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MR of Neuronal Migration Anomalies

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Migration anomalies are congenital malformations caused by insults to migrating neuroblasts during the third to fifth gestational months. Included in this group are agyria, pachygyria, polymicrogyria, unilateral megalencephaly, schizencephaly, and gray matter heterotopias. Patients who have these conditions present clinically with developmental delay and seizures, and abnormal motor skills are noted in the more severely affected infants. To determine the utility of MR as a method for imaging in these patients, we used MR to evaluate 13 patients who had the full spectrum of migration anomalies. MR was more sensitive than CT in detecting these anomalies because of its better contrast between gray and white matter. We found that MR was particularly more sensitive in detecting schizencephaly, where recognizing the presence of gray matter lining the cleft is critical to distinguishing that disease from porencephaly, and in detecting polymicrogyria, where critical details of cortical architecture are obscured on CT by the overlying bone. Multiplanar capabilities were also found to be essential, since narrow clefts may not be detected when the imaging plane is parallel to the cleft.

MR should be the primary imaging method for infants who have seizures or developmental delay.

Abnormalities of cell migration are characterized by ectopic location of neurons in the cerebral cortex. This broad group of anomalies includes agyria, pachygyria, polymicrogyria, schizencephaly, unilateral megalencephaly, and gray matter heterotopias. All these entities have been characterized pathologically and in vivo by sonography and CT. MR is an imaging technique uniquely suited to study these anomalies because of its exceptional differentiation between gray and white matter and its high-resolution multiplanar display of anatomy.

In a review of 537 MR studies in the pediatric age group, we identified 13 patients with migration anomalies. We review the salient features of these anomalies and their MR appearance. The relationship of the pathologic anatomy to theories of pathogenesis is emphasized.

Subjects and Methods

Thirteen patients with migration anomalies were scanned, including two with lissencephaly, four with schizencephaly, two with unilateral megalencephaly, two with isolated polymicrogyria, and three with isolated gray matter heterotopias. The four patients with schizencephaly also had foci of polymicrogyria. One of the patients with unilateral megalencephaly had foci of ectopic gray matter. The patients' ages ranged from 4 months to 21 years, with a mean of 6.6 years and a median age of 3.5 years. The mean age is skewed by two patients with schizencephaly who were 17 and 21 years old. The patients were referred for imaging because of seizures, mental retardation, developmental delay, or enlarging head size (see Table 1).

Ten patients were examined on a 1.5-T GE Signa unit. Three patients 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) images were obtained with a TR of 2000 msec and TE of 35–40 msec and 70–80 msec in the transverse and coronal planes and a TR of 600 msec and TE of 25 msec

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TABLE 1: Summary of Patient Data

Patient	Age	Presenting Symptoms[a]	MR Diagnosis
1	4 mo	S	Lissencephaly
2	4 y	S, DD	Lissencephaly
3	8 y	DD	Polymicrogyria
4	2 y	S, DD	Polymicrogyria
5	12 mo	S, DD	Schizencephaly (bilateral vertical clefts: one narrow, one wide); polymicrogyria in and adjacent to clefts
6	7 mo	S, DD	Schizencephaly (bilateral horizontal clefts: both narrow); polymicrogyria and pachygyria in adjacent brain
7	17 y	S, DD	Schizencephaly (unilateral horizontal wide cleft); polymicrogyria in and adjacent to cleft; ectopic gray matter
8	21 y	S	Schizencephaly (unilateral vertical cleft with fused lips)
9	2 y	S, DD, H	Unilateral megalencephaly
10	8 y	S, DD	Unilateral megalencephaly
11	7 y	S	Heterotopic gray matter
12	2 y	S	Heterotopic gray matter
13	3 y	S	Heterotopic gray matter

[a] Abbreviations: S = seizures; DD = developmental delay; H = hemiplegia.

in the axial, coronal, or sagittal plane, as indicated. The results of these studies are included in the Discussion section.

Pathologic confirmation was not obtained. Migration anomalies were diagnosed from the characteristic gross morphology of the affected brains, which has been established from pathologic and CT experience.

Discussion

The phenomenon of neuronal migration has been known since the turn of the century [1]. The neurons that constitute the mammalian brain are generated in proliferative zones situated along the ventricular surface of the developing brain [1–4]. At the end of the second gestational month, the neurons migrate from their site of origin along radially aligned glial cells to relatively distant final positions [3, 4] (Figs. 1 and 2). At this point they differentiate further, grow axons and dendrites, and develop synaptic contacts with other neurons [4].

The final position of the neurons within the cortex varies inversely with the time of cell origin. Those cells generated earlier migrate to the deeper cortical layers relatively quickly (3–4 days). The cells generated later end their migration in the more superficial cortex; this migration takes place over several weeks. The major cell migration activity lasts about 2 months, beginning in the eighth fetal week and ending at about week 16 [4, 5]. Smaller waves of cell migration continue up to week 25. Any insult to the brain during this period results in a migration anomaly.

The normal human cerebral cortex is six-layered, the sizes of the layers varying with the location. There is a marginal layer (I), external granular layer (II), external pyramidal layer (III), internal granular layer (IV), internal pyramidal layer (V), and fusiform layer (VI) (Fig. 3). The common underlying feature

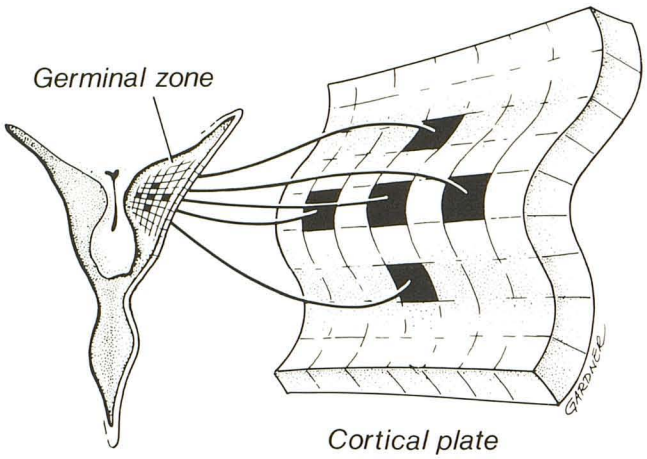


Fig. 1.—Schematic drawing shows relationship of the germinal matrix in wall of lateral ventricle to the developing cortical plate. There is a one-to-one correspondence between the site of cell proliferation within the germinal zone and its eventual destination within the cortical plate. Corresponding regions are connected by radial glial cells that span entire thickness of hemisphere. Neurons migrate along these radial cells, eventually arriving at predestined locations on the enlarged, convoluted cortical surface. (Adapted from [4].)

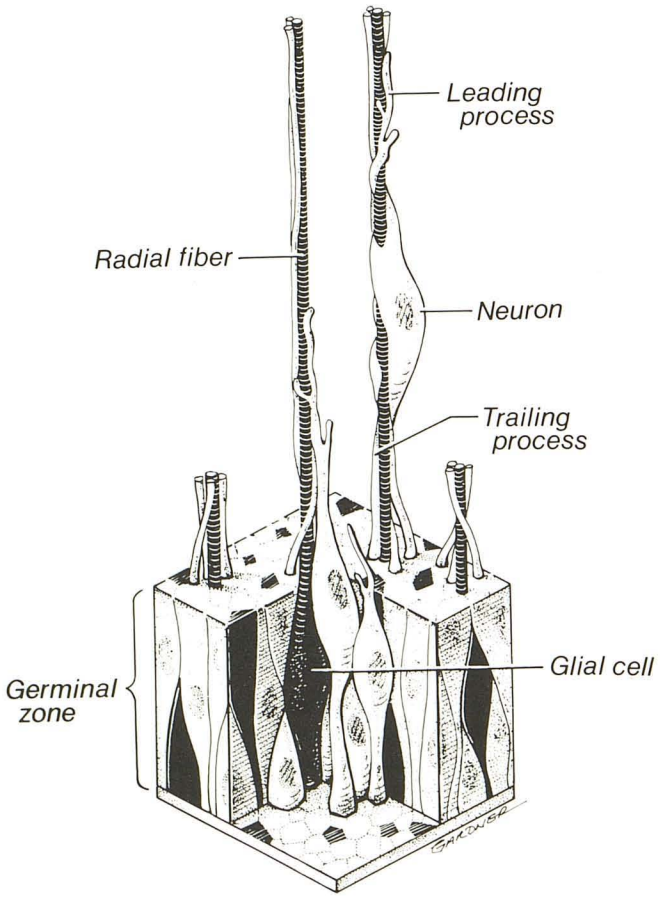


Fig. 2.—Illustration of relationship of migrating neurons to fibers of the radial glial cells. Migrating neuron is seen ascending the glial fiber (radial fiber) led by multiple pseudopodia. Any damage to radial glial fiber will presumably cause an arrest of cell migration at that point. (Adapted from [4].)

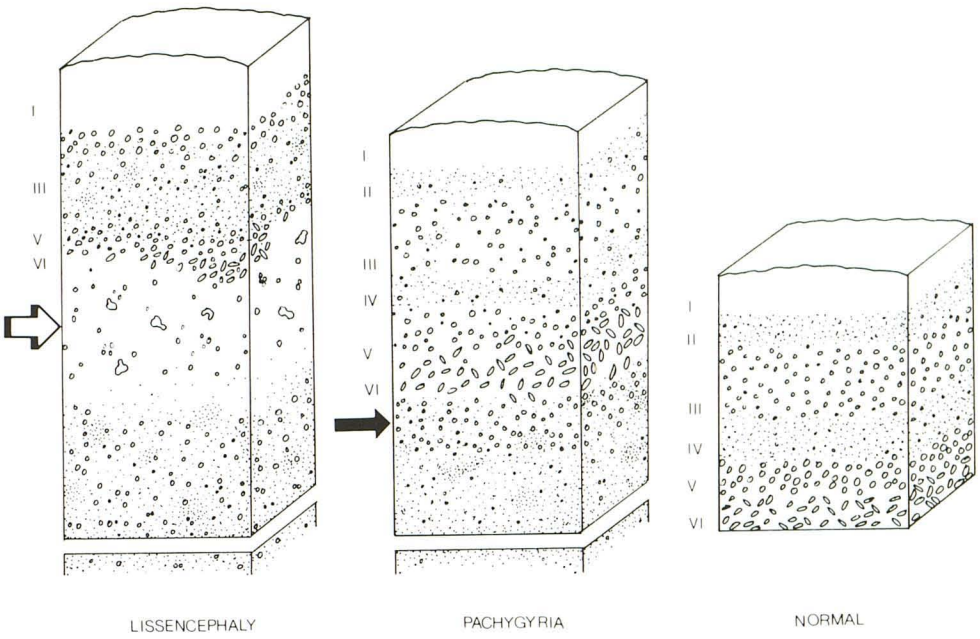


Fig. 3.—Cortical architecture in agyric (labeled lissencephaly) and pachygyric regions of brain as compared with normal cortical architecture. In agyric cortex there is a large cell-sparse layer (*open arrow*) that separates a disorganized cortex (outer cellular layer) from a thick layer of ectopic neurons located medially. Pachygyric cortex is more organized into normal cortical layers and cell-sparse layer (*closed arrow*) is thinner and populated by more cells. In general, there is a thinner layer of heterotopic neurons in the pachygyric cortex. (Adapted from [11].)

of the migration anomalies is an abnormal location of neurons both within and outside of the cortex. In general the cortex is thickened by a large, disorganized layer of neurons whose migration has been prematurely halted. The subcortical layer of white matter is thinned because organization of the neurons, which subsequently stimulates axonal growth, has not occurred [1–4].

It was generally believed that migration anomalies were sporadic events that occurred secondary to environmental insults during the first two trimesters. There is now increasing evidence of a genetic transmission or at least a genetic susceptibility to many of these anomalies [5–10]. Thus, the expression of an insult (vascular, infectious, teratogenic, etc.) is influenced both by the stage of brain development and the underlying genetic susceptibility of the fetus.

Agyria/Pachygyria (Lissencephaly)

The term agyria refers to an absence of cortical gyri. In fact, most "agyric" brains have at least small areas of gyral formation [1, 2]. These areas of broad, flat, shallow gyri are referred to as areas of pachygyria. The term lissencephaly ("smooth brain") is sometimes used as a synonym for agyria and at other times as a more general term encompassing the agyria/pachygyria complex. We shall use the term in the latter sense.

Pathologically, both agyric and pachygyric regions of brain have a so-called four-layered cortex, composed of a molecular layer, an outer cellular layer, a cell-sparse layer, and an inner cellular layer. The cell-sparse zone is believed to be an area of laminar necrosis occurring secondary to metabolic insult of the brain during the period of neuronal migration. Neuronal migration through this region is thereafter impaired; moreover, degeneration occurs in neurons that have already migrated but have their axonal and dendritic connections interrupted within the layer of necrosis [11]. The cortex remains thick because it encompasses the radial columns of migrating cells that are arrested in mid-migration. The subcortical white matter is thin because the organization phase during which axonal and dendritic connections are established is markedly diminished (Fig. 4).

Dobyns and associates [9, 10, 12] have recently described this entity as a series of "syndromes with lissencephaly." They describe three separate classes based on gross pathologic features that they attempt to correlate with specific clinical syndromes. The clinical and CT findings in these classes have been thoroughly discussed [9, 10, 12]. Van Allen and Clarren [13] and Alvarez et al. [14] have disputed these classifications, demonstrating similar clinical manifestations in children whose brains had quite dissimilar gross morphology, although all the brains were within the lissencephaly spectrum. Moreover, Alvarez has suggested that the clinical syndrome may be related more to cytoarchitectonic abnormalities of the brainstem than to cortical anomalies [14]. It is clear that the understanding of these anomalies is at a very early stage.

In the case that we imaged, MR exquisitely demonstrated the abnormal cytoarchitecture. The normal ratio of gray to white matter is reversed (Fig. 5). Within the thickened cortex can be seen a circumferential band of high intensity on the T2-weighted images, which is thicker and more prominent in the parietooccipital region. This is believed to represent the cell-sparse layer that is known to have diminished numbers of neurons and myelinated fibers and increased glial tissue [11, 15, 16], and presumably therefore it has an increased water content. The gray and white matter are otherwise of normal intensity. Coronal images show the temporal lobes to be less affected, as is commonly seen pathologically. In the sagittal plane, a small brainstem is seen, reflecting the lack of development of the corticospinal tracts.

The pattern of brain involvement with the more severely

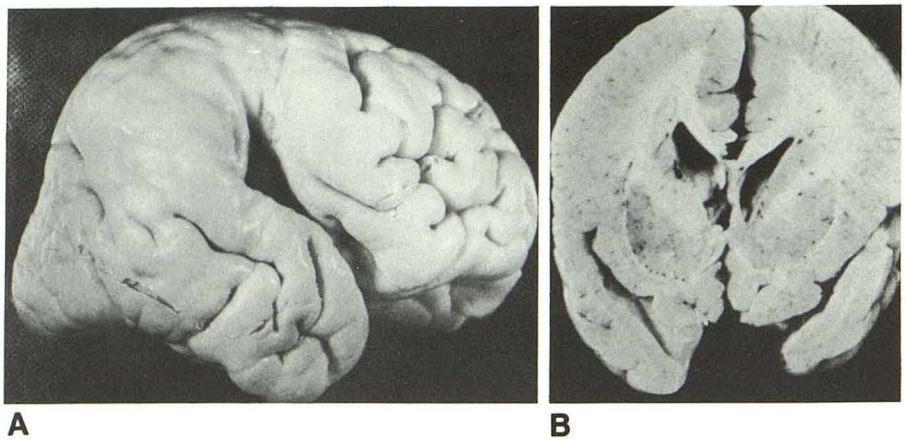


Fig. 4.—Lateral view (*A*) and coronal section (*B*) demonstrate characteristic features of lissencephaly. There is pachygyria in frontal and temporal regions with an agyric cortex in posterior temporoparietal watershed area. This distribution suggests a vascular component in the etiology of the malformation. There is thickening of the cortex due to arrested neuronal migration with corresponding reduction of white matter. (Reprinted with permission from [2].)

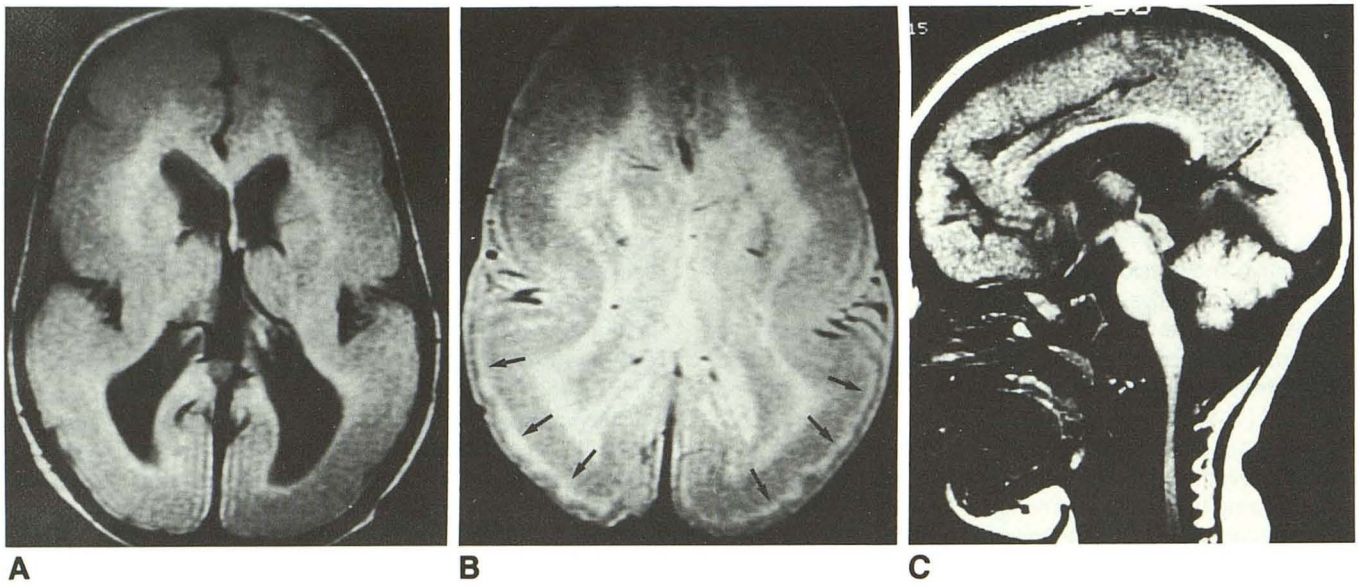


Fig. 5.—Patient 1. *A*, SE 2000/35. Axial image demonstrates thickening of gray matter and thinning of white matter in this patient who has lissencephaly. There is pachygyria in frontal lobes with agyria in temporoparietooccipital region that suggests a vascular etiology as explained in the text.

***B*, SE 2000/70. Axial image again demonstrates a thickened cortex. An irregular rim of high intensity in outer cortex (*arrows*) probably represents an area of laminar necrosis, the cell-sparse layer.**

***C*, SE 600/25. Sagittal image shows a thin corpus callosum and narrow brainstem. These are secondary to a lack of development of association and corticospinal tracts.**

affected (agyric) regions in the posterior parietal watershed area and the less severely affected pachygyric regions more frontally would seem to support the hypothesis by Stewart et al. [11] of a vascular component in the etiology of our particular cases of lissencephaly. Stewart theorizes that the cell-sparse layer is a region of laminar necrosis impeding the migration of neuroblasts. In the watershed area, the ischemia and therefore the area of laminar necrosis is most severe, hence the barrier to migration is most severe. Indeed, we saw increased thickness of the cell-sparse layer in this region on MR. In view of this evidence and the strong evidence for genetic etiologic factors as well [7–10, 12], it is likely that a complex combination of genetic susceptibility and in utero insult is involved in the development of this entity.

Polymicrogyria

Polymicrogyria (PMG) is an anomaly characterized by excessive cerebral convolutions, increased cortical thickness, and abnormal cortical histology. It is a relatively common malformation, reported in one study [17] in 5% of 500 consecutive autopsies of patients that had mental deficiencies. It is frequently found at autopsy in patients with other congenital cerebral anomalies such as schizencephaly or the Chiari II malformation. The location is commonly in the insular area, invoking the possibility of a vascular etiology [18].

Histologically, one sees a four-layered cortex composed of a marginal layer, an outer cellular layer, a cell-sparse layer, and an inner cellular layer. The outer cellular layer is laminated

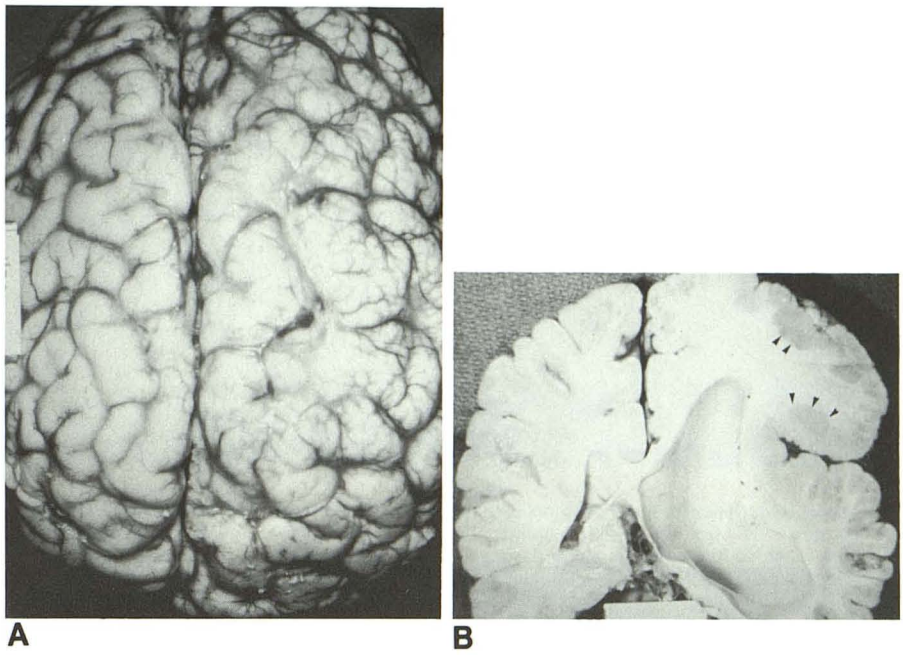


Fig. 6.—Superior view (*A*) and coronal section (*B*) demonstrate polymicrogyria in a patient who has unilateral megalencephaly. There are an increased number of closely set, miniature, shallow gyri over the cortical surface. In some places, because of fusion of adjacent gyri, sulci are shallow or absent and cortical surface becomes paradoxically smooth.

***B*, Cut section reveals a thickened cortex with a flattened inner cortical border (*arrowheads*). Also notice marked overgrowth of left hemisphere with enlargement of ipsilateral lateral ventricle. These findings are characteristic of unilateral megalencephaly. (Courtesy of Dr. Richard Davis, Neuropathology Section, University of California, San Francisco.)**

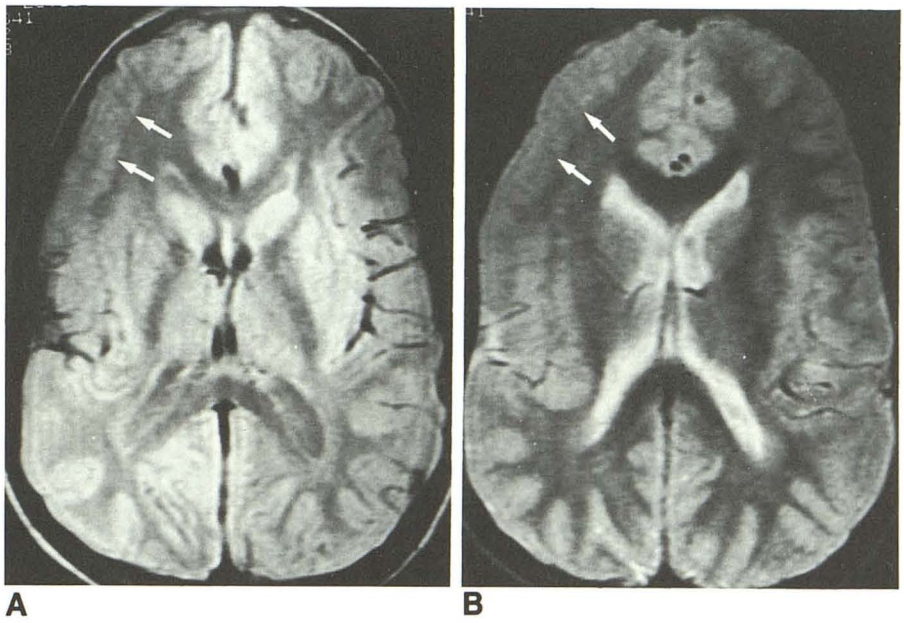
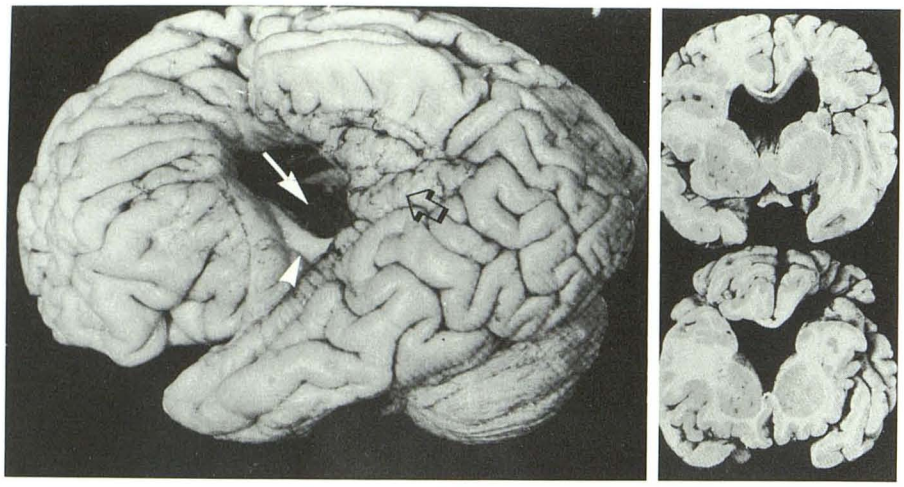


Fig. 7.—Patient 3. *A*, SE 2000/35 and *B*, SE 2000/70. Axial images reveal thickening of right posterior frontal cortex (*arrows*). No gyri are seen in this region; instead, there is a paradoxically smooth cortex as was seen in all cases of polymicrogyria. Normal fingerlike extensions of white matter (compare the left side) are absent.

with sublayers corresponding to and contiguous with layers II, III, and IV of the normal cortex, while the inner cellular layer is contiguous with and architecturally similar to layer VI. It is uncertain whether the insult causing the laminar necrosis of layer V occurs during or after the completion of cell migration [18, 19]. In either event, the resulting gross pathologic picture is of multiple small, shallow convolutions on the brain surface. In the topographic center of the lesion, the convolutional folding of the deep cortical layers are often so exaggerated that the surface of the brain becomes paradoxically smooth [18] (Fig. 6).

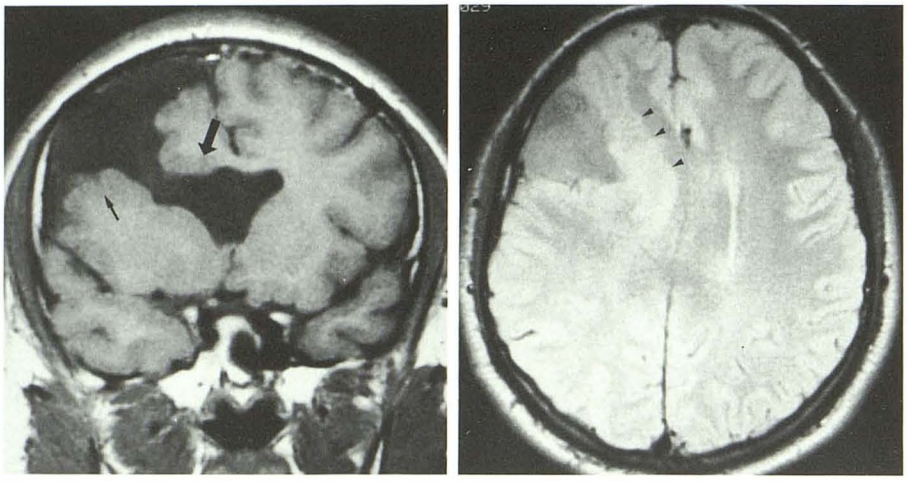
CT findings of PMG have not been described, possibly because the overlying calvarium causes beam hardening that makes detailed evaluation of the cortex difficult. Moreover, pathologic proof is difficult to obtain and the CT appearance is not so distinctive as, for example, schizencephaly, to allow confident diagnosis on the CT findings alone. In our cases, although not pathologically proved, we saw many of the gross pathologic characteristics of PMG (Fig. 7), which included a thickening of the cortex with absence of detectable gyri within the region. Moreover, the underlying white matter appeared somewhat diminished, and we saw characteristic involvement



A B

Fig. 8.—Schizencephaly. *A*, Holohemispheric cleft can be seen in left cerebral hemisphere. Cleft has choroid plexus in its floor (*closed arrow*) and ependyma lining the wall (*arrowhead*). There is surrounding polymicrogyria (*open arrow*).

B, Coronal sections show bilateral clefts lined by gray matter. Septum pellucidum is absent. (Reprinted with permission from [2].)



A B

Fig. 9.—Patient 8. *A*, Coronal SE 600/20 and *B*, axial SE 2000/35 images reveal a large unilateral holohemispheric cleft lined by cortex. Cortex is thickened along cleft (*arrowheads*) and adjacent gyri are abnormal (*small arrow*). Ectopic gray matter lines frontal horn (*large arrow*). This patient was 17 years old when scanned, presenting with mild developmental delay and seizures.

of the opercular region [18]. The fact that no zone of long T2 is seen corresponding to a cell-sparse layer may be explained by the fact that this layer is smaller and less "sparse" in PMG than in the agyric cortex; more neurons and axons are present, and therefore little change in signal intensity would be expected.

In three of our cases, the PMG was associated with schizencephaly. In these patients, PMG was manifested as areas of abnormal gyri and thickened cortex lining the hemispheric clefts and in the cortex immediately adjacent to the clefts. In two patients, the PMG was isolated; the posterior frontal region was involved in one and the posterior temporal region in the other.

Schizencephaly

The term schizencephaly was introduced by Yakovlev and Wadsworth [20, 21] in 1946 to describe bilateral, nearly symmetrical, full-thickness clefts within the cerebral hemispheres. Pathologically, these clefts are characterized by an infolding of cortical gray matter along the cleft (Fig. 8) with a fusion of the pial lining of the brain and the ependyma of the ventricle forming a characteristic "pial-ependymal seam." Moreover, gray matter heterotopias and areas of polymicrogyria are found within and near the cleft. The lips of the defects may be separated or fused.

The most widely accepted theory for the pathogenesis of this anomaly is that a segmental failure occurs in the formation of a portion of the germinal matrix or in the migration of the primitive neuroblasts contained therein [20, 22, 23]. Alternative theories include (1) destruction of the previously formed hemisphere sometime before the sixth gestational month [24] and (2) a spectrum of encephaloclastic disorders, ranging from hydranencephaly to porencephaly to schizencephaly [25–27].

Clinically, the patients demonstrate a broad range of neurologic disability that may be related to the amount of brain tissue involved [23, 28]. Clinical features include microce-

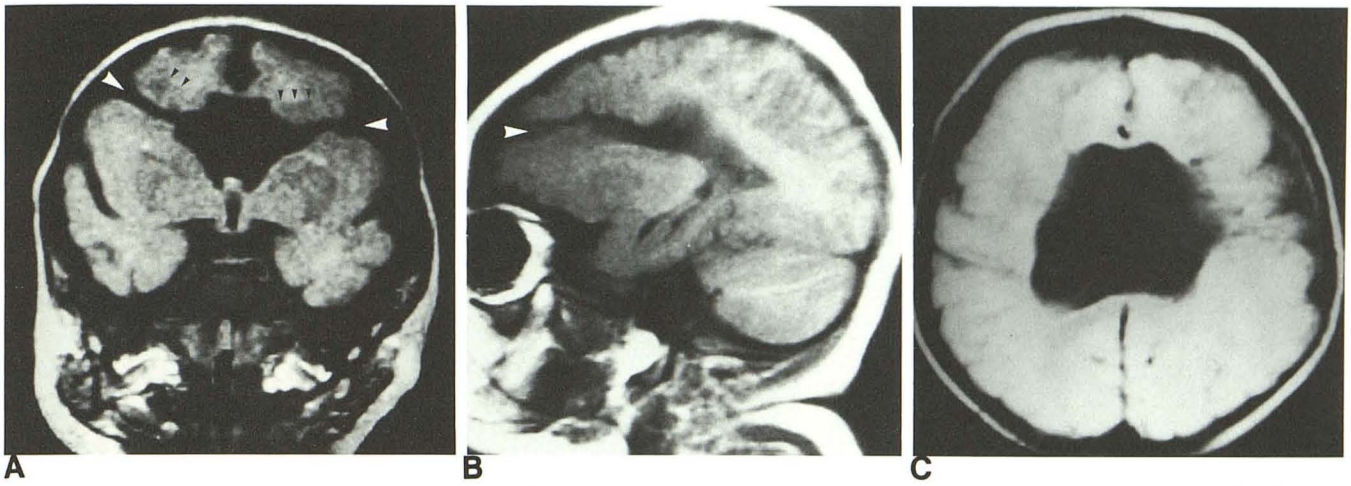


Fig. 10.—Patient 6. *A*, Coronal SE 1500/40, *B*, sagittal SE 500/30, and *C*, axial SE 2000/30 images demonstrate bilateral, cortex-lined holohemispheric clefts (*white arrowheads*) diagnostic of schizencephaly. Cortex is thickened within clefts (*A*, *black arrowheads*), compatible with polymicrogyria that is usually seen within and near the clefts pathologically. Septum pellucidum is absent, a frequent finding in schizencephaly. Significantly, the narrow, horizontally oriented clefts are not seen on axial image (*C*). These images emphasize that imaging in at least two planes is necessary for proper evaluation of congenital anomalies.

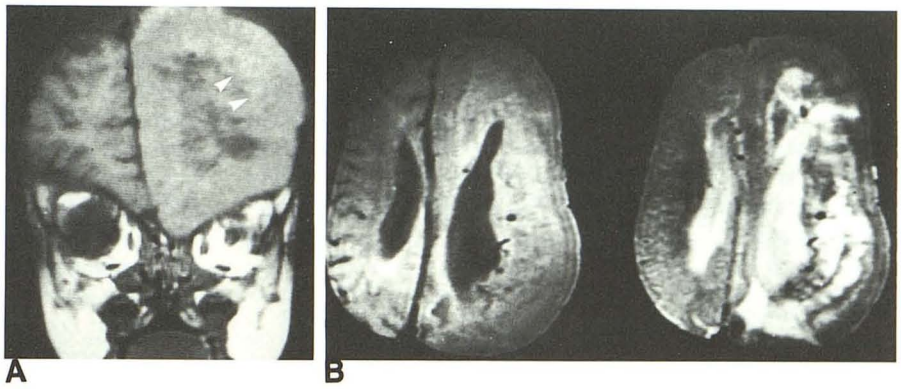


Fig. 11.—Patient 9. *A*, Coronal SE 600/25 and *B*, axial SE 2000/35-70. There is marked overgrowth of left hemisphere with shift of interhemispheric fissure, falx, and superior sagittal sinus to the right. Cortex is markedly thickened (*arrowheads*). White matter is of abnormally low intensity on T1-weighted image (*A*) and high intensity on T2-weighted image (*B*), suggesting decreased myelination and increased water content. *B* shows enlargement of ipsilateral lateral ventricle, characteristic of this anomaly.

phaly, retardation, abnormal motor function, and seizures. Miller et al. [23] report three patients with schizencephaly who have survived into their twenties and thirties, demonstrating only mild neurologic deficits. Both of our patients with unilateral clefts presented near the end of their second decade with mild clinical symptoms, one with seizures and the other with seizures and mild retardation, further supporting this observation. Both patients with bilateral clefts presented in their first year of life with severe developmental delay and seizures.

Our cases of schizencephaly have in common holohemispheric clefts in the region of the pre- and postcentral gyri, which are characteristic of both the pathologic and CT appearance of this entity. Moreover, the finding of continuity of the gray matter from the cortex through the cleft to the subependymal region of the lateral ventricle is clearly shown (Fig. 9). The abnormal gyral pattern surrounding the clefts is consistent with the known pathologic finding of PMG in this region [21]. These findings are crucial in differentiating schizencephaly from porencephaly and other destructive anomalies. This differentiation is of practical importance in terms of genetic counseling, since when a child has a disorder of cell migration 5–20% of subsequent siblings may have brain anomalies [9, 10, 23]. Although there continues to be debate in the literature as to the existence of unilateral schizencephaly [26], our cases clearly show continuity of the gray matter through the cleft into the ventricle. The fact that Yakovlev's initial description included only bilateral cases, therefore, does not exclude unilateral cases from the category but most probably reflects the small size of his original sample. Perhaps the relatively mild symptomatology of the unilateral variant has kept most of these cases from the pathologist's table. If these clefts are indeed due to focal destruction of the germinal matrix, unilateral clefts should be as common or more common than bilateral clefts, and the multiplanar imaging capability and gray/white contrast resolution of MR should allow more unilateral clefts to be found.

The fact that the narrow clefts are identified in only one imaging plane and missed in another is important. These lesions will be overlooked in a significant number of cases if

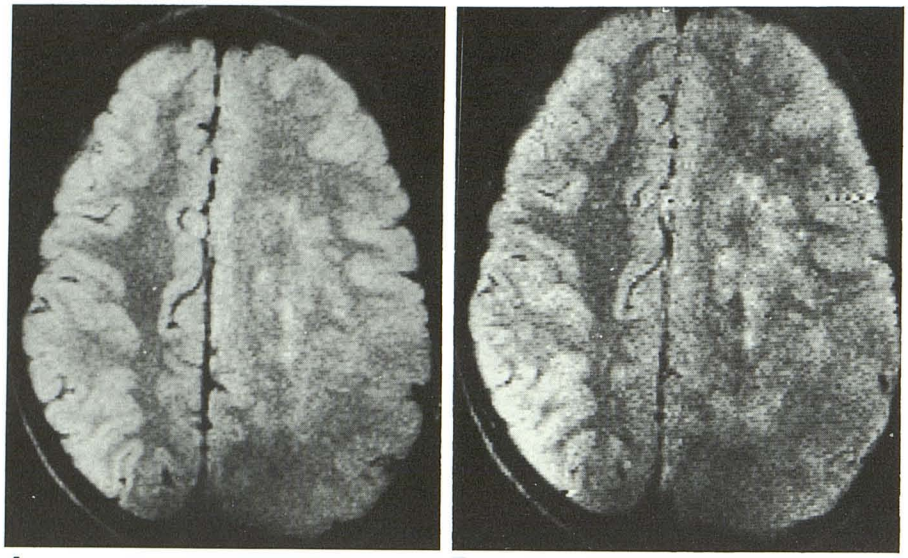


Fig. 12.—Patient 11. Axial SE 2000/30-60 images reveal foci that are isointense with gray matter lying within centrum semiovale. This is characteristic of ectopic gray matter—collections of neurons that have been arrested during migration through the cortex.

imaging is performed in only one plane. In our patient who had bilateral narrow clefts with a horizontal orientation, the abnormality would have been missed entirely or misdiagnosed had the coronal sequences not been obtained (Fig. 10). Similarly, the vertically oriented narrow clefts in the left hemispheres of our first and fourth patients would have been missed had only coronal images been obtained. We believe that imaging of the pediatric patient with early onset of seizures and developmental delay should be performed using 5-mm slice thickness in at least two planes in order to avert such mistakes.

Unilateral Megalencephaly

Unilateral megalencephaly is a rare anomaly of the brain characterized by the early onset of intractable seizures, hemiplegia, and severe developmental delay. There is marked overgrowth of part or all of a cerebral hemisphere with defects in cell migration in the affected areas. The severity ranges from mild lobar enlargement to marked enlargement and architectural distortion of the entire cerebral and cerebellar hemispheres and the ipsilateral brainstem. This anomaly is not associated with corporal hemihypertrophy [29, 30].

Pathologically, severe cases of this anomaly demonstrate areas of lissencephaly and polymicrogyria with a thickened cortex and disorganization of cortical layers without alignment into distinct laminae. Ectopic gray matter is scattered throughout the hemisphere. Mild cases are more focal, often roughly lobar in distribution. Sulcal enlargement is seen and there are foci of PMG (see Fig. 6). Microscopically, in mild cases the architectural distortion of the cortex is less severe and the deeper cortical layers are more severely affected [31].

The MR findings in this anomaly are quite characteristic (Fig. 11). Although enlargement of all or part of a hemisphere can be seen associated with corporal hemihypertrophy or a hemispheric mass lesion, only unilateral megalencephaly is associated with a distorted, thickened cortex and ipsilateral ventricular dilation. The long T1 and long T2 of the ipsilateral centrum semiovale have been noted to correlate with the low density seen in this region on CT, probably representing decreased myelination and increased water content as compared with normal white matter. The perimeter of high-signal intensity in the deep cortex on the T2-weighted images in our first case corresponds with a similar rim of high intensity in our case of lissencephaly, which represents, we believe, gliosis in the cell-sparse layer. Our second case of unilateral megalencephaly, which was less severe and more localized to the temporal lobe, did not show this perimeter of high intensity, perhaps reflecting a less severe anomaly of migration, as in our case of PMG. Moreover, the less extensive case showed less cortical thickening, a more distinct corticomedullary junction, and more distinct foci of heterotopic gray matter in the centrum semiovale.

The recommended therapy for unilateral megalencephaly is surgical resection of the involved lobe or hemisphere [32]. The increased sensitivity of MR in localizing the involved segments should prove quite valuable for surgical planning so that as much viable brain as possible can be preserved.

Heterotopic Gray Matter

Heterotopic gray matter consists of collections of neurons in abnormal locations, which are thought to result from arrest of radial migration of the neuroblasts. Although it is not uncommon to see ectopic single neurons in newborn infants, these aberrations usually disappear within the first few months of life either by regression or by completion of their migration, and they are not considered true heterotopias. True heterotopic nodules vary widely in size and location, appearing anywhere from the subependymal zone to the cortex [1]. They may be isolated anomalies or may be associated with other CNS derangements such as the Chiari II

malformation or PMG. The major clinical symptom is seizures.

The key to recognizing heterotopias is in the use of imaging sequences in which the signal intensity of gray matter is distinct from that of white matter, and section thickness is 5 mm to minimize partial-volume effects. With these parameters, even small heterotopias are easily recognized as foci isointense with gray matter but positioned in the corona radiata or subependymal region (Fig. 12). They are much more readily identified on MR than on CT. The increased sensitivity with MR should enable us to arrive at improved clinical correlation with clinical defects and heterotopias.

Summary

The anomalies of cell migration are readily identified with MR, which is in general more sensitive and more specific than CT. Recognition depends on awareness of the characteristic appearance of the entities and use of the proper imaging technique. Images should be obtained in at least two planes, using a 5-mm slice thickness and both T1- and T2-weighted imaging sequences. The degree to which migration has been impaired is related to the thickness of the cell-sparse layer, which may be visualized on T2-weighted images. Recognition is important for planning proper treatment and for genetic counseling.

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