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Partial Development of the Corpus Callosum

David Rubinstein, Vicky Youngman, Joseph H. Hise, and Thomas R. Damiano

PURPOSE: To determine whether the MR findings of callosal dysgenesis suggest that the partially formed corpus callosum in humans is the result of arrested growth or delayed continued development. **METHODS:** The MR scans of 25 patients with callosal dysgenesis were reviewed to determine whether the observed corpus callosum corresponded to the form and position of a portion of a normal corpus callosum, as suggested by a theory of arrested growth. **RESULTS:** In 10 of the 25 cases, the partially formed corpus callosum corresponded to a portion of a normal corpus callosum. In the remaining 15 cases, the partially formed corpus callosum was located posterior to the expected location of a normal genu and inferior to the expected location of a normal body. **CONCLUSIONS:** Corpus callosum dysgenesis in humans may be caused by arrested growth in some cases; in other cases it is most likely caused by delayed continued development that attempts to compensate for earlier abnormalities in the evolution of midline structures.

Index terms: Corpus callosum, abnormalities and anomalies; Corpus callosum, anatomy; Corpus callosum, magnetic resonance; Brain, growth and development

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The concept that a partially formed corpus callosum is the result of arrested midline development is more than a century old (1). The current theory of callosal dysgenesis extends this to state that a partially formed corpus callosum consists of those portions of a normal corpus callosum known to develop first (2–6). As a result, a partially developed corpus callosum should consist of at least a genu or anterior body.

Recent studies using mice with hereditary callosal defects suggest another hypothesis. These studies demonstrate that the initial abnormalities leading to a partially developed corpus callosum are delayed midline fusion at the expected location of pioneer callosal fibers and absence of at least some of the guiding glial cells (7, 8). These abnormalities could be considered an arrest of midline growth, but the studies indicate that despite these initial deficiencies, callosal axons manage to cross the midline in a delayed and unorganized fashion (7–9). The resulting partially formed corpus callosum represents an attempt to compensate for the initial failure of midline fusion. This structure may not correspond to the position and morphology of a portion of a normal corpus callosum. The purpose of our study was to review the magnetic resonance studies of patients with developmental abnormalities of the corpus callosum to determine whether a similar process occurs in humans.

Materials and Methods

The databases of several hospitals were searched for patients with abnormalities of the corpus callosum demonstrated by magnetic resonance. The magnetic resonance scans of these patients were reviewed, and patients who were felt to demonstrate partial development of the corpus callosum were identified. All of the magnetic resonance studies included a T1-weighted sagittal scan. A structure identified as the corpus callosum was confirmed to be a structure crossing the midline on either T1- or T2-weighted axial or coronal scans. The abnormal corpus callosum in each case was evaluated by two of the authors (D.R. and

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From the University of Colorado Health Sciences Center, Department of Radiology, Section of Neuroradiology, Denver (D.R., V.Y.); Department of Radiology, Scott & White Memorial Hospital, Temple, Tex (J.H.H.); and Department of Radiology, Fitzsimons Army Medical Center, Aurora, Colo (T.R.D.).

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Address reprint requests to David Rubinstein, MD, University of Colorado Health Sciences Center, Department of Radiology, Section of Neuroradiology, 4200 E Ninth Ave, Campus Box A-034, Denver, CO 80262.

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V.Y.) for size, shape, and location to determine whether the commissure which had developed corresponded to a portion of a normal corpus callosum. In order to be considered part of a normal corpus-callosum genu or anterior body, the structure needed to extend anterior to the lamina terminalis or anterior commissure and, at one point, be separated from the fornices by at least the width of the spinal cord. The criteria were designed to exclude extreme cases but not equivocal cases from being judged as having a portion of a normal corpus callosum. In our review of 100 cases without callosal abnormality, the criteria were easily met.

Results

Twenty-five patients were identified with partial development of the corpus callosum. In 10 cases, the observed corpus callosum corresponded to portions of a normal corpus callosum. Despite the normal relationship of the corpus callosum to the fornices, a septum pellucidum was identified in only five cases (Fig 1). In 15 cases, the partially formed corpus callosum did not correspond to a portion of a normal corpus callosum. The corpus callosum in these cases was always located more inferior than a normal corpus callosum body and was closely apposed to the fornices with little or no septi pellucidi. The anterior-posterior position of the corpus callosum in these 15 cases varied. In four cases, the corpus callosum was located mainly anterior to the anterior commissure, but because the structure was closely apposed to the fornices, it was posterior to the expected position of a normal genu (Fig 2). In eight cases the corpus callosum was closely apposed to the superior surface of a short segment of the forniceal bodies (Fig 3). Of these, five had a small portion of the corpus callosum extending anterior to the anterior commissure, and three did not have an extension anterior to the anterior commissure. In three cases, the corpus callosum was closely apposed to the superior surface of the entire length of the bodies of the fornices (Fig 4).

Each corpus callosum that corresponded to a portion of a normal corpus callosum and 10 of the 15 that did not were sufficiently thick to

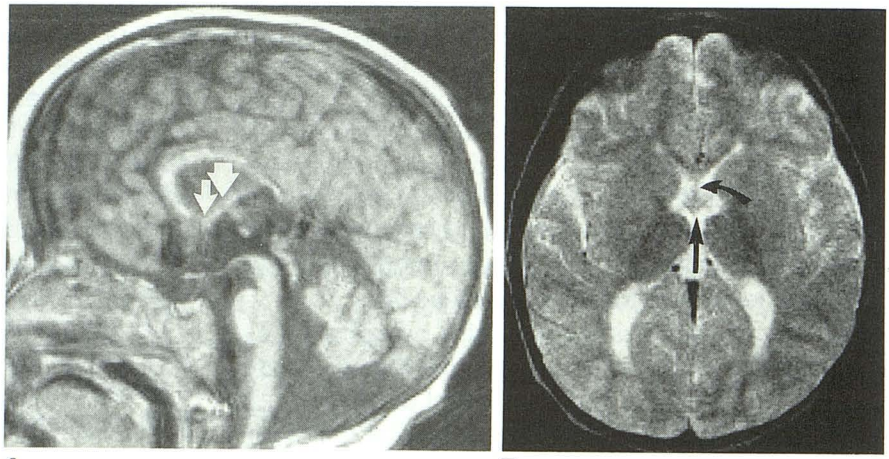

Fig. 1. A patient with a partially developed corpus callosum corresponding to a normal anterior portion of the corpus callosum.

A, The sagittal scan demonstrates that the posterior body and splenium are deficient. A cingulate gyrus has developed over the body of the corpus callosum. The corpus callosum extends well anterior to the anterior commissure (*thin arrow*), and the corpus callosum is well separated from the fornices (*thick arrow*).

B, On the axial scan the forniceal columns (*arrow*) are separated from the corpus callosum by a thin septum pellucidum (*curved arrow*).

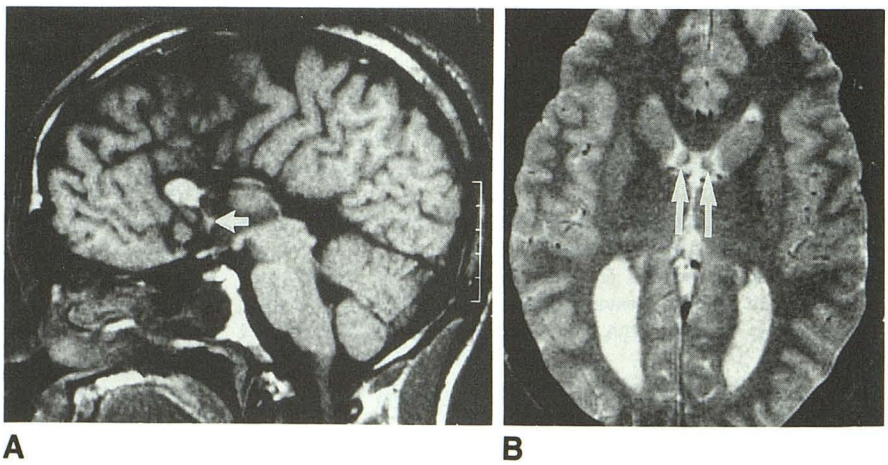

Fig. 2. A patient with a corpus callosum that does not correspond to a portion of a normal corpus callosum.

A, On the sagittal image the corpus callosum is located just anterior to the anterior commissure (*arrow*) but cannot be separated from the fornices. The position of the corpus callosum is posterior to the normal position of the genu.

B, The axial image demonstrates that the corpus callosum lies just anterior to the fornices (*arrows*) with no septum pellucidum separating them, in contrast to the relationship of the corpus callosum and fornices in Figure 1.

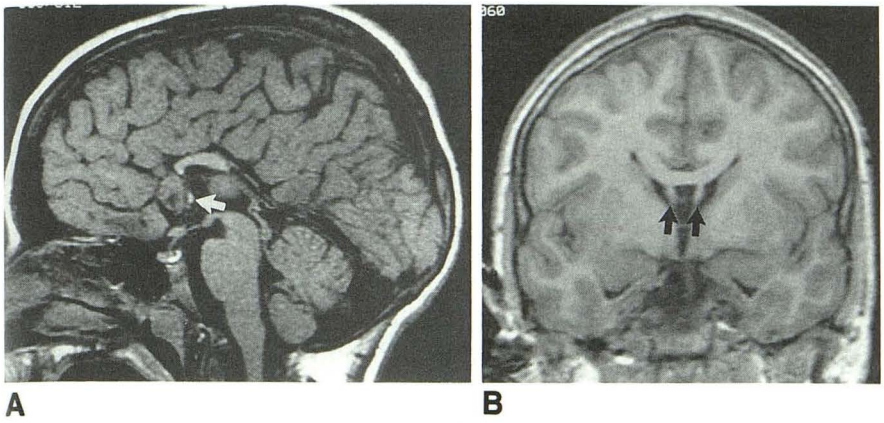

Fig. 3. The corpus callosum in this patient is short and closely apposed to the fornices.

A, The sagittal image shows that the corpus callosum extends just anterior to the anterior commissure (*arrow*) but cannot be separated from the fornices.

B, On the coronal image the corpus callosum is just superior to the forniceal bodies (*arrows*) with no intervening septum pellucidum. A cingulate gyrus has formed superior to the dysgenetic corpus callosum.

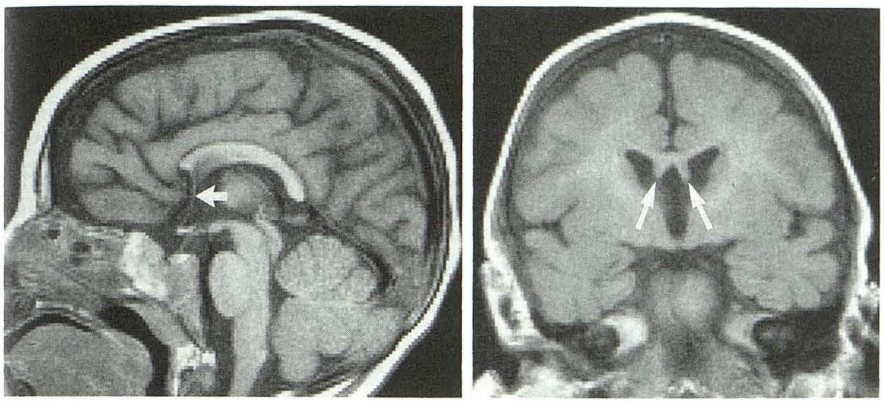

Fig. 4. The corpus callosum in this patient lies along the length of the fornices.

A, On the sagittal image the corpus callosum extends just anterior to the lamina terminalis (*arrow*) and cannot be separated from the fornices. A cingulate gyrus has formed over the anterior portion of the dysgenetic corpus callosum.

B, The coronal image demonstrates that the corpus callosum lies directly superior to the fornices (*arrows*) with no intervening septum pellucidum as in Figures 2 and 3.

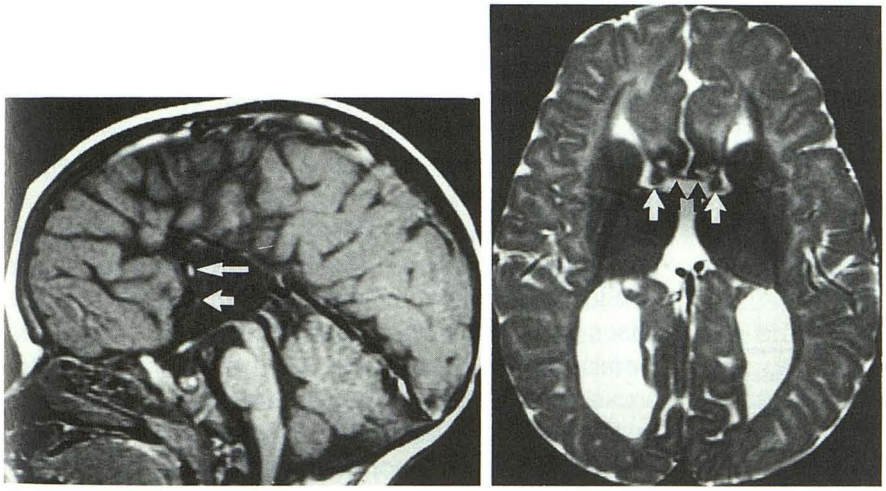

Fig. 5. This patient has the smallest corpus callosum of our series. On the sagittal image the corpus callosum (*long arrow*) lies in the same position relative to the anterior commissure (*short arrow*) as the corpus callosum in Figure 2. On the axial image the corpus callosum (*black arrows*) lies anterior to the fornices (*white arrows*) with no intervening septum pellucidum.

appear as a structure crossing the midline which was continuous with the white matter of the hemispheres. Although individual axons could not be followed, it is assumed that these structures contained axons that connected the cortex of one hemisphere with the other. In the remaining five cases the direction of axons composing the thin corpus callosum could not be determined with certainty. All five of these commissures were located in positions similar to the position of the corpus callosum in one of the 10 cases, in which the corpus callosum did not correspond to a portion of a normal corpus callosum (Fig 5). In four of the five cases the crossing structure appeared superior or anterior to the fornices; in only one the structure could not be identified separate from the forniceal bodies along its course laterally from the midline. The other brain abnormalities

occurring in these cases of corpus callosum dysgenesis are listed in the Table.

Discussion

According to Rakic and Yakovlev, the normal formation of the corpus callosum is a result of several events occurring in the midline between 6 and 20 weeks of gestation. From 6 to 8 weeks the dorsal part of the thin rostral wall of the telencephalon thickens to form the lamina reuniens. At 8 weeks the dorsal part of the lamina reuniens begins to fold to form the sulcus medianus telencephali medii. The banks of the sulcus medianus telencephali medii then fuse by 10 weeks, forming the massa commissuralis. The fusion occurs with the migration of cells of probable "spongioblastic" origin, which obliterate the small strip of meninx primitiva in the sulcus. At approximately the same time, fibers cross the midline in the ventral portion of the lamina reuniens to form the anterior commissure. Meanwhile, at approximately 9 weeks the fornices have begun to develop in the ventral lamina reuniens extending dorsally. By 11 weeks interlacing fibers between the fornices form the hippocampal commissure, and the pioneer fibers of the corpus callosum have begun to cross the massa commissuralis. A definitive corpus callosum is identified in the 12th week. The corpus callosum then grows mainly in a caudal (posterior) direction paralleling the growth of the cerebral hemispheres. As the hemispheres expand and the corpus callosum grows, the anterior corpus callosum separates from the fornices, stretching the folds of the septum pellucidum. At 14 to 16 weeks the knee shape of the genu is formed. Finally, by 20 weeks the corpus callosum has obtained a form similar to an adult corpus callosum as the rostrum is formed (10).

Abnormalities Associated with a Partial Corpus Callosum

	Number of Cases Corresponding to Portions of a Normal Corpus Callosum	Number of Cases Not Corresponding to Portions of a Normal Corpus Callosum
Chiari II Malformation	3	0
Dandy-Walker Variant	2	1
Dandy-Walker	0	1
Schizencephaly	1	0
Porencephaly	1	0
Mild focal cortical damage and mild white matter lesions	0	1
Gray matter heterotopia	0	1
Lipoma	1	1
None	2	10
Total	10	15

The theory of arrested midline growth predicts that the form of a dysgenetic corpus callosum should include the portion of the corpus callosum that normally develops first, the genu or anterior body (2–6). As a result, the corpus callosum that develops should have a constant anterior-posterior relationship to the anterior commissure. Additionally, if the separation of the corpus callosum from the fornices is the result of expansion of the cerebral hemispheres, the normally formed portion of the corpus callosum should obtain a normal adult location unless the migration is impeded by a structure such as a lipoma or cyst. Previous discussions of partial development of the corpus callosum did not take into account the position of the corpus callosum relative to the anterior commissure and fornices. Consequently, every anterior portion of the corpus callosum that formed was called either a genu or genu and body (2–4). The use of this terminology produces cases that erroneously support a theory of arrested midline growth. In only 10 of our 25 cases did the partially formed corpus callosum consist of at least a normal genu or anterior body as predicted by a theory of arrested growth.

In 10 of the 15 remaining cases the interhemispheric commissure was sufficiently thick to suggest that the crossing fibers were connecting the cortex of the hemispheres and therefore represented the corpus callosum. We believe that each of the five thinner commissures also represents a corpus callosum for three reasons. First, each of the thinner commissures is located in a position similar to the corpus callosum in one of the 10 cases with a malpositioned thick corpus callosum. Second, in four of the five cases the crossing structure appeared superior or anterior to the forniceal bodies (Fig 5) and therefore did not appear to be connecting them. In the fifth case, the structure extended the entire length of the forniceal bodies but could not be delineated from them at its lateral borders on the coronal images. The apparent lack of separation may have been attributable to image quality. Ten-millimeter coronal sections were obtained in this case, our only case in which the patient was imaged as a newborn. Finally, the hippocampal commissure normally is a small structure. An enlargement of this structure is unlikely after an insult in the region of the lamina reuniens. Such

an insult should hinder the development of this commissure.

A theory of arrested midline growth does not explain the appearance of the corpus callosum in these 15 cases. The range and location of the corpus callosum from anterior to posterior relative to the anterior commissure and the lack of separation of the corpus callosum from the fornices are not predicted by that theory. Several animal experiments suggest a theory of the appearance of the corpus callosum in these cases: that continued development to overcome initial abnormalities in the evolution of midline structures can result in cases demonstrating a wide variety in the shape, size, and location of the corpus callosum.

The most conclusive of these experiments is a study of the partial development of the corpus callosum in fetal mice. Wahlsten compared normal mice with a strain of mice with incomplete penetrance of hereditary agenesis of the corpus callosum. In the abnormal strain, adults demonstrate a wide variety of callosal anatomy, with 40% having normal morphology, yet almost all fetuses at 17 days after conception have a gap, a lack of fusion dorsal to the hippocampal commissure that is not seen in normal fetuses of the same developmental stage. This gap most likely corresponds to the human sulcus medianus telencephali medii, which is obliterated as its walls fuse to form the massa commissuralis. Fusion in this area occurs later in the fetuses of the abnormal strain. In addition, these fetuses have varying degrees of deficiency of the glial "sling" (7), the structure that usually guides callosal axons over the midline (11). Despite the delay in fusion and the abnormalities of the glial sling, most mice are able to develop a corpus callosum because axons are able to cross the midline later than usual. In fact, in some mice with complete absence of the sling, the delayed crossing of callosal axons occurs directly on the dorsal surface of the hippocampal commissure (7). The mice develop a full or partial corpus callosum because of continued midline development. A partial corpus callosum is not the result of arrested growth of a structure which had crossed the midline.

Interestingly, Wahlsten originally believed that dysgenesis of the corpus callosum was caused by arrested growth of the commissure. This belief was based on his observation that when the corpus callosum is partially formed, the structure is in the same location relative to the center of the hippocampal commissure as the pioneer callosal fibers in normal fetal mice (12). Only with the study of different aged fetuses of mice destined to have partial development of the corpus callosum did he reach the conclusion that a partially developed corpus callosum results from compensation for earlier abnormalities in the evolution of midline structures and is the consequence of continued development (7).

Wahlsten's work is supported by experiments that demonstrate that callosal axons have the ability to cross the midline over structures other than the glial sling (13, 14). In mice with surgical destruction of the sling or the immature corpus callosum, axons can cross the midline on cellulose bridges even when the implants are introduced in the first few postnatal days. The implants are first covered by glial cells and then crossed by callosal axons (13). Glial-coated implants, removed after 2 days and placed in surgically acallosal 17- or 34-day-old mice, produced crossing callosal axons in two of 20 animals (14). These experiments prove that callosal axons have the ability to cross the midline on structures other than the glial sling and that they maintain that ability for some time.

Another set of experiments supporting Wahlsten's findings traced axons of the corpus callosum in normal mice and in mice with hereditary deficiencies of the corpus callosum. Earlier experiments on newborn and adult rats (15) and fetal and adult monkeys (16) suggest the topography of the recently formed corpus callosum is similar to the adult callosum. A corpus callosum with arrested development should be an organized structure with fibers found in the first-formed portions of a normal corpus callosum. However, in mice with partial development of the corpus callosum, callosal fibers connect all portions of the brain. In addition, the organization of fibers in the corpus callosum is different in mice with partial development of the corpus callosum than in normal mice. In normal adult mice as might be expected, the axons connecting anterior portions of the brain are located more anterior in the corpus callosum, and the axons connecting the more posterior portions of the brain are located more posterior in the corpus callosum. In the abnormal mice, the corpus callosum demonstrates less organization. Axons connecting the frontal lobes were identified in all but the most posterior portion of the partially developed corpus callosum in one mouse, and axons connecting the occipital lobes were identified in the most anterior portion of the corpus callosum in another

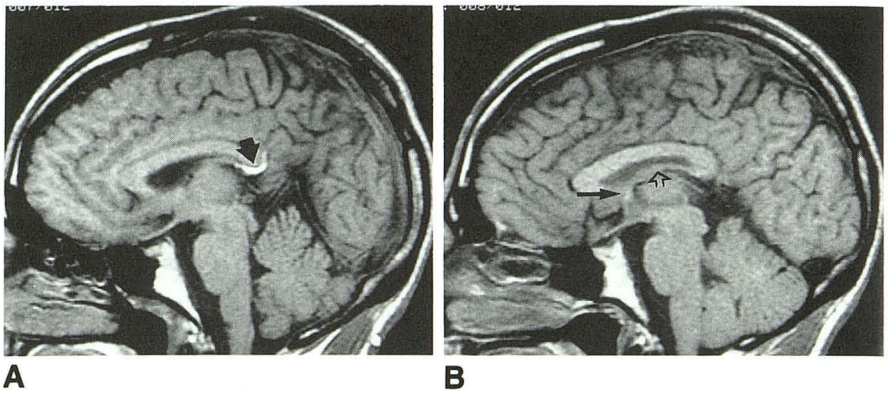

Fig. 6. Sagittal images (*A* and *B*) of the patient with a small lipoma (*thick arrow*) wrapping around a mildly deficient splenium. The corpus callosum extends well anterior to the anterior commissure (*thin arrow*) and is well separated from the fornices (*open arrow*). The cingulate gyrus is well formed.

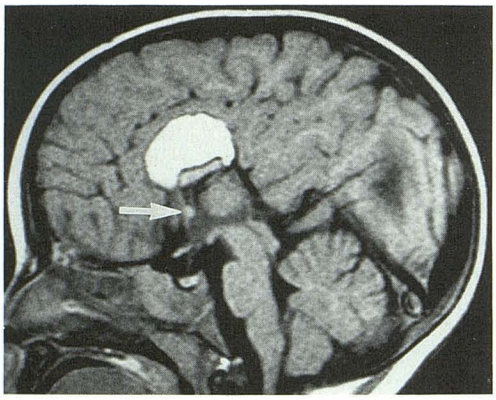

Fig. 7. A sagittal image of the patient with a lipoma just superior to the lamina terminalis. In contrast to Figure 6, the corpus callosum extends anteriorly just to the level of the anterior commissure (*arrow*) and cannot be separated from the fornices. A cingulate gyrus has formed superior to the lipoma.

(9). Additionally, in mice having very small corpora callosa, axons have been identified leaving Probst longitudinal bundles and crossing over the hippocampal commissure, a course that normal crossing axons do not take (9, 17, 18). The topography of the partially developed corpus callosum in these mice is most likely the result of continued development in which fibers reaching the midline and still having the ability to cross the midline do so when an opportunity presents.

Ongoing development of the corpus callosum, with axons crossing the midline where they find a suitable bridge, could produce a corpus callosum of almost any form and certainly could account for our cases of partially developed corpora callosa that do not correspond to a portion of a normal corpus callosum. The variable anterior-posterior position of the corpus callosum in these cases could be explained by axons' finding different routes across the midline. Furthermore, it is possible that in our cases, as in some mice that have a deficient corpus callosum, callosal axons crossed the midline more closely to the hippocampal commissure than normal or used the developing hippocampal commissure for a bridge (7, 9, 17, 18). A fetal corpus callosum that forms more closely to the fornices or hippocampal commissure than usual would have less tissue to form a septum pellucidum. The lack of tissue to form a septum pellucidum could prevent the separation of the corpus callosum from the fornices as the cerebral hemispheres enlarge, and would explain the close apposition of the corpus callosum to the fornices in our 15 cases. It is also possible that when the early midline abnormalities are mild or when callosal axons are extremely successful in overcoming these abnormalities, a corpus callosum is formed that is similar in shape, size, and location to portions of a normal corpus callosum.

More likely, both continued development and arrested growth play a part to produce the wide variety of morphology in callosal dysgenesis. Our two cases of pericallosal lipoma illustrate the extremes. In our case in which a small lipoma wrapped around the splenium, the splenium was mildly deficient (Fig 6). The most likely cause of the deficiency is arrested growth caused by obstruction by the lipoma. Obstruction causing arrested growth of the corpus callosum has been suggested by several authors (4, 10, 19–21) but does not explain our case in which the lipoma was located superior to the lamina terminalis (Fig 7). This lipoma most likely developed in the residual meninx primitiva of the sulcus medianus telecephalii medii (10, 21) and obstructed formation of the massa commissuralis. If development had been arrested, no corpus callosum would have formed. A dysplastic corpus callosum, however, did form, most likely as a result of continued development compensating for the obstruction.

In the remaining nine cases in which the partial corpus callosum corresponded to a portion of a

normal corpus callosum, we do not know when the insult to midline evolution occurred. The lack of a septum pellucidum in some cases despite a normal position of the corpus callosum suggests an insult during the formation of the corpus callosum, but the insult causing Dandy-Walker malformations is thought to occur before the formation of the corpus callosum (3). Because the exact timing of the abnormalities accompanying the dysgenetic corpus callosum in these cases is in doubt, it is uncertain whether the morphology of the corpus callosum in these cases is caused by arrested growth or by successful compensation for initial abnormalities in midline evolution.

Our collection of cases suggests that insults early in the evolution of midline structures produce a spectrum of callosal morphology and location because of the variability of continued midline development. Insults that occur during the formation of the corpus callosum may result in arrested growth and a predictable callosal shape and location more closely corresponding to a normal corpus callosum.

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References

1. Bruce A. On the absence of the corpus callosum in the human brain, with the description of a new case. *Brain* 1889;12:171–190
2. Davidson HD, Abraham R, Steiner RE. Agenesis of the corpus callosum: magnetic resonance imaging. *Radiology* 1985;155:371–373
3. Barkovich AJ, Norman D. Anomalies of the corpus callosum: correlation with further anomalies of the brain. *AJNR Am J Neuroradiol* 1988;9:493–501
4. Jinkins JR, Whittemore AR, Bradley WG. MR imaging of callosal and corticocallosal dysgenesis. *AJNR Am J Neuroradiol* 1989;10:339–344
5. Barkovich AJ. Apparent atypical callosal dysgenesis: analysis of MR findings in six cases and their relationship to holoprosencephaly. *AJNR Am J Neuroradiol* 1990;11:333–339
6. Barkovich AJ, Lyon G, Evard P. Formation, maturation, and disorders of white matter. *AJNR Am J Neuroradiol* 1992;13:447–461
7. Wahlsten D. Growth of the mouse corpus callosum. *Dev Brain Res* 1984;15:59–67
8. Wahlsten D. Defects of the fetal forebrain in mice with hereditary agenesis of the corpus callosum. *J Comp Neurol* 1987;262:227–241
9. Olavarria J, Serra-Oller MM, Yee KT, Van Sluyters RC. Topography of interhemispheric connections in neocortex of mice with congenital deficiencies of the callosal commissure. *J Comp Neurol* 1988;280:575–590
10. Rakic P, Yakolev PI. Development of the corpus callosum and cavum septi in man. *J Comp Neurol* 1968;32:45–72
11. Silver J, Lorenz SE, Wahlsten D, Coughlin J. Axonal guidance during development of the great cerebral commissures: descriptive and experimental studies, in vivo, on the role of preformed glial pathways. *J Comp Neurol* 1982;210:10–29
12. Wahlsten D. Prenatal schedule of appearance of mouse brain commissures. *Dev Brain Res* 1981;1:461–473
13. Silver J, Ogawa MY. Postnatally induced formation of the corpus callosum in acallosal mice on glia-coated cellulose bridges. *Science* 1983;220:1067–1069
14. Smith GM, Miller RH, Silver J. Astrocyte transplantation induces callosal regeneration in postnatal acallosal mice. *Ann NY Acad Sci* 1987;495:185–206
15. Olavarria, Van Sluyters RC. Axons from restricted regions of the cortex pass through restricted portions of the corpus callosum in adult and neonatal rats. *Dev Brain Res* 1986;25:309–313
16. Killackey HP, Chalupa LM. Ontogenetic change in the distribution of callosal projection neurons in the postcentral gyrus of the fetal Rhesus monkey. *J Comp Neurol* 1986;244:331–348
17. Ozaki HS, Murakami TH, Toyoshima T, Shimada M. The fibers which leave the Probst's longitudinal bundle seen in the brain of an acallosal mouse: a study with the horseradish peroxidase technique. *Brain Res* 1987;400:239–246
18. Ozaki HS, Shimada M. The fibers which course within the Probst's longitudinal bundle seen in the brain of a congenitally acallosal mouse: a study with the horseradish peroxidase technique. *Brain Res* 1988;441:5–14
19. Loser JD, Alvord EC. Agenesis of the corpus callosum. *Brain* 1968;91:553–570
20. Kendall BE. Dysgenesis of the corpus callosum. *Neuroradiology* 1983;25:239–256
21. Truwit CL, Barkovich AJ. Pathogenesis of intracranial lipoma: an MR study in 42 patients. *AJNR Am J Neuroradiol* 1990;11:665–674