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Apparent Atypical Callosal Dysgenesis: Analysis of MR Findings in Six Cases and Their Relationship to Holoprosencephaly

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The MR scans of six pediatric patients with apparent atypical callosal dysgenesis (presence of the dorsal corpus callosum in the absence of a rostral corpus callosum) were critically analyzed and correlated with developmental information in order to assess the anatomic, embryologic, and developmental implications of this unusual anomaly. Four patients had semilobar holoprosencephaly; the dorsal interhemispheric commissure in these four infants resembled a true callosal splenium. All patients in this group had severe developmental delay. The other two patients had complete callosal agenesis with an enlarged hippocampal commissure mimicking a callosal splenium; both were developmentally and neurologically normal. The embryologic implications of the presence of these atypical interhemispheric connections are discussed.

Differentiation between semilobar holoprosencephaly and agenesis of the corpus callosum with enlarged hippocampal commissure—two types of apparent atypical callosal dysgenesis—can be made by obtaining coronal, short TR/TE MR images through the frontal lobes. Such differentiation has critical prognostic implications.

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Abnormalities of the corpus callosum are frequently seen in patients with congenital brain malformations [1–5]; a recent publication [5] reports an incidence of 47%. The corpus callosum normally develops in an anterior to posterior direction. The genu forms first, followed by the body, splenium, and rostrum. Dysgenesis of the corpus callosum is manifested by the presence of the earlier-formed segments (genu, body) and absence of the later-formed segments (splenium, rostrum) [4–6].

We have recently encountered six patients with findings suggestive of atypical callosal dysgenesis in whom there was apparent formation of the callosal splenium in the absence of the genu and body. We analyzed the MR anatomy in the six patients in an attempt to clarify the embryologic, radiologic, and clinical implications.

Patients and Methods

The six patients ranged in age from 1 month to 9 years (average, 2.3 years) (Table 1). There were two males and four females. The four patients with holoprosencephaly (patients 1–4) presented with microcephaly (three), developmental delay (two), seizures (two), and associated findings (Table 1). Patient 5 was imaged because of a large (>95th percentile) head size. Patient 6 presented after minor head trauma and had an abnormal CT, which led to the MR examination. Both patient 5 and patient 6 were neurologically and developmentally normal.

Five MR scans were performed at 1.5 T (Signa, General Electric) and one at 0.5 T (Magnatom, Siemens). Sagittal spin-echo (SE) images were obtained by using parameters of 500–600/17–20/1 (TR/TE/excitations) 256 × 192 acquisition matrix, and 5-mm section thickness (1 mm gap). Axial 5-mm (2.5-mm gap) SE images, 2500–3000/30–60, 70–120/2, were also obtained in all patients. Coronal 5-mm SE images, 600/20/1, were obtained in patients 1–4 and 6.

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TABLE 1: Patient Information

Case No.	Age	Reason for Scan	Radiologic Diagnosis	Telencephalic Commissures
1	1 mo	Abnormal facies, seizures, small head	Semilobar holoprosencephaly	Pseudosplenium
2	1 mo	Small head, hypotelorism	Semilobar holoprosencephaly	Pseudosplenium
3	14 mo	Small head, developmental delay	Lobar holoprosencephaly	Pseudosplenium
4	3 yr	Seizures, developmental delay, spastic diplegia	Semilobar holoprosencephaly	Pseudosplenium
5	6 mo	Large head, r/o hydrocephalus	Agenesis of the corpus callosum	Hippocampal commissure
6	9 yr	Minor head trauma	Agenesis of the corpus callosum	Anterior commissure, hippocampal commissure

All the patients had a large interhemispheric commissure superior to the posterior aspect of the bodies of the lateral ventricles in the region normally occupied by the splenium of the corpus callosum. The MR scans were assessed for all other anomalies of brain formation. Specifically, the four portions of the corpus callosum (rostrum, genu, body, splenium) and the other telencephalic interhemispheric commissures (anterior commissure and hippocampal commissure) were sought. The posterior commissure was not analyzed critically because its development is completely separate from the other three interhemispheric commissures. The interhemispheric fissure was assessed to look for interhemispheric fusion at any point other than the four interhemispheric commissures (anterior commissure, hippocampal commissure, corpus callosum, posterior commissure). If interhemispheric fusion was present, other features of holoprosencephaly such as absence of the septum pellucidum, dysplastic frontal horns, thalamic fusion, hypotelorism, and facial clefts [7] were sought specifically.

Results

All patients had an interhemispheric commissure in the dorsal telencephalon, above the posterior borders of the lateral ventricles. In patients 3, 4, and 6, who were old enough for myelination to have occurred, the commissure was myelinated. Myelination was otherwise appropriate for age in all patients [8]. In patients 1–4, the commissure was slightly thicker posteriorly than anteriorly, was curved around the posterior aspects of the lateral ventricles, and was positioned near the normal position of the callosal splenium (Figs. 1–3). The appearance was therefore that of a pseudosplenium, as described in holoprosencephaly [7]. In patients 5 and 6, the commissure was more anterior in position and connected the widely separated fornices at the junction of their bodies and crura (Figs. 4 and 5); that is, the position of the hippocampal commissure. The appearance, therefore, was that of an enlarged hippocampal commissure. In patient 6, this commis-

sure appeared egg-shaped on sagittal images whereas in patient 5 it was more linear in configuration. Moreover, in patient 6, the body and column of the right fornix was enlarged (Fig. 5); this enlarged forniceal body was initially misinterpreted as a dysgenetic corpus callosum.

Patients 1–4 had hypotelorism and fusion of the frontal lobes across the interhemispheric fissure, as well as absence of the anterior falx cerebri. The interhemispheric fissure was normal and the falx cerebri present in the posterior parietal and occipital region in all of these patients (Fig. 3). Additionally, all had small frontal lobes with abnormal gyral patterns in the affected regions. Patients 1 and 2 had partial fusion of the thalami. The frontal horns were completely absent in patients 1, 2, and 4; patient 3 had extremely rudimentary frontal horns (Fig. 3). All of these findings are typical of holoprosencephaly [3, 7].

The anterior commissure was present and slightly enlarged in patient 6. No anterior commissure could be detected in patient 5. Except for the anomalies of the interhemispheric commissures mentioned above, the scans of patients 5 and 6 were unremarkable.

Discussion

It is clear from the anatomic analysis in the results that patients 5 and 6 do not have atypical callosal dysgenesis; in fact, both these patients have complete callosal agenesis. The anatomic structure that was initially interpreted as the splenium of the corpus callosum is actually an enlarged hippocampal commissure (psalterium). Presence of the hippocampal commissure in callosal agenesis is apparently extremely uncommon [3, 4] and hypertrophy of the hippocampal commissure in agenesis of the corpus callosum has not been described. Loeser and Alvord [1] have, in fact, stated that "the hippocampal commissure is never hypertrophied" in

Fig. 1.—Patient 1.

A, Sagittal SE 600/20 MR image shows an apparent callosal splenium (*arrows*) dorsally. No callosal body, genu, or rostrum is seen.

B, Axial SE 600/20 MR image at basal fore-brain level shows absence of ventral interhemispheric fissure. This fusion of the frontal lobes is diagnostic of holoprosencephaly.

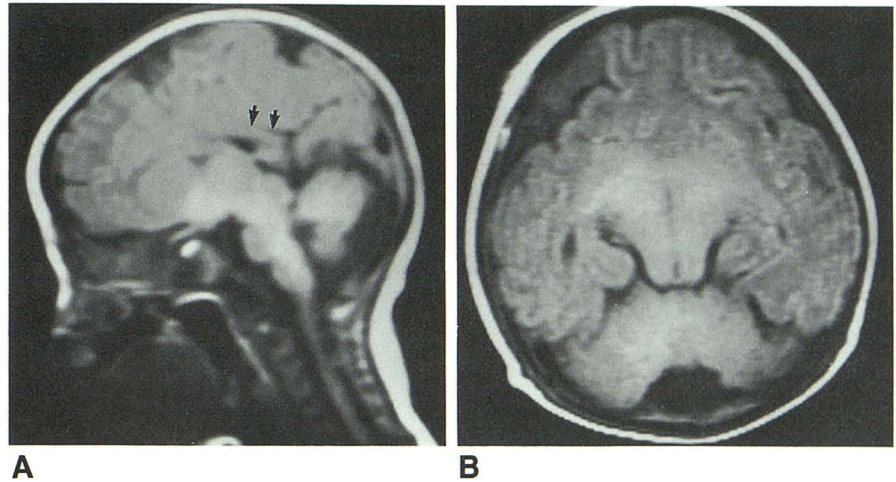


Fig. 2.—Patient 2.

A, Sagittal SE 600/20 MR image shows an apparent callosal splenium (*arrows*). Notice that gyral formation is quite abnormal in this patient and there is an obvious lack of development of the frontal lobes.

B, Axial SE 600/20 MR image shows fusion of frontal lobes, diagnostic of holoprosencephaly. There is no falx cerebri anteriorly. Gyral pattern in frontal region is extremely abnormal.

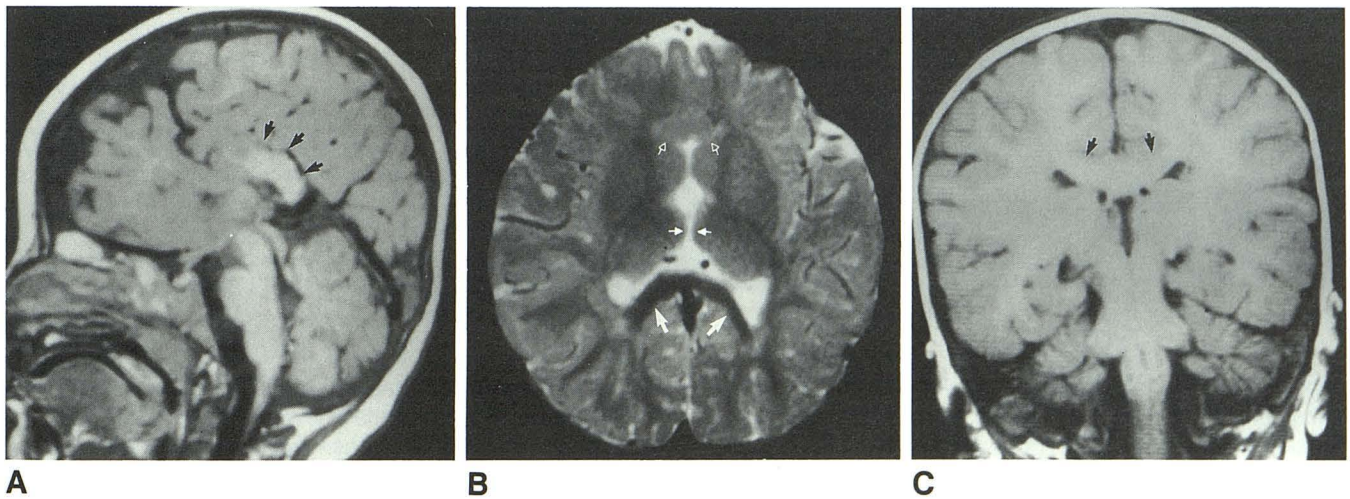
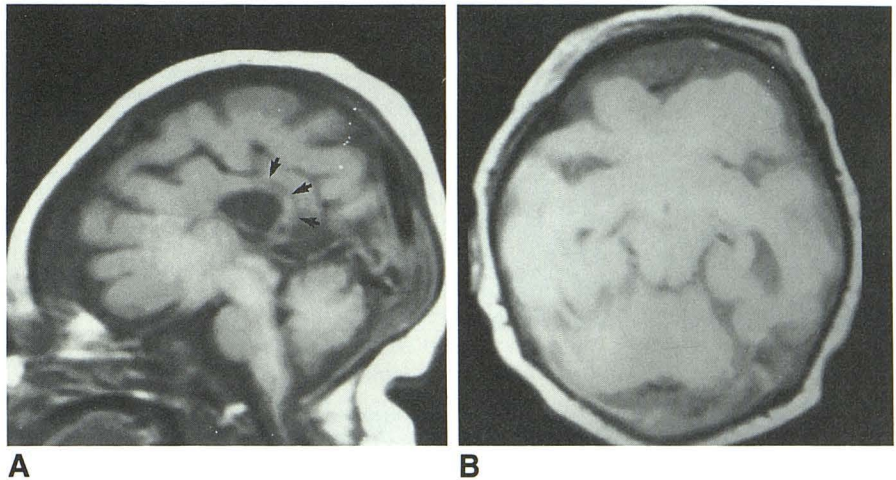


Fig. 3.—Patient 3.

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

B, Axial SE 2800/70 MR image shows that the spleniumlike commissure (*large arrows*) has normal myelination. As with patients 1, 2, and 4, there is fusion of the frontal lobes, diagnostic of holoprosencephaly. This patient, however, has rudimentary frontal horn formation (*open arrows*) and separation of the thalami (*small closed arrows*); therefore, a diagnosis of lobar holoprosencephaly, instead of semilobar holoprosencephaly, was made.

C, Coronal SE 600/20 MR image shows that dorsal interhemispheric fissure contains neocortical fibers from cerebral hemispheres and has the appearance of a true callosal splenium (*arrows*).

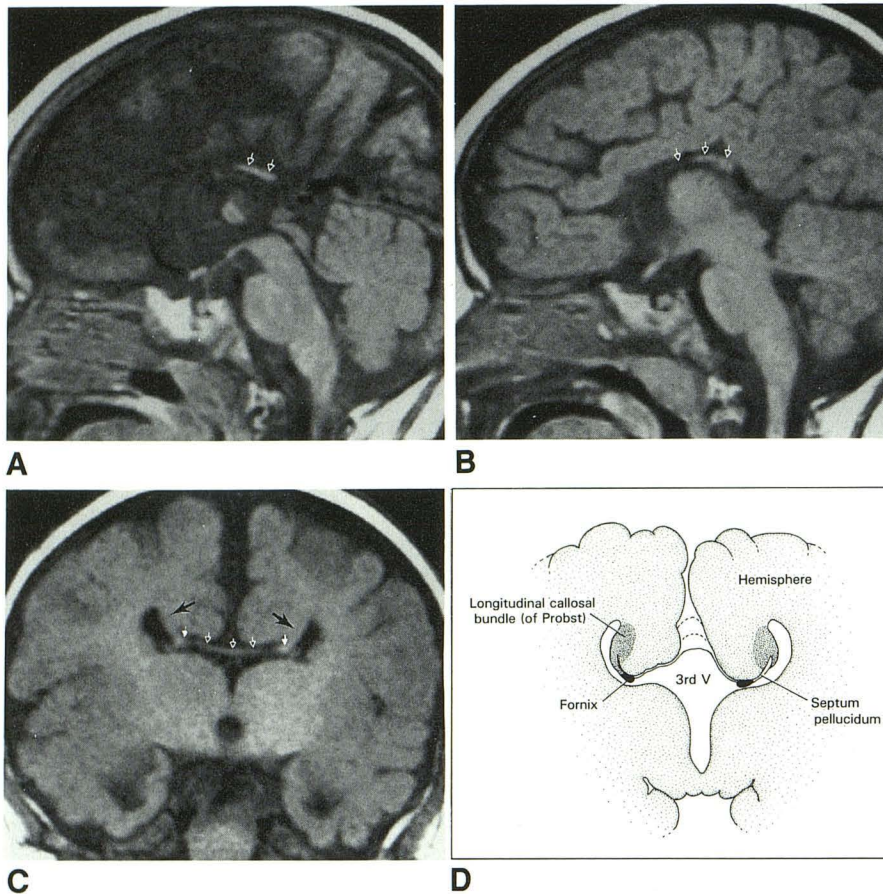


Fig. 4.—Patient 5.

A, Midline sagittal SE 600/20 MR image shows a linear, soft-tissue-intensity structure (arrows) resembling the splenium of the corpus callosum.

B, Parasagittal SE 600/20 MR image 6 mm lateral to A. The dorsal commissure is seen to connect with a structure that runs along the path of the body of the fornix (arrows).

C, Coronal SE 600/20 MR image shows inter-hemispheric commissure (open arrows) extending from the body of one fornix to the body of the other fornix (closed arrows). Note the crescentic shape of the ventricles resulting from their compression by the bundles of Probst (black arrows) in this patient with absence of corpus callosum.

D, Schematic showing the normal relationship of the lateral ventricles, bundles of Probst, and fornices in patients with absence of corpus callosum.

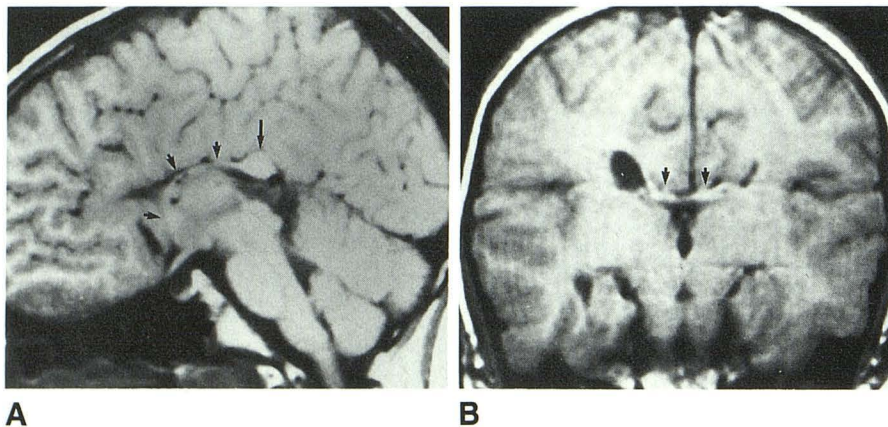


Fig. 5.—Patient 6.

A, Sagittal SE 600/20 MR image shows a large dorsal interhemispheric commissure (long arrow) with a structure resembling the fornix (short arrows) extending anteriorly from it.

B, Coronal SE 600/20 MR image with some motion artifact shows interhemispheric commissure (arrows) extending between the bodies of the fornices, similar to Fig. 4C.

agenesis of the corpus callosum. This is in contradistinction to the anterior commissure, which is usually present and occasionally hypertrophied (11%) or hypoplastic (18%) in patients with callosal agenesis [1, 3].

The usual presence of the anterior commissure and uncommon presence of the hippocampal commissure in callosal agenesis can be explained embryologically. As summarized in a recent paper [5], the telencephalic commissures (anterior commissure, hippocampal commissure, and corpus callosum) form when axons from the developing hemispheres migrate

through a commissural plate [2] or massa commissuralis [6] in the developing brain. If the commissural plate, the bed for in-growth of the developing hemispheric axons, fails to develop in a certain area, a commissure will not form in that area. Because the commissural plate forms in an anterior to posterior direction, the anterior commissure (the most rostral of the three) forms first, the first fibers crossing in the rostral portion of the commissural plate at about 10 weeks of gestation. The first fibers of the hippocampal commissure begin to cross in the dorsal portion of the commissural plate at

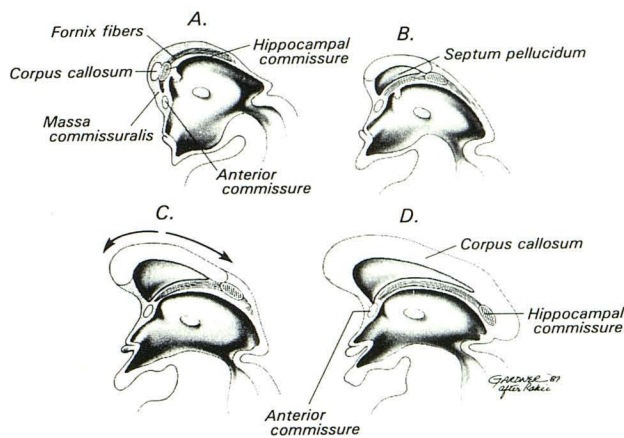


Fig. 6.—Development of the interhemispheric commissures. The anterior commissure, corpus callosum, and hippocampal commissure all form as a result of commissuration of fibers through the massa commissuralis (also known as the commissural plate). The anterior commissure forms first, with the first fibers crossing in the anterior portion of the massa at approximately 10 gestational weeks. The first fibers of the hippocampal commissure cross further dorsally at about the 11th gestational week. The first fibers of the corpus callosum begin to cross in the midline at approximately 12 gestational weeks in close association with the hippocampal commissure.

about 11 gestational weeks. The pioneer callosal fibers then begin to cross slightly anterior to the hippocampal commissure at about the 12th gestational week (Fig. 6). One might postulate that the temporal and anatomic proximity of the crossing of the archicortical (hippocampal commissure) and neocortical (corpus callosum) fibers within the commissural plate makes it likely that both would be damaged by a teratogenic insult. In contradistinction, the fibers of the anterior commissure cross earlier and in a more rostral portion of the commissural plate; the temporal and geographic separation of the developing anterior commissure from the developing corpus callosum is the probable reason that these fibers are often spared in callosal agenesis. Whatever the reason, it appears that in the two cases described (patients 5 and 6) the hippocampal commissure is spared and enlarged. Although this might be explained as an extremely focal insult to the developing corpus callosum in patient 6 (in whom the anterior commissure was also spared), it is hard to explain the sparing of the hippocampal commissure in the absence of an anterior commissure and corpus callosum, as in patient 5. It is furthermore difficult to explain the cause of the enlargement of the hippocampal commissure. Compensatory enlargement of the hippocampal commissure in order to increase interhemispheric communication is unlikely because the hippocampal commissure connects the fornices, which are a part of the archicortex and therefore embryologically and anatomically separate from the neocortex (connected by the corpus callosum) [9]. The enlargement of the hippocampal commissure in patient 6 may be related to the enlarged right fornix. However, the reason for the forniceal enlargement remains obscure.

The presence of a spleniumlike bundle of interhemispheric white matter fibers has been described in patients with holoprosencephaly of the intermediate or semilobar type [5, 7, 10, 11]. Fleming and Norman [11] describe one such pseudo-splenium 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. Kautzky [10] considered a similar structure in a similarly malformed brain to be a true splenium and proposed that the anomalous brain was a hybrid between holoprosencephaly and agenesis of the corpus callosum. Most authors [7, 11–13], however, consider the corpus callosum to be absent by definition in the holoprosencephalies because of the lack of induction of the normal commissural plate. This lack of induction and formation of the commissural plate is unquestionably related to the other facial and brain anomalies of holoprosencephaly, which are the result of a poorly understood lack of induction of the rostral forebrain and the central portions of the face.

The facial anomalies of holoprosencephaly are complex and will not be discussed in this paper except to say that they result from varying degrees of agenesis of the central (premaxillary) segments of the face. In an architectonic study of holoprosencephalic brains, Yakovlev [14] showed that the prefrontal cortex (homotypical granular cortex) that normally makes up the bulk of the frontal lobes is absent in holoprosencephaly. Moreover, the hypothalamus, neurohypophysis, and adenohypophysis are usually hypoplastic and hypofunctional, and the olfactory system tends to be unformed [7]. This combination of anomalies involving the face, rostral diencephalon, and rostral telencephalon, can be explained in light of recent work by Couly and LeDouarin [15], who have mapped the rostral end of the neural tube in very young chick embryos (Fig. 7). The anlage of all the most commonly affected structures of holoprosencephalic brains are situated at the most rostral end of the neural tube; therefore, either an injury to or a lack of induction of the rostral tip of the neural tube could result in the abnormalities of the face, hypothala-

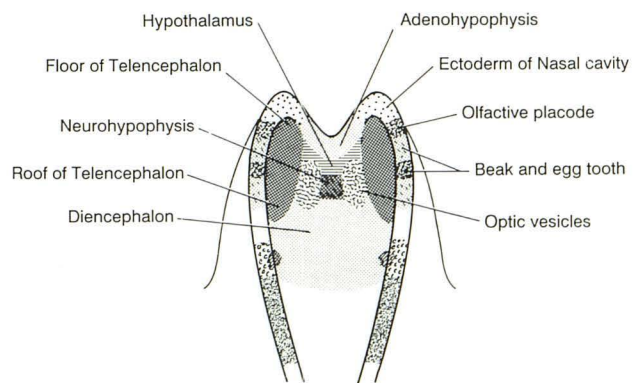


Fig. 7.—Location of the anlage of the brain and face in the developing neural tube (adapted from Couly and LeDouarin [15]).

mus, and frontal lobes in holoprosencephaly. An injury to or lack of induction of the most rostral neural tube, however, would necessitate lack of development or abnormal development of the primitive lamina terminalis, which is at the site of closure of the anterior neuropore. It is because the dorsal aspect of the lamina terminalis forms the substrate for the development of the commissure plate [5, 6] that embryologists have remarked on the inconsistency of the corpus callosum existing in holoprosencephaly [7]. Furthermore, since the commissural plate forms in an anterior to posterior direction, it seems anatomically inconsistent that a splenium should form in the absence of a genu and body.

Another possibility exists, however, that could explain the development of a dorsal interhemispheric commissure in holoprosencephalies. Marin-Padilla [16, 17] has postulated that incoming (corticopetal) axons from the brainstem induce the development of the cerebrum, in that they induce mitotic activity in the germinal matrix and the subsequent migration of these young neurons to form the cortical plate (Fig. 8). He has shown that essentially no developmental activity occurs in a region until the in-growth of these corticopetal fibers is detected. It is therefore plausible that holoprosencephalies result from either injury to or lack of development of the most rostral of these pioneer axons, those that go to the anterior hypothalamus and frontal lobes. The facial anomalies can be explained by this theory if one postulates that the lack of induction of the more rostral pioneer fibers results from a

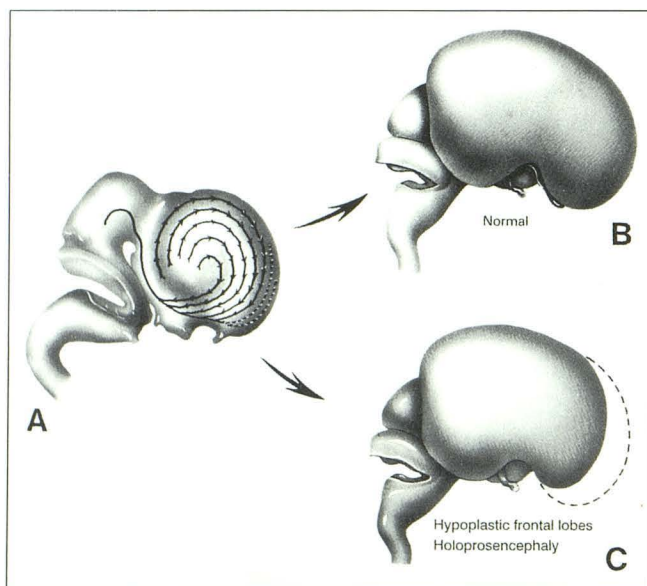


Fig. 8.—Induction of the cortical plate. Development of the telencephalon may be induced by incoming fibers from the brainstem. These incoming fibers (shown by curvilinear lines in A) in some way initiate the process of mitosis in the germinal matrix and the subsequent migration of young neurons to the cortical plate to form a normal brain (B). If the most rostral of these pioneer axons from the mesencephalon do not form or are destroyed (dotted lines in A), the neurons that will form the frontal lobes are not induced to form or migrate. Hypoplasia of the frontal lobes, ventral diencephalon, and midline portions of the face result (C); these are the features of holoprosencephaly.

deficient rostral notochord [18] or deficient precordial mesoderm [9], because the midline facial structures are believed to form as a result of a complex interaction of the superficial ectoderm, neuroectoderm, and precordial mesoderm in that region [18].

This postulate could also explain how apparently normal callosal fibers commissurate dorsally in the absence of a callosal genu and body. If induction of brain development is the result of interaction of embryonic brain substrate with corticopetal fibers from the brainstem, then induction of the dorsal cerebrum does not depend upon previous induction of the more rostral cerebrum; dorsal induction is dependent only upon contact with the dorsal corticopetal axons, which develop normally. Consequently, 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 pseudosplenium. This type of commissural malformation could only occur, however, when the frontal lobes are hypoplastic owing to a lack of induction; that is, in holoprosencephaly.

Whatever the cause, it is important to recognize that a callosalike bundle of interhemispheric fibers is frequently present in many patients with intermediate forms of holoprosencephaly. It is even more important to distinguish these patients, who are almost invariably moderately to severely developmentally delayed, from patients with agenesis of the corpus callosum and a large hippocampal commissure, who seem to be developmentally normal. Therefore, when a large interhemispheric commissure is seen superiorly to the dorsal bodies of the lateral ventricles in the absence of a normal corpus callosum, coronal images should be obtained through the frontal lobes to assess the integrity of the interhemispheric fissure. If there is fusion of the frontal lobes across the interhemispheric fissure (Figs. 1–3), a diagnosis of holoprosencephaly can be made. If the interhemispheric fissure is intact (Figs. 4 and 5), the patient has agenesis of the corpus callosum with an enlarged hippocampal commissure and a much better, probably normal, prognosis (in the absence of other associated anomalies).

In summary, we have described the findings in six patients with apparently atypical callosal dysgenesis (presence of the posterior corpus callosum in the absence of an anterior corpus callosum on midline sagittal images). Four of these patients have intermediate forms of holoprosencephaly, and a dismal developmental prognosis, whereas two have agenesis of the corpus callosum with a large hippocampal commissure and are developmentally normal. These two anomalies can be differentiated by obtaining coronal, short TR/TE MR images through the frontal lobes. Such differentiation has critical prognostic implications.

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