

Holoprosencephaly: An Analysis of Callosal Formation and Its Relation to Development of the Interhemispheric Fissure

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PURPOSE: To correlate the degree of hemispheric fusion in holoprosencephaly with degree of callosal formation, with degree of thalamic and basal ganglia fusion, and with presence or absence of dorsal cyst. **METHODS:** MR, CT, and ultrasonography from 19 patients with holoprosencephaly was retrospectively reviewed. The imaging studies were graded according to extent of the hemispheric fusion, thalamic fusion, corpus striatum fusion, callosal formation, and the presence or absence of a dorsal cyst. These factors were statistically correlated with each other using Kendall rank correlation coefficient. **RESULTS:** There were significant correlations between hemispheric fusion and failure of corpus callosum formation, presence of dorsal cyst and failure of corpus callosum formation, and hemispheric fusion and presence of dorsal cyst. Additional correlations were noted between thalamic fusion and corpus striatum fusion. **CONCLUSIONS:** Our results suggest that the presence of an interhemispheric fissure is necessary for callosal formation, and the presence of a dorsal cyst may interfere with callosal formation in holoprosencephaly.

Index terms: Holoprosencephaly; Brain, abnormalities and anomalies; Brain, longitudinal fissure; Corpus callosum, abnormalities and anomalies

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In the normal brain, the corpus callosum develops primarily from anterior to posterior; the genu forms first, followed by the body, splenium, and rostrum. The most common callosal anomalies are agenesis and hypogenesis, the latter manifested by the presence of the earlier-formed segments (genu, body) and absence of the later-formed segments (splenium, rostrum). Patients with holoprosencephaly also have callosal anomalies. In holoprosencephalies, however, the posterior portion of the corpus callosum is formed and the anterior portion absent; this configuration has been called *atypical callosal dysgenesis* (1).

The purpose of the present study was to gain a better understanding of the relationship of the callosal dysgenesis in holoprosencephaly with

other features characteristic of the malformation, such as hemispheric fusion, thalamic fusion, basal ganglia fusion, and presence of a dorsal cyst. From these relationships, we were able to postulate the potential embryological basis of these relationships.

Patients and Methods

Magnetic resonance (MR), computed tomography (CT), and ultrasonography findings from 19 patients with holoprosencephaly (alobar holoprosencephaly, 2; semilobar holoprosencephaly, 7; lobar holoprosencephaly, 6; syntelencephaly, 4) were retrospectively reviewed. Two patients (patients 18 and 19) have been reported in a previous communication (2). Their ages at the time of the MR or CT examination ranged from 3 days to 6 years. Nine patients had imaging at 1.5 T, in which sagittal 3- to 5-mm spin-echo (400-800/11-25 [repetition time/echo time] images and axial 5-mm spin-echo (2300-3000/30-60, 80-120) images and 5-mm spin-echo (500-600/20) images were obtained using a 128, 192, or 256 × 256 matrix. Coronal 5-mm spin-echo (600-800/20-25) images were obtained in 7 patients. Coronal 5-mm spin-echo (2500-2800/17-30, 80-119) images were obtained in 3 patients. Four patients had imaging at 0.5 T and 1 at 0.3 T, using a variety of T1- and T2-weighted pulse sequences. Sagittal, coronal, and axial images, with section thickness

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Nineteen patients with holoprosencephaly: degree of abnormality (grade)

Patient/Imaging	Classification	Hemispheric Fusion	Thalamic Fusion	Corpus Striatum Fusion	Corpus Callosum Formation	Dorsal Cyst
1/MR	Alobar	Severe (4)	Moderate (3)	Severe (4)	None (4)	Dorsal cyst (2)
2/CT,US	Alobar	Severe (4)	Severe (4)	Severe (4)	None (4)	Dorsal cyst (2)
3/MR	Semilobar	Severe (4)	None (1)	Severe (4)	None (4)	Dorsal cyst (2)
4/MR	Semilobar	Moderate (3)	Severe (4)	Severe (4)	Splenium (3)	None (1)
5/CT	Semilobar	Moderate (3)	Mild (2)	Severe (4)	Splenium (3)	None (1)
6/MR	Semilobar	Moderate (3)	Severe (4)	Severe (4)	Splenium (3)	None (1)
7/MR	Semilobar	Moderate (3)	None (1)	None (1)	Splenium (3)	None (1)
8/MR	Semilobar	Mild (2)	Mild (2)	Moderate (3)	Body, splenium (2)	None (1)
9/CT	Semilobar	Severe (4)	Mild (2)	Mild (2)	None (4)	Dorsal cyst (2)
10/MR	Lobar	Mild (2)	None (1)	Moderate (3)	Body, splenium (2)	None (1)
11/CT	Lobar	Moderate (3)	Mild (2)	None (1)	Splenium (3)	None (1)
12/CT,US	Lobar	Moderate (3)	None (1)	None (1)	None (4)	Dorsal cyst (2)
13/MR	Lobar	Moderate (3)	None (1)	None (1)	Splenium (3)	None (1)
14/MR	Lobar	Mild (2)	None (1)	Moderate (3)	Body, splenium (2)	None (1)
15/CT	Lobar	Moderate (3)	None (1)	None (1)	Splenium (3)	None (1)
16/MR	Syntelencephaly	Moderate (3)	None (1)	None (1)	Genu, splenium (3)	None (1)
17/MR	Syntelencephaly	Moderate (3)	Mild (2)	None (1)	Genu, splenium (3)	None (1)
18/MR	Syntelencephaly	Moderate (3)	Severe (4)	Severe (4)	None (4)	Dorsal cyst (2)
19/MR	Syntelencephaly	Moderate (3)	None (1)	None (1)	Genu, splenium (3)	None (1)

Note.—US indicates ultrasound.

varying from 5 to 10 mm, were obtained in these examinations. Six patients had CT imaging but not MR. Coronal images were obtained in addition to axial images in four of these patients. Two patients in whom coronal CT images were not obtained had ultrasonography in addition to CT.

We classified holoprosencephaly into four types (alobar, semilobar, lobar holoprosencephaly, and syntelencephaly) with reference to the criteria of DeMyer (2, 3) and Barkovich (4). *Alobar holoprosencephaly* was assigned when the interhemispheric fissure and falx cerebri were absent and the thalami were fused so that there was only a large holovertricle (no third ventricle). Patients were classified as having *semilobar holoprosencephaly* when interhemispheric fissure and falx cerebri were formed posteriorly, the thalami were partially separated, creating a rudimentary third ventricle, and rudimentary temporal horn formation was present within the holovertricle. *Lobar holoprosencephaly* was assigned when the interhemispheric fissure extended well forward into the frontal area and the frontal horns of the lateral ventricles were at least partly formed. *Syntelencephaly* (middle interhemispheric fusion), another variant of holoprosencephaly (4), was assigned when the interhemispheric fissure was present anteriorly (in the anterior frontal region) and posteriorly (in the occipital region) without separation of the hemispheres in the posterior frontal and parietal regions.

The images were evaluated with special attention to the size and location of hemispheric fusion, interhemispheric fissure, thalamic fusion, corpus striatum fusion, corpus callosum formation, and the presence or absence of dorsal cyst. The extent of callosal myelination was evaluated in those patients in whom MR showed callosal formation.

For purposes of statistical analysis, the hemispheric fusions, thalamic fusions, corpus striatum fusions, and

corpus callosum formations were each separated into four grades based upon the extent of the abnormality. Hemispheric fusions were judged as grade 1 if the cerebral hemispheric fusion was absent or minimum, grade 2 if the hemispheric fusion was mild, grade 3 if the hemispheric fusion was moderate, and grade 4 if the hemispheric fusion was severe. In the statistical analysis of the present study, we regarded patients with syntelencephaly as grade 3. The severity of thalamic and corpus striatum fusions ranged from no fusion (grade 1), to mild (grade 2), to moderate (grade 3), to severe (grade 4). Corpus callosum formations were judged as grade 1 if genu, body, and splenium were formed; grade 2 if body and splenium were formed; grade 3 if only splenium was formed; and grade 4 if corpus callosum was absent. Dorsal cyst formation was graded in two categories: grade 1 if dorsal cyst formation was absent, grade 2 if dorsal cyst was formed. These factors were correlated with each other using Kendall rank correlation coefficient.

The images were analyzed retrospectively and independently by the authors. Any disagreements were resolved by discussion until a consensus was attained.

Results

Imaging Analysis

The imaging findings, categorized by grade, of the 19 patients are summarized in the Table.

Ten patients had atypical callosal dysgenesis, with the posterior corpus formed in the absence of the anterior portion. Seven showed callosal splenium formation in the absence of

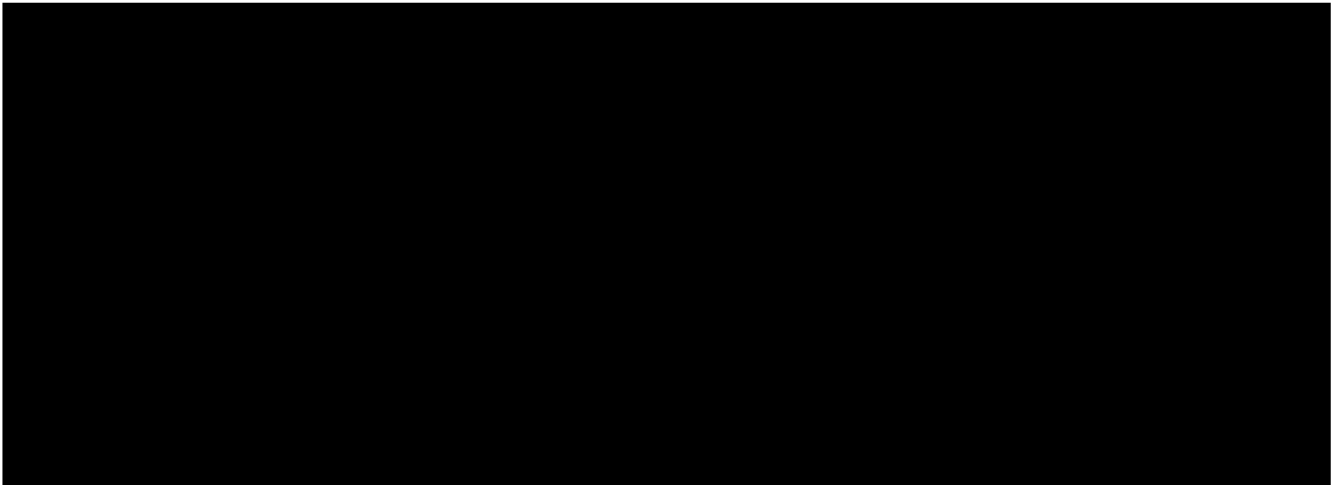


Fig. 1. Patient 13, lobar holoprosencephaly (this patient had rudimentary frontal horn formation).

A, Sagittal spin-echo (600/20) MR image shows callosal splenium formation (*arrows*). Frontal lobes are noted to be extremely dysgenetic. The parietooccipital region of the brain and the cerebellum have a more normal appearance.

B, Axial spin-echo (2300/70) MR image shows the callosal splenium (*arrows*) has normal myelination. There is fusion of the frontal lobes and dysgenesis of the frontal horns, diagnostic of holoprosencephaly. The interhemispheric fissure is normal posteriorly. The thalami and basal ganglia are separated.

C, Coronal spin-echo (600/20) MR image shows neocortical fibers from the cerebral hemispheres are crossing immediately below the bottom of the dorsal interhemispheric fissure and have the appearance of a true callosal splenium.

the body and genu (Fig 1). Three patients showed formation of the callosal body and splenium in the absence of the genu (Fig 2). In these 10 patients, the interhemispheric fissure was present in the occipital regions, and the corpus callosum appeared partially formed at the site of an almost completely formed interhemispheric fissure. Five of these patients had thalamic fusion, grade 2 in 3 patients and grade 4 in 2 patients. Six had corpus striatum fusion, grade 4 in 3 and grade 3 in 3. None had dorsal cysts.

Four patients (patients 16, 17, 18, and 19) showed syntelencephaly (Fig 3) (4). The imag-

ing studies of these four patients were characterized by the presence of an interhemispheric fissure anteriorly and posteriorly (in the occipital region) without separation of the hemispheres in the posterior frontal and parietal regions. A well-defined corpus callosum was absent in the portions of brain at the level of the fused portions of the cerebral hemispheres. Three of these four patients showed genu and splenium formation. One patient showed absence of corpus callosum. As discussed in "Patients and Methods," we classified these patients as grade 3 hemispheric fusion. Two patients with syntelencephaly had thalamic fu-

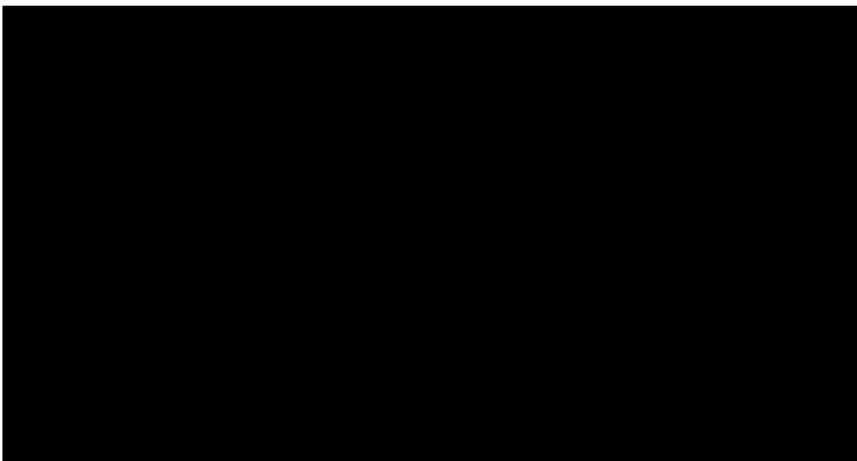


Fig. 2. Patient 8, semilobar holoprosencephaly.

A, Sagittal spin-echo (500/11) MR image shows callosal body and splenium formation (*arrows*).

B, Axial spin-echo (2500/100) MR image shows the callosal splenium has normal myelination. There is fusion of frontal lobes. A small degree of thalamic fusion (grade 1) is noted (*arrow*). An azygous anterior cerebral artery (*curved arrow*) is present.

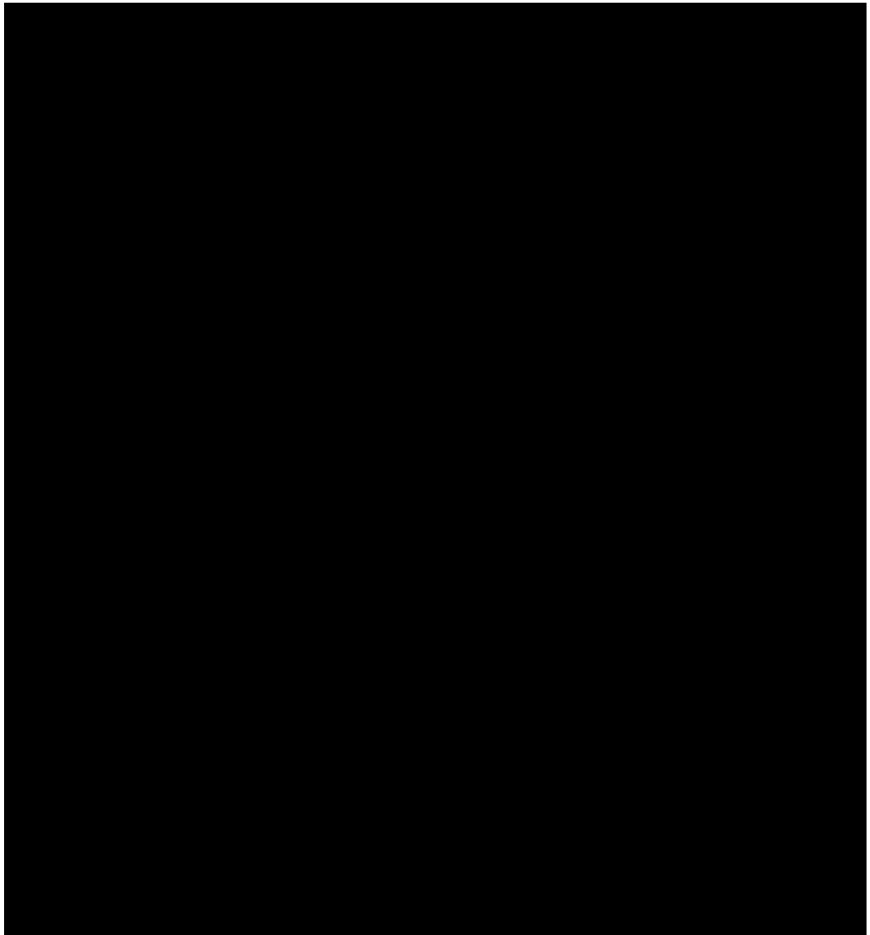
Fig. 3. Patient 16, syntelencephaly.

A, Sagittal spin-echo (550/14) image shows presence of callosal genu (*arrow*) and splenium (*arrowheads*), but callosal body cannot be identified. Instead, a bizarrely shaped region of gray and white matter is seen among the mass of interhemispheric fusion.

B, Coronal fast spin-echo (5738/90) MR image at the level of the genu shows neocortical fibers from cerebral hemispheres cross immediately below the bottom of the anterior interhemispheric fissure and have the appearance of a true callosal genu (*small arrows*). The callosal genu has normal myelination. The anterior falx is absent. *Curved arrow* shows an azygous anterior cerebral artery.

C, Coronal fast spin-echo (5738/90) MR image at the level of the splenium shows neocortical fibers from the cerebral hemispheres cross immediately below the bottom of the dorsal interhemispheric fissure and have the appearance of a true callosal splenium (*small arrows*). The callosal splenium has normal myelination. The falx is absent at this location.

D, Axial fast spin-echo (6000/90) MR image at the level of the centrum ovale shows interhemispheric fusion is present in the posterior frontal and parietal lobes, but an interhemispheric fissure is present more anteriorly and posteriorly. The falx is deficient anteriorly and posteriorly.



sion (one grade 4 and one grade 2), and one had corpus striatum fusion (grade 4). One had a dorsal cyst.

The dysgenetic corpus callosum in these 14 patients showed appropriate myelination for age (Figs 1B, 2B, and 3B and C). The coronal views in seven patients disclosed that these callosumlike structures had the appearance of normal transverse neocortical callosal fibers (Figs 1C and 3B and C).

Almost complete hemispheric fusion (lack of normal interhemispheric fissure) was seen in four patients (Fig 4A). All of these patients showed complete absence of corpus callosum (Fig 4B). Three of the four had thalamic fusion (one in each of grade 2, 3, and 4) (Fig 4C), and all had corpus striatum fusion (grade 4 in three, grade 2 in one). Dorsal cyst formation was present in all four patients (Fig 4A and B).

Statistical Analysis

There were highly significant correlations between severity of hemispheric fusion and failure

of corpus callosum formation ($P = .0001$); severity of hemispheric fusion and presence of dorsal cyst ($P = .0001$); and presence of dorsal cyst and failure of corpus splenium formation ($P = .0001$).

There was significant correlation between thalamic fusion and corpus striatum fusion ($P = .0004$).

The statistical analysis was performed on the computer (Macintosh PowerBook 170, Apple Computer, Cupertino, Calif) using the program StatView II (Abacus Concepts, Berkeley, Calif).

Discussion

The corpus callosum is the major pathway of association fibers between the two cerebral hemispheres. The anatomy and embryology of the commissure have been studied extensively. Development occurs between approximately 8 and 17 weeks of gestation (5). The corpus callosum normally develops in an anterior-to-posterior direction. The genu forms first, followed by the body, splenium, and rostrum. Dysgene-

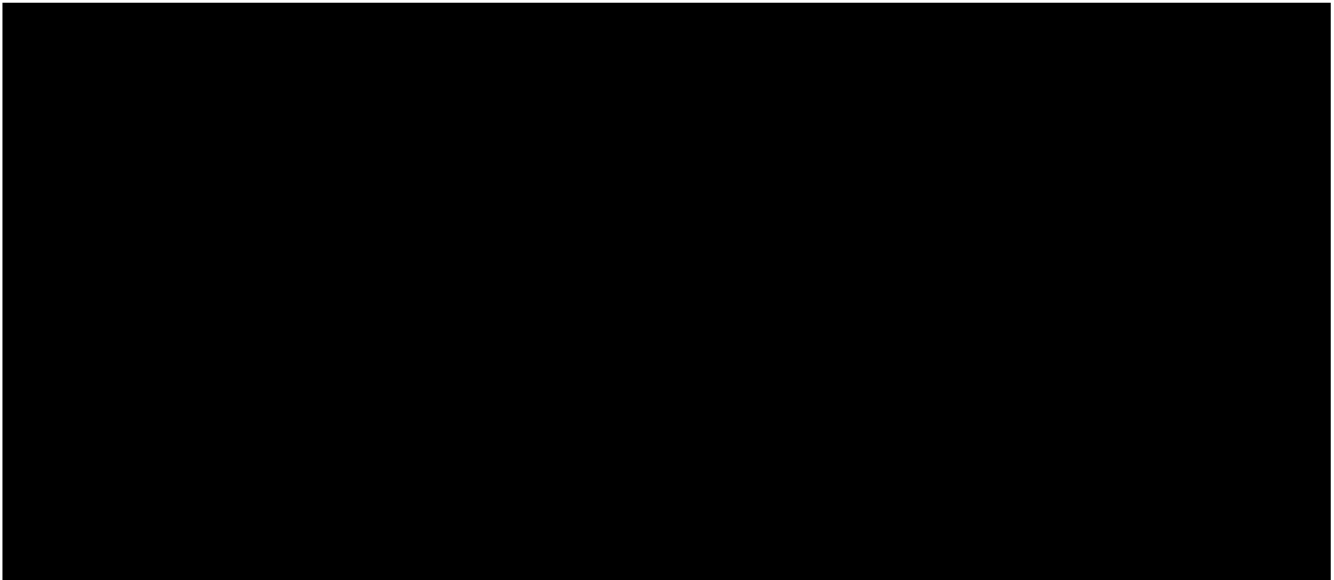


Fig. 4. Patient 1, alobar holoprosencephaly.

A, Sagittal spin-echo (616/12) MR image shows complete absence of corpus callosum and presence of large dorsal cyst.

B, Axial spin-echo (600/16) image shows the cerebrum is composed of a pancakelike mass of tissue in the rostral cranial vault. A crescent-shaped holovertricle is continuous with a large dorsal cyst.

C, Coronal spoiled gradient-echo (35/14) image shows a central monoventricle. Thalami are fused. A shallow "pseudo"-interhemispheric fissure (arrow) is seen.

sis of the corpus callosum (better termed *hypogenesis*) is manifested by the presence of the earlier-formed segments (genu, body) and absence of the later-formed segments (splenium, rostrum) (5–7). The sole exceptions to this rule that we have found are patients with holoprosencephaly, in which the posterior corpus callosum appears to form in the absence of the genu, rostrum, and, usually, anterior body (1, 8). It has been noted in the literature that the interhemispheric fissure is an important structure that forms, not simply a space that results from the separation of the brain parenchyma into two hemispheres. Callosal formation does not seem to occur in the absence of a normal interhemispheric fissure (1, 4, 9). The present study supports this hypothesis, revealing significant correlation between extent of hemispheric fusion and failure of corpus callosum formation ($P = .0001$) in this group of patients with holoprosencephaly.

Previous authors (5, 10, 11) have speculated that callosal formation results from the navigation of specialized pioneer axons through the developing hemispheres and commissural plate (8). Other axons are believed to follow surface markers on the surface of the pioneer axons by a process known as *fasciculation* (12, 13). An

important concept of these theories is that the special "signals," in the form of molecules on the cell surface or extra cellular space, are necessary to guide the pioneer axons to the contralateral hemisphere. These signals may be within the meninx primitiva, the mesenchyme that fills the primitive subarachnoid space, or on glial bridges or "slings" that cross the interhemispheric fissure (14). Recent studies (15,16) in laboratory animals (*drosophila*) have located the genes for these cells and shown that if expression of these genes is inhibited, an acallosal brain results. Our results demonstrating the correlation between the formation of the interhemispheric fissure and that of the corpus callosum strongly suggest that the corpus callosum is dysgenetic in holoprosencephaly primarily because the lack of development of the interhemispheric fissure prevents the proper signals from reaching their necessary location. It is known that axonal growth cones respond to a number of molecular signals; they interact more strongly with some than with others. Presumably, when the pioneer callosal axons reach the midline and the normal signals are absent, they follow other molecular signals to other brain regions or regress.

The Pseudocallosum

The presence of a spleniumlike bundle of interhemispheric white matter fibers has been described in patients with holoprosencephaly of the intermediate or semilobar type (1, 4, 10, 17–19). Fleming and Norman (19) described one such pseudosplenium in depth. This structure, formed by myelinated and unmyelinated transverse axons, differed from a normal corpus callosum in that it was in direct contact with each hippocampus, and the posterior pillars of the fornix came in contact with its dorsal and not its ventral surface. This location would suggest that the commissure they described was, in fact, an enlarged hippocampal commissure (1) and not a true splenium. Moreover, the presence of the posterior pillars of the fornices imply that the brain they studied was not, in fact, a true holoprosencephaly; the fornices are always absent in holoprosencephaly (17). Many authors (17, 19, 20–22) consider the corpus callosum to be absent by definition in the holoprosencephalies. Others have suggested a normal dorsal commissural plate could be induced in the absence of a rostral commissural plate, and axons from the developing dorsal telencephalon would commissurate to form a splenium (1). Our data suggest that the presence of the posterior interhemispheric fissure is a prerequisite for formation of the splenium. Previous authors have described a callosumlike structure that appears to consist of nearly normal transverse neocortical callosal fibers (1, 17). In our cases, the callosumlike structure seemed to be continuous with neocortical white matter on coronal images, suggesting that they are truly callosal.

Fusion of the Corpora Striata and the Thalami

Our study revealed varying degrees of fusion of the basal ganglia and thalami in holoprosencephalies. Holoprosencephaly is considered to be a result of a disturbance of developmental planning of normal telencephalization. Failure of bilateral division of the telencephalon would occur at or before 4 weeks of gestation (23). Likewise, fusion of the corpus striatum and thalamus or, more correctly, a lack of separation of the structures, is considered to occur at or before 4 weeks of gestation (23). The developing corpus striatum appears in the embryo as medial and lateral elevations known as the medial

and lateral eminences. The medial eminence, which will become the globus pallidus, is derived from an area of the diencephalic germinal matrix that lies adjacent to the thalamus. The topographical relationship between the corpus striatum and the thalamus during embryogenesis is a likely cause for the high correlation between thalamic fusion and corpus striatum fusion ($P = .0004$) in the present study.

Thalamic fusion, however, does not necessarily result from an event prior to formation of the third ventricle. The thalamus increases greatly in size during the late first trimester and bulges towards the opposite thalamus, with which it commonly fuses during the second trimester to form the interthalamic adhesion, also called the massa intermedia. The relatively large massa intermedia in the Chiari II malformation is likely the result of this secondary fusion (24). When the thalami are completely fused into a single mass of gray matter, obliterating the third ventricle (Fig 4B), or the corpora striata are fused, we believe the cause is likely an early event resulting in lack of separation of the thalami. Lesser degrees of thalamic fusion (Fig 2), however, may not be distinguishable from a large massa intermedia by imaging.

Dorsal Cyst Formation

The dorsal cyst of holoprosencephaly is a large cerebrospinal fluid cavity that occupies the area above the dorsocaudal aspect of the diencephalon and communicates directly with the prosencephalic, telencephalic, or diencephalic ventricle. This cavity usually abuts the cranial vault in the midline parietooccipital area and lies directly on the cerebellum because of tentorial dysplasia (25). The wall of the cyst is a thin transparent membrane consisting of ependymal epithelium and leptomeninges, in which, occasionally, a layer of cerebral tissue or heterotopic glial rest is seen (26, 27).

The term *dorsal cyst* has been traditionally reserved for holoprosencephaly, but histologically identical cavities are also found in other dorsal midline anomalies (27–29). Dysplasia of the tentorium cerebelli is the only characteristic by which the dorsal cyst is distinguished from other similar midline cysts such as diencephalic cyst (29) and primary interhemispheric cyst associated with absent corpus callosum (28):

these cysts were interpreted as protrusions of the roof of the third ventricle (28, 29) and some types of porencephaly (27).

In his system of classification of the holoprosencephaly, Probst (17) uses the dorsal sac to define the most severe forms of the malformation. Our results support this statement by showing a statistically significant association of dorsal cyst formation with the severity of interhemispheric fusion and degree of callosal dysgenesis. Moreover, the strong correlation of the dorsal cyst formation with complete absence of the corpus callosum suggests one of three possibilities:

1) Cyst formation may be facilitated by absence of the splenium.

2) Conversely, the splenium may inhibit cyst formation.

3) Cyst formation may inhibit formation of the splenium.

A dorsal cyst was present in every patient who lacked a splenium in this series, whereas no patient with a splenium had a dorsal cyst.

We know of no long-term studies to determine the neurodevelopmental prognosis of patients with syntelencephaly. Such studies would be of interest to determine whether the outcome of these patients might be different than those of patients with the more classic forms of holoprosencephaly. If so, reclassification of these disorders outside of the spectrum of holoprosencephaly may be a more rational system. A collaborative multiinstitutional study will probably be necessary to find an adequate number of patients.

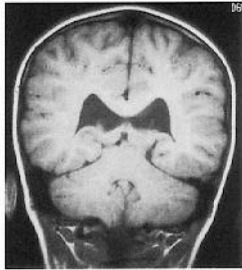
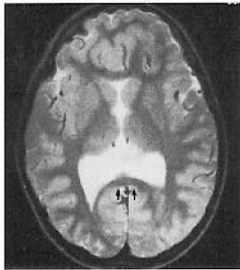
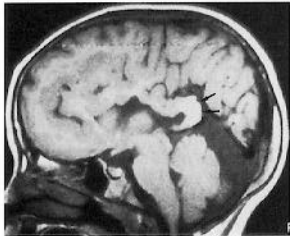
In summary, we have correlated the degree of hemispheric fusion in holoprosencephaly with degree of callosal formation, with degree of thalamic and basal ganglia fusion, and with presence or absence of dorsal cyst in 19 patients with holoprosencephaly. There were significant correlations between hemispheric fusion and corpus callosum formation and between presence of dorsal cyst and corpus callosum formation. Based on this and prior studies, we postulate that a normal interhemispheric fissure is a necessary prerequisite for corpus callosum formation and suggest that dorsal cyst formation in holoprosencephaly is facilitated by absence of the callosal splenium. Moreover, we have shown that subcategories of holoprosencephaly, which we have termed *syntelencephaly*, can be segregated on the basis of morphological features. It will be important

to study larger numbers of these patients to determine whether specific clinical phenotypes are associated with the specific anomalies.

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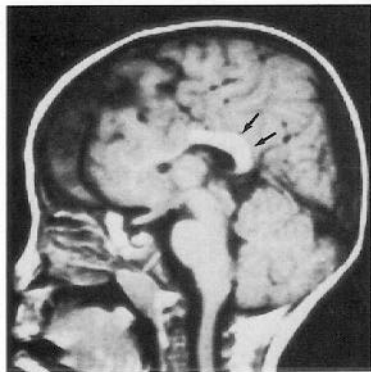
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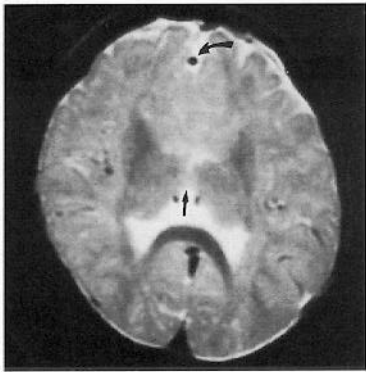
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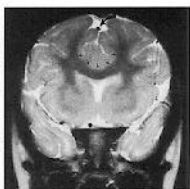
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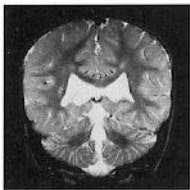
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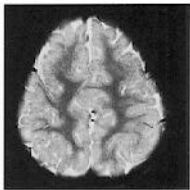
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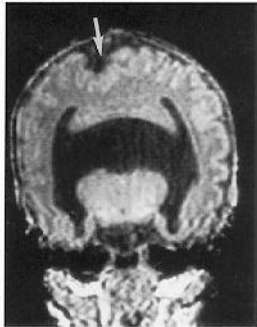
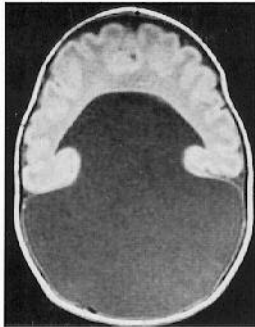
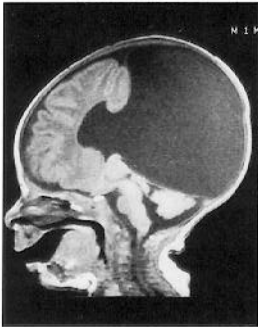
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