Middle Interhemispheric Fusion: An Unusual Variant of Holoprosencephaly

A. James Barkovich and Douglas J. Quint

PURPOSE: To describe the imaging features of a brain anomaly found on studies of three patients, and to speculate on the embryologic basis leading to the development of this abnormality.

PATIENTS AND METHODS: Clinical records (three patients), MR scans (two patients), and CT scans (two patients) of three patients with fusion of the middle portions of the cerebral hemispheres in the presence of nearly normal anterior interhemispheric fissures were retrospectively reviewed. The results were correlated with the present theories of brain development in an attempt to classify the anomaly and define the underlying embryologic abnormalities. RESULTS: All three patients with middle interhemispheric fusion were severely developmentally delayed. Associated anomalies were identified in all three and included neuronal migration anomalies, callosal dysgenesis, and hypoplasia of the anterior falx cerebri. Correlation of the imaging findings with theories of brain development lead to the suggestion that this anomaly is the result of deficient or dysplastic mesenchyme, which leads to disordered brain development. CONCLUSION: Middle interhemispheric fusion may be considered as a variant of holoprosencephaly. It is suggested that the mesenchyme formed by the prechordal plate, notochord, and neural crest play an important part in the early development of the brain and that anomalies of the mesenchyme underlie this disorder as well as other forms of holoprosencephaly.

Index terms: Brain, abnormalities and anomalies; Brain, growth and development; Holoprosencephaly; Pediatric neuroradiology

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Lack of separation of the cerebral hemispheres is an unusual condition in humans. It is most commonly seen in holoprosencephaly, a condition representing a spectrum of forebrain dysgenesis that results from a lack of induction of the base of the forebrain and the middle portions of the face (1–9). A key feature of holoprosencephaly is that the rostral basal regions of the brain are the most severely affected and seem to be involved in all cases (2, 5, 6, 8). We report three patients in whom the posterior frontal and parietal regions of the brain are continuous across the midline, in spite of separation and nearly normal development of the base of the forebrain, and speculate on the embryologic mechanisms of this anomaly.

Patients and Methods

The three patients ranged in age from 5 months to 22 months at the time of their imaging studies (Table 1). All three patients presented with failure to achieve normal milestones in the first year of life. All had normal facies with normal interorbital distance and normal hypothalamic-pituitary function. No focal neurologic signs or symptoms were present in any of the patients. None of the patients displayed any seizure activity. The eldest patient (patient 3) had poor gross and fine motor control, delayed speech, and hyperreflexia with increased tone in the lower extremities at age 22 months.

Patient 1 was studied with computed tomography (CT) and magnetic resonance (MR), patient 2 was studied with CT alone, and patient 3 with MR alone. CT scans consisted of 10-mm contiguous axial images without administration of intravenous contrast. MR scans consisted of 5-mm (1-mm gap) sagittal and coronal spin-echo (SE) 500-600/20/
TABLE 1: Imaging findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (mo)</th>
<th>Reason for Presentation</th>
<th>Dorsal Cyst</th>
<th>Thalamic Fusion</th>
<th>Septum Pellucidum</th>
<th>Choroid Plexus</th>
<th>Cortical Dysplasia</th>
<th>Hippocampal Formation</th>
<th>Corpus Callosum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Developmental delay</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Bilateral diffuse</td>
<td>Hypoplastic</td>
<td>Absent</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>Developmental delay</td>
<td>Absent</td>
<td>Mild</td>
<td>Absent</td>
<td>Poorly evaluated</td>
<td>Not conclusive</td>
<td>Poorly evaluated</td>
<td>Absent</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>Developmental delay</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Only in trigone</td>
<td>Bilateral frontal</td>
<td>Hypoplastic</td>
<td>Absent</td>
</tr>
</tbody>
</table>

2 (TR/TE/excitations) images and axial 5-mm (2.5-mm gap) SE 2800-3000/30, 80-90/2 images using a 192 × 256 sampling size. Patient 3 had sagittal and coronal sequences repeated after intravenous administration of gadolinium-DTPA.

The images were analyzed retrospectively and independently by the authors. When referring to areas of the brain, common anatomical terms such as “frontal” and “parietal” are used in reference to the portions of the brain that normally occupy that area within the calvarium. The authors are aware, however, that the distribution of specific types of cortex within the brain is altered in holoprosencephaly, as shown by Yakovlev (9); however, no better terminology has been developed for discussion of the anatomy of the holoprosencephalic brain.

Results (Table 1)

The imaging studies of all three patients were characterized by the presence of an interhemispheric fissure anteriorly (in the prefrontal region) without separation of the hemispheres in the posterior frontal and parietal regions (Figs. 1–3). In patients 2 and 3, an interhemispheric fissure was present in the occipital region as well (Figs. 2 and 3). The anterior falx cerebri was hypoplastic in all three patients (Figs. 1–3). Moreover, a well-defined corpus callosum and the choroid plexuses were absent in the portions of brain at the level of the fused portions of the cerebral hemispheres. The choroid plexuses were present in the trigones, subacute to the separated occipital lobes, in patients 2 and 3. No definite choroid plexus was present in the lateral ventricles or third ventricle of patient 1. However, a small area of tissue isointense to white matter is located just above the thalamus (Fig. 1C) that may represent some rudimentary choroid plexus extending rostrally from the trigone. The hippocampal formations were very small in the two patients (patients 1 and 3) in whom they were adequately visualized (Figs. 1 and 3). The olfactory sulci were poorly formed in patients 1 and 3, indicating hypoplasia or dysplasia of the rhinencephalon.

In addition to the aforementioned similarities, many significant differences were noted on the scans. Patient 1 had a dorsal cyst, a characteristic finding in severe holoprosencephalies that is believed by many (5, 10, 11) to be a dorsal extension of the third ventricle. Patient 1 also had nearly complete thalamic fusion, another characteristic of the more severe end of the holoprosencephaly spectrum. Less complete thalamic fusion was present in patient 2 (Fig. 2B). Anomalies of neuronal migration were present in patients 1 and 3, with patient 1 much more severely affected (Fig. 1C). Patient 2 did not show normal arborization of the white matter and the cortex may be slightly thickened (Figs. 2B and 2C). However, we did not feel that the CT images were adequate to allow definitive diagnosis of a migration anomaly. Multiple large masses of heterotopic gray matter were present bilaterally in the frontal regions of patient 1, with the right side being more affected than the left. A large infolding of gray matter extended upward and to the left from the base of the right frontal lobe, displacing the holoventricle to the left (Fig. 1C). A subdural hematoma was present on the right as a result of shunt placement. Patient 3 had abnormal infoldings of dysplastic cortex in the frontal regions bilaterally and a stripe of gray matter lining the superior aspect of the holoventricle in the midline (Fig. 3D). Two other findings of note in patient 3 were the presence of an apparent callosal genu and splenium in the absence of a callosal body (Figs. 3A and 3E) and absence of the velum interpositum. Other than the interhemispheric fusion, no significant abnormalities were detected in the CT scan of patient 2. However, as only an
adjusted axial CT scan (with 10-mm-thick images) was available, it is entirely possible that other abnormalities were present, but not detectable.

Discussion

Although the associated facial deformities (cyclopia, ethmocephaly, cebocephaly) have been known since antiquity, the holoprosencephalic brain was first described by Kundrat (12), who named the malformation arhinencephaly. Although the name given to the disorder has changed several times since then (holotelencephaly (9), holoprosencephaly (4)), the description by Kundrat remains an excellent reminder of the basic defects in patients with holoprosencephaly—lack of formation of the central midline structures of the face and the rostral medial portions of the brain. Although the severity of the malformation can range from mild ("lobar" holoprosencephaly) to moderate ("semilobar" holoprosencephaly) to severe ("alobar" holoprosencephaly), the most severely affected region of the brain has consistently been the basal forebrain (2, 4, 6, 7), leading many authors to postulate that the primary defect is in the rostral notochord and the prechordal plate, which produce mesenchyme that is believed to influence strongly the development of the central portions of the face and the basal forebrain (3, 6, 9).

A lack of induction of the basal forebrain, however, would be expected to result in a lack of separation of the rostro-basal portions of the brain and does not explain the abnormality of the interhemispheric fissure in the three patients described in the present series. Indeed, imaging studies in all of these patients show separation of the hemispheres in the basal forebrain region, but a lack of separation of the cerebral hemispheres (interhemispheric fusion) in the posterior frontal and parietal regions. Moreover, the patients in this study all had normal interorbital distances, lack of facial deformity, normal hypothalamic-
pituitary function, and normal pituitary glands, although mild hypoplasia or dysplasia of the rhinencephalon was present in patients 1 and 3. These findings suggest that the brain was less involved rostrally and basally than dorsally and posteriorly.

From a clinical perspective, these patients are difficult to classify; all have clearly dysfunctional brains, with severe developmental delay evident from early childhood, and the oldest child manifested spasticity, which might lead to categorization as "cerebral palsy." This combination of clinical findings is quite nonspecific and can be present in acquired disease (hypoxic-ischemic encephalopathy) and a number of congenital malformations. From a gross pathologic perspective, however, the presence of interhemispheric fusion at any part of the cerebrum seems essentially pathognomonic for some form of holoprosencephaly (6). Moreover, the underlying developmental defect in this disorder may be similar to that in holoprosencephaly, as outlined below. We have, therefore, classified this anomaly within the holoprosencephalies, although we acknowledge that the diencephalon is separated from the telencephalon in these patients and that "syntelenencephaly" may be a more appropriate term for this disorder.

The embryologic question of how this anomaly develops and how it relates to more typical holoprosencephalies is complex. In order to speculate upon the causes and mechanisms involved in the anomalous formations of these brains, it is necessary to review some basic embryology of the developing brain and its surrounding mesenchyme. In this discussion, we will refer to the timing of events by both their time of occurrence and the corresponding developmental stage. The stages are based upon a division of the embryonic period into 23 consistent stages, as outlined by O'Rahilly and Muller (13).

The central nervous system is composed of neuroectodermal tissue that differentiates from surrounding ectoderm under the influence of the underlying notochordal process, notochordal plate, and notochord (14-18). These three structures are all midline condensations of mesoderm derived from the primitive streak (15, 16, 19). The notochordal process, the most rostral of the three, evolves into the notochordal plate, which subsequently forms the notochord (15, 16, 19). Rostral to the notochordal elements lies the pre-
Fig. 3. Patient 3; 22-month-old with developmental delay.

A, Sagittal SE 500/20 image shows presence of an anterior corpus callosum (genu, open white arrow) and posterior corpus callosum (splenium, closed white arrow) but the middle portion cannot be identified. Some heterotopic gray matter (open black arrows) lies above the lateral ventricle where the corpus is absent. Note that the high signal of myelinated white matter is seen above the heterotopia in the midline, marking the area in which the hemispheres are fused.

B, Coronal SE 500/20 image shows the intact anterior interhemispheric fissure, absence of the olfactory sulci, absence of the anterior falx, and an azygous anterior cerebral artery (arrow). Compare with normal brain in C.

C, Coronal SE 600/20 image in a normal patient. Arrows point to olfactory sulci. (Compare with B.)

D, Coronal SE 500/20 image shows absence of the middle portion of the falx, interhemispheric fusion, heterotopic gray matter (open black arrow) overlying the mid portion of the holoventricle, and markedly hypoplastic hippocampi (open white arrows). The lateral periventricular gray matter (closed black arrows) are the caudate bodies.

E, Axial SE 3000/90 image shows the absence of falx anteriorly, normal falx posteriorly, azygous anterior cerebral artery (white arrow), and absent septum pellucidum. The small island of gray matter (black arrows) anterior to the callosal splenium may be an extension of the midline heterotopias seen in D.

Chordal plate, a source of mesoderm for the face, rostral meninges, and cardiac structures (15, 16).

As the midline neural plate thickens, cells at the junction of the neural ectoderm and more peripheral cutaneous ectoderm differentiate into specialized cells, known as the neural crest. The first neural crest cells can be identified in the area of the rhombencephalon at embryos of stage 9 (21 days) (16). At stage 10 (22–23 days), during the initial closure of the neural plate into a neural tube (17), neural crest cells from the region of the rhombencephalon begin to migrate ventrolaterally to form the ganglia of the cranial nerves (17).

After closure of the rostral neuropore at stage 11 (23–26 days) and the caudal neuropore at
stage 12 (26–30 days) (18, 20, 21), neural crest cells differentiate in the neural tube at the level of the mesencephalon and caudal diencephalon. Moreover, mesenchyme, perhaps from the mesencephalic neural crest or from the prechordal plate, is present ventral to mesencephalon (22).

Stage 13 (28–32 days) is noteworthy for the development of a "sheath" of mesenchyme around the notochord (22), further extension of the mesenchyme around the base of the brain (23), and the initial appearance of the commissural plate in the most rostral portion of the brain (23). The commissural plate lies between the anterior portions of evaginating cerebral hemispheres. It differentiates from the posterior aspect of the primitive lamina terminalis (which remains thin and undeveloped) and will eventually become an area that promotes ingrowth of developing commissural fibres (24, 25).

Mesenchyme continues to engulf the brain and, by stage 14 (31–34 days), surrounds the entire telencephalon, even ventrally (22). Mesoderm from the prechordal plate and mesenchymal sheath of the notochord migrate to the area where the medial part of the tentorium will form. The initial portion of the interhemispheric fissure develops at the most rostral telencephalon at this time (26).

During stages 15–17 (35–44 days), the interhemispheric fissure develops further posteriorly and deepens as a result of disproportionate growth of the evaginating cerebral hemispheres (which are expanding posterolaterally) and the midline telencephalic structures (lamina terminalis, commissural plate, and telencephalon medium) (18, 22, 25, 27–29). At the same time that the interhemispheric fissure is developing posteriorly, the commissural plate is growing posteriorly, and the interhemispheric fissure is becoming filled by mesenchyme (Figs. 4A and 4B) (18, 22, 27–29). The commissural plate seems to form as a result of transformation of the thin
midline wall of the telencephalon known as the velum transversum (18, 25). Immediately lateral to the velum transversum and medial to the developing hippocampus in the region of the paraphysis (immediately posterior to the commissural plate), the velum transversum differentiates into the epithelial lamina, a very thin layer of tissue from which the choroid plexuses will develop (30, 31). The mesenchyme for the future chondrocranium is in the process of condensing (22).

During stages 18–21 (44–54 days), the epithelial lamina bilaterally begin to evaginate into the developing lateral ventricles, together with meninx from the interhemispheric fissure, to form the plexus folds, which will become the choroid plexuses of the lateral ventricles (Figs. 4C and 4D) (30, 31). The falx cerebri begins to form in two separate portions, condensing from mesenchyme in continuity with the developing anterior skullbase rostrally and from a continuation of the tentorium cerebelli caudally (22, 32). The two portions unite in the early fetal period.

With this embryologic background, it is possible to speculate upon the events that lead to the brain deformities in the patients reported herein. The key question in this regard concerns the normal mechanism of formation of the interhemispheric fissure. The absence of the interhemispheric fissure is clearly the key to the overall deformity. In its absence, the falx cerebri cannot form, the commissural plate (and thus the corpus callosum) cannot form, and the epithelial laminae cannot evaginate into the ventricles to form the choroid plexuses. Moreover, as the hippocampus forms within the medial telencephalon directly lateral to the epithelial lamina (i.e., within the interhemispheric fissure), the lack of interhemispheric fissure development is likely related to the hypoplastic hippocampi in these patients, as well.

We suggest that the lack of formation of the interhemispheric fissure is the result of a paucity of mesenchyme surrounding the telencephalon, both in the patients described herein and in classical cases of holoprosencephaly. Abundant evidence exists for a paucity of mesenchyme in classical holoprosencephaly. The mid portions of the face, anterior skullbase and anterior falx cerebri, which are deficient in holoprosencephalies, normally arise from mesenchyme of the prechordal plate, possibly augmented by mesenchyme from neural crest cells (5, 22, 32, 33). The ganglia of the cranial nerves have been found to be of reduced size in holoprosencephaly embryos; these ganglia are composed of mesenchyme that derives from mesencephalic neural crest (7). The medial aspects of the tentorium cerebelli, also deficient in holoprosencephalic embryos (7), derive from mesenchyme of the prechordal plate, mesencephalic neural crest, and, perhaps, the notochordal sheath (7, 22). The olfactory axons develop from prechordal mesenchyme in nasal mucosa, then elongate toward the ventral surface of the telencephalon where they induce the olfactory tracts and bulbs to evaginate (3, 34); the olfactory system, too, is deficient in most cases of classical holoprosencephaly. Moreover, mesenchyme from the prechordal plate is suspected to have a large role in the induction of the basal medial forebrain, including the optic, commissural, and septal primordia, as well as the adenohypophysis (3, 33, 35–37).

The question that has not been addressed previously concerns the role of mesenchyme in the differentiation of the telencephalon. That is, why do germinal matrices normally form in regions away from the midline, resulting in formation of the cerebral hemispheres, while the midline of the telencephalon (velum transversum) persists as a thin layer of tissue? The cerebral hemispheres begin to evaginate from the telencephalon at stage 14 (26) at the same time that the telencephalon becomes completely surrounded by mesenchyme (22), an association that is unlikely to be coincidental. Indeed, precedent exists for the influence of mesenchyme upon the developing neural ectoderm, including induction of the differentiation of neural cells. In addition to the aforementioned examples of mesenchymal induction of the rostral medial forebrain and the olfactory bulbs, the mesenchyme surrounding the rhombencephalon has been shown to influence strongly cerebellar development (38, 39) and the notochord induces the differentiation of the floor plate of the neural tube (14). Whether the mesenchyme promotes the differentiation and evagination of the developing hemisphere, inhibits the differentiation of the velum transversum, or both, cannot be deduced from the available data.

Based upon data available in embryologic, pathologic, and radiologic literature, one can postulate that the degree of brain development in classical holoprosencephaly correlates with the severity of deficiency of mesenchyme. The most severely affected individuals have absence of
midfacial structures, absence of many medial basal forebrain structures, deficiency of the skull base, absence of the interhemispheric fissure, absent telencephalic commissures, and absent falx cerebri; whereas less severely affected patients have less severe facial and skull base deformities, presence of more normal medial basal forebrain structures, a posterior interhemispheric fissure, a posterior falx cerebri, and a posterior corpus callosum (2, 5, 8). The less severely affected patients of the holoprosencephaly spectrum, it appears, have more mesenchyme posteriorly, where the mesenchyme is of mesencephalic neural crest and notochordal sheath, as opposed to prechordal plate, origin. In contradistinction, the patients reported herein appeared to have relatively normal formation of the face, skullbase, and basal forebrain (areas that derive from the more rostral prechordal mesenchyme) and significant abnormalities more posteriorly in the posterior frontal and parietal regions. Therefore, we suggest that the malformations of these patients resulted from a deficiency of mesenchyme that was predominantly restricted to the posterior frontal and parietal regions.

The fact that other brain anomalies are present in the same region as the interhemispheric fusion supports the concept of the localized lack of mesenchyme as the underlying disorder in the patients of this series. The anterior falx is hypoplastic in all three patients and the anterior cerebral artery is azygous in two of the three. Both the cerebral arteries and the falx derive from mesenchyme, pointing to a mesenchymal abnormality anterior to the site, as well as at the site, of hemispheric fusion. The corpus callosum is absent at the site of hemispheric fusion, which may result from the lack of interhemispheric fissure formation or, possibly, a lack of direct interaction of the velum transversum with the mesenchyme. This point will be elaborated upon below. Finally, two of our patients have heterotopic gray matter on the superior surface of the ventricle in the midline (where the corpus callosum is normally located). As a germinal zone is not present in the dorsal midline in normal brains, this heterotopic gray matter most likely resulted from ectopic germinal tissue, which we suggest is caused by abnormality of the surrounding midline mesenchyme. Putting all this information together, we postulate that these patients had diminished migration of mesenchyme to the midportion of the midline telencephalon, most likely as a result of slightly diminished or faulty mesenchymal production by the prechordal plate. The localized lack of mesenchyme results in disturbed development of the underlying brain with germinal matrix developing in the midline and the formation of a continuous cerebral hemisphere without an interhemispheric fissure (interhemispheric fusion). The localized lack of interhemispheric fissure and mesenchyme results in a localized lack of formation of the epithelial lamina, with subsequent absence of local choroid plexus development, lack of formation of the corresponding portion of the commissural plate, and lack of formation of a portion of the corpus callosum.

The presence of the anterior and posterior portions of the corpus callosum in the setting of absence of the callosal body in patient 3 raises questions concerning the proposed mechanisms of callosal formation. Previous authors (24, 40–42) have speculated that callosal formation results from the navigation of specialized pioneer axons through the developing hemispheres and commissural plate (43). Other axons are believed to follow surface markers on the surface of the pioneer axons by a process known as fasciculation (44, 45). An important concept of these theories is that the corpus callosum forms as a result of, and in continuity with, the previously formed adjacent portions. The findings in patient 3 suggest that, to the contrary, the formation of the corpus callosum may be related more to the formation of the interhemispheric fissure than to the presence of adjacent callosal bundles. Indeed, patient 3 and other cases we have examined (2, 46), suggest that a discrete callosal bundle will not form in the absence of a normal interhemispheric fissure containing normal mesenchyme. If the interhemispheric fissure contains abnormal mesenchyme that ultimately forms a lipoma, the corpus does not form in the area of the lipoma (46). Moreover, when the interhemispheric fissure and normal mesenchyme reappeared more posteriorly in patient 3, the discrete interhemispheric callosal bundle reappeared as well. Thus, it appears that the “guideposts” in the developing brain and interhemispheric fissure that interact with the growth cones and guide the pioneer callosal axons across the midline of the brain (43) are dependent upon the formation of an interhemispheric fissure and the normal mesenchyme within it. It is not clear whether transhemispheric association axons migrate across the midline to
their normal destinations on the contralateral side of the holoprosencephalic brain in the absence of a true corpus callosum. Tracer experiments using horseradish peroxidase in holoprosencephalic brains would be useful in answering this question. (When horseradish peroxidase is deposited upon the surface of the brain, it is absorbed into axons by pinocytosis. It then is transported via retrograde axonal transport to the cell body. It can, therefore, be used as a means to find the cell body from which an axon arises.)

To summarize, we describe imaging findings in three patients who have apparently normal anterior interhemispheric fissures in the rostral medial aspects of the cerebral hemispheres and interhemispheric fusion further posteriorly. Although these patients seem to be best classified as having holoprosencephaly, the pattern of fusion in their brains is clearly different from the patterns seen in all previously reported cases of holoprosencephaly, in which the rostral medial portions of the brain have been the most severely affected and the dorsal lateral portions the least affected. An embryologic explanation for this pattern of brain malformation is postulated in which the primary defect may be deficiency or dysplasia of mesenchyme.

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