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Case Report

Advanced MR Imaging of Cortical Dysplasia with or without Neoplasm: A Report of Two Cases

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Summary: We herein describe two cases of patients with epilepsy with occipital lobe cortical dysplasia who were studied with both MR spectroscopy and MR diffusion imaging in addition to conventional MR imaging. Greater diffusion abnormalities, as well as more marked decreases in *N*-acetylaspartate, were observed to occur in the patient harboring a low grade neoplasm within an area of cortical dysplasia than in the patient with cortical dysplasia alone.

Cortical developmental malformations are a well-recognized cause of medically refractory epilepsy. We describe two cases of young patients with epilepsy with occipital lobe cortical dysplasia who underwent MR diffusion imaging and MR spectroscopy in addition to conventional MR imaging.

Case Reports

Case 1

A 10-year-old white female patient, who was born full-term, had been well from birth until 2.5 years of age, when her mother noted staring spells. A diagnosis of complex partial seizures was made. Since that time, the patient had been receiving antiepileptic drug(s), achieving fair seizure control. In addition, at 8 to 10 months of age, she was noted to have hyperpigmented areas on her trunk and the diagnosis of neurofibromatosis type I was made. However, considering the continuing seizures and the diagnostic possibility of brain tumor, her condition was further investigated for possible cortical resection at our institution at the age of 10 years.

Serial MR images revealed a lesion involving the right mesial occipital lobe, displaying marked hyperintensity on fluid-attenuated inversion recovery (FLAIR) coronal view images, as shown in Figure 1, without interval changes noted. Two nodular foci of enhancement within the dysplastic thickened right occipital cortex were noted on contrast-enhanced T1-weighted images. A neurologic examination revealed a left homonymous hemianopsia.

The seizures consisted of an aura of vision of an approaching locomotive and then a period of unresponsiveness and behavioral automatisms. The frequency of seizures immediately before surgery was four to six per week. Interictal EEG showed frequent epileptiform discharges from the right temporo-occipital region and seizures that originated from the right posterior occipitotemporal region. Subsequently, recordings from implanted subdural EEG electrodes revealed that the habitual seizures originated from the right mesial and suboccipital areas. These regions were resected without additional neurologic deficit. The patient remained seizure free without receiving antiepileptic drugs during 2 years of follow-up.

^{1}H MR spectroscopy was performed before surgery, using the single voxel point-resolved spectroscopy technique with 1500/270 (TR/TE) and voxel sizes of $2 \times 2 \times 2$ cm. The voxels were placed over abnormal right occipital cortex (displaying structural abnormalities on conventional FLAIR, magnetization-prepared rapid acquisition gradient-echo, and spin-echo T1-weighted images) and homologous areas of normal contralateral occipital cortex (Fig 2). In addition, these cases were studied by using trace echo-planar diffusion-weighted MR imaging. Apparent diffusion coefficient (ADC) maps were also generated. Diffusion-sensitizing gradients applied in three orthogonal directions (x, y, and z) with b values of 0, 500, and 1000 s/mm^2 were used for ADC computation. Regions of interest centered on the abnormal right occipital lobe and on the normal left occipital lobe were generated for each patient by using the ADC map images (Fig 3). Quantitative assessments of average ADC values within each chosen region of interest were made, and the ratio of the mean ADC value in the abnormal side to the mean ADC value of the normal side is presented in Table 1.

Histologic examination revealed a 0.5-cm neoplasm characterized by a vascular, reticulin-positive stroma, abundant dysplastic, often binucleate, neurons, and a glial fibrillary acidic protein-positive astrocytic component, consistent with the diagnosis of ganglioglioma (1) (Fig 4). Immunohistochemistry for neurofilament highlighted the dysplastic neurons within the neoplasm as well as widespread severe cortical dysplasia with neuronal cytoskeletal abnormalities in the adjacent cortex. Cortical dysplasia was noted in the specimen containing the neoplasm as well as adjacent resected cortex. Other features of cortical dysplasia noted were loss of normal cortical architecture, persistent subpial granular layer, and a number of glioneuronal hamartia. The coexistence of cortical dysplasia and neoplasia is a well-described phenomenon that occurs in patients with epilepsy (2).

Case 2

A 20-year-old white female patient had suffered from medically intractable simple and complex partial seizures since 4.5 years of age. Seizures were characterized by an expression of fear and then by head turning to the left and facial twitching with or without secondary generalization. The frequency of seizures was four to six per day. At the age of 8 years, she was evaluated with chronic subdural EEG electrodes at another institution, which failed to localize her seizure focus. Subsequent presurgical evaluation showed frequent epileptiform discharges from the right occipital-posterior temporal region with intermittent diffuse bilateral spikes and slow activity. Scalp ictal EEG did not reveal seizure localization. An intracarotid amobarbital test (Wada test) revealed left language dominance and memory dysfunction on the right compared with the left. No visual field defect was documented preoperatively. Thus, subdural electrodes were placed over the right medial and suboccipital regions and the posterior temporal lobe. The ictal zone

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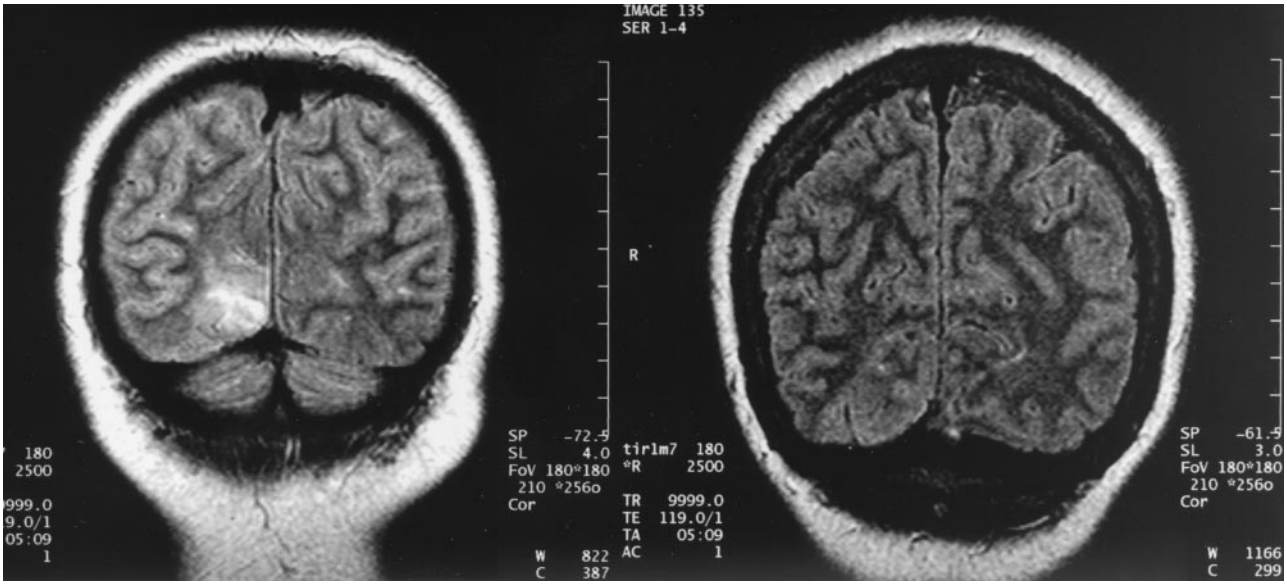

FIG 1. Coronal view FLAIR images from case 1 (*left*) and case 2 (*right*) (9999/119/1 [TR/TE/NEX]) show hyperintensity in the ganglioglioma within the right occipital lobe in case 1 and isointensity to normal gray matter in the benign cortical dysplasia in case 2.

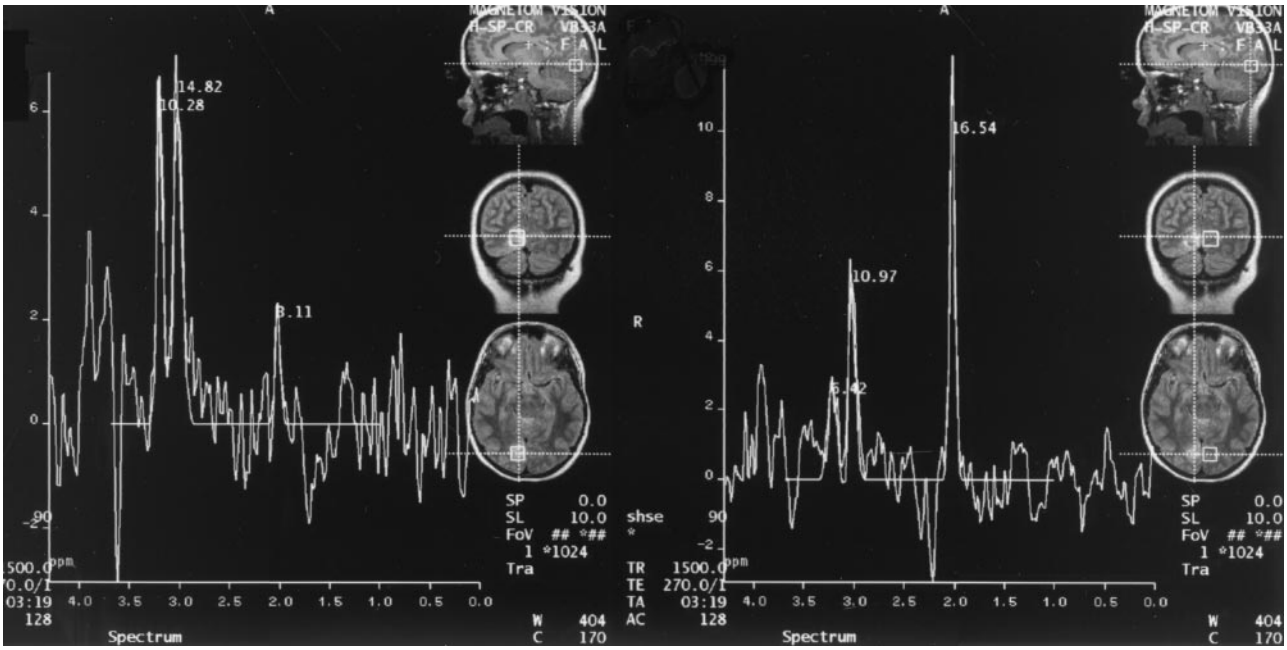

FIG 2. MR spectra from case 1 (1500/270; number of signals acquired, 128), obtained by using a 2 × 2 × 2 cm voxel centered within abnormal right occipital tissue (*left*) and within normal left occipital tissue (*right*), show reduced NAA/Cr and NAA/Cho ratios in the abnormal right occipital tissue compared with the normal left occipital tissue.

localized to the right suboccipital, medial, and lateral occipital region diffusely. This patient's MR imaging showed abnormally thickened isointense cortex on both FLAIR (Fig 1) and magnetization-prepared rapid acquisition gradient-echo images. A right inferior occipital lobectomy was performed. The patient experienced significant seizure reduction (Engel class III) with a complete homonymous hemianopsia during the first 18 months of clinical follow-up.

MR spectroscopy and MR diffusion imaging with ADC mapping was performed before surgical resection of the lesion by using the same techniques as described above for case 1 (Figs 3 and 5). When compared with case 1, absence of significant FLAIR hyperintensity, as well as lower ratio of *N*-acetylaspartate (NAA)/creatine (Cr) in the normal side to NAA/Cr in the abnormal (lesion) side (1.06 versus 7.19), lower ratio of NAA/choline (Cho) in the normal side to NAA/Cho in the abnormal side (2.99 versus 8.60), and lower ratio of mean ADC value in the abnormal side to mean ADC value in the normal side were noted (Table 1).

Histologic examination of the surgical specimen revealed most of the specimen to exhibit widespread disruption of the normal cortical architecture with numerous enlarged, malaligned neurons (Fig 6). The abnormal neurons were shown to be accumulating cytoplasmic neurofilaments by immunohistochemistry and the Bielschowsky silver impregnation stain. These changes were interpreted as being diagnostic of severe cortical dysplasia with neuronal cytoskeletal abnormalities by the grading system proposed by Mischel et al (3).

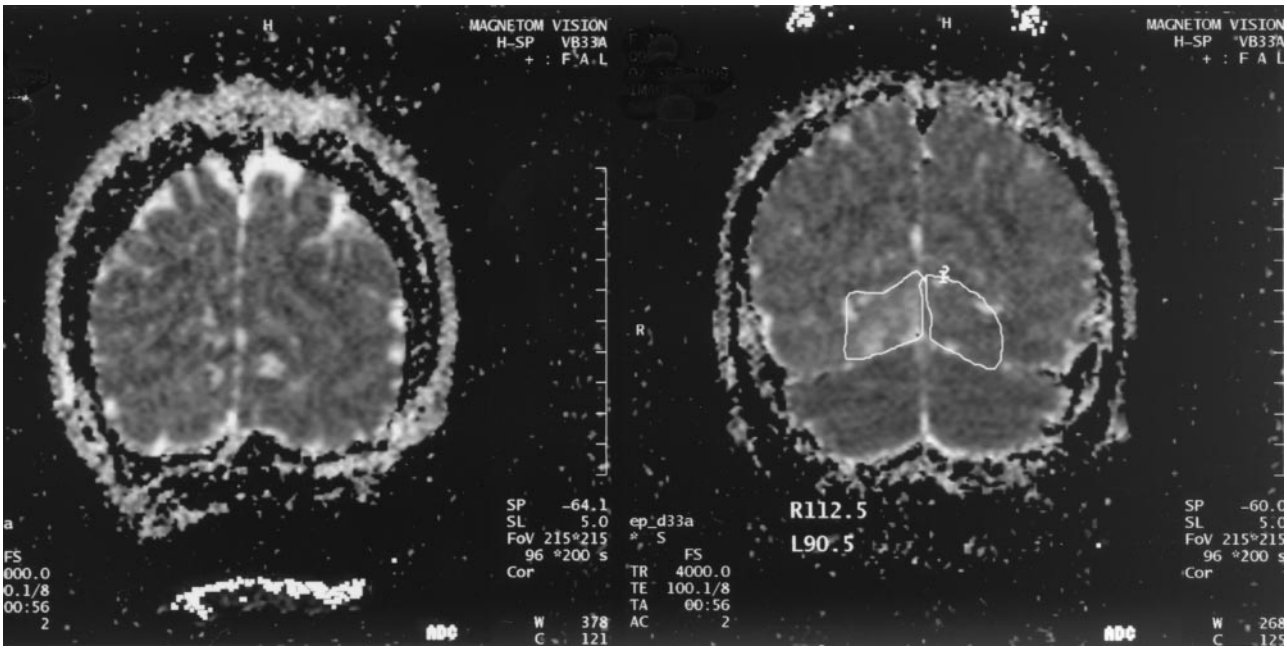

FIG 3. ADC maps (4000/100/2) from case 2 (*left*) and case 1 (*right*). Mean ADC measurements within regions of interest encompassing the dysplastic right occipital cortex and normal contralateral homologous region in case 1 are displayed. Note the hyperintensity (indicative of increased ADC values) in the right occipital cortex in case 1 and the isointensity in case 2.

Metabolite ratios and ratios of mean ADC values in abnormal occipital cortex versus those in contralateral homologous normal occipital cortex

	Case 1	Case 2
NAA/Cr, normal side	1.51	1.52
NAA/Cr, abnormal side	0.21	1.43
Ratio of NAA/Cr, normal side to ratio of NAA/Cr, abnormal side	7.19	1.06
NAA/Cho, normal side	2.58	4.01
NAA/Cho, abnormal side	0.30	1.34
Ratio of NAA/Cho, normal side to ratio of NAA/Cho, abnormal side	8.60	2.99
Cho/Cr, normal side	0.58	0.38
Cho/Cr, abnormal side	0.70	1.06
Ratio of Cho/Cr, normal side to ratio of Cho/Cr, abnormal side	1.21	2.79
Ratio of mean ADC value, abnormal side to mean ADC value, normal side	1.22	1.04

Discussion

Malformations of cortical development are thought to be integral in the pathogenesis of epilepsy in >75% of children and in approximately 20% of adults undergoing epilepsy surgery (4). The structural abnormalities noted on structural MR images may not reflect the true extent and functional status of these malformations, because the abnormal metabolic areas may extend beyond the structural lesions in some cases (4). In addition, normal gray matter metabolic activity may be seen in displaced but otherwise normal tissue present within these malformations (4). Although MR spectroscopy has established itself as a sensitive indicator for the lateralization of temporal lobe seizures, less is known about metabolic abnormalities in patients with epilepsy with malformations of cortical development (4). Although many pediatric epilepsy surgery candidates are treated adequately with single stage surgical resection, patients with focal epilepsy secondary to malformations of cortical development often require invasive EEG recording with subdural and depth electrodes to adequately plan surgery and maximize outcome (5). For these reasons, MR spectroscopy may prove to be an important imaging tool to delineate the true extent of these often ill-defined lesions.

Malformations of cortical development may be broadly described as neuronal migrational disorders (and represent a heterogeneous group of cortical abnormalities manifested by anomalies of site, thickness, shape, and organization of cerebral cortex due to complete or partial failure of the neuroblast migration process, which occurs between 8 and 15 weeks of gestation (6). The causes include genetic and chromosomal factors and environmental factors such as hypoxic-ischemic, toxic, and infectious causes (6, 7). An association between such cortical malformations and hippocampal atrophy has also been described, particularly with occipitoparietal epilepsy (8).

Focal cortical dysplasia is associated with characteristic MR imaging features that distinguish them from other malformations of cortical development, which are found in the broader spectrum of neuronal migrational disorders (9). Lee et al (9) reported the following structural features in their series of nine cases of focal cortical dysplasia: gyral thickening (macrogyria), varying degrees of cortical hyperintensity on heavily T1-weighted images (such as magnetization-prepared rapid acquisition gradient-echo images), indistinct gray matter-white matter junctions, hypointensity on T1-weighted images, and hyperin-

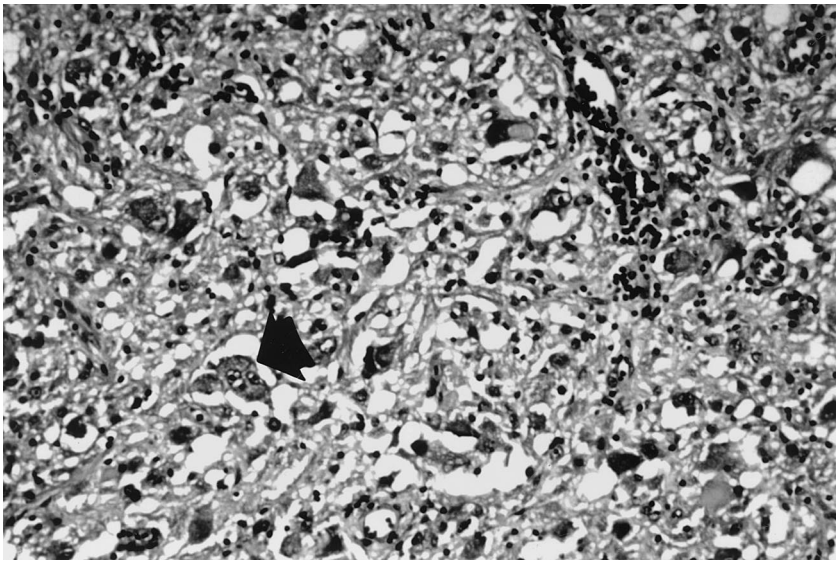

FIG 4. A binucleate neoplastic neuron (*arrow*) is seen in the ganglioglioma (hematoxylin and eosin; original magnification, ×400) in case 1.

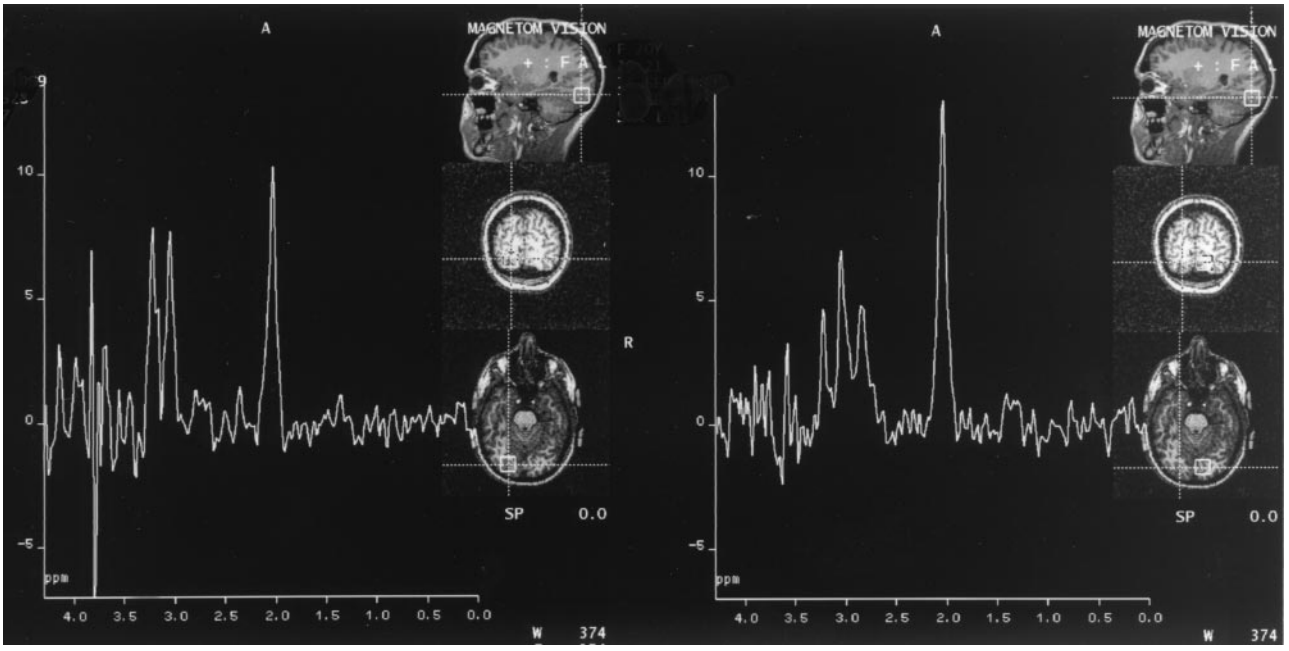

FIG 5. Case 2 spectra (1500/270/128), obtained by using a 2 × 2 × 2 cm voxel size (*left*, right occipital lobe voxel; *right*, left occipital lobe voxel), show reduced NAA/Cr and NAA/Cho ratios in the voxel placed within the abnormal right occipital tissue compared with those obtained in the contralateral normal occipital lobe. However, the degree of the relative reduction is less than that seen in case 1.

tensity on T2-weighted and FLAIR images within the subcortical white matter of affected areas. One of their cases even showed enhancement after the administration of contrast material. They reported that the cortical hyperintensity seen on magnetization-prepared rapid acquisition gradient-echo and other heavily T1-weighted sequences is specific to focal cortical dysplasia, because it is not seen in most cerebral neoplasms and is not present in other neuronal migrational disorders.

Our findings showed greater NAA decrease (decreased NAA/Cr and NAA/Cho ratios) and greater diffusion relative to normal contralateral cerebral tissue in the patient with cortical dysplasia with ganglioglioma as compared with the patient with cortical dysplasia alone. The spectral findings alone are nonspecific, because NAA decreases may be observed in both cortical developmental malformations and low grade neoplasms. In addition, the inclusion of both the neoplastic component and surrounding dysplastic tissue in the sampled voxel in case 1 clearly diminishes the contribution of the neoplastic component to the overall spectrum. The diffusion differences between the lesions in the two cases, however, probably reflect inherent structural and physiological differences rather than transient changes attributable to recent seizure activity, because the patient showing the diffusion abnormality (case 1) showed lower seizure frequency and because neither patient was postictal at the time of imaging. The combined diffusion and spectral findings provide imaging evidence of

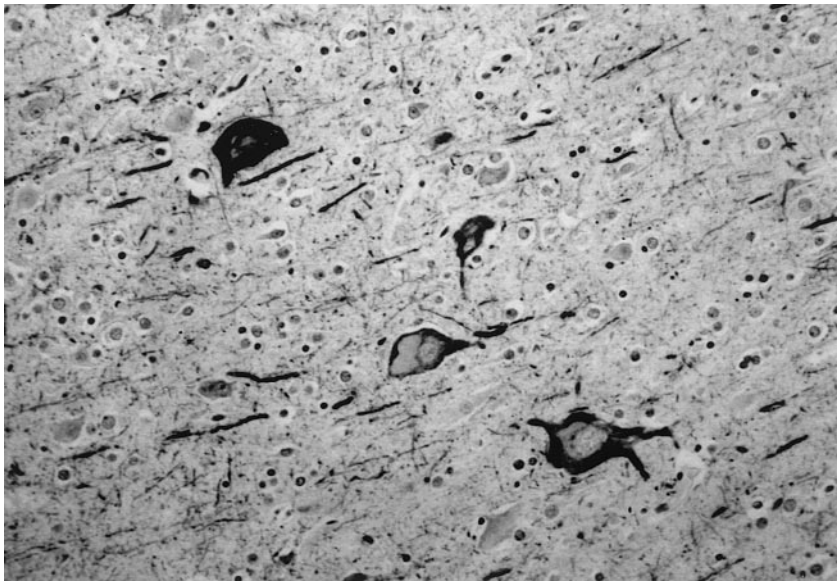

FIG 6. Neurofilament immunohistochemistry shows the enlarged, atypical neurons characteristic of severe cortical dysplasia with neuronal cytoskeletal abnormalities (neurofilament stain with hematoxylin counterstain; original magnification, ×400) in case 2.

pathophysiological differences between the two anatomically similar structural lesions. The presence of FLAIR hyperintensity and contrast enhancement in our case of cortical dysplasia with focal ganglioglioma (case 1) clearly establishes that this structural abnormality represents, at least partially, a neoplastic process; the ADC and spectral findings, however, further elucidate biochemical and diffusion differences between the lesions in the two cases. Thus, although it is clear that further investigation is necessary, it seems that the combination of diffusion MR imaging and proton MR spectroscopy may supplement conventional structural MR imaging in the noninvasive characterization of cortical dysplasia. However, few reports in the literature to date have explored MR spectral findings in cases of malformations of cortical development, and MEDLINE search results suggest that no reports to date have explored diffusion abnormalities associated with such lesions.

Li et al (10) noted different degrees of NAA reduction in different subgroups within the broad category of malformations of cortical development. They found very low NAA/Cr ratios in cases of focal cortical dysplasia, compared with normal NAA/Cr ratios in patients with polymicrogyria and variably normal or abnormal ratios in those with heterotopic gray matter (10). Kuzniecky et al (4) also found in their series that Cr/NAA and Cho/NAA ratios were abnormal in patients with focal cortical dysplasia but not in those with heterotopias or polymicrogyria. In addition, they found a relationship between the frequency of seizures and the presence of metabolic changes; such metabolic abnormalities tended to occur in patients with frequent or intractable seizures (4).

However, the results obtained by Simone et al (6) are somewhat different in that heterotopias were characterized by very low NAA/Cr and Cho/Cr ratios in comparison with the gray and white matter of neurologic controls, whereas no significant differences were found between patients with focal cortical dysplasia and neurologic controls. This group has noted that the reduction in NAA/Cr ratios is directly related to decreases in NAA, because no significant differences in the areas of the Cr peaks were noted in patients with neuronal migrational disorders (6). They also noted reduction of the Cho/Cr ratio both in the hemisphere containing the neuronal migrational disorders and in the contralateral hemisphere, which would suggest a more diffuse bilateral abnormality of brain metabolism in these patients, both within and outside the neuronal migrational disorder lesion itself (6). They also speculated that the disparity between their results regarding NAA reduction in focal cortical dysplasia and those of Li et al (10) and Kuzniecky et al (4) may be related to sampling error associated with their use of spectroscopic voxel sizes, which exceeded the size of the actual metabolic abnormality in their cases of focal cortical dysplasia. Kuzniecky et al had shown that the spatial extent of the metabolic abnormality in focal cortical dysplasia may not be as great as the spatial extent of the morphologic abnormality detected on MR images (4, 6).

Preul et al (11) described a single case of a giant right hemispheric heterotopia that showed markedly decreased NAA compared with normal gray matter. They noted, however, that although the NAA decrease within the heterotopia may reflect the presence of disorganized, dysfunctional nodules of neurons (increased in actual number), the ongoing epileptogenicity of the lesion may also account for the NAA decrease. In addition, this group noted that not only was the extent of the metabolic abnormality greater than the extent of the structural lesion noted on MR images but that the areas of greatest NAA and Cr decrease corresponded to the structurally abnormal regions seen on MR images.

Furthermore, Li et al (12) showed in their group of 51 patients with localization-related epilepsy that 40% to 50% of these patients (38% of the patients with TLE and 50% of those with extra-temporal epilepsy) had MR spectroscopy evidence (ie, abnormal decrease of NAA/Cr ratios on long TE proton spec-

tra) of neuronal metabolic dysfunction, which extended beyond the epileptogenic zone defined by clinical findings, EEG, and/or the structural abnormality defined by MR imaging.

Diffusion MR imaging has been used recently to study both status epilepticus and brain tumors, in addition to the well-known applications in stroke imaging. Reversible cytotoxic edema producing hyperintensity on diffusion-weighted images and decreased ADC values have been noted (13). Furthermore, Gupta et al (14) reported an inverse correlation between Cho signal on proton MR spectra and ADC values in human gliomas. They suggested that although even the more cellular portions of intracranial gliomas show slightly increased ADC values relative to normal tissue, more cellular tumors display relatively decreased ADC values compared with less cellular (with larger components of cyst, necrosis, or edema) tumors. However, no study to date has examined the combined diffusion MR imaging and MR spectroscopy findings in cases of malformations of cortical development.

Although our very small sample size and the histologic heterogeneity of cortical developmental malformations preclude definitive assessment of the usefulness of MR spectroscopy and MR diffusion imaging in the evaluation of cortical dysplasia, we hope that our study will serve as a catalyst for further evaluation of cortical dysplasia with these modalities.

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