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Microscopic Cortical Dysplasia in Infantile Spasms: Evolution of White Matter Abnormalities

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PURPOSE: To determine whether microscopic cortical lamination defects in patients with infantile spasms, not initially identifiable on MR, may be inferred from evolving changes in the adjacent white matter. **METHODS:** Three infants between 3 and 6 months of age presented with infantile spasms. Based on negative metabolic assessment and normal MR findings, they were classified as cryptogenic. Despite therapy the children deteriorated with seizure recurrence and the advent of lateralizing clinical and neurophysiologic findings. MR studies were repeated and positron emission tomography was done. **RESULTS:** The second MR studies demonstrated abnormalities of myelination, corresponding to localized clinical and neurophysiologic findings. Positron emission tomography findings did not show a strong correlation; one was normal, one showed no abnormality in the major area of MR abnormality, and one showed significantly less abnormality than on MR. Two patients have undergone surgery, both with good response. **DISCUSSION:** Subtle lamination defects may be identifiable on positron emission tomography but are usually not detectable on MR. White matter abnormality on MR images is usually attributable to primary disease. We suggest that in certain cases progressive white matter changes may be induced as a secondary phenomenon by overlying microscopic cortical lamination defects. Serial MR imaging may be beneficial in children with infantile spasms in whom signs of laterality evolve.

Index terms: Seizures, in infants and children; White matter, abnormalities and anomalies

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The causes of infantile spasms are varied and complex. The syndrome has been traditionally classified as a generalized age-specific seizure disorder with a peak age of onset of 3 to 8 months (1). Historically two subtypes of infantile spasms, namely, the symptomatic and the cryptogenic, have been defined based on the ability of available diagnostic tests to show a cause (1–3). The proportion of infants with infantile spasms assigned to the cryptogenic subtype has been steadily diminishing in recent years, largely as a result of improvements in neuroimaging. The recognition that some cases of infantile spasms may result from focal rather than diffuse cortical abnormalities (4–6) and may be amenable to a cure by focal resection (7–12) has underscored the need for sensitive diagnostic modalities in detecting focal cortical microdysgenesis.

In view of the maturational changes in the white matter signal of the magnetic resonance (MR) of the developing human brain that have been described (13–18), we hypothesized that focal cortical microdysgenesis not readily detectable on the MR of a 3- to 6-month-old infant might manifest later by secondary focal changes in white matter maturation. We report the results of serial MR studies in three children who had seemingly normal MR findings between the ages of 4 and 6 months but who

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showed focal white matter changes in a later study. This focal finding correlated well with both the clinical examination and the electrophysiologic studies of these children. In two of these children, the focal MR findings also correlated with the histopathologic findings from surgically resected tissue.

Materials and Methods

Three patients ages 4½ to 6 months of age who presented with infantile spasms were examined serially with MR. All patients initially met the criteria for cryptogenic infantile spasms; they had nonlateralizing neurologic findings, normal results of screening for metabolic abnormalities, and MR brain scans reported as normal. The initial and follow-up MR examinations were performed on a 1.5-T system and included T1-weighted and T2-weighted conventional spin-echo sequences. The T1-weighted images had been obtained using repetition times in the range of 300 to 600 milliseconds and echo times in the range of 15 to 20 milliseconds. The T2-weighted images were obtained with repetition times of 2500 to 3500 milliseconds and echo times of 80 to 120 seconds. The follow-up MR images were compared with the results from functional neuroimaging studies with fludeoxyglucose F 18 (FDG) positron emission tomography (PET) studies. The follow-up MRs were obtained within 1 or 2 months of the FDG PET studies. Correlations of asymmetric findings in the follow-up MR images were sought with findings of clinical neurophysiologic tests such as electroencephalograms and median nerve somatosensory evoked potential studies, as well as neurologic examinations.

Results

Case 1

This male infant presented with infantile spasms at 6 months of age. His neurologic examination was notable for hypotonia but was nonlateralizing. All metabolic studies were normal. The MR was read as normal (Fig 1A). His electroencephalogram initially displayed generalized hypsarrhythmia. After standard therapy with corticotropin, pyridoxine, benzodiazepines, and valproic acid failed, he was admitted for an in-patient evaluation with continuous electroencephalographic and video telemetry, and FDG PET for the detection of a possible lateralized and resectable abnormality. This decision was prompted by the development of early left-hand preference in this child. A repeat MR performed at 16 months of age (Fig 1B–D) showed a dramatic difference in the white matter signal between the two hemispheres, with a paucity of myelin on the left. There was corresponding electroencephalographic slowing over the left hemisphere and abnormal cortical potential on right median nerve somatosensory evoked potential testing. His FDG PET showed subtle relative hypometabolism of the left hemisphere by visual inspection, much less striking than the asymmetry of the myelin signal in the MR (Fig 1E). Formal region-of-interest analysis of the PET images did not enhance the degree of lateralization of FDG uptake (data not shown). This patient has since undergone a left functional hemispherectomy with complete resolution of his seizures and resumption of his neurodevelopment. Pathologic examination of the resected tissue was consistent with cortical microdysgenesis. A whole-mount section of the tissue stained for myelin (Fig 1F) demonstrates patchy dysmyelination of the subcortical white matter. The region of cortex with nearly normal lamination and cellularity (Fig 1G) contrasts with the severely dysplastic cortex (Fig 1H) from an area overlying the white matter with severe dysmyelination.

Case 2

This female infant experienced the onset of infantile spasms at 4½ months of age. Her initial evaluation resulted in the classification of her infantile spasms as cryptogenic. Her first MR evaluation (Figs 2A and B) was obtained at 6 months of age and was judged to be normal. She responded favorably to early treatment with corticotropin for a few weeks. However, subtle left hemiparesis developed around 8 months of age, and her spasms recurred by 11 months of age. An FDG PET scan at about 11 months of age appeared normal (Fig 2C). Analysis by region of interest did not support the inference of asymmetry in FDG uptake. Nevertheless, because of her hemiparesis, she underwent further evaluation with a repeat MR study (Figs 2D and E) as well as continuous electroencephalographic and video monitoring. The follow-up MR images showed asymmetric development of white matter with increased signal on T2 evident in the right hemisphere. Consistent with her MR and her hemiparesis, electroencephalography showed several abnormal features in the right hemisphere, and the right cortical evoked potential on stimulation of the left median nerve was likewise abnormal. Surgery has been deferred because of favorable response of seizures

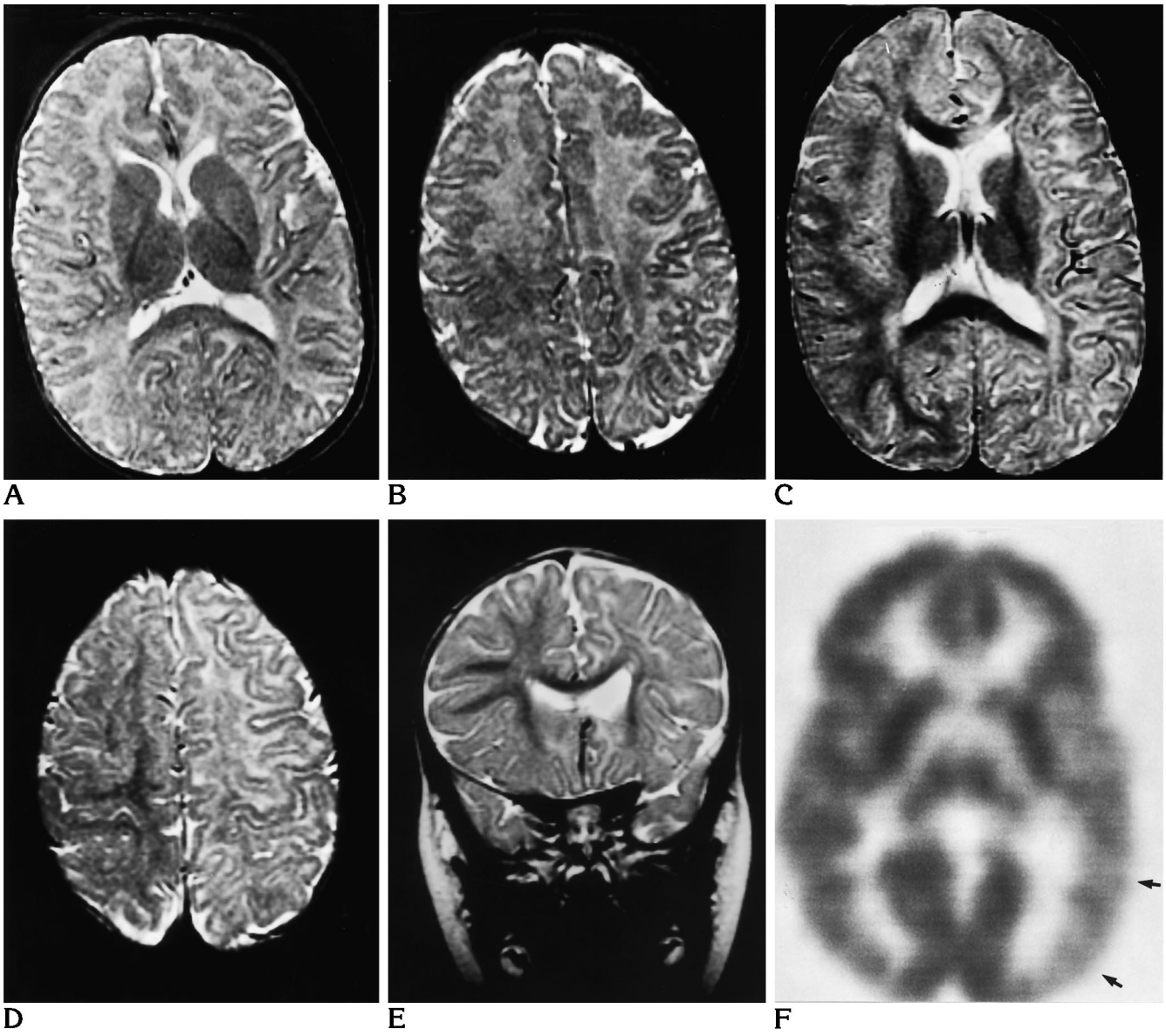

Fig 1. *A* and *B*, MR at 6 months of age. *A*, Axial T2-weighted image (2200/80/1 [repetition time/echo time/excitations]), at the level of the internal capsule. T2 myelination changes are present in the splenium of the corpus callosum and in the internal capsule bilaterally. Overall white matter development was reported as normal, although in retrospect some early mild asymmetry in the genu of the corpus callosum may have been present.

B, Axial T2-weighted image (2200/80/1) at the level of the centrum semiovale. Again no gross asymmetry of white matter signal was detected, although in retrospect the periphery of the left hemisphere was relatively hyperintense compared with the right.

C–F, Imaging studies at 16 months of age. *C*, Axial T2-weighted image (2500/80/1) at the level of the internal capsule demonstrating marked asymmetry of white matter signal reflecting abnormal myelination in the left hemisphere. There is extensive involvement of white matter including external and extreme capsules and the left side of the genu of the corpus callosum. The internal capsule, together with restricted portions of frontal and occipital lobe white matter, seems unaffected.

D, Axial T2 weighted image (2500/80/1) through the centrum semiovale from the same examination. Similar asymmetry of white matter signal reflecting abnormal myelination in the left hemisphere is evident.

E, Coronal T2-weighted (2300/90/1) image through the frontal lobes again demonstrating marked asymmetry of myelination. The abnormality extends out into the gyri to the cortex, affecting the entire spectrum of white matter tracts.

F, FDG PET image illustrating relative cortical hypometabolism in the posterior two thirds of the left hemisphere (*arrows*).

(Figure continues.)

Fig 1, continued.

G, Whole-mount myelin-stained section of the right frontal lobe. The tissue demonstrates patchy dysmyelination of the subcortical white matter with and indistinct cortex–white matter junction (*arrows*).

H and *I*, Representative sections from the resection specimen stained with Kluver-Barrera stain (which highlights myelinated fibers and cortical cytoarchitecture). The pial surface is at the *top* of the section. *H*, Section from relatively normal area of cortex shows well-laminated cortex composed of normally oriented neurons. *I*, Section (by comparison) shows severe cortical dyslamination and clusters of maloriented slightly atypical neuronal cell bodies (*arrows*) (magnification, × 95).

to valproic acid, but her neurologic development continues to be subnormal.

Case 3

This male infant experienced his first spasms at 6 months of age. His initial studies, with the exception of electroencephalography showing hypsarrhythmia, were normal. MR obtained at 6 months of age was normal (Figs 3A and B). This patient had transient responses to therapy with corticosteroids and corticotropin and had been treated with benzodiazepines. He was referred to our center because of the evolution of focal features in his electroencephalogram that had not been present earlier. The repeat MR study, obtained at 3 years of age, clearly showed (Figs 3C and D) asymmetry in signal on T2-weighted images that was limited to the right frontal lobe and corresponded very well with localized right frontal lobe electroencephalographic abnormalities. His median nerve somatosensory evoked potentials were symmetric, and he had no hemiparesis, suggesting a lesion in the right frontal lobe anterior to the primary sensory and motor areas, corresponding to the MR. His PET scan (Fig 3E) did not demonstrate asymmetric FDG uptake in the frontal lobes but showed slight asymmetry in the temporal lobes and thus does not correspond to the electrophysiology as closely as does the MR. This patient recently underwent resection of his right frontal lobe sparing the motor strip and has been seizure-free during this brief period of follow-up. Figures 3F and G are photomicrographs of the resected right frontal lobe from an area near the edge of the resection, and microscopic cortical dysplasia is seen in Figure 3G.

Discussion

Because infantile spasms are a developmental stage–sensitive syndrome with a wide range of causes, neuroimaging studies have concentrated mainly on infants with a visible structural lesion. The MR appearances of gross neuronal migrational anomalies such as agyria, pachy-

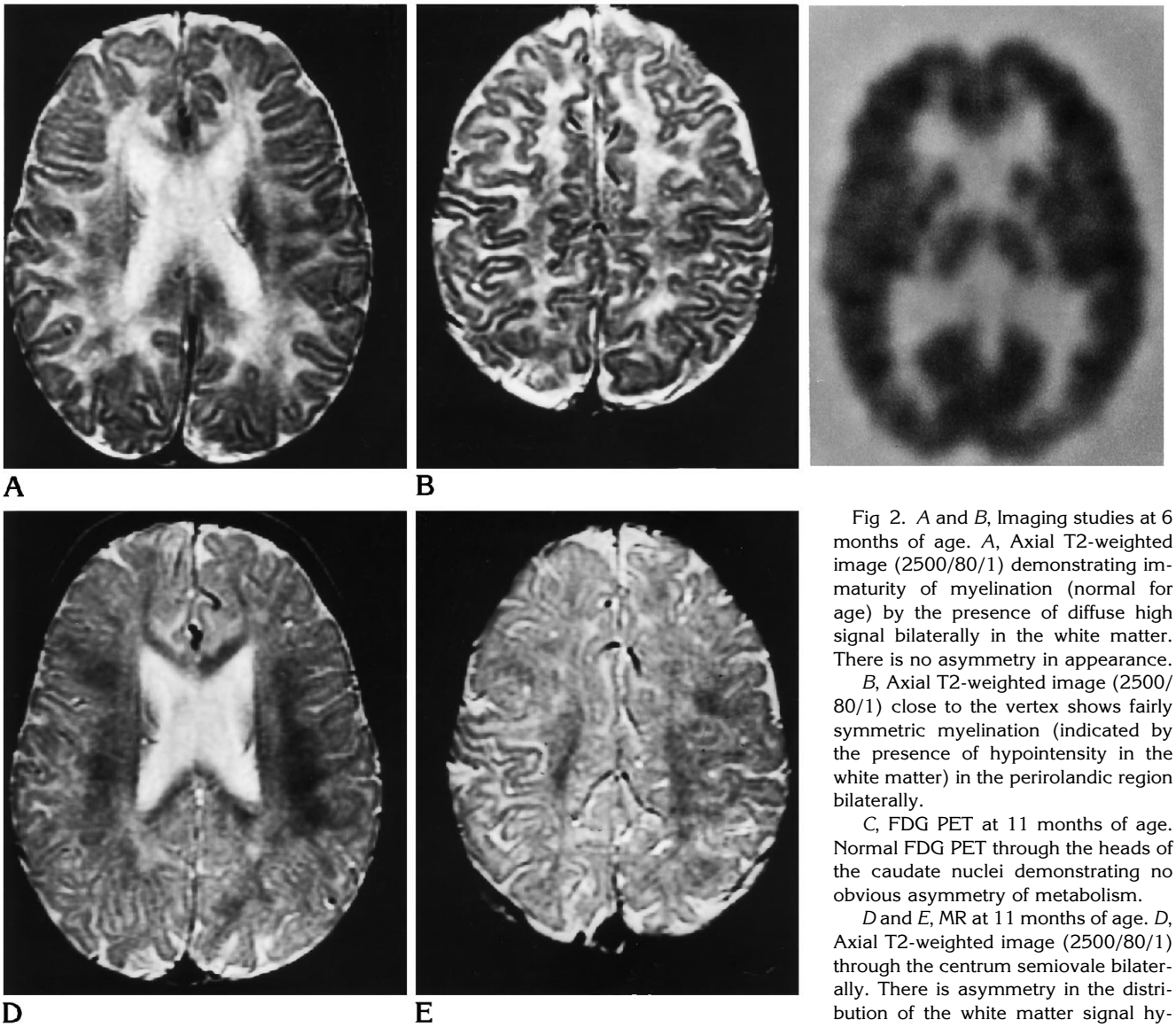

Fig 2. *A* and *B*, Imaging studies at 6 months of age. *A*, Axial T2-weighted image (2500/80/1) demonstrating immaturity of myelination (normal for age) by the presence of diffuse high signal bilaterally in the white matter. There is no asymmetry in appearance.

B, Axial T2-weighted image (2500/80/1) close to the vertex shows fairly symmetric myelination (indicated by the presence of hypointensity in the white matter) in the perirolandic region bilaterally.

C, FDG PET at 11 months of age. Normal FDG PET through the heads of the caudate nuclei demonstrating no obvious asymmetry of metabolism.

D and *E*, MR at 11 months of age. *D*, Axial T2-weighted image (2500/80/1) through the centrum semiovale bilaterally. There is asymmetry in the distribution of the white matter signal hypointensity, particularly peripherally, a change reflecting poorly developed myelination on the right.

E, Axial T2-weighted image (2500/80/1) through the region of the vertex. Again noted is asymmetry of myelination, the left being more abundant than the right.

gyria, polymicrogyria, hemimegalencephaly, and different types of gray matter heterotopias have been well described (19–27). However, subtle lamination defects of the cortex that do not involve significant variance in the thickness of the cortical mantle may not be readily identifiable in the MR of infants at the typical age of onset of infantile spasms (3 to 6 months). Functional neuroimaging with PET of local cerebral glucose metabolism has been considered the imaging modality of choice in defining focal cortical microdysgenesis in cryptogenic cases (10–12). There have been several reports describing the utility of FDG PET in delineating regions of focal cortical microdysgenesis (10–12) that have been missed by computed tomography or MR. Careful review of the data in the reports describing the use of PET to identify cortical microdysgenesis that was not detected by computed tomography or MR revealed that the PET scan had been generally obtained several months (sometimes years) after the initial MR.

Cryptogenic cases in which MR findings are normal are not likely to be reimaged. Such cases, if they continue to be refractory for an

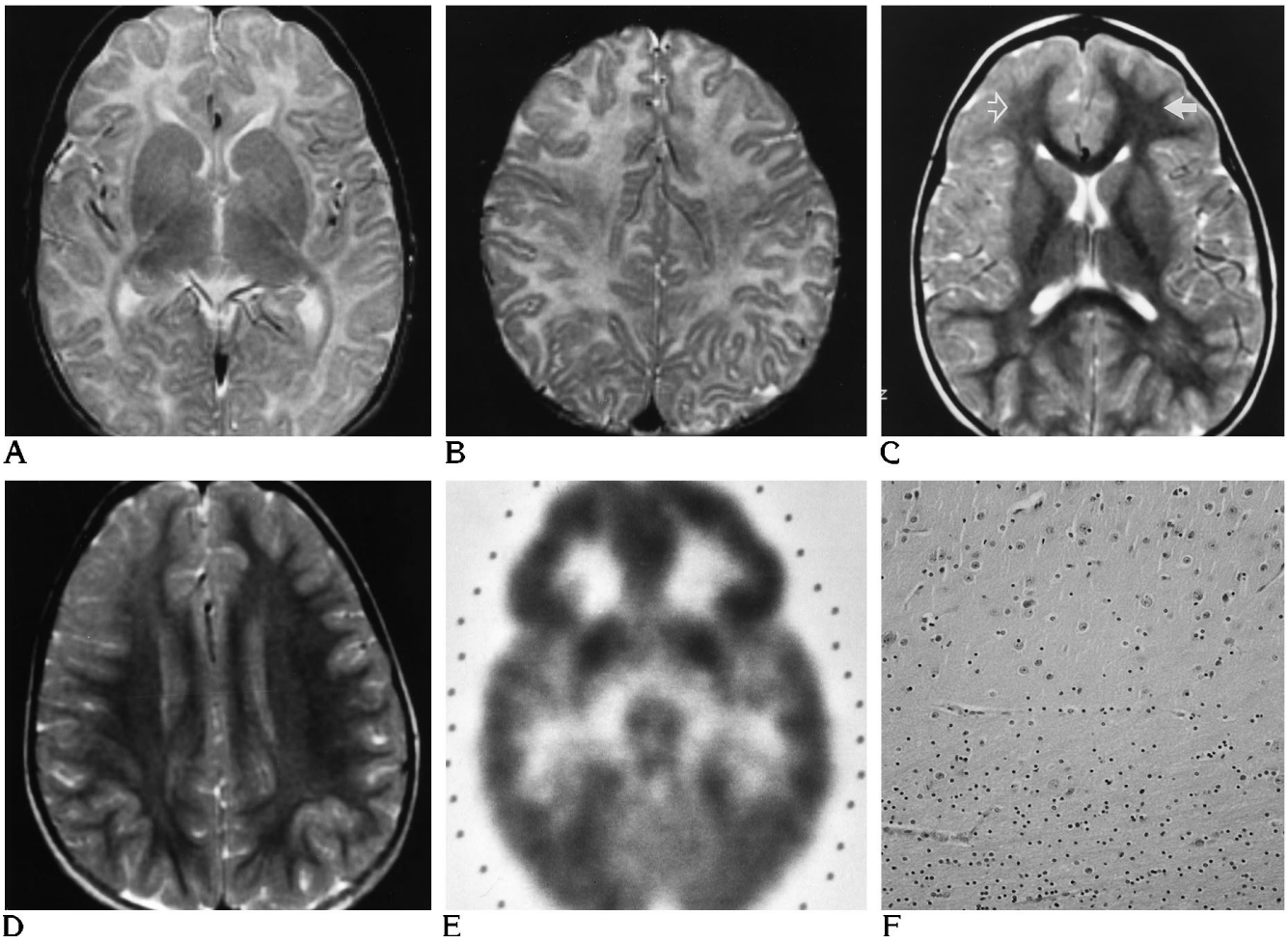

Fig 3. *A* and *B*, MR at 6 months of age. *A*, Axial T2-weighted image (2500/80/1) at the level of the internal capsule. The gray matter–white matter boundary is well delineated, and there is no inequality of distribution of white matter.

B, Axial T2-weighted image (2500/80/1) through the region of the vertex. No asymmetry is noted in the distribution or myelination of white matter between the two hemispheres.

C and *D*, MR at 36 months of age. *C*, Axial T2-weighted image (2300/80/1) through the internal capsule. There is symmetric myelination throughout the white matter except in the frontal lobes. The left frontal lobe white matter is normal (*solid arrow*); the right lobe white matter is relatively hyperintense (*open arrow*) with loss of the gray matter–white matter junction. This latter appearance is consistent with an area of cortical dysplasia.

D, Axial T2-weighted image (2500/80/1) through the vertex again demonstrating the asymmetry of myelination in the frontal lobes and the loss of gray matter–white matter discrimination in the right frontal lobe.

E, FDG PET (at 36 months of age) demonstrating no asymmetry of metabolism in the frontal lobes.

F and *G*, Two sections stained with hematoxylin and eosin from the right frontal lobe after surgical resection (magnification, × 220). In both cases the pial surface is at the top of the section outside of the field of the micrograph.

F, Section of the cortical mantle and adjacent white matter. The normal cortex–white matter junction is well demarcated and shows relative paucity of neuronal cell bodies.

G, Section of the cortical mantle and adjacent white matter. This demonstrate a collection of abnormally oriented and slightly atypical neurons (ie, the area that lies transversely between the *two arrows*) in a comparable location, affected by mild cortical dysplasia. The normal topography between the white and gray matter seen on the previous section is lost.

extended period, get referred to tertiary centers where functional imaging is often obtained in the course of evaluation.

In a study on the MR of neuronal migrational disorders, Barkovich et al (19) had noted the appearance of diminished white matter underlying the abnormal cortex in cases of polymicrogyria. Poor myelination of the white matter adjacent to a diffusely abnormal and thickened cortex has been demonstrated by brain biopsy in a report by Marchal et al (20). White matter abnormalities have also been reported by Palmini et al (22) in the MR of patients with macrogyria. In the presurgical evaluation of several cases of lateralized neuronal migrational disorders such as hemimegalencephaly, we have observed asymmetries in the white matter signal on MR, which corresponded to abnormal white matter maturation in the resected hemisphere.

Several studies (13–18) have described in detail the substantial and predictable signal changes in the MR of the developing human brain during the first 2 years of life. These changes in the MR signal pattern of the white matter are considered to represent maturational changes in the myelination of the developing brain. We hypothesize that maturation of the subcortical white matter is influenced by the overlying cortex, and that any abnormality of the maturation of this white matter secondary to a microdysplastic cortex would not be evident on MR at the age of presentation of infantile spasms but may become readily discernible at a stage when myelination would be expected to have advanced in a manner described by the above (13–18) studies. Therefore we interpret the relatively high signal in the white matter on T2-weighted MR as evidence of dysmyelination. We chose to reimage cryptogenic patients with MR at a time when FDG PET was being contemplated, to make a more meaningful comparison of these two different imaging modalities in delineating microscopic cortical dysplasia.

Our results demonstrate that the ability to discern microscopic cortical dysplasia by MR in these cases is strongly influenced by the timing of the study. At least in these cases, the follow-up MR seems superior to FDG PET in delineating the abnormality. It has been suggested (12) that the detection of such lesions on PET scans may be enhanced by the application of region-of-interest analysis. Although enhanced detection by the application of such semiquantitative methods has indeed been reported by Theodore et al (28) in cases of adult temporal lobe epilepsy, this has not been the case in our limited experience with the application of region-of-interest methods to the PET scans of these children. We suspect that the adult temporal lobe images in cases of mesial temporal sclerosis are much more amenable to use of a standardized template for region-of-interest analysis as reported by Theodore et al (28). It is difficult to establish the region of interest in a standardized manner in the type of lesions encountered in infants, because of the wide variation in the extent of cortical abnormalities in these cases. It is possible that FDG PET may show subtle foci at a later stage, as stated by Chugani et al (12). However, in the cases described in this report, it is clear that MR provided a clear delineation of abnormalities that correlated with the clinical presentation and electrophysiology at a stage when PET did not. A similar progression of focal abnormality in the white matter signal by 3 years of age in a patient whose MR had not been considered abnormal at the age of 6 months is described in a very recent report by van Bogaert et al (29), but comparison with functional imaging was not available. It is also possible that phase-sensitive inversion recovery pulse sequences as used by Christophe et al (17) in studying normal maturation may provide a means of earlier identification of subtle asymmetries in the maturation of myelin.

We conclude that an infant with intractable seizures who shows focal or lateralized features on follow-up neurologic examinations and/or focal or lateralized findings in clinical electrophysiologic testing in the setting of a previously diagnosed cryptogenic infantile spasms deserves follow-up MR imaging. Our three cases suggest that MR may be more sensitive than PET in detecting certain types of microscopic cortical dysplasia.

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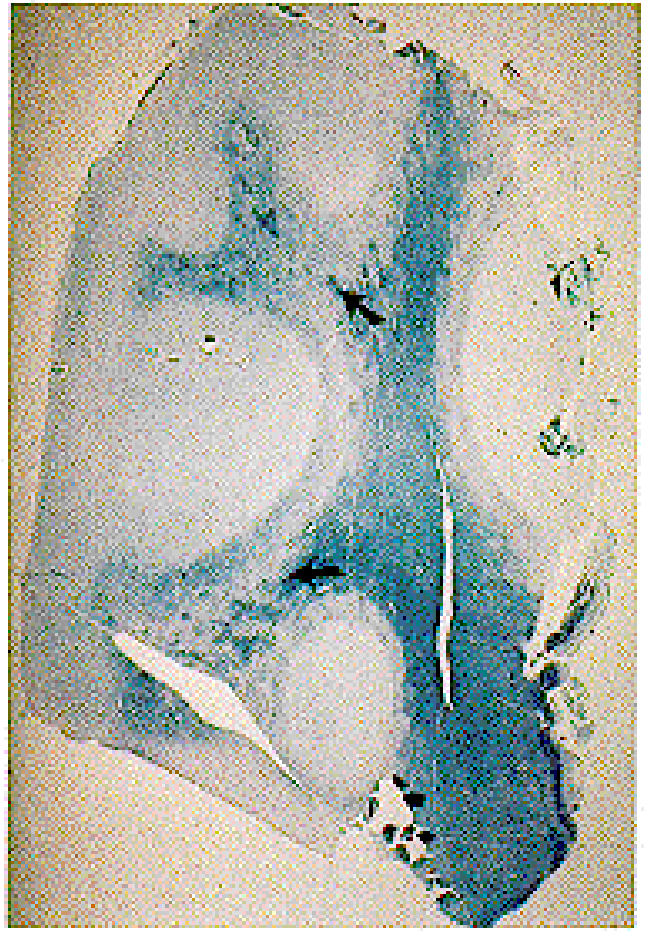

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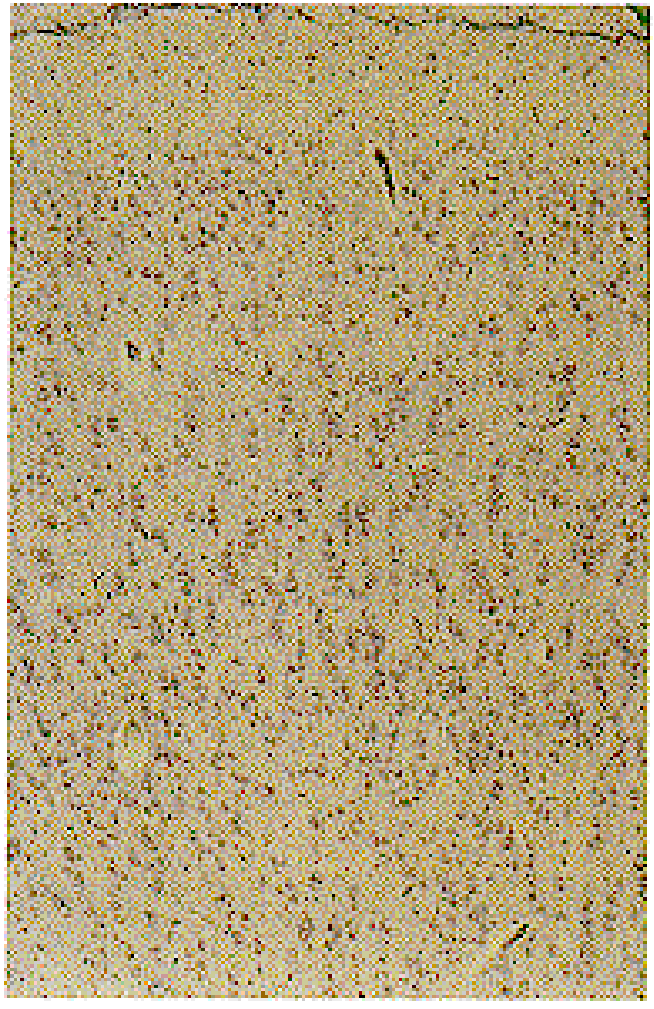

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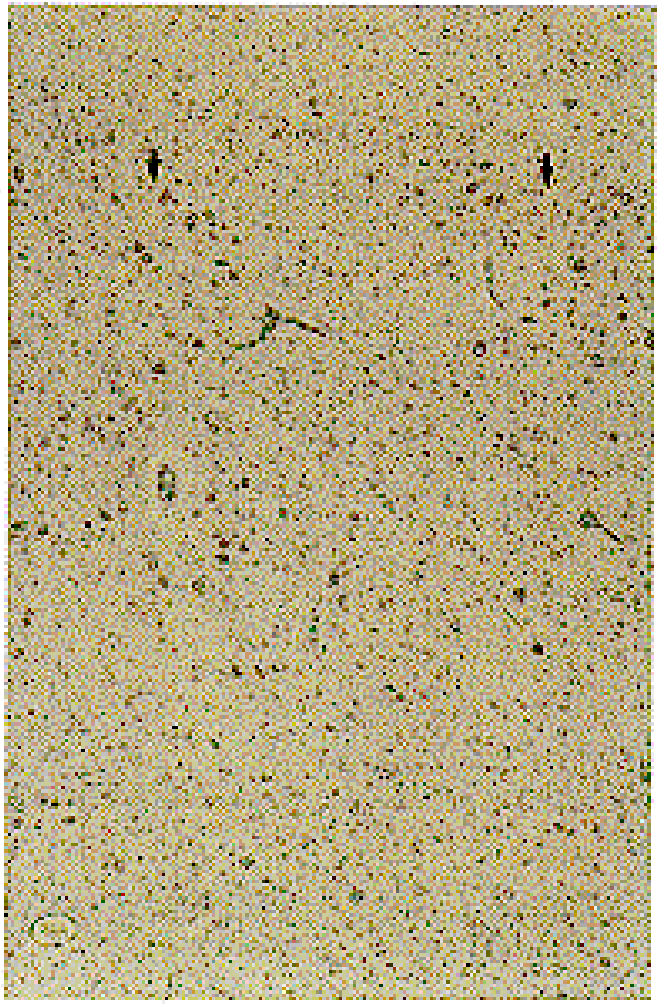

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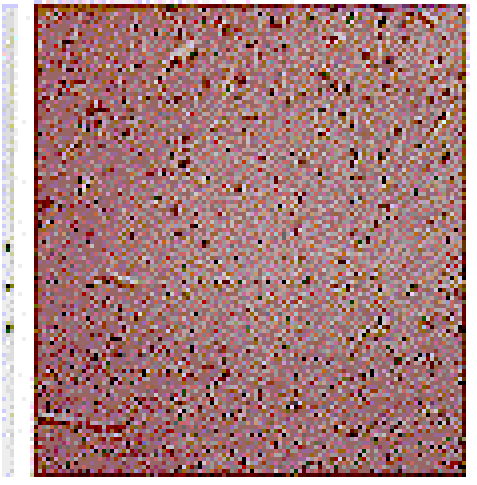

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