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Radiologic-Pathologic Correlation
Alobar Holoprosencephaly

Mauricio Castillo,[1] *Thomas W. Bouldin, James H. Scatliff, and Kinuko Suzuki*

Case Report

After 37 weeks of gestation, a girl was born at another institution to a 33-year-old mother. Apgar scores were 8 at 1 minute and 9 at 5 minutes. Prenatal history included occasional use of alcohol and a 7-year-old sibling with a brain-stem glioma and secondary hydrocephalus. Ultrasound obtained during the second trimester showed a single cerebral ventricle and microcephaly.

Physical examination of the infant showed a head circumference of 29.7 cm (expected: 35.9 cm), cleft upper lip and palate, one nostril, poor muscle tone, and poor sucking reflex (Fig 1). Ultrasound showed a large monoventricle and fused thalami compatible with alobar holoprosencephaly (Fig 2). During the second day of life she developed generalized tonic-clonic seizures and tachycardia, both refractory to multiple medications. Her karyotype was normal (46XX). The patient was discharged and died at 5 months of age. The body was sent to our institution for autopsy.

Postmortem examination revealed a small, malformed brain weighing 184 g (expected weight: 730 g). The cerebrum lacked an interhemispheric fissure (Fig 3). There was a single ventricle with no septum pellucidum (Fig 4A). The corpus callosum and the olfactory tracts were absent. Sections of the brain stem and spinal cord showed severe hypoplasia of the corticospinal tracts.

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Before sectioning of the brain, a magnetic resonance (MR) study was done. Coronal and axial T1-weighted images showed a large horseshoe-shaped monoventricle, continuation of the gray and white matter across the midline, and fused thalami (Figs 4B and 4C). Sagittal T1-weighted images better demonstrated the small size of the cerebrum as well as a smooth cortex (Fig 4D).

Discussion

The anterior neuropore closes at approximately the 25th day of intrauterine life (1). At this time, three distinct brain vesicles develop. The most rostral one is known as the prosencephalon or forebrain. The forebrain then divides into the telencephalon, which gives origin to the cerebral hemispheres and the striatum (putamina and caudate nuclei) and into the diencephalon, which gives origin to the thalami, hypothalamus, and globus pallidus. Complete division of the telencephalon into cerebral hemispheres occurs by the fifth month of gestation. Portions of the brain located in the midline of the early differentiating hemispheres form the lamina terminalis, whose presence is imperative for the formation of a normal corpus callosum (2). In the holoprosencephalies there is failure of "cleavage" of the prosencephalon into discrete telencephalic and diencephalic structures (1). The failure of cleavage may vary from partial to complete and thus may give rise to a spectrum of abnormalities ranging from a brain with simple fusion of the thalami to a brain with unrecognizable hemispheres and the presence of a single horseshoe-shaped monoventricle (Fig 5). In the most severe expressions of holoprosencephaly, the interhemispheric fissure is absent and the falx is not formed. This lack of midline separation leads to abnormal formation of the lamina terminalis (and therefore the lamina reuniens), which in turn results in abnormalities of the corpus callosum ranging from total absence to abnormal formation of its anterior aspects (ros-

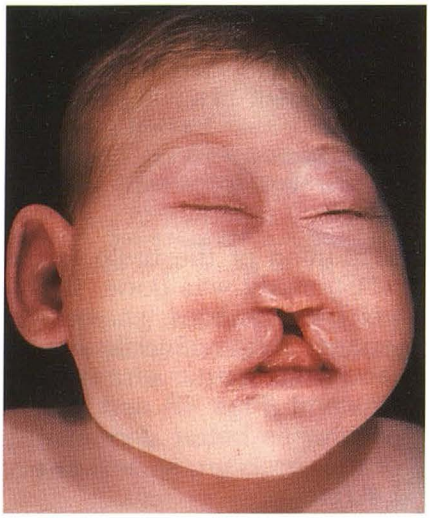


Fig. 1. Photograph of the child showing marked microcephaly and a rudimentary nose with a single enlarged nostril (cebocephaly). Hypotelorism and a cleft upper lip are also seen.

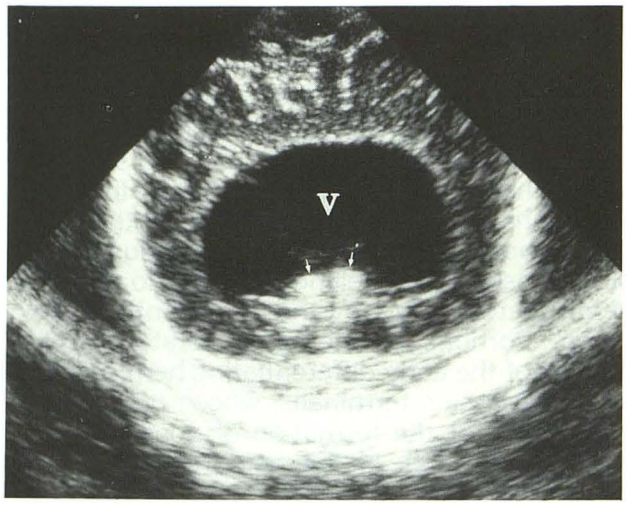


Fig. 2. Transfontanelle coronal sonogram demonstrates a large horseshoe-shaped monoventricle (*v*). The thalami are fused (*arrows*). There is no corpus callosum, and there is continuation of the gray and white matter across the midline, as well as absence of the interhemispheric fissure.

trum and genu). The holoprosencephalies are the only anomalies in which isolated agenesis of the anterior segments of the corpus callosum are present, whereas it is typically the posterior aspect of the corpus callosum that is malformed in partial agenesis of the corpus callosum (1). The corpus callosum is, however, normally formed in the mildest forms of holoprosencephaly.

The formation of the face parallels the formation of the forebrain, with which it is intimately associated. As the rostral neuropore closes, paired nasal and optic fields appear (3). Normal formation of the prosencephalon induces the adjacent ectoderm to form the nasal placodes. Similarly, the prosencephalon also induces the formation of the optic placodes. Stimulation of the surrounding mesenchyme eventually leads to the formation of the frontonasal processes and of the nasal passages. In turn, the formation of the optic and olfactory centers induces maturation of the maxillary processes, which are the structures ultimately responsible for the formation of the face. Alterations in this sequence of events leads to hypoplastic facial features that may accompany holoprosencephaly.

Holoprosencephaly occurs in 1 in 16,000 live births and is associated with the presence of maternal diabetes, bleeding during early pregnancy, dizygotic twinning, in vitro radiation exposure, and several chromosomal abnormalities (trisomies 13 and 15, 13q syndrome, deletion of the short arm of chromosome 18, and Meckel and Kallmann syndromes) (4, 5).

Classification and Clinical Features

Traditionally, holoprosencephalies have been divided into three distinct types: alobar, semilobar, and lobar. Alobar holoprosencephaly is the most severe type and has the worst prognosis (6). In these patients, facial anomalies are common, although occasionally the face may be normal. Greater differentiation of the brain is present in the semilobar type, with partial separation of the hemispheres and ru-

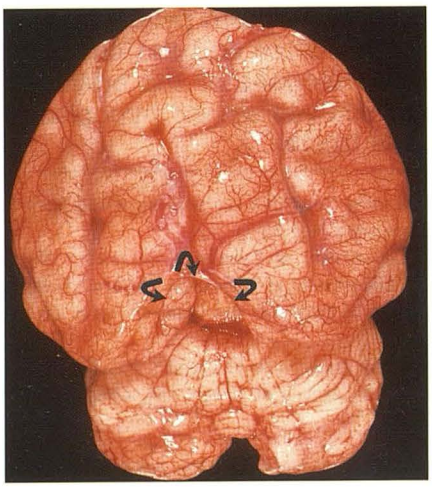


Fig. 3. View of the brain from above shows the presence of a shallow and underdeveloped interhemispheric fissure (*curved arrows*) posteriorly. The interhemispheric fissure is absent anteriorly. The gyral pattern is abnormal in that normal gyri are replaced by broad, somewhat smooth gyri, suggesting pachygyria.

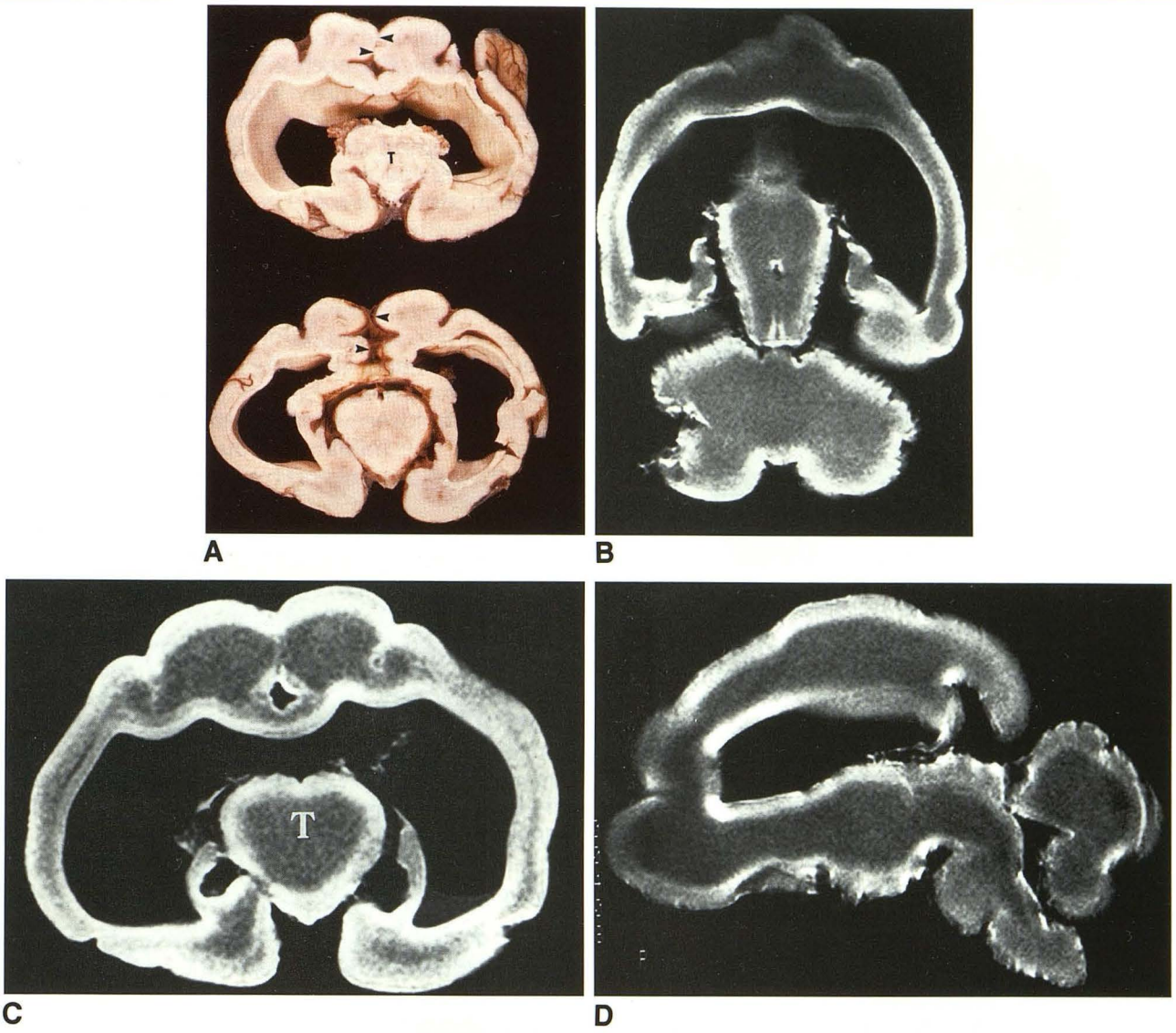


Fig. 4. *A,* Two coronal sections of the fixed brain. The *upper section* shows the fused thalami (*T*) as well as the monoventricle. There is continuation of white matter across the midline but no corpus callosum. A rudimentary interhemispheric fissure (*arrowheads*) is present and seen in both sections.

B, Postmortem axial MR T1-weighted image (600/20) clearly shows continuation of the gray and white matter in the frontal lobes and the monoventricle. No septum pellucidum or interhemispheric fissure are seen.

C, Postmortem coronal MR T1-weighted image (600/20/2) (repetition time/echo time/excitations) at a level comparable to the section of the brain shown superiorly in Fig 1A. The thalami (*T*) are fused. Pachygyria is present.

D, Postmortem sagittal MR T1-weighted image (600/20) shows pachygyria and absence of the third ventricle.

dimentary lobes (7). The olfactory bulbs and tracts are typically absent in the holoprosencephalies, hence the term arrhinencephaly (4). The lobar type is the least severe of the holoprosencephalies. Facial abnormalities are commonly absent, and some authors group it together with the septo-optic dysplasias (8)

It has been stated that the "face predicts the brain" (9). However, the opposite is not true. Facial abnormalities are associated only with the alobar and semilobar types of holoprosencephalies. DeMyer (9) has classified these facial anomalies into: 1) cyclopia—median single rudimentary orbit, may also have a proboscis; 2) ethmocephaly—two orbits and a proboscis; 3) cebocephaly—two orbits, rudimentary nose with a single nostril; 4) median cleft lip with hypotelorism; and 5) hypotelorism.

Holoprosencephalies need to be distinguished from the median cleft-face syndrome, in which there is nose and/or lip clefting, hypertelorism, dysgenesis of the corpus callosum, and midline intracranial lipomas (6). In alobar and semilobar holoprosencephalies the nasal

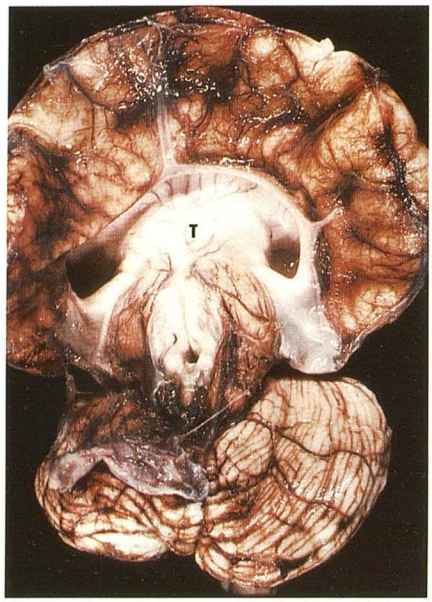


Fig. 5. Axial view of a fixed brain specimen from a different patient with alobar holoprosencephaly. The monoventricle is well seen. Anteriorly, there is continuation of gray and white matter with no interhemispheric fissure. The thalami (*T*) are fused. Pachygyria is present. (Reprinted with permission from Ref. 6.)

bridge is always flat. A proboscis (from the Greek *proboscis* for trunk) refers to a tubular soft-tissue structure situated in the midline of the face and always associated with abnormal formation of the nasal passages (3). A lateral proboscis is not associated with holoprosencephaly. In alobar and semilobar holoprosencephalies the premaxillary segment of the face is hypoplastic and leads to hypotelorism (1). The premaxillary segment also may be involved, giving origin to maxillary agenesis. A single midline incisor may be present.

Patients with alobar holoprosencephaly exhibit minimal motor and sensory activities and always have seizures (6). As stated earlier, the prognosis is very poor. Other common clinical features (which also can be seen in the less severe holoprosencephalies) include spasticity, athetoid movements, and mental retardation.

Imaging Features

Alobar Holoprosencephaly

Patients are microcephalic, and the brain resembles a single, somewhat flattened bulb (10). Externally, the interhemispheric fissure and the falx cerebri are absent. The brain itself is located in the rostral-most aspect of the cranial vault. Midline sections show continuation (fusion) of gray and white matter across the midline (Figs 2, 4A, 4B, and 4C). The cortical sulci are not well formed (Fig 4D). Histologically, the cortex is abnormally formed (11). Heterotopic gray matter may be seen, especially in the region of the suprasellar structures, the lateral ventricles, and the cerebellum. The corpus callosum is absent. A dorsal interhemispheric cyst may be present (1). These cysts may attain very large size, and they may be isolated or arise from a ballooned third ventricle. A large horseshoe-shaped, single ventricle is present (4) (Fig 5). The septum pellucidum is absent. Inferiorly, the thalami are fused (Figs 2 and 4B). The olfactory bulbs and tracts are not present (4).

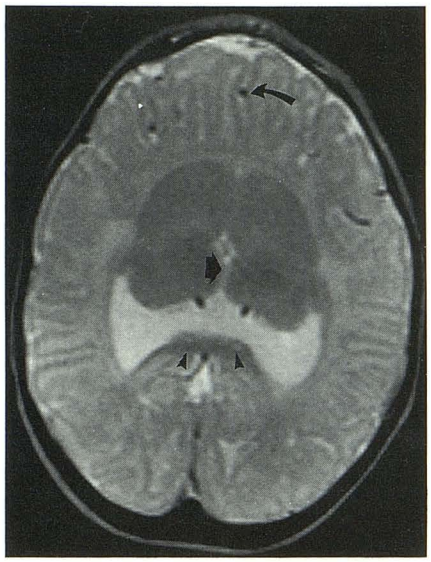
The anterior cerebral artery is single (azygous), and the midline venous structures (particularly the internal cerebral veins, the superior sagittal sinus, and the straight sinus) may be absent. Lack of condensation of the embryonic veins is responsible for the absence of the superior sagittal sinus. The embryonic veins may be seen as large abnormal cortical veins in these cases. We have seen two cases in which the torcula was very high in location, and the transverse sinuses assumed an almost vertical course (Fig 6). If a cerebrospinal fluid shunt is to be inserted using a posterior approach, this important variation of the venous structures can be evaluated readily using MR venography.

Semilobar Holoprosencephaly

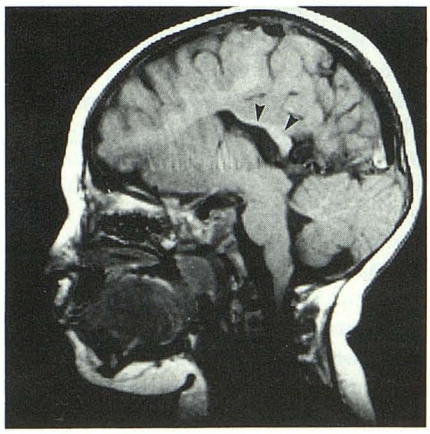
In this less severe anomaly, there is some differentiation of the forebrain. The posterior aspect of the interhemispheric fissure and the falx cerebri are partially present (1). The overall

Fig. 6. Oblique view from the two-dimensional time-of-flight MR venogram (32/10) (flip angle = 50) in a patient with alobar holoprosencephaly shows the high insertion of the torcula (*arrow*) and almost vertical course of the transverse sinuses (*arrowheads*). Note absence of deep venous system.

volume of the brain is still reduced. Externally, there is some sulcation, especially in the occipitoparietal regions (4). The monoventricle shows some minimal differentiation, and rudimentary temporal horns may be present. The septum pellucidum is always absent (1). Although the thalami are fused, there may be some cleavage, giving rise to a small third ventricle (Fig 7A). The hippocampal formations are incomplete (1). When the corpus callosum is completely absent, the posterior commissure may be prominent, giving origin to a "splenium-like" structure (12). In some cases, the anterior aspect of the corpus callosum is absent, but the posterior body and splenium are present (Fig 7B). The olfactory bulbs and tracts are absent.



A



B

Fig. 7. *A,* Axial T2-weighted image (2500/80) in a child with semilobar holoprosencephaly. The anterior corpus callosum is absent; however, the splenium (*arrowheads*) is present. A rudimentary third ventricle (*arrow*) is seen. Note the azygous anterior cerebral artery (*curved arrow*).

B, Midline sagittal T1-weighted image (600/15) in the same case shows the posterior corpus callosum (*arrowheads*).

Facial anomalies are less severe and are not a constant feature; a median cleft lip and hypotelorism are the most common ones. Prognosis varies.

Lobar Holoprosencephaly

This is the least severe type. At times, there is only minimal deviation from the normal brain and therefore may be difficult to appreciate (1). The brain is of normal size. The interhemispheric fissure is well formed, as is the falx (although the anterior falx may be dysgenetic) (Fig 8A). The lateral ventricles assume an almost normal shape with well-differentiated occipital and temporal horns. The septum pellucidum is absent (Fig 8B). The third ventricle is small but present. The anterior aspect of the corpus callosum may be deficient, and occasionally the entire corpus callosum may be dysgenetic. Lack of frontal cleavage and fusion of the midline at the level of the cingulate gyri may be present (1). The hippocampal formations are normal or nearly normal. The face is usually normal.

Absent septum pellucidum is also seen in many of patients with septo-optic dysplasia. Indeed, well-differentiated lobar holoprosencephaly might be the same as septo-optic dysplasia. Therefore, a short discussion of the imaging features of septo-optic dysplasia is pertinent here.

Septo-optic dysplasia (DeMorsier syndrome) is a group of disorders characterized by pituitary and hypothalamic insufficiencies and by anomalies of the septum pellucidum, fornices, and corpus callosum (8). The initial diagnosis is clinically made when hypoplasia of the optic discs is encountered. These patients are usually hypotonic and have wandering nystagmus if blindness is present. Hormonal insufficiency characterized by inadequate production of growth hormone, adrenocorticotropin, and antidiuretic hormone is usually present (4). This syndrome is more commonly seen in first-born patients and has been found in association with maternal diabetes, quinidine ingestion, antiseizure medications, drug abuse, and cytomegalovirus infection (4). Imaging studies always show agenesis of septum pellucidum (13). The frontal horns of the lateral ventricles show a flattened roof, resulting in the so-called box-like ventricles (1) (Fig 9). The inferior aspect of the frontal horns is pointed. These latter changes are nonspecific (1). The cisterns surrounding a hypoplastic optic chiasm are large.

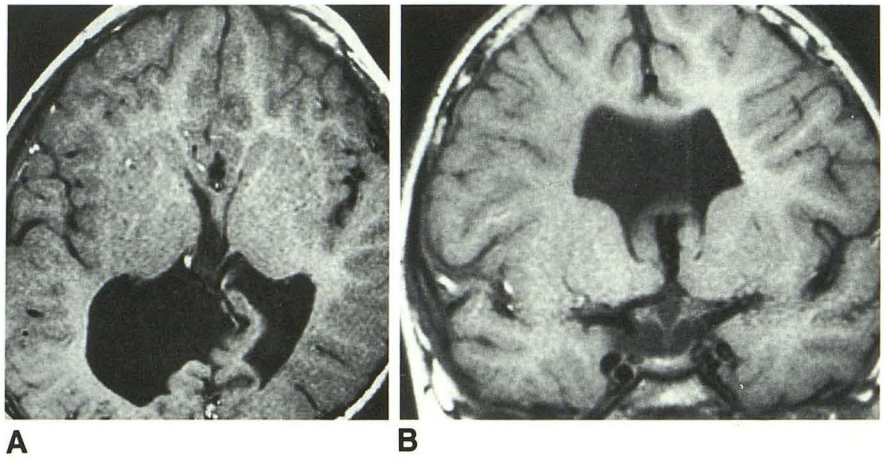


Fig. 8. *A,* Axial T1-weighted image (600/15) in a case of lobar holoprosencephaly shows fusion of the lateral ventricles and no septum pellucidum. The corpus callosum is dysgenetic. Posteriorly, the lateral ventricles show differentiation into two discreet, but dilated (colpocephaly) occipital horns. The frontal horns are small. The interhemispheric fissure is present.

B, Coronal T1-weighted image (600/15) confirms the absent septum pellucidum. The inferior aspect of both frontal horns points down. The chiasm is normal. (Case courtesy of Anne Osborn, MD, University of Utah Medical Center, Salt Lake City, Utah.)

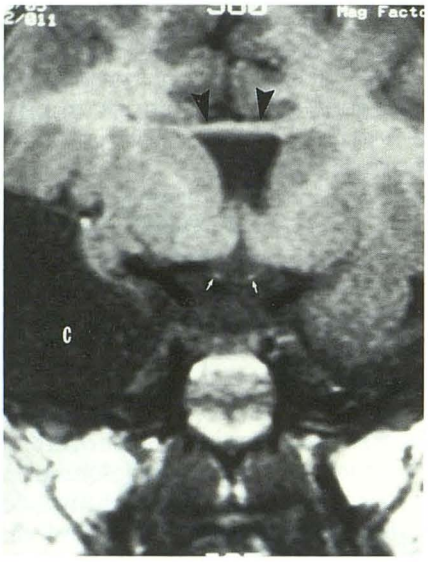


Fig. 9. Coronal T1-weighted image (600/15) in a patient with septo-optic dysplasia. Note the flattened superior aspect of the lateral ventricles (*arrowheads*) giving them a box-like appearance. The septum pellucidum is absent. The optic nerves (*arrows*) are extremely small, and the suprasellar cistern is prominent. Incidentally seen is an arachnoid cyst in the right middle cranial fossa (*c*).

The optic nerves are small, but in our experience exact assessment of the size of the optic nerves is difficult and not always possible by either computed tomography and/or MR imaging (Fig 9). The fornices are abnormally formed, and the corpus callosum is dysgenetic. The pituitary infundibulum may be thinned or absent. Approximately 50% of patients with septo-optic dysplasia will harbor a schizencephaly (1).

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