MR Imaging of Schizencephaly

A. James Barkovich and David Norman

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MR Imaging of Schizencephaly

A. James Barkovich1,2
David Norman2

MR imaging was used to evaluate six patients who had schizencephaly, a disorder of cell migration characterized by holohemispheric, gray-matter-lined clefts. Clinically, these patients presented with intractable seizures and variable developmental delay. Although three of these patients had previous CT scans, the diagnosis was made only by MR. MR was more sensitive than CT in detecting the clefts as well as the accompanying abnormalities, including areas of pachgyria, polymicrogyria, and heterotopic gray matter. The possible pathogenesis of schizencephaly is discussed.

MR provides excellent demonstration of the anatomic changes in schizencephaly.

Schizencephaly is a congenital brain anomaly characterized by clefts spanning the cerebral hemispheres. This disorder has been detected in vivo by CT [1, 2] and sonography [3] and is well-characterized pathologically [4-6]. MR imaging is uniquely suited to the study of this anomaly because of its superior differentiation of gray and white matter and its high-resolution, multiplanar display of anatomy. In a review of 980 MR examinations of the brain, we identified six patients who had schizencephaly. Here, we discuss the characteristic clinical, pathologic, and radiographic features of schizencephaly, compare the efficacy of CT and MR in its detection, and relate the pathologic anatomy to proposed theories of pathogenesis.

Patients and Methods

The six patients in our study included five males and one female, ages 7 months, 12 months, 3 years, 17 years, 21 years, and 23 years, respectively (see Table 1). All patients had intractable seizures. Two of the patients (ages 3 years and 17 years) had hypoplastic optic nerves and hypothalamic dysfunction, and were diagnosed as having septooptic dysplasia. Three of the patients were included in a previous report dealing with migration anomalies [7].

Patients 3, 4, 5, and 6 were imaged on a 1.5-T General Electric Signa unit; patients 1 and 2 were examined on a 0.35-T Diasonics MT/S scanner. Slice thickness was 5 mm with a 2.5-mm interslice gap. Spin echo (SE) sequences with repetition/echo times (TR/TE) of 2000 msec/35 and 70 msec were obtained in the transverse plane. Sagittal SE 600/20 sequences were obtained in five patients and coronal (SE 600/20) images were acquired in three patients. All patients were imaged in a minimum of two orthogonal planes. Postcontrast CT scans using 10-mm sections were available on three of the six patients.

Pathologic confirmation was not possible. The diagnosis of schizencephaly was determined from the characteristic gross morphology of the affected brains, which has been established from pathologic and CT experience.

Results

Two patients (patients 5 and 6) had unilateral, vertically oriented clefts with fused lips; that is, in one spot the opposing walls touched across the cleft (Fig. 1). In both
TABLE 1: Summary of Patient Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Clinical Findings</th>
<th>Radiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 mo</td>
<td>M</td>
<td>Seizures; moderate developmental delay</td>
<td>Bilateral, narrow, horizontal frontal clefts; frontal pachygyria; polymicrogyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>along cleft; absent septum pellucidum</td>
</tr>
<tr>
<td>2</td>
<td>12 mo</td>
<td>M</td>
<td>Seizures; severe developmental delay</td>
<td>Large right cleft, separated lips; small left cleft, separated lips; polymicrogyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>along cleft; absent septum pellucidum</td>
</tr>
<tr>
<td>3</td>
<td>3 yr</td>
<td>M</td>
<td>Seizures; severe developmental delay; hypoplastic optic nerves; hypothalamic dysfunction</td>
<td>Large right cleft, separated lips; small left cleft, separated lips; polymicrogyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>along cleft; absent septum pellucidum</td>
</tr>
<tr>
<td>4</td>
<td>17 yr</td>
<td>M</td>
<td>Seizures; severe developmental delay; hypoplastic optic nerves; hypothalamic dysfunction</td>
<td>Large right cleft, separated lips; subependymal heterotopia; polymicrogyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>along cleft; absent septum pellucidum</td>
</tr>
<tr>
<td>5</td>
<td>21 yr</td>
<td>M</td>
<td>Seizures; normal development</td>
<td>Right unilateral cleft, fused lips; polymicrogyria along cleft; absent septum pellucidum</td>
</tr>
<tr>
<td>6</td>
<td>23 yr</td>
<td>F</td>
<td>Seizures; normal development</td>
<td>Left unilateral cleft, fused lips</td>
</tr>
</tbody>
</table>

Fig. 1.—Patient 5. Unilateral schizencephaly with fused lips.
A, Axial contrast-enhanced CT scan. Cortex is seen to extend down to lateral wall of the body of lateral ventricle (arrowheads). A true "cleft" is not appreciated. Septum pellucidum is absent, as it was in five of the six patients imaged in this study.
B, Axial SE 2000/35 MR image shows vertical holohemispheric cleft extending into lateral ventricle. Irregularity of gray matter lining cleft (arrowheads) suggests polymicrogyria and heterotopias, common findings along clefts in schizencephaly.
C, Coronal SE 2000/35 MR image through region of cleft reveals dimple along the ependymal wall and asymmetry of opercular gray matter; the cleft, however, is not appreciated. Clefts with fused lips were not seen in any patients when plane of image was parallel to cleft.

patients, the CT scans were interpreted prospectively as normal. In retrospect, one patient had what appeared to be an abnormally deep sulcus in the appropriate hemisphere, but the entire cleft and its communication with the lateral ventricle could not be appreciated (Fig. 1A). The CT scan (obtained with an EMI 1010 model scanner) in the other patient was normal on retrospective evaluation. The MR images of both these patients showed a cleft lined with gray matter extending from the cortex to the ipsilateral lateral ventricle (Fig. 1B). In both cases, a small dimple was seen in the lateral wall of the ventricle where the cleft communicated. The cortex within and adjacent to the cleft was irregularly thickened. Although coronal images obtained in one patient failed to show the cleft, an abnormal contour of the ventricular wall was apparent.

Patient 4 had a large unilateral cleft with unfused lips. In this patient, the CT scan showed the midportion of the cleft but failed to show communication of the cleft with the lateral ventricle medially and the subarachnoid space laterally; the continuity of the gray matter along the cleft was not initially recognized. The MR scan clearly showed communication with the lateral ventricle, gray matter lining the cleft, and thickened cortex adjacent to the cleft. Medially, there was a focus of subependymal heterotopic gray matter. These findings were not detected on retrospective review of the CT scan (Fig. 2).

The three youngest patients had bilateral nonfused clefts. In patient 1, the clefts were narrow and oriented horizontally.
Sagittal and coronal MR images showed gray matter lining the clefts; the clefts were not apparent in the axial images. The gray matter at the lateral margins of the clefts was thick and the gyri consequently enlarged. In patients 2 and 3, the clefts were wide on the right and vertical and narrow on the left. MR clearly showed gray-matter-lined clefts bilaterally with thickening and irregularity of the gray matter within the narrow clefts (Fig. 3). The latter three patients were not evaluated with CT.

Gyral anomalies were noted within and adjacent to the clefts in five of the six patients. In these cases, irregular thickening of the gray matter evident within the cleft was believed to represent foci of polymicrogyria [7]. Patients 2 and 6 had nodules of heterotopic gray matter adjacent to the clefts, deep to the gray matter lining the cleft (Fig. 1), and patients 4 and 5 had subependymal heterotopias lining a portion of the lateral ventricle (Fig. 2). Patient 1 had extensive areas of thickened cortex with large, broad gyri consistent with pachygyria in the frontal lobes. In the four patients who had clefts with separated (nonfused) lips, the septum pellucidum was completely absent. The most rostral 1 cm of the septum was present in one of the patients who had a small fused unilateral cleft, and the entire septum was present in the other. The corpus callosum, to which the septum pellucidum is attached superiorly, was fully formed in all patients, although there was some thinning of this commissure in the region of clefts, as previously reported [7]. The fornix, with which the septum pellucidum is continuous inferiorly, was present and appeared normal in all patients, although its position was low in those with absence of the septum.

Fig. 2.—Patient 4. Unilateral schizencephaly with separated lips.
A, Contrast-enhanced axial CT scan shows deep infolding of cortex in right frontal region, apparently pressing upon right lateral ventricle (arrowheads).
B, Coronal SE 600/20 MR image shows this infolding to be a large cleft in continuity with lateral ventricle. Continuity of gray matter through cleft is clearly shown (arrowheads) as is the focus of heterotopic gray matter along roof of right lateral ventricle (open arrow). Once again, there is absence of septum pellucidum. This patient also carries a diagnosis of septooptic dysplasia.

Fig. 3.—Patient 3. Bilateral schizencephaly with separated lips. Axial (A) and coronal (B) SE 600/20 MR images show a thick layer of gray matter within clefts (open arrows) and thickened, broad, flat gyri (arrowheads) adjacent to clefts, which presumably represent pachygyria or polymicrogyria. Notice in larger cleft that the arc of missing cortex is proportionally larger, which suggests that destruction of a portion of the subependymal germinal matrix is the origin of the cleft.
Discussion

The term schizencephaly refers to full-thickness clefts within the cerebral hemispheres. Pathologically, these clefts are characterized by an infolding of gray matter along the cleft from the cortex into the ventricles and a fusion of the cortical pia and ventricular ependyma within the cleft, the so-called pial-ependymal seam [4]. Gray-matter heterotopias and areas of polymicrogyria are frequently found within and near the cleft [4–6].

In their 1946 articles, in which they coined the term, Yakovlev and Wadsworth [4, 5] described a broad range of schizencephalies. In seven brain specimens, the clefts ranged from extremely narrow with actual fusion of the gray-matter-lined walls of the cleft (fused lips) to quite large with wide separation of the walls and absence of large portions of the involved hemispheres. The cases they classified as bilateral large clefts would today be classified as hydranencephaly. On the basis of this series of seven specimens, Yakovlev and Wadsworth defined schizencephaly as being characterized by bilateral clefts that are fairly symmetrical and that characteristically occur along the course of normal sulci.

Over the past 40 years, the understanding of schizencephaly has slowly evolved as advances in imaging techniques have resulted in a steady improvement in the in vivo evaluation of this anomaly. Holohemispheric clefts, both unilateral and bilateral, have been demonstrated in patients who have minimal symptoms [1], or no symptoms (personal communication, Dr. Steve Holmes). These patients may exhibit a broad range of neurologic disability, which is presumably related to the amount of brain tissue involved [1, 8]. Our data further support this concept. The two patients in our study who had unilateral clefts with fused lips were of normal intelligence. The patient with the large unilateral cleft had moderate developmental delay. The patients with bilateral clefts had severe developmental delay. All the patients, however, had seizure disorders that were refractory to medical therapy, and all had motor dysfunction, ranging from mild unilateral weakness in the patients who had unilateral, fused clefts to severe spastic diplegia in the patients who had bilateral clefts.

The pathogenesis of schizencephaly has not been firmly established. The fact that there is continuity of the gray matter through the cleft plus the high frequency of associated heterotopias and polymicrogyria led Yakovlev and Wadsworth [5] to classify schizencephaly as a dysgenetic (as opposed to encephaloclastic) process. It is known that schizencephaly and septo optic dysplasia frequently coexist [9] and that both are associated with absence of the septum pellucidum in 75–100% of patients [1, 2]. In view of these associations and the known embryologic facts discussed below, we propose that an ischemic episode occurring during the seventh week of gestation is the underlying cause of these anomalies. This proposal is a hypothesis based on review of previous discussions [9–14] and not based on the results presented in this paper.

In the normal embryo, beginning at the seventh week of gestation, neuroblasts are generated in the proliferative zones situated along the ventricular surface of the developing brain, the so-called germinal matrix. During the eighth week these primitive cells begin to migrate along radially oriented glial cells to predetermined, relatively distant final positions, forming the cerebral cortex (Figs. 4 and 5) [10]. Detailed anatomic evaluation of the cerebral vascular system in fetal life is not available; however, DeReuck and associates [11] and Takashima and Tanaka [12] have shown that in premature infants there are watershed zones between the ventriculofugal and ventriculopetal arteries in and around the walls of the lateral ventricles. Moreover, the ventriculofugal branches (leading from the ventricle toward the cortex) are not developed until the seventh month, suggesting that, before the third trimester, watershed zones are situated along the ventricular walls.

On the basis of these observations, we hypothesize that a gray-matter-lined cleft can develop secondary to an episode of hypotension, causing infarction of the watershed area—in this case, a focus of the germinal matrix in the wall of the lateral ventricle. The areas of polymicrogyria and heterotopias commonly seen surrounding the cleft could then be secondary to ischemic changes in the less severely affected surrounding areas of germinal matrix. The association of optic nerve hypoplasia with schizencephaly [9] could also be explained in this schema, since the retinal layers and optic nerve fibers also form during the seventh week of gestation.

Skarf and Hoyt [13] have presented clinical, experimental, and embryologic evidence that hypoplastic optic nerves result from an excessive degeneration of optic nerve axons and retinal ganglion cells during the development of the eye and visual pathway. A hypotensive episode during the seventh week of gestation, when the retinas and nerves are forming, could cause such a degeneration. The frequent absence of

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**Fig. 4.** Schematic drawing shows relationship of the germinal matrix in wall of lateral ventricle to the developing cortical plate. There is a one-to-one correspondence between the site of cell proliferation within the germinal zone and its eventual destination within the cortical plate. Corresponding regions are connected by radial glial cells that span entire thickness of hemisphere. Neurons migrate along these radial cells, eventually arriving at pre destined locations on the enlarged, convoluted cortical surface. If there is damage to a portion of the germinal matrix before migration begins, a cleft will necessarily result from the ventricle to the corresponding section of cortex. The larger the area of destruction in the germinal matrix, the proportionately larger the arc of missing cortex. (Adapted from [10]. Reprinted with permission from [7].)
Germinal the diagnosis of three cases of factor may be present. Further investigations in abnormalities mapping may analogous old genes for the optic nerves and septum destruction of the fiber (radial fiber).

Further definition of the basis, if one nerve is presumably lines migration at that point. Incomplete destruction of the germinal matrix cells will result in an abnormal migration of neuroblasts, this presumably is the cause of the abnormal cortex that lines and frequently surrounds the cleft. (Adapted from [10]. Reprinted with permission from [7].)

Fig. 5.—Illustration of relationship of migrating neurons to fibers of the radial glial cells. Migrating neuron is seen ascending the glial fiber (radial fiber) led by multiple pseudopodia. Any damage to radial glial fiber will presumably cause an arrest of cell migration at that point. Incomplete destruction of the germinal matrix cells will result in an abnormal migration of neuroblasts, this presumably is the cause of the abnormal cortex that lines and frequently surrounds the cleft. (Adapted from [10]. Reprinted with permission from [7].)

the septum pellucidum, in both schizencephaly and optic nerve hypoplasia [1, 2], can also be explained on an ischemic basis, if one postulates that the developing septum pellucidum is also a watershed area that is supplied by tenuous transcallosal branches of median artery of the corpus callosum, which Padget [14] has shown to be present in the 7-week-old embryo. This vascular supply in the embryo would be analogous to that in the adult whereby the septum pellucidum is supplied by transcallosal branches of the pericallosal artery. Further definition of the cerebral blood supply of the 7-week-old fetus is necessary if this theory is to be verified.

An alternative explanation may be offered as well. If the genes for the optic nerves and septum pellucidum lie near to one another and to the gene for the germinal matrix, a genetic factor may be present. Further investigations in chromosomal mapping may clarify this matter.

Our investigation showed that MR was superior to CT in the diagnosis of three cases of schizencephaly. The abnormalities were not detected in the three patients examined with CT. In one case, this might be attributed to suboptimal resolution of a first-generation scan; in the other cases, interpretation of the CT images was limited as a result of poor differentiation of gray and white matter, imaging in a single plane, and the use of a 10-mm slice thickness. Although the abnormality probably should have been recognized on CT in patient 5, the diagnosis was more obvious and more easily made on MR.

Identification of the gray-matter lining of the cleft is critical in differentiating schizencephaly from porencephaly. This differentiation may be important for genetic counseling, since the reported incidence of brain anomalies is 5–20% in subsequent siblings of children who have anomalies of cell migration [15, 16]. The improved differentiation of gray and white matter with MR also aids in the identification of associated anomalies. Pachygyria was well-demonstrated by MR in one of our patients. Pachygyria is sometimes difficult to diagnose by CT because of beam hardening by the overlying calvarium as well as the lower contrast resolution. Gray-matter heterotopias and foci of polymicrogyria were shown on MR in three patients, but not detected on CT.

All of the patients in our series had seizure disorders, and four of six were developmentally delayed. In addition to schizencephaly, seizure disorders in children and young adults can be caused by a variety of congenital and acquired disorders, including the other anomalies of cell migration, phakomatoses, vascular accidents, asphyxia, trauma, infections, degenerative disorders, metabolic derangements, and tumors [17]. MR has been shown to be efficacious in the evaluation of migration anomalies [7], tuberous sclerosis [18], trauma [19], and tumors [20, 21]. Moreover, assessment of brain myelination by MR imaging [22–24] promises to be useful in the assessment of developmentally delayed patients. In view of this increased sensitivity and specificity, we believe that MR imaging should be the primary method of screening children who have seizures or developmental delay. We recommend 5-mm thick (2.5-mm gap) SE 2500/35–70 images in both the axial and coronal planes as a screening exam for patients older than 18 months. In patients between 8 and 18 months of age, there is little contrast between gray and white matter on these sequences [24]. For optimal evaluation, therefore, we recommend imaging patients in this age group with an SE 600/20 sequence in at least one plane.

In summary, schizencephaly is probably more common and more frequently unilateral than it has been generally accepted. This anomaly presents with a variably severe clinical picture, depending on the amount of brain involved, but nearly all patients have intractable seizures. MR provides excellent demonstration of the anatomic changes in schizencephaly. Evidence is mounting that MR should be the imaging method of choice in the evaluation of patients who have seizures or developmental delay.

REFERENCES

2. Zimmerman RA, Bilaniuk LT, Grossman RI. Computed tomography in