

Are your **MRI contrast agents** cost-effective?

Learn more about generic **Gadolinium-Based Contrast Agents**.



FRESENIUS  
KABI

caring for life

**AJNR**

**Schizencephaly: correlation of clinical findings with MR characteristics.**

A J Barkovich and B O Kjos

*AJNR Am J Neuroradiol* 1992, 13 (1) 85-94

<http://www.ajnr.org/content/13/1/85>

This information is current as of April 19, 2024.

# Schizencephaly: Correlation of Clinical Findings with MR Characteristics

A. James Barkovich<sup>1</sup> and Bent O. Kjos<sup>2</sup>

**Purpose:** To correlate clinical outcome with the size and location of clefts in patients with schizencephaly. **Patients and Methods:** MR scans and clinical records of 20 patients with schizencephaly were retrospectively reviewed. Seven patients had bilateral clefts (10 open lip clefts, 4 closed lip clefts), eight patients had right-sided unilateral clefts (5 open lip clefts, 3 closed lip clefts), and five patients had left-sided unilateral clefts (3 open lip clefts, 2 closed lip clefts). **Results:** Statistically significant correlations were found as follows: Patients with bilateral schizencephalies had significantly worse intellectual ( $P = .004$ ) and speech ( $P = .03$ ) development than those with unilateral clefts; patients with unilateral large or medium open lip schizencephalies had significantly worse motor ( $P = .003$ ) and intellectual ( $P = .008$ ) impairment than those with unilateral closed lip or small open-lip schizencephalies; patients with frontal lobe involvement had a significantly higher incidence of motor dysfunction than those without frontal lobe involvement ( $P = .01$ ). Strong similarities were noted in the patient outcomes and the locations of cortical anomalies of patients with schizencephaly and those with nonschizencephaly focal cortical dysplasias. **Conclusion:** A common pathogenetic origin for the formation of focal cortical dysplasia in the form of polymicrogyria and schizencephalies is proposed. Patients with small unilateral schizencephalies have a good developmental prognosis, particularly when the motor cortex is not involved.

**Index terms:** Migration anomalies; Magnetic resonance in infants and children

AJNR 13:85-94, January/February 1992

Until relatively recently, schizencephaly was thought to be an extremely rare developmental disorder, seen primarily in institutionalized patients with severe motor and intellectual disabilities. The rapid improvement of computed tomography (CT) and magnetic resonance (MR) imaging and an enhanced awareness of the disorder have resulted in an increasing recognition thereof. The increasing number of patients being diagnosed with schizencephaly has revealed a paucity of information concerning their anticipated motor, intellectual, and neurologic deficits. The purpose of this study was to correlate clinical data with anatomic data as assessed by MR in an attempt to find those MR characteristics that are most useful in predicting clinical course.

## Patients and Methods

MR scans and clinical records of 20 patients with schizencephaly were retrospectively reviewed. Patients ranged in age from 3 months to 23 years old at the time of their scan (mean age was 11 years old, median age was 3 years old). Seventeen patients were male and three were female. Patients 3, 6, 12, 18, and 20 have been reported previously (1). Patient charts were reviewed with specific attention to the following: presence or absence of seizures and type of seizures; presence or absence of motor deficits, type of motor deficit (spastic vs flaccid), and areas of body involved (quadripareisis vs hemipareisis vs monopareisis); developmental level (percent of developmental age as determined by the Denver Developmental Screening Test) in younger patients; intelligence quotient in older patients; and level of speech development. MRs were evaluated with special attention to the location, size, and characteristics of the cleft and for the presence or absence of associated anomalies. Lobar involvement (location) was assessed by examination of a combination of sagittal, axial, and coronal images, with the sagittal images usually being the most useful. Schizencephalic clefts were classified as closed lip schizencephaly if the gray matter-lined walls of the cleft were in apposition at one or more points on images in more than one plane. In open lip schizencephaly, cerebrospinal fluid (CSF) could be seen between the gray matter-

---

Received May 2, 1991; revision requested June 11; revision received June 24, final acceptance June 28.

<sup>1</sup> Department of Radiology, Neuroradiology Section L371, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143-0628. Address reprint requests to A. J. Barkovich.

<sup>2</sup> Department of Radiology, Swedish Hospital, Seattle, WA 98116.

AJNR 13: 85-94, Jan/Feb 1992 0195-6108/92/1301-0085

© American Society of Neuroradiology

lined walls through the entire length of the cleft. Open lip schizencephalies were judged as large if they occupied more than two-thirds of a lobe or involved more than one lobe, medium if they occupied more than one-third but less than two-thirds of a single lobe, and small if they occupied less than one-third of a single lobe. Closed lip schizencephalies were, by definition, small.

Films were reviewed separately by the authors without knowledge of detailed clinical history. Clinical data were then obtained for each patient. The imaging data was not known by the clinician at the time of their initial examination.

Sixteen patients were imaged at 1.5 T. Sagittal 3–5 mm (0.5–1.0 mm “gap”) spin echo (SE) 400–600/11–20/2 (TR/TE/excitations) and axial 5 mm (2.5 mm “gap”) SE 2500–3000/30–60, 80–120 images were obtained using a 128, 192, or 256 × 256 matrix in all patients scanned at 1.5 T. Coronal 5 mm SE 600–800/20 images were obtained in 15 patients. Coronal 5 mm SE 2800/30, 80 were obtained in one. Two patients were imaged at 0.35 T and two at 0.5 T, using a variety of T1- and T2-weighted pulse sequences. Sagittal, coronal, and axial images, with slice thickness varying from 5 to 10 mm were obtained in these examinations.

Statistical analyses were performed using the Fisher exact test (2). Abnormalities or retardation of development, motor function, and speech were correlated with the extent of cortical involvement (bilateral vs unilateral), location (left hemisphere, right hemisphere, individual lobes), size of involved area, presence of open lip versus closed lip clefts, and presence or absence of seizures.

## Results

Tables 1–3 list pertinent data from the 20 patients in this study. A key to the abbreviations used in the tables is provided. The 20 patients (27 hemispheres) involved in this study included involvement of 12 frontal lobes, one parietal lobe, one temporal lobe, and four occipital lobes. Eight

hemispheres had both frontal and parietal lobe involvement and one hemisphere had both temporal and occipital lobe involvement. Variably sized areas of cortical dysplasia were present in the cortex surrounding the clefts in all patients (Figs. 1–5). Seven patients had bilateral schizencephalies (Fig. 1), which were symmetric or nearly symmetric in six patients, whereas 13 patients had unilateral schizencephalies, five closed lip (Fig. 2), and eight open lip (Figs. 3–5). Four patients with unilateral schizencephalies had migration anomalies contralateral to the schizencephaly (three patients with contralateral cortical dysplasia and one patient with bilateral heterotopias (Figs. 4 and 5)); in each patient with contralateral cortical dysplasia, the dysplasia was symmetrical or nearly symmetrical to the schizencephaly.

### *Bilateral Schizencephalies*

The seven patients with bilateral schizencephalies were scanned at a median age of 7 months old. Ten of the hemispheres had open lip clefts (five large, one medium, four small (Fig. 1)) and four had closed lip clefts. Five of the seven patients had motor dysfunction manifest as a spastic quadriplegia; motor dysfunction was present on the side of the body contralateral to all open lip schizencephalies involving the frontal lobes. Marked developmental delay or severe mental retardation were present in all six patients old enough to evaluate. Language was severely impaired in the two patients old enough to have developed speech. All seven patients had seizure disorders. In the two youngest patients, these consisted only of infantile spasms. The other five had various combinations of focal motor, partial

TABLE 1: Bilateral Schizencephalies

| Patient | Age   | Sex | Right Hemisphere | Left Hemisphere | Motor                 | Speech    | C/D        | Seizures                 | Comments           |
|---------|-------|-----|------------------|-----------------|-----------------------|-----------|------------|--------------------------|--------------------|
| 1       | 3 mo  | M   | Fr, C            | Fr, C           | Hypotonia             | Y         | Y          | Spasms                   | SOD                |
| 2       | 6 mo  | F   | Temp, O(L)       | Fr, O(L)        | Axial hypotonia<br>QP | Y         | DQ = 50    | Spasms                   |                    |
| 3       | 7 mo  | F   | Fr-Par, O(S)     | Fr, O(L)        | QP                    | Y         | DQ = 70    | FM                       |                    |
| 4       | 7 mo  | M   | Fr, O(L)         | Fr, O(L)        | Axial hypotonia<br>QP | Y         | DQ < 50    | Mixed FM,<br>minor motor | SOD                |
| 5       | 10 mo | M   | Fr-Par, C        | Fr-Par, O(S)    | RHP                   | Y         | DQ = 50–70 | FM                       |                    |
| 6       | 3 yr  | M   | Fr-Par, O(M)     | Fr, O(S)        | QP                    | D         | DQ = 50    | Mixed FM,<br>PC          |                    |
| 7       | 23 yr | M   | Occ, C           | Occ, O(S)       | NL                    | Few words | IQ < 50    | Mixed                    | Multiple anomalies |

TABLE 2: Left Unilateral Schizencephalies

| Patient | Age   | Sex | Location       | Motor | Speech | C/D     | Seizures | Comments               |
|---------|-------|-----|----------------|-------|--------|---------|----------|------------------------|
| 8       | 4 mo  | M   | Fr-Par, O(L)   | RHP   | Y      | Y       |          |                        |
| 9       | 8 mo  | M   | Fr, O(M)       | RHP   | Y      | DQ = 70 | FM       |                        |
| 10      | 10 yr | F   | Occ, C         | NL    | NL     | NL      | FM       |                        |
| 11      | 17 yr | M   | Temp-Occ, O(L) | QP    | NL     | IQ < 50 | FM, TC   | Bilateral heterotopias |
| 12      | 23 yr | F   | Fr, C          | RHP   | NL     | IQ = 80 | FM       |                        |

TABLE 3: Right Unilateral Schizencephalies

| Patient | Age   | Sex | Location     | Motor | Speech | C/D     | Seizures | Comments                       |
|---------|-------|-----|--------------|-------|--------|---------|----------|--------------------------------|
| 13      | 8 mo  | M   | Fr-Par, O(L) | LHP   | Y      | DQ = 70 |          | Dyplastic cortex on left       |
| 14      | 8 mo  | M   | Fr-Par, O(S) | LHP   | Y      | DQ = 80 |          | SOD                            |
| 15      | 16 mo | M   | Fr-Par, O(L) | QP    | Y      | DQ = 50 |          | Dysplastic cortex on left      |
| 16      | 6 yr  | M   | Par, C       | NL    | NL     | DQ = 70 | FM       | Dysplastic cortex on left, SOD |
| 17      | 8 yr  | M   | Occ, C       | NL    | NL     | NL      | FM       |                                |
| 18      | 11 yr | M   | Fr, C        | LHP   | NL     | NL      | FM       |                                |
| 19      | 15 yr | M   | Fr, O(S)     | LHP   | NL     | NL      | FM, PC   |                                |
| 20      | 18 yr | M   | Fr, O(L)     | LHP   | NL     | IQ = 70 | FM       | Subependymal heterotopias, SOD |

## Key to Abbreviations in Tables

|     |                        |      |                          |
|-----|------------------------|------|--------------------------|
| C   | Closed lipped          | O    | Open lipped              |
| C/D | Cognition/development  | Occ  | Occipital                |
| D   | Delayed                | Par  | Parietal                 |
| DQ  | Developmental quotient | PC   | Partial complex seizures |
| FM  | Focal motor seizures   | QP   | Quadriparesis            |
| Fr  | Frontal                | RHP  | Right hemiparesis        |
| IQ  | Intelligence quotient  | (S)  | Small cleft              |
| (L) | Large cleft            | SOD  | Septo-optic dysplasia    |
| LHP | Left hemiparesis       | TC   | Tonic clonic seizures    |
| (M) | Medium cleft           | Temp | Temporal                 |
| NL  | Normal                 | Y    | Too young to evaluate    |

complex, and generalized (tonic clonic) seizures; only two of these five were controlled well by medication.

*Right Hemisphere Schizencephaly*

The eight patients with schizencephaly involving the right hemisphere had a median age of 6 years old. Five patients had open lip clefts (three large (Figs. 3 and 5), two small) and three had closed lip schizencephalies. Six patients had spastic hemiparesis on the side opposite the cleft, four were developmentally delayed or intellectually impaired (including three patients with neu-

ronal migration anomalies involving the contralateral hemisphere), and five manifested seizure disorders. The seizures were focal motor in nature in four patients and both focal motor and partial complex in the fifth. Four of the five were well controlled and essentially seizure-free on antiseizure mediations. All patients in this group had normal language development.

*Left Hemisphere Schizencephaly*

The five patients with left sided unilateral schizencephaly had a median age of 10 years old. Three had open lip schizencephalies (two large,

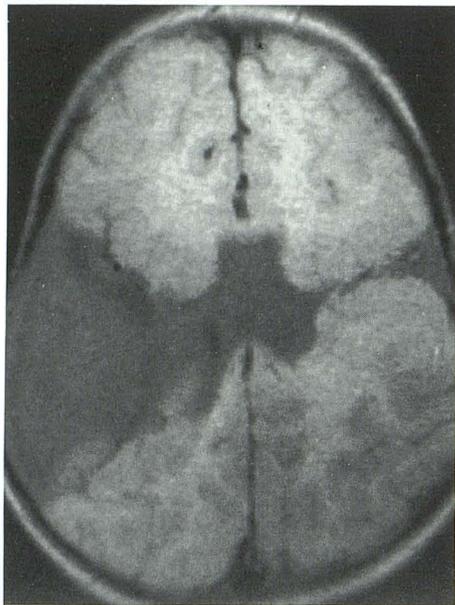


Fig. 1. Patient 6; bilateral schizencephaly. This boy had quadriplegia and severe developmental delay. Axial SE 600/20 image shows a large open lip fronto-parietal schizencephaly on the right and a smaller open lip cleft in the left frontal lobe. The characteristic gray matter lining of the clefts is well seen. The left hemispheric lesion was larger superiorly.

one medium (Fig. 4)) and two had closed lip schizencephalies (Fig. 2). Four of the five patients had spastic right hemiparesis, three were developmentally delayed or intellectually impaired, and four had focal motor seizures. Three of the four with seizure disorders were well controlled on antiepileptic medications. The three older patients had all developed speech normally.

#### Statistical Analyses

Several relationships were found to have statistical significance:

1. All patients (100%) with bilateral clefts who were old enough to evaluate had developmental dysphasia, whereas all patients (100%) with unilateral schizencephalies had normal speech development ( $P = .03$ ).

2. All six patients (100%) with bilateral clefts who were old enough to evaluate had moderate or severe developmental delay (DQ or IQ less than 70), whereas only two of 13 patients (15%) with unilateral schizencephaly had DQ or IQ less than 70 and six of 13 (46%) had DQ or IQ less than or equal to 70 ( $P = .04$ ).

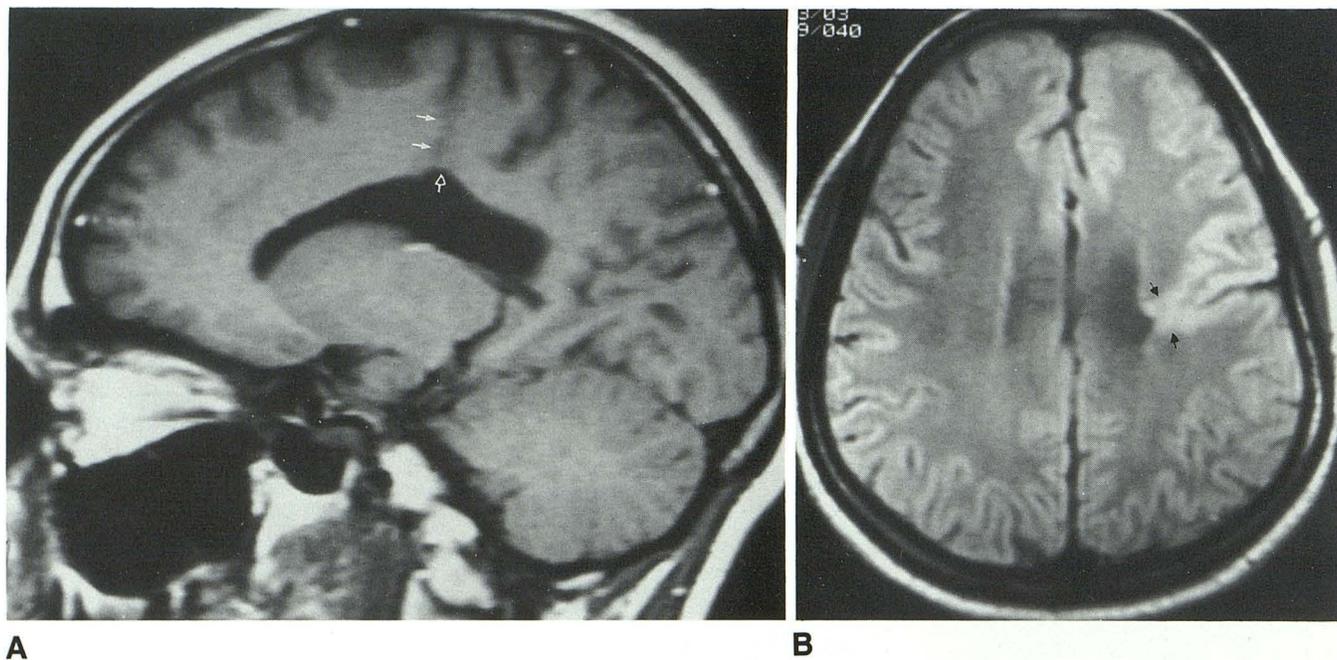
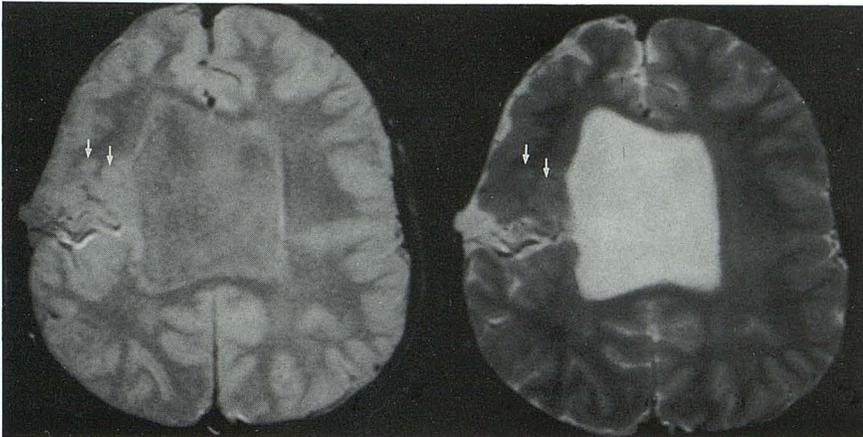


Fig. 2. Patient 12; closed lip schizencephaly. This patient had an IQ slightly below normal and a right hemiplegia.  
 A, Sagittal SE 600/20 image shows a dimple (*open arrow*) in the superior aspect of the body of the left lateral ventricle with a track of gray matter (*closed arrows*) extending vertically upward from it.  
 B, Axial SE 2500/25 image shows gray matter (*arrows*) extending from the ventricular dimple laterally to the region of the posterior frontal cortex. The gray matter walls of the cleft are apposed in the midline, making this a closed lip schizencephaly.



A

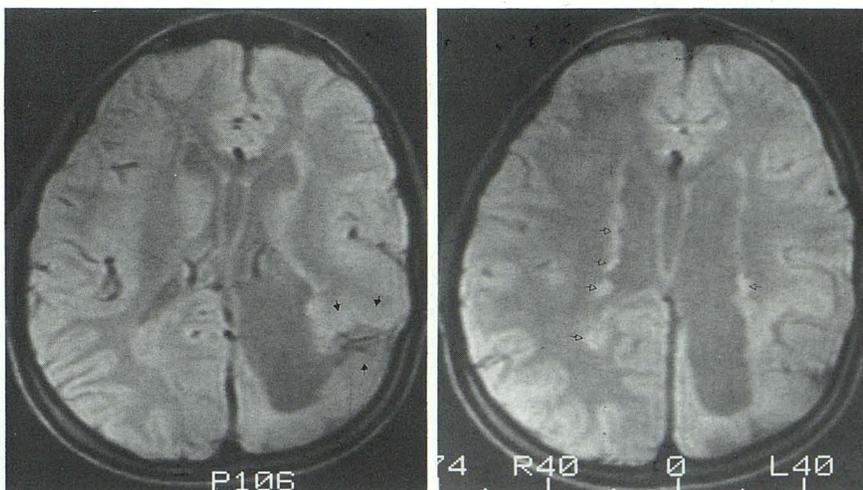


B

Fig. 3. Patient 19; small open lip schizencephaly. This patient had normal intelligence and left hemiplegia.

A, Coronal SE 600/20 images show CSF within the small cleft (*closed arrows*) from the cortical surface to the ventricular dimple. The cortex anterior to the cleft (*open arrows*), is dysplastic.

B, Axial SE 2800/30, 80 images show thickened, irregular gray matter lining the cleft with scattered nodules of heterotopic gray matter (*arrows*) surrounding it.



A

B

Fig. 4. Patient 11; open lip schizencephaly with bilateral subependymal heterotopias. The presence of the bilateral heterotopias, in addition to the schizencephaly, indicates a diffuse brain injury during the period of neuronal migration and may explain the severity of this young man's disability. This patient is severely retarded with spasticity in all extremities.

A, Axial SE 2000/35 image show an open-lip, gray matter-lined cleft (*arrows*). Vascular flow voids are present within the cleft.

B, Axial SE 2000/35 image at a higher level shows small gray-matter heterotopias (*arrows*) in the subependymal region lining the ventricles.

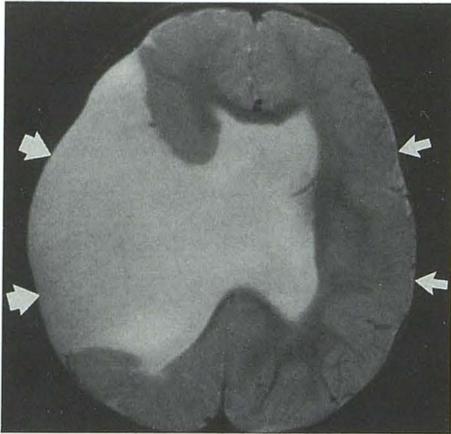


Fig. 5. Patient 15; open lip schizencephaly with contralateral cortical dysplasia. This 16-month-old boy had severe developmental delay and quadriplegia, with the left side of the body being more severely affected. SE 2800/700 image shows the large open lip cleft on the right, with expansion of the ipsilateral hemispheric volume (*large arrows*). The contralateral frontal cortex (*small arrows*) is abnormally thick with shallow sulci and a bumpy surface, indicating a neuronal migration anomaly.

3. Motor impairment was present contralateral to brain involvement in 16 of 19 hemispheres (84%) with frontal lobe involvement, whereas motor impairment was present contralateral to only two of seven hemispheres (29%) without frontal lobe involvement ( $P = .01$ ).

4. Motor dysfunction was present contralateral to 17 of 18 open lip schizencephalies (94%) but contralateral to only two of nine (22%) closed lip schizencephalies ( $P = .0003$ ).

5. Motor dysfunction was present contralateral to all 12 hemispheres (100%) with large or medium open lip schizencephalies, but contralateral to only 7 of 15 hemispheres (47%) with closed lip or small open lip schizencephalies ( $P = .003$ ).

6. Of patients with unilateral clefts, all five with large or medium open clefts (100%) were moderately or severely retarded (IQ or DQ less than or equal to 70), whereas only one of seven with a small or closed lip (14%) was moderately or severely retarded ( $P = .008$ ).

## Discussion

Few studies have addressed the clinical outcome of a large number of patients with schizencephaly, probably because most studies have been small (1, 3–7). Patients have been reported as having nonspecific clinical features including microcephaly, seizures, retardation, and motor dysfunction (1, 3, 7). Miller et al (8) used CT to

evaluate 11 patients with schizencephaly. They found various combinations of delayed development, mental retardation, motor dysfunction, seizures, and microcephaly in the affected patients; however, they reported that “no clinical findings could be consistently predicted based on CT findings.” Aniskiewicz et al (9) recently studied neurobehavioral correlates of schizencephaly in three patients. They found that the level of general intellectual functioning related to the amount of brain involved. Moreover, they noted that variations in specific neurobehavioral abilities reflected both the location of the involved brain and the prenatal nature of the injury, the deficits being less than would have been expected in an older child or adult with a similar degree of injury. In other words, they felt that the increased plasticity of the immature brain allowed a greater degree of functional recovery as compared to the more mature brain, a concept that has been discussed by others (10, 11).

Our findings agree with those of Aniskiewicz et al (9), in that certain clinical manifestations were statistically correlated with the size and locations of the clefts. Motor dysfunction correlated with involvement of the frontal lobes and with the size of the clefts: patients with medium or large open lip clefts were significantly more likely to have hemiparesis of the contralateral side of the body than those with small or closed lip clefts. Patients with bilateral schizencephalies and those with large or medium unilateral schizencephalies had a significantly higher incidence of moderate and severe developmental delay and mental retardation than patients with small open lip unilateral schizencephalies or closed lip unilateral schizencephalies. Although four of the six patients with small, unilateral schizencephalies were in special education classes at one time, all were eventually “mainstreamed” into normal classes. Two (patients 18 and 19) are honor students. All have achieved good seizure control on antiepileptic medications. Therefore, it appears that patients with small unilateral clefts, particularly those not involving the frontal lobes, have an excellent prognosis.

Classification was made somewhat difficult by the presence of contralateral cortical dysplasia in three patients (Fig. 5). These three patients presented at an earlier age and had lower developmental levels than the patients with unilateral disease, although the difference was not statistically significant. Moreover, two patients with unilateral schizencephaly and contralateral gyral dys-

plasia (patients 11 and 15) were quadriparetic, with the hemiparesis ipsilateral to the cleft presumably a result of the contralateral cortical dysplasia. Definite correlation of intellectual impairment with the combination of schizencephaly and contralateral cortical dysplasia is not possible because the large clefts themselves were associated with a poorer intellectual outcome. Thus, the prognosis for intellectual development in those patients with unilateral schizencephaly and contralateral cortical dysplasia may depend upon the size of the cleft, the extent of the dysplasia, or a combination of the two. We look forward to a report concerning patients with cortical dysplasia contralateral to a small schizencephaly to clarify this matter.

It is interesting to note that the patients with cortical dysplasia contralateral to the clefts had cortical dysplasia in a hemispheric location similar to the contralateral schizencephalies. This finding raises an interesting possibility concerning the pathogenesis of both schizencephaly and cortical dysplasias: could they be the result of the same process in some patients? Evidence from anatomic and clinical studies support this theory. Cortical dysplasias and schizencephalies reportedly occur in the same locations, primarily around the sylvian fissures but occasionally in other locations such as the occipital, prefrontal, and temporal lobes (1, 7, 8, 12–17). Moreover, areas of cortical dysplasia are often in the form of an infolding of polymicrogyria cortex (18, 19). Some authors have labeled such cortical infoldings as “Type I schizencephaly” (7), although such designation is incorrect according to the original definition of the term by Yakovlev and Wadsworth (7, 15, 16). (Yakovlev and Wadsworth define the hallmark of schizencephaly as a “pial-ependymal seam”, a region where the ependymal lining of the ventricle contacts the pial lining of the gray matter-lined cleft. Clearly, if the infolding of cortex does not communicate with the ventricle, the pial-ependymal seam cannot be present.) Nonetheless, the fact that the cortical infoldings occur in approximately the same locations as the transhemispheric clefts of schizencephaly, the presence of infoldings of various depths, and the fact that both schizencephalies and cortical infoldings are lined by polymicrogyria certainly suggests a common mechanism of formation.

An understanding of the pathogenetic mechanism that will be proposed to relate these two disorders necessitates a discussion of the proposed pathogeneses of schizencephaly and pol-

ymicrogyria. To start, it is necessary to assume that the cortical dysplasias (contralateral to the schizencephalies) reported in this paper are polymicrogyria. This assumption is justified by the following: 1) Biopsy specimens from patients with focal cortical dysplasias of identical MR appearances in previous studies (20) and from this institution (21) were identified histologically as polymicrogyria. 2) Areas of cortical dysplasia with identical gross pathologic appearance to those in this study and a previous study (21) have been reported in the pathology literature (14, 18, 22). 3) Cortex within schizencephalies and in the regions of brain immediately surrounding schizencephalies have been identified as polymicrogyria pathologically (7, 13, 15, 16, 23).

The term polymicrogyria refers to small, irregular gyri without intervening sulci or with intervening sulci obliterated and bridged by fusion of the overlying molecular layer (12, 14). Histologically, two principle patterns are recognized: layered and unlayered. The layered pattern consists of a marginal zone (most external), a disorganized outer molecular layer, a cell sparse layer with astrocytes, and an inner molecular layer (22). Elegant experiments by Dvorak et al (24, 25) in rats led to their contention that the cell sparse layer is the result of a cortical laminar necrosis in the immature brain and that the disorganized outer molecular layer consists of cells that arrived after the cortical injury has destroyed the normal organizational mechanisms within the cortex. In the unlayered form of polymicrogyria, no cell sparse layer is present (12, 18), making laminar necrosis less likely. Nonetheless (and despite the fact that polymicrogyria can be caused by chromosomal disorders (12)), most authors suggest ischemic cortical damage as the cause of many, if not most cases of polymicrogyria (12, 13, 18, 24–27). Indirect evidence suggests that, even in cases of intrauterine infection, polymicrogyria is the result of cerebral perfusion failure (12, 14, 28).

A few isolated case reports give clues to the timing of insults that result in polymicrogyria. Barth (12) has made the observation that two accidents involving carbon monoxide poisoning of mothers at 18–24 weeks of gestation resulted in layered polymicrogyria, whereas two cases involving injuries at 12–17 weeks of gestation resulted in unlayered polymicrogyria. On the basis of these observations, he postulates that unlayered polymicrogyria is the result of early second trimester injury and that layered polymicro-

gyria results from a late second trimester injury. Evrard et al (26, 27) postulate that polymicrogyria is caused by prenatal perfusion failure after neuronal migration and before the establishment of gyration (20–30 weeks).

Concerning schizencephalies, Yakovlev and Wadsworth (15, 16) postulated that schizencephalies were "agenetic porencephalies" that formed as the result of failure of growth and differentiation of areas of the germinal matrix. They estimated that such an injury must have occurred in the first half of the first trimester. They reported unlayered polymicrogyria lining the clefts in all five of their autopsy cases. Norman (23) reported bilateral schizencephalies in a child born at 26 weeks gestational age to a woman who had an episode of severe bleeding during the 12th gestational week. As the crown-rump length of a macerated twin suggested that it had died at 17 weeks gestational age, the author postulated that the clefts must have occurred as the result of an insult between 12 and 17 weeks. The gray matter lining and surrounding the cleft in this case was in the form of unlayered polymicrogyria. In Dekaban's autopsy series (13) of four patients with bilateral schizencephalies, all had polymicrogyria lining the cleft and extending into the surrounding brain. Upon reviewing his illustrations, cases 1 and 4 appeared to be layered polymicrogyria, whereas case 3 appears unlayered and case 2 is indeterminate.

Our results support the concept put forth by Barth (12) that cortical dysplasias in the form of polymicrogyria and schizencephalies result from the same pathogenetic processes. The schizencephalies in the present series have a very similar anatomic distribution to the focal cortical dysplasias in our previous study (21). Thirty-nine percent of patients with focal cortical dysplasias had bilateral lesions; 35% of schizencephalies were bilateral. Cortical dysplasias were located primarily in the frontal (37%) and frontoparietal (23%) areas, with another 25% involving the parietal and occipital lobes. Schizencephalies also primarily involve the frontal (44%) and frontoparietal (30%) regions, with significant involvement (19%) of the parietal and occipital lobes. Moreover, upon studying a large number of these lesions, one appreciates a spectrum of depth of cortical infolding among those with focal cortical dysplasias. In the study of cortical dysplasias (21), we noted that infolding of thickened, irregular cortex was apparent in 28 of 43 hemispheres (65%) affected with focal cortical dysplasia and

that thickened, irregular cortex lined the adjacent hemisphere in nine (32%) of these. Similar cortical infoldings have been reported in the pathology literature (18); the gray matter lining the infolding was polymicrogyria. Moreover, a patient from our series of cortical dysplasias (21) had surgical removal of a region of cortical infolding that was identified as polymicrogyria on histologic examination. As these infoldings of dysplastic cortex become deeper and deeper, they resemble more and more the type I schizencephaly as originally defined by Yakovlev and Wadsworth (15, 16).

The task now arises of finding the common pathogenetic mechanisms for these cortical dysplasias and true schizencephalies. To do so, we apply the results of Dvorak et al (24, 25). Any injury that results in cortical necrosis (24, 25) and damages the radial glial fibers or other normal organizational mechanisms (26, 27) will result in polymicrogyria. The high incidence of bilateral lesions in the perisylvian region has been used as evidence for fetal hypotension and ischemic cortical damage as the underlying factor (22), but toxic and direct infectious damage certainly cannot be excluded on the basis of existing evidence, particularly in the case of unilateral lesions. We suggest that superficial cortical injury will result in flat polymicrogyria without cortical infolding (Fig. 6). More severe injuries that extend more deeply into the hemisphere and destroy radial glial fibers (or their surface molecules that promote neuronal migration (29)) result in cortical infoldings lined by polymicrogyria (Fig. 6). If the injury involves the entire thickness of the hemisphere from the pia to the ependyma, a true schizencephaly, with a pial-ependymal seam, is formed (Fig. 6). As the pathologic studies cited earlier (13, 15, 16, 23) indicate that most schizencephalies are lined by unlayered polymicrogyria, it seems likely that most form in the first half of the second trimester.

Although the three patients in this series with schizencephaly and contralateral cortical dysplasia had symmetrical lesions (ie, the cortical dysplasia was in the same region of the brain as the schizencephaly), multifocal injuries to the brain are not necessarily symmetrical. Therefore, one can envision, and perhaps predict, that cortical dysplasia will sometimes occur in conjunction with schizencephaly in an asymmetrical location. Such an occurrence in no way invalidates the theory proposed in this communication, however, as asymmetrical schizencephalies also occur (patient 2 in this series, for example).

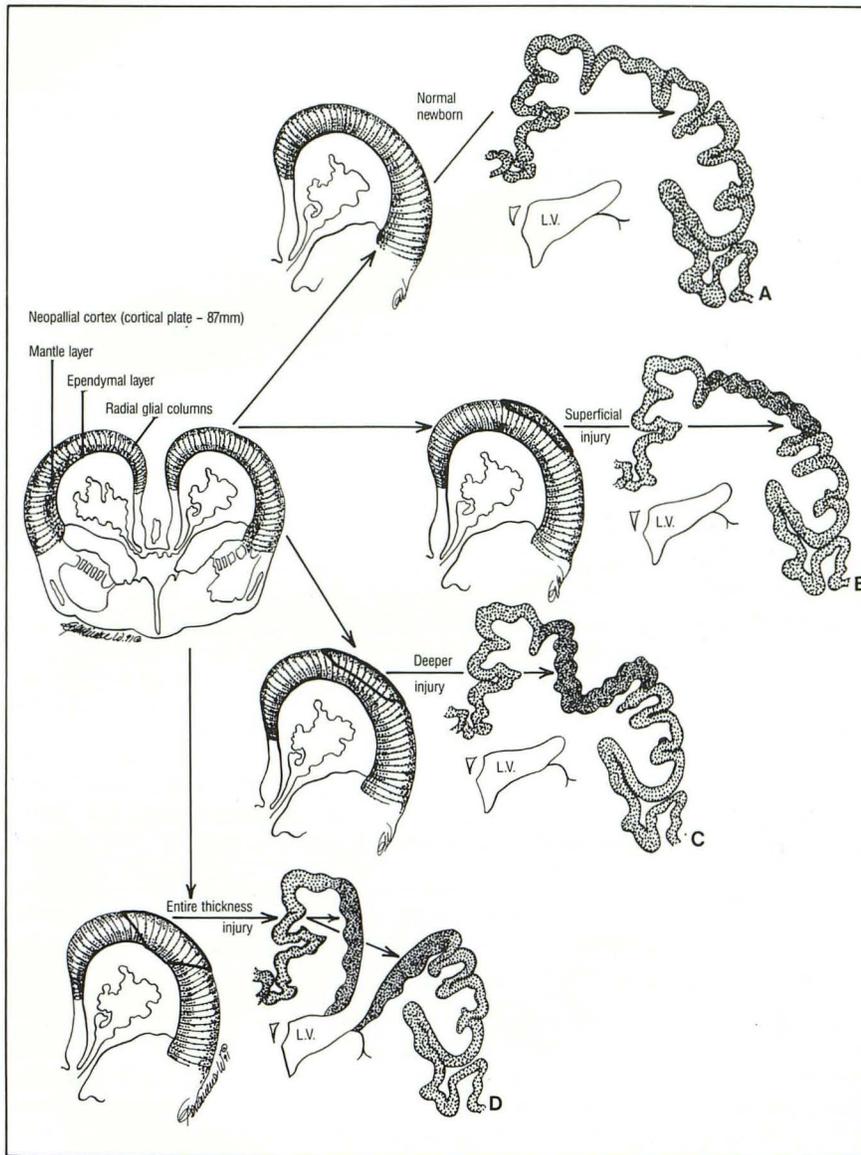


Fig. 6. Schematic illustrating the proposed relationship among superficial polymicrogyria, infoldings of polymicrogyria, and schizencephaly. In normal development (A), neurons migrate radially along radial glial cells (RGCs) from the germinal zone lining the lateral ventricle to form the cerebral cortex. When the fetus suffers an injury that results in a superficial brain injury (B), either the RGCs or the surface molecules guiding the neurons along the RGCs are damaged, resulting in a disorganized and slightly thickened-appearing cortex. A deeper injury to the fetal brain (C) results in destruction of the RGCs or surface molecules at a deeper level. The result is an infolding of a slightly thickened and irregular, disorganized cortex and a thinner layer of underlying white matter. However, the infolding of cortex is not in contact with the ependyma of the lateral ventricle and is, therefore, not a true schizencephaly. Finally, if the entire thickness of the cerebral hemisphere is affected (D), the result is a true schizencephaly, in which the pia lining the cleft comes in contact with the ependyma of the lateral ventricle and the subarachnoid space is in continuity with the ventricular CSF.

From the perspective of the imaging physician and the referring clinician, the importance of this study lies in the recognition that prenatal cortical destruction or dysplasia, whether in the form of schizencephaly, infoldings of polymicrogyria, or the "bumpy", superficial form of polymicrogyria, can occur anywhere in the brain. Moreover, bilateral disease is common and seems to imply a poorer prognosis for the patient. Therefore, the physician performing or interpreting the images must have a high index of suspicion for bilateral, as well as unilateral, disease.

It is important to note that the patient selection for this study was not random; the study is therefore biased by the decision of the clinicians

to obtain imaging studies of the patients included in this study. At our institution, images are obtained for all patients with seizures or developmental delay; however, it is possible that some patients initially seen at other institutions may not have been scanned if they exhibited extremely mild clinical signs and symptoms. Therefore, it is possible that mildly symptomatic patients, most likely those with small unilateral schizencephalies, may be underrepresented in this series. Conversely, patients with bilateral schizencephalies may have been overrepresented because of their severe clinical manifestations and patients with frontal schizencephalies overrepresented because of their motor problems. Finally,

the study is limited by the diagnostic acuity and the indices of suspicion of the radiologists who originally reviewed these scans. Some abnormalities may not be apparent on MR if images in the proper plane are not obtained.

To summarize, we have reviewed MR scans and clinical records of 20 patients with schizencephaly. The results indicate that the size and locations of the clefts are very important in the determination of the patients' prognoses. Patients with bilateral schizencephalies and those with large or medium unilateral schizencephalies have a very poor prognosis for intellectual development. Patients with bilateral clefts also have a poor prognosis in terms of the development of speech. Patients with unilateral closed lip or small open lip schizencephalies have a good prognosis for intellectual development. Impaired motor function correlated significantly with contralateral frontal lobe involvement. Similarities were noted in the anatomy, location, and clinical outcome of patients with focal cortical dysplasia and those with schizencephaly. A common pathogenetic mechanism for their formation is proposed.

## References

1. Barkovich AJ, Norman D. MR of schizencephaly. *AJNR* 1988;9:297-302
2. Fried R. Introduction to statistics. New York: Gardner Press, 1976:304
3. Page L, Brown S, Gargano F, Shortz R. Schizencephaly: a clinical study and review. *Child's Brain* 1975;1:348-358
4. Williams J, Blalock C, Cunaway C, Chalub E. Schizencephaly. *J Comput Assist Tomogr* 1983;7:135-139
5. Byrd S, Osborn R, Bohan T, Naidich T. The CT and MR evaluation of migration disorders of the brain. II. Schizencephaly, heterotopia, and polymicrogyria. *Pediatr Radiol* 1989;19:219-222
6. Barkovich AJ, Chuang SH, Norman D. MR of neuronal migration anomalies. *AJNR* 1987;8:1009-1017
7. Bird C, Gilles F. Type I schizencephaly: CT and neuropathologic findings. *AJNR* 1987;8:451-454
8. Miller G, Stears J, Guggenheim M, Wilkening G. Schizencephaly: a clinical and CT study. *Neurology* 1984;34:997-1001
9. Aniskiewicz A, Frumkin N, Brady D, Moore J, Pera A. Magnetic resonance imaging and neurobehavioral correlates in schizencephaly. *Arch Neurol* 1990;47:911-916
10. Lenn N. Neuroplasticity and the developing brain: implications for therapy. *Pediatr Neurosci* 1987;13:176-183
11. Perry V, Maffei L. Dendritic competition: competition for what? *Dev Brain Res* 1988;41:195-208
12. Barth PG. Disorders of neuronal migration. *Can J Neurol Sci* 1987;14:1-16
13. Dekaban A. Large defects in cerebral hemispheres associated with cortical dysgenesis. *J Neuropathol Exp Neurol* 1965;24:512-530
14. Friede RL. *Developmental neuropathology*, 2nd ed. Berlin: Springer-Verlag, 1989
15. Yakovlev PI, Wadsworth RC. Schizencephalies: a study of the congenital clefts in the cerebral mantle. I. Clefts with fused lips. *J Neuropathol Exp Neurol* 1946;5:116-130
16. Yakovlev PI, Wadsworth RC. Schizencephalies: a study of the congenital clefts in the cerebral mantle. II. Clefts with hydrocephalus and lips separated. *J Neuropathol Exp Neurol* 1946;5:169-206
17. Zimmerman R, Bilaniuk L, Grossman R. Computed tomography in migration disorders of human brain development. *Neuroradiology* 1983;25:257-263
18. Ferrer I. A golgi analysis of unlayered polymicrogyria. *Acta Neuropathol* 1984;65:69-76
19. Barkovich A. Abnormal vascular drainage in anomalies of neuronal migration. *AJNR* 1988;9:939-942
20. Kuzniecky R, Berkovic S, Andermann F, Melanson D, Olivier A, Robitaille Y. Focal cortical myoclonus and rolandic cortical dysplasia: clarification by magnetic resonance imaging. *Ann Neurol* 1988; 23:317-325
21. Barkovich A, Kjos B. Nonlissencephalic cortical dysplasia: correlation of imaging findings with clinical deficits. *AJNR* 1992;95-103
22. Richman DP, Stewart RM, Caviness VS. Cerebral microgyria in a 27 week fetus: an architectonic and topographic analysis. *J Neuropathol Exp Neurol* 1974;33:374-384
23. Norman M. Bilateral encephaloclastic lesions in a 26 week gestation fetus: effect on neuroblast migration. *Can J Neurol Sci* 1980;7:191-194
24. Dvorak K, Feit J. Migration of neuroblasts through partial necrosis of the cerebral cortex in newborn rats: contribution to the problems of morphological development and developmental period of cerebral microgyria. *Acta Neuropathol* 1977;38:203-212
25. Dvorak K, Feit J, Jurankova Z. Experimentally induced focal microgyria and status verrucosus deformis in rats: pathogenesis and interrelational, histological and autoradiographical study. *Acta Neuropathol* 1978;44:121-129
26. Evrard P, de Saint-Georges P, Kadhim H, Gadsseux J-F. Pathology of prenatal encephalopathies. In: French J, ed. *Child neurology and developmental disabilities*. Baltimore: Paul H. Brookes, 1989:153-176
27. Evrard P, Kadhim H, de Saint-Georges P, Gadsseux J-F. Abnormal development and destructive processes of the human brain during the second half of gestation. In: Evrard P, Minkowski A, ed. *Developmental neurobiology*. New York: Vevey-Raven Press, 1989:21-41
28. Marques-Dias M, Harmant-van Rijckevorsel G, Landrieu C, et al. Prenatal cytomegalovirus disease and cerebral microgyria: evidence for perfusion failure, not disturbance of histogenesis, as the major cause of fetal cytomegalovirus encephalopathy. *Neuropediatrics* 1984;15:18-24
29. Rakic P. Contact regulation of neuronal migration. In: Edelman G, Thiery J, ed. *The cell in contact: adhesions and junctions as morphogenetic determinants*. New York: Neuroscience Research Foundation, 1985:67-91

Note: Please see the Commentary by Barth on page 104 in this issue.