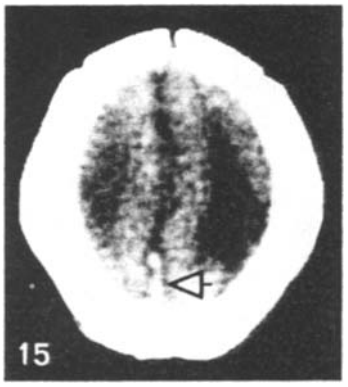


Fig. 14a and b. Semilobar holoprosencephaly. **a** AP tomogram of PEG in a poorly differentiated case shows early development of the temporal horns beneath thalami that are better separated than in the alobar form. Rudimentary third ventricle *(arrows)* is visible. **b** PEG in better differentiated semilobar type shows narrower, more well-defined temporal horns *(open arrows)* and superior midline indentation *(solid arrow)*. Third and fourth ventricles are visible in the midline

Fig. 15. Semilobar holoprosencephaly. High axial CT slice. A posterior falx is present *(arrow)*, and the interhemispheric fissure extends forward from it (same patient as Fig. 20)

in the coronal view (Fig. 19). No septum pellucidum is present. When the ventricles are small, as they often are, the findings described may not be easily appreciated.

There are no good descriptions of the angiographic features of lobar holoprosencephaly in the literature, probably because they were thought to be variations of normal. One would expect a minor deviation of the pericallosal artery over the fused portion of the frontal cortex, and perhaps, no other diagnostic findings. Osaka et al. [29] reported a case they felt to be lobar holoprosencephaly in which they describe a lack of the inferior sagittal sinus. To this author, the ventriculogram might well be interpreted as agenesis of the corpus callosum with a midline cyst. Moreover, in this case, there is also a posterior fossa cyst, a finding that has been reported with agenesis of the corpus callosum [30], but never previously with holoprosencephaly.

Miscellaneous findings

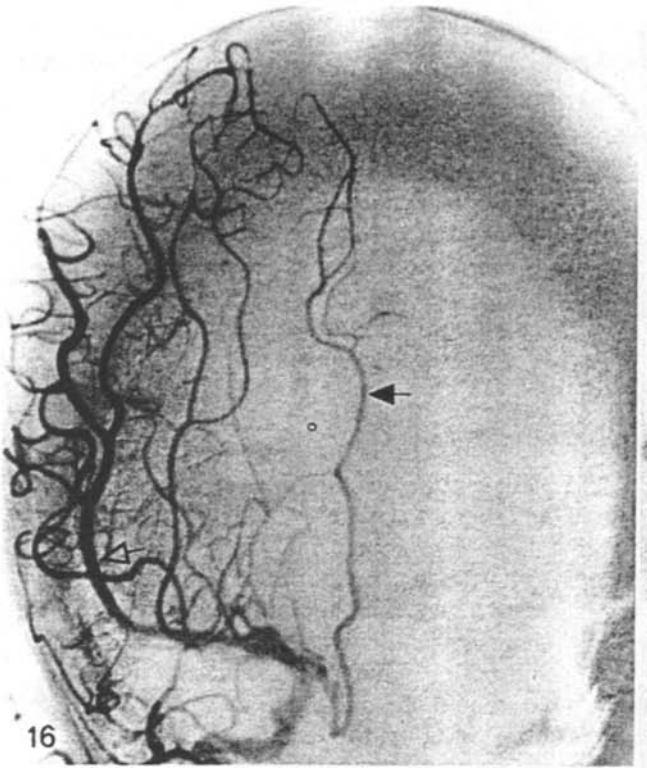
The author found calcifications in the anterior, inferior cortex just ahead of the thalami, possibly in the basal ganglia or at the gray-white matter border, in 2 of 15 cases (Fig. 20). They resembled the course of a normal proximal MCA. One occurred in a semilobar form without dorsal cyst, and the other in an alobar form with a dorsal cyst.

Two cases had an unusually large posterior fossa and high incomplete tentorium (Fig. 21). The dorsal sac appeared to communicate with the infratentorial compartment above the normal appearing cerebellum.

Differential diagnosis

Agenesis of the corpus callosum

The most likely mistake in diagnosis is to confuse a semilobar holoprosencephaly with agenesis of the corpus callosum accompanied by a midline cyst. Careful observation shows differences in these two entities. Probst [6] has emphasized that the dorsal cyst of holoprosencephaly is not of the same origin as the interhemispheric cyst of agenesis of the corpus callosum. They also do not appear alike. The dorsal



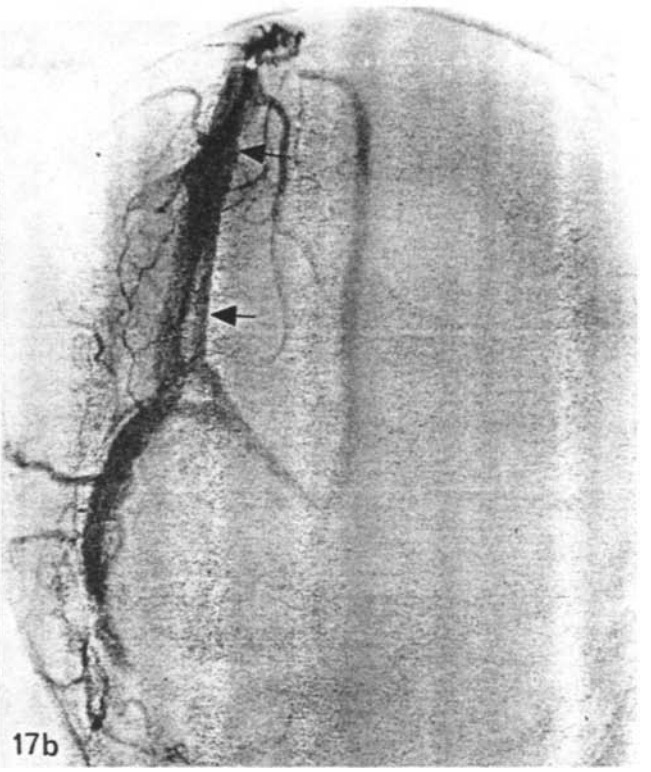


Fig. 16. Semilobar holoprosencephaly, carotid arteriogram, AP projection. The hypoplastic ACA *(solid arrow)* ascends centrally. The major portion of the MCA follows the curve of the primitive sylvian fissure *(open arrow)*, though the operculum is not developed superiorly

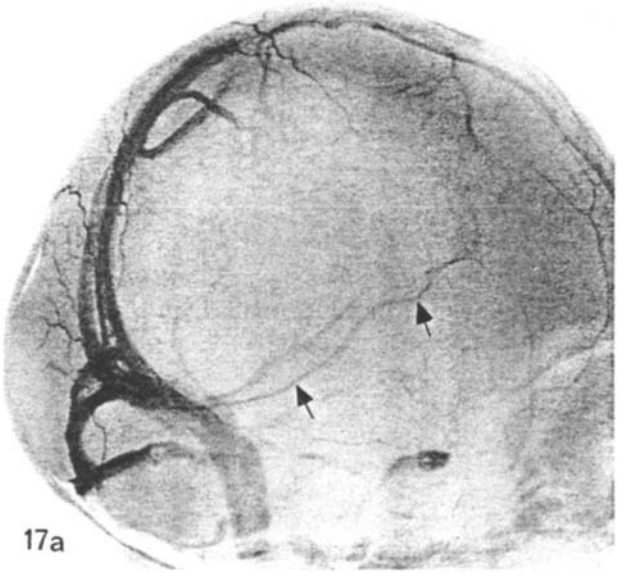


Fig. 17 a and b. Semilobar holoprosencephaly, venous phase of carotid arteriography (same patient as Fig. 16). **a** Lateral projection. The internal cerebral vein *(arrows)* is clearly visible along the ventricular floor. **b** AP projection. The posterior portion of the sagittal sinus *(arrows)* is displaced to the right by the midline dorsal sac

cyst, even in the alobar form, is as the name describes it, behind or dorsal to the holosphere, whereas the interhemispheric cyst is between the hemispheres. When the cyst is extensive, some confusion may occur (Fig. 22).

The lateral ventricles of the callosal agenesis have a distinctive pattern in the coronal view. They often have a goblet or horn configuration with pointed superolateral margins (Fig. 23). The holospheric ventricle, even when partly separated, is shaped in the reverse manner with the superolateral margins being rounded off (Fig. 14). In axial view, the lateral ventricles of callosal agenesis are widely separated and parallel (Fig. 24). Such differentiation of the lateral ventricles has not been described in holoprosencephaly with a dorsal sac.

Another differential feature is the falx, which is always present in callosal agenesis and is often unusually deep, sometimes splitting the cyst (Fig. 23). With this is the interhemispheric fissure itself, which is always present and easily identifiable ahead or behind any cyst.

Lastly, patient appearance also aids differential diagnosis. Patients with agenesis are likely to have hypertelorism; those with holoprosencephaly are likely to have hypotelorism.

Absent septum pellucidum

This finding, generally thought to be a normal variant when occurring alone, may be very difficult to

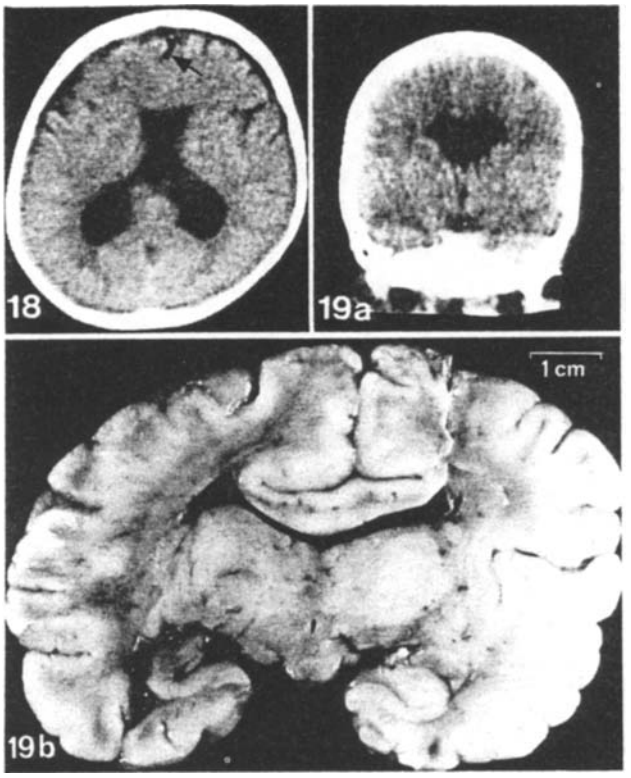


Fig. 18. Lobar holoprosencephaly. Axial CT slice through ventricular bodies shows the narrow appearance due to the continued fusion of the bodies. The frontal horns have a square shape. There is no septum pellucidum. A shallow interhemispheric fissure *(arrow)* is present anteriorly

Fig. 19. Lobar holoprosencephaly. **a** Coronal CT through the frontal horns shows the flat roof. No septum pellucidum is present. **b** Coronal section from lobar holoprosencephaly demonstrates continuity of cerebral cortex underneath interhemispheric fissure, fused basal gray matter, and absent septum pellucidum and fornix (Courtesy of Dr. R. E. Schmidt, St Louis, MO]

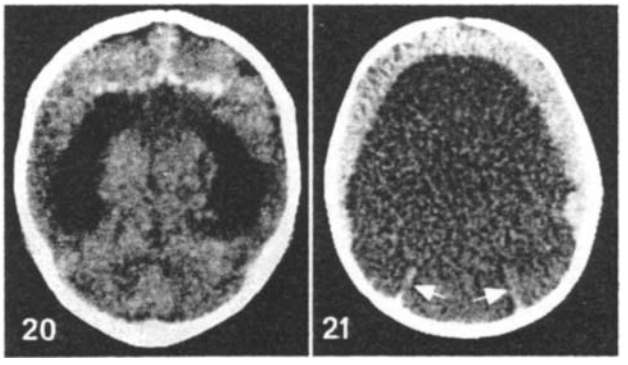


Fig. 20. Cerebral calcifications. Axial CT in semilobar holoprosencephaly. A line of calcifications is visible extending laterally from the midline, anterior to each side of the partially separated ventricle

Fig. 21. High tentorium. The tentorial leaves *(arrows)* are vertically oriented, with the infratentorial space connected to the supratentorial space. The top of the tent was at the posterior fontanelle

differentiate from mild lobar holoprosencephaly. In patients with absent septum pellucidum, coronal and axial views of CT or PEG usually demonstrate that the frontal horns are less square-shaped than those of lobar holoprosencephaly and have a more nearly normal indentation of the roof and anterior border in the midline. As Probst [6] points out, visualization of the fornices at the floor of the anterior horns also helps to identify patients with absent septum pellucidum, since the fornices are absent in holoprosencephaly. However, high-resolution CT is usually necessary to visualize the fornices.

Hydranencephaly

Hydranencephaly usually does not present a problem in differential diagnosis. The dysplastic brain remnants of hydranencephaly have a distinctive pattern in most cases. In addition, the presence of a falx projecting down from the skull vault makes a mistaken diagnosis of alobar holoprosencephaly unlikely.

On occasion, when residual brain is in a different location than in the customary occipital and inferior temporal locations, the usually clear difference between the two entities is less easily appreciated (Fig. 25). While the absence of a falx in such a case is supportive of the diagnosis of holoprosencephaly, the same process that destroyed brain might, theoretically, destroy the falx.

Septo-optic dysplasia

De Morsier [31] described a syndrome consisting of blindness or near blindness with hypoplasia of the optic discs and absence of the septum pellucidum in females. Hoyt et al. [32] added the finding of hypopituitarism.

The radiographic findings include the enlargement of the anterior recess of the third ventricle [33], and enlargement of the chiasmatic cistern [34]. Although the infundibular stalk is usually described as thin, Manelfe and Rochiccoli [35], in the first CT description of the entity, thought that their case showed an enlarged stalk. Hypotelorism may be present [34].

Pathologically and on CT, the septum pellucidum is absent. The falx and interhemispheric fissure are normal (Fig. 26). The optic nerves are small bilaterally (Fig. 27). The enlarged anterior recess of the third ventricle is not usually visible on CT, but the enlarged chiasmatic cistern commonly is.

While the clinical findings are not the same as those of holoprosencephaly, the combination of the facial features, absent septum pellucidum, and hypopituitarism suggest there may be a common or similar origin with holoprosencephaly. The falx and

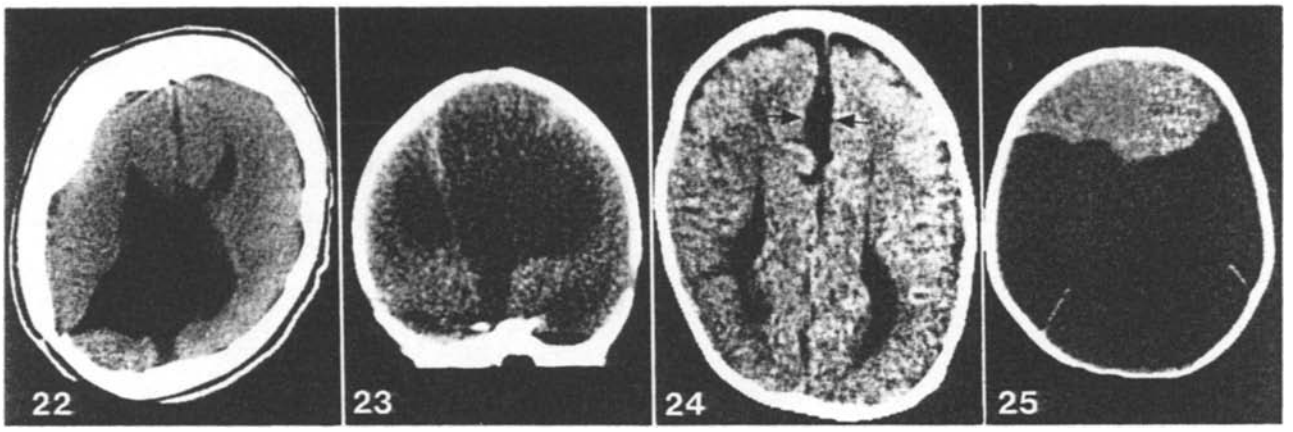


Fig. 22. Agenesis of the corpus callosum with interhemispheric cyst. Axial CT slice reveals a large interhemispheric cyst between and somewhat behind the lateral ventricles. The interhemispheric fissure is well seen anteriorly and posteriorly. The frontal horns are pointed, without any suggestion of the flattened appearance of the holoprosencephaly

Fig. 23. Agenesis of the corpus callosum with interhemispheric cyst. Coronal CT shows a large cyst extending upward from the well-developed third ventricle between and above the lateral ventricles. In spite of marked dilatation, the superior borders of the lateral ventricles are somewhat pointed in contrast to those of holoprosencephaly (Fig. 14)

Fig. 24. Agenesis of the corpus callosum. Axial CT slice. The bodies of the lateral ventricles are parallel, and somewhat narrow in this case. A narrow anterior interhemispheric cyst is present *(arrows)*. The deep falx can faintly be seen well into the cyst

Fig. 25. Indeterminant brain; 10-day-old infant with a large head. CT demonstrates some frontal lobe anteriorly, with the remainder of the cranium filled with "cyst". No ventricle was identified. No falx is present. The cerebellum is hypoplastic. The tentorium resembles that in Figure 21. No other studies were performed

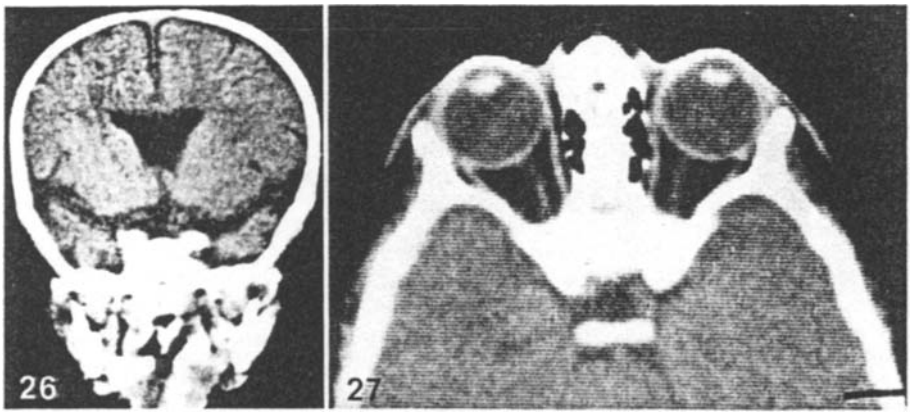


Fig. 26. Septo-optic dysplasia. Coronal CT. The septum pellucidum is absent. The falx and interhemispheric fissure are normal. Although the suprasellar cisterns are slightly large, this may be accounted for by the generalized cortical atrophy or hypoplasia

Fig. 27. Septo-optic dysplasia. Axial CT through the orbits shows small optic nerves bilaterally

interhemispheric fissure have been normal in all the author's cases of septo-optic dysplasia. No olfactory defects have been reported, but the same is true of some cases of lobar holoprosencephaly. In the author's experience, this disease is about as common as holoprosencephaly.

Arhinencephaly

Hypoplasia or absence of the olfactory bulbs and tracts may occur without other brain abnormalities [36]. Dekaban [36] uses this term, and divides it into four categories of which types II–IV are clearly the three types of holoprosencephaly. The mildest, type I, is not radiologically detectable, and often goes undetected clinically. Patients with arhinencephaly are often diagnosed only at autopsy. In Dekaban's series [36], 3 of the 20 patients with type I arhinencephaly also had callosal agenesis; 7 had cleft lip or palate, and 4 had gonadal agenesis.

Conclusion

The more severe semilobar and alobar forms of holoprosencephaly are clearly separable from other en-

tities by radiological means. Accurate radiographic differential diagnosis of the lobar form from septo-optic dysplasia and from absent septum pellucidum may be more difficult, though it is usually possible. While the exact cause of these anomalies is unknown, the similarity of their radiological and clinical features and their similar endocrine problems suggest a related origin.

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