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## Focal Cortical Dysplasia with Glioproliferative Changes Causing Seizures: Report of 3 Cases

### Abstract

In contrast to neoplasia, lesions of focal cerebral dysplasia are thought to be completed developmental processes of abnormal neuronal migration. We present three children with seizures resulting from brain lesions which pathologically demonstrate regions of both clearcut focal cortical dysplasia and also hypercellularity and monomorphism typical of proliferative lesions such as low grade glial tumor. These cases suggest the existence of a distinct subgroup of patients with prominent glioproliferative changes in association with focal cortical dysplasia, challenging the conventional dichotomy between dysplastic and proliferative categories of brain lesions. Recognition of patients with dual pathology may be of practical as well as theoretical importance.

### Key Words

Neoplasia

Cortical dysplasia

Epilepsy

### Introduction

Focal cerebral dysplasia is a recognized cerebral lesion of childhood which gives rise to seizures. This disorder is generally interpreted as a developmental process of abnormal neuronal migration, with minimal risk of subsequent neoplastic transformation [1–10]. In contrast, epileptogenic neoplastic lesions, even if low grade, are known to have a potential for growth and recurrence [3, 8, 11, 12]. We recently treated 3 children who presented with seizures arising from lesions found on resection to demonstrate both focal cortical dysplasia and regions of hypercellular and monomorphic glial proliferation resembling glioma. The 3 patients shared several clinical and radiographic features. We suggest that there is a subgroup of patients with seizures and mass lesions who have a distinctive histopathologic picture characterized by focal cortical dysplasia and glioproliferation. This entity challenges a strict dichotomy between dysplastic and proliferative disorders. Recognition of these cases depends on

histological observation of focal dysplasia in normal-appearing tissue adjacent to the glial proliferation, and may be overlooked if resection is less extensive.

### Case Reports

*Case 1.* A 4-year-old Asian girl presented with a 6-month history of intermittent episodes lasting 1 or 2 min, with typically 10–15 episodes per day. These episodes consisted of abnormal feelings in her abdomen, hyperventilation, some automatic activity with her left hand with subsequent fatigue. Her neurological examination, reading skills and school performance were normal. An EEG 1 month prior to surgery showed an area of focal spike activity in the right temporal lobe, and an MRI scan showed a right temporal lobe mass (fig. 1). An ill-defined extensive T<sub>2</sub> signal abnormality in the right medial temporal lobe was found to extend across the Sylvian fissure into the medial subfrontal area and into the basal ganglia and external capsule. There was no enhancement with gadolinium, and the preoperative impression was that this was most likely an infiltrative glial tumor. The tumor was removed with a postoperative scan showing a small area of bright signal on the T<sub>2</sub> studies in the posterior

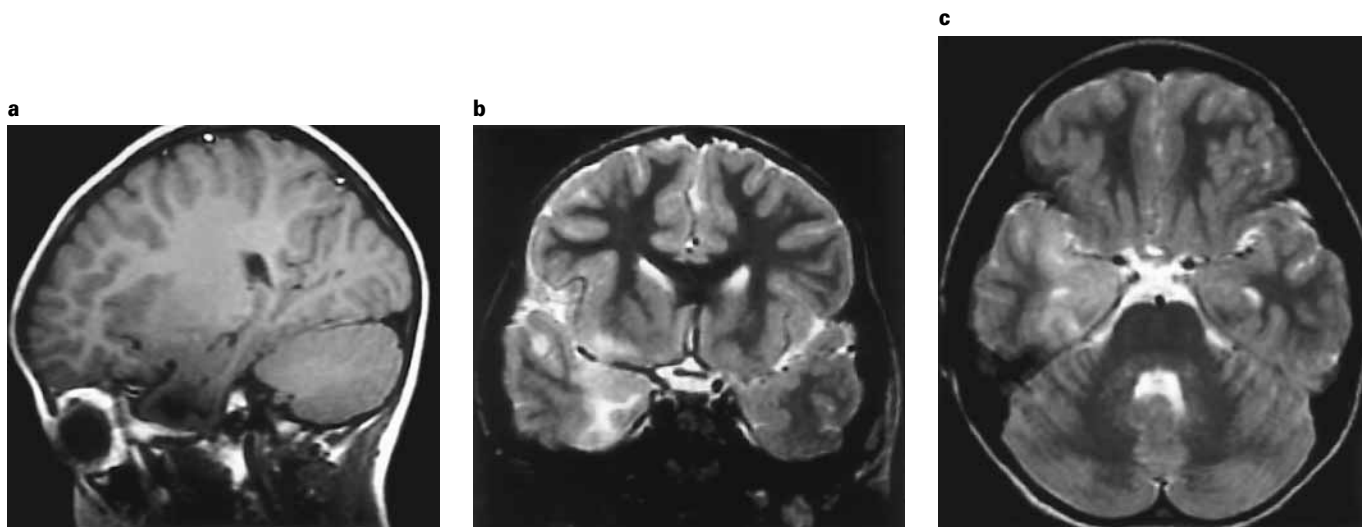
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**Fig. 1.** MR images of case 1. Sagittal (**a**) demonstrates a hypointense lesion in the right temporal lobe. Coronal (**b**) and axial (**c**) fast spin echo (FSE) images show an ill-defined hyperintense  $T_2$  signal abnormality extending across the Sylvian fissure into the medial subfrontal area and into the basal ganglia and external capsule. There was no enhancement with gadolinium (not shown).

temporal lobe, which remained entirely stable on a scan 6 months later with no evidence of residual or recurrent mass. She remains seizure-free after withdrawal of anticonvulsants with no neurological abnormalities.

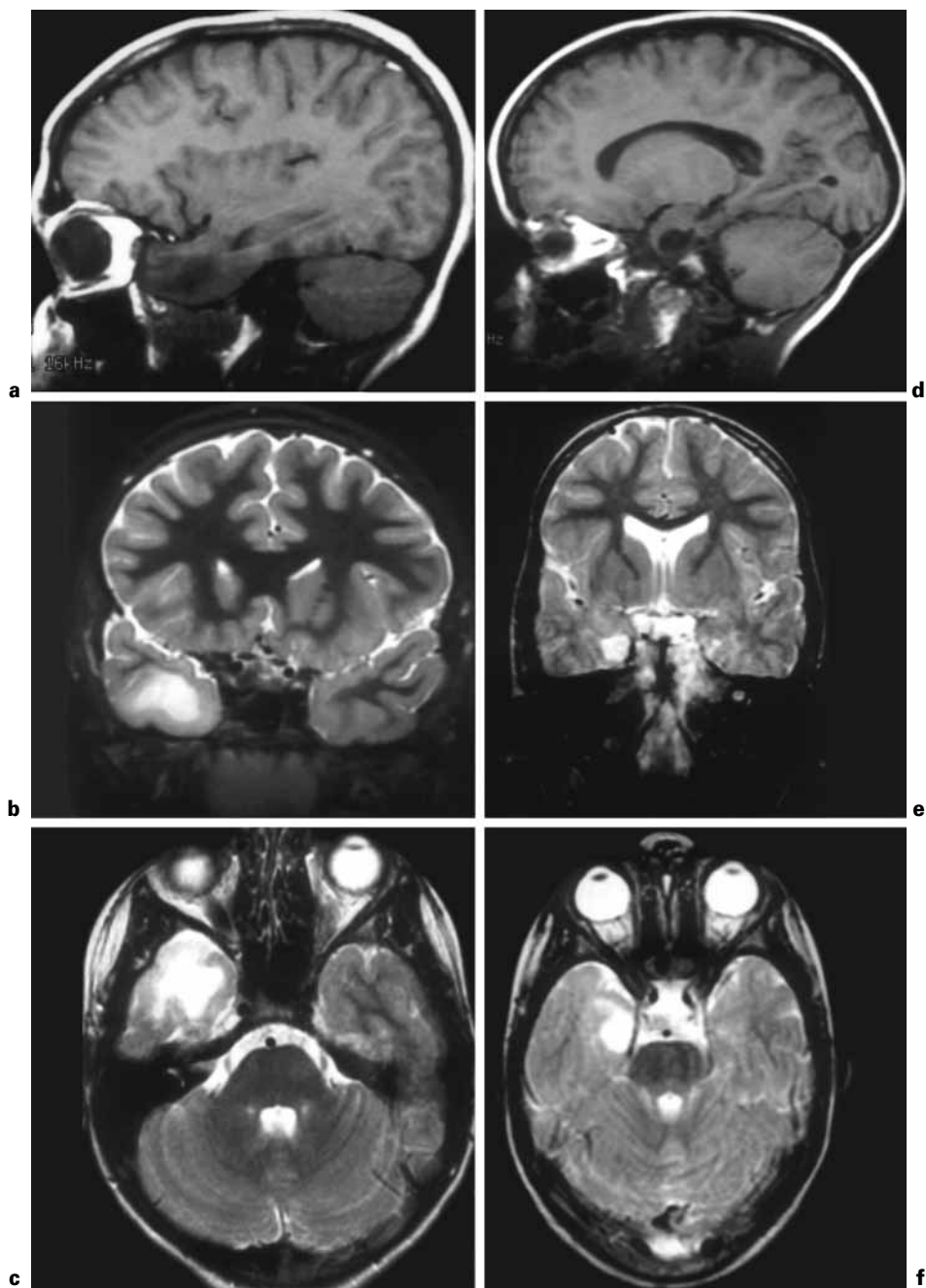
*Case 2.* A 9-year-old Caucasian girl was healthy until 3 months prior to presentation, when, after a febrile illness, she began having 1- to 2-min episodes of staring, repetitive movements with her hands, and occasional mumbling. Up to 2 episodes would occur per day and up to 5 in 1 week. She would report feeling tired after each episode, but there were otherwise no neurological sequelae. There was no specific aura. On one occasion, she fell while climbing a jungle gym in school. Two EEG studies were performed; the first was apparently normal but the second was abnormal with slowing over the right frontal and temporal regions. The neurological examination was otherwise entirely normal. An MRI study demonstrated an area of  $T_2$  signal abnormality in the right temporal lobe that extended virtually from the tip of the temporal lobe posteriorly for a distance of 3.2 cm (fig. 2). The lesion spared the superior temporal gyrus and the middle cerebral artery, and did not involve the Sylvian fissure. It did not enhance with gadolinium. The remainder of the brain appeared normal. The lesion was resected through a right temporal craniotomy without difficulty. A postoperative MRI scan and one repeated 1 year later showed no evidence of recurrent or residual mass. The patient was tapered off of anticonvulsants and is free of seizures.

*Case 3.* A 3-year-old Hispanic girl presented with a 5-month history of seizure episodes during which she would look straight ahead, become pale, develop a stiff facial expression, and then extend her arms with wrists flexed and fingers spread apart and stiff. This would last for about 1 min and she would be unresponsive without memory of the event. After the spell, she would complain of being tired and needing to sleep. Carbamazepine was started 3 months prior to the surgery, with seizures stopping for 1 month and then recurring in the same pattern. On medications, she continued to have approximately one seizure per day. An MRI scan obtained 2 months prior to surgery

demonstrated a right medial temporal lobe lesion. There was no gadolinium enhancement. She was felt by her parents to have a somewhat diminished attention span and overactivity, but was otherwise neurologically normal. EEG demonstrated a tendency for slow high-amplitude background 6-Hz alpha-like activity of widespread extent, and with drowsiness, runs of slowing, and paroxysmal theta activity and frank spikes originating in the right mid- and posterior temporal electrodes. She underwent surgical resection of the lesion. A postoperative MRI scan showed complete resection of the lesion, and she remains entirely seizure-free after surgery, without recurrence of seizures after withdrawal of anticonvulsants at 10 months postoperatively. An MRI scan obtained at that time showed no evidence of recurrent or residual tumor. The postoperative EEG showed resolution of the focal right temporal abnormality, but the generalized posterior predominant discharges remain unchanged.

#### *Radiologic Findings*

MR imaging using a 1.5-Tesla system was performed in all 3 patients. Imaging consisting of sagittal  $T_1$ , FSE (fast spin echo) axial proton density, FSE axial  $T_2$ , and coronal FSE  $T_2$  was done. After the administration of gadolinium, axial  $T_1$  and coronal  $T_1$  images were obtained. All lesions were hypointense compared to gray matter on  $T_1$  images and hyperintense on  $T_2$ -weighted images. There was no enhancement after intravenous contrast in any of the three lesions. In 2 patients (cases 1 and 2) the lesions were hyperintense on proton density images. In 1 patient (case 3) the central portion of the lesion was hypointense on proton density with peripheral hyperintense signal. In 2 of the patients (cases 2 and 3), the lesions were well circumscribed involving the medial portions of the temporal lobes, involving the gray and white matter and the hippocampus. In these 2 patients the abnormality measured respectively 3.2(AP), 3.2(TX), 2.3(SI) (case 2) and 1.2(AP), 1.0(TX), 1.0(SI) (case 3). In 1 patient (case 1), the lesion was ill-defined involving the right medial temporal lobe gray matter and white matter and the hippocampus with



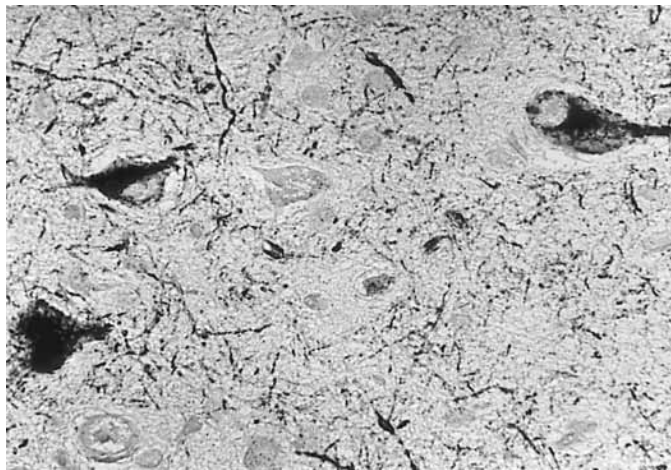
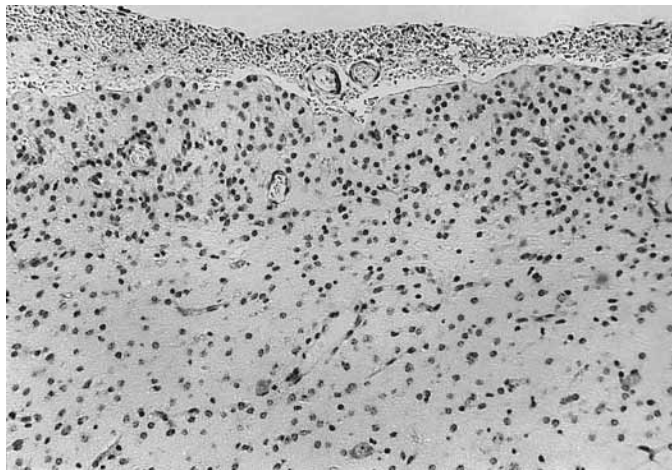
**Fig. 2.** MRI of case 2 (**a-c**) and case 3 (**d-f**). Sagittal T<sub>1</sub> weighted images (**a, d**) demonstrate a well-circumscribed hypointense lesion in the right temporal lobe in each case. Coronal (**b, e**) and axial (**c, f**) FSE T<sub>2</sub> images show a hyperintense lesion in medial right temporal lobe including gray and white matter. The lesion spared the superior temporal gyri and the middle cerebral artery and did not involve the Sylvian fissure. Neither enhanced with gadolinium (not shown).

extension into the right external and extreme capsules. In this patient the lesion could not be measured accurately because of the ill-defined borders. All patients underwent resection of the right temporal lobe, without significant postsurgical findings on followup MR images. There have been follow-up scans in each patient at 7–12 months after surgery, with none showing persistent or recurrent tumor.

#### *Pathologic Findings*

The microscopic findings in these 3 cases were remarkably similar. Two distinctive abnormalities characterized the histopathology

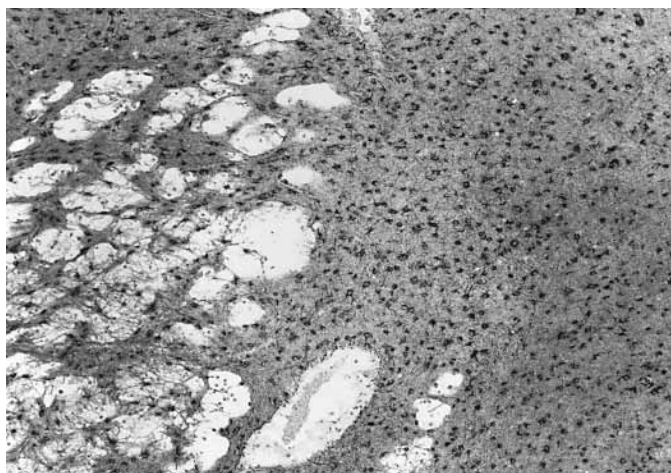
of the lesion: a lesion characterized best as cortical dysplasia, and a lesion characterized by prominent glial hypercellularity (fig. 3). The dysplastic lesion consisted of a remarkable cytoarchitectural abnormality with lack of normal neuronal lamination in the cerebral isocortex and cytologic abnormalities (fig. 4), suggesting a maldevelopmental disorder of neuronal migration and maturation [2, 4]. In the glial proliferative lesion, multifocal regions of hypercellularity were present in both the white and gray matter of the cerebral cortex with a variable amount of nuclear atypia, involving both the abnormally formed gray matter and also the underlying white matter. The densi-



**Fig. 3.** Photomicrograph of a subpial region of cerebral cortex from case 1 showing multiple small nuclei of the proliferating glial cells, with disorganized layering of neurons. Proliferation of glial cell nuclei is evident all the way up into the subpial region of the molecular layer.

**Fig. 4.** A higher power view of cerebral cortex showing abnormally shaped neurons with presence of immunoreactivity for phosphorylated neurofilament in perikarya (case 1). These neurons demonstrate disorganized layers and architecture, demonstrated by immunostaining for neurofilament.

**Fig. 5.** Dramatic proliferation of glial cells with microcystic changes and positivity for glial fibrillary acidic protein in white matter adjacent to lesion. This appearance with this stain could be consistent with a low-grade glial neoplasm (case 1).



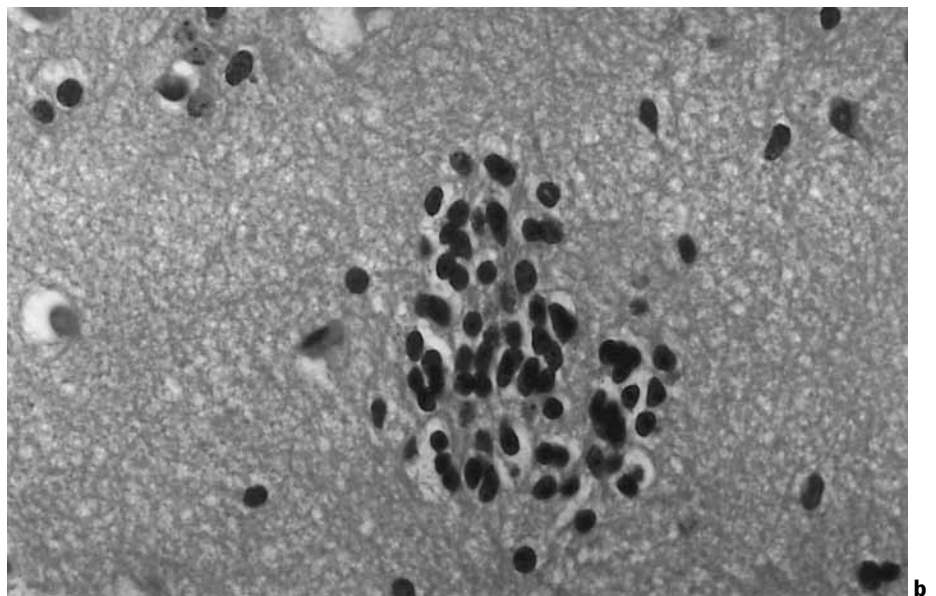
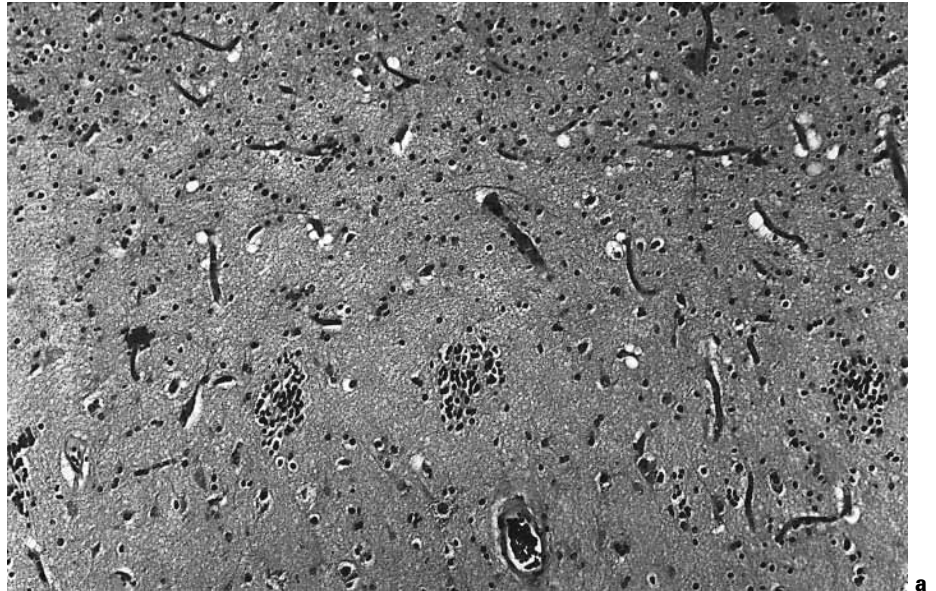
**Table 1.** Radiographic, histological, and clinical characteristics of the three cases

Case	Boundary	Cell density mm <sup>-2</sup>	MIB1 index %	Dysplasia	Follow-up months	Outcome
1	diffuse	1,247	0.039	+	18	seizure-free/no recurrence
2	circumscribed	1,980	0.054	+	24	seizure-free/no recurrence
3	circumscribed	877	0.022	+	21	seizure-free/no recurrence

ty of the glial proliferation raised the possibility of a low-grade astrocytoma (fig. 3, 5). Frequently, these two aspects of the lesion were intermixed or found adjacent to one another. Detailed immunohistochemical and histopathologic analysis of the lesion with special stains revealed that the dysplastic lesion was characterized by abnormalities in neuronal distribution (clustering of neurons, abnormal spacing, cell bodies of large neurons in the molecular layer), neuronal cell size (disproportionately large cell bodies for nuclear size), shape (cell bodies with bizarre shapes) and orientation (neurons with abnormal polarity, such as apical dendrites misdirected parallel to the pial surface or downward; fig. 4). Scattered hypertrophic neurons were seen

in the white matter and aggregates of small round neurons (neuroblast-like) were found in the dysplastic cortex (fig. 6). The abnormally shaped neurons were well demonstrated with the Bielschowsky silver impregnation technique and immunocytochemical studies showed blotchy and irregular immunoreactivity of the neuropil with the antisynaptophysin antibody and immunoreactivity against phosphorylated neurofilaments in the perikaryon of dysplastic neurons.

The proliferative component of the lesion consisted of multifocal and irregularly distributed glial cell nuclei with astrocytic nuclear characteristics. Astrocytic proliferation was noted both in the cerebral cortex and the subcortical white matter. Sometimes the cellular



**Fig. 6.** Scattered hypertrophic neurons were seen in the white matter and aggregates of primitive neurons ('residual neuroblasts') were found in the dysplastic cortex (case 2). Lower (**a**) and higher magnification (**b**) views are shown.

density was especially prominent in the subpial areas where it was associated with capillary proliferation. The GFAP immunocytochemical reaction was intensely positive in these regions whilst the MIB-1 proliferation marker showed a very low proliferative index (<0.1% in each of the cases; table 1). Expression of CD68 cell surface antigen was also present in some cells in the more cellular areas.

### Discussion

The clinical, radiographic, and pathological aspects of the 3 cases presented were strikingly similar. The seizure disorders were all typical partial complex seizures which

came on with multiple brief seizures per day, all with a history of approximately 6 months prior to treatment. With greater than 12 months' follow-up in each case, the short-term results of lesion resection appear excellent, with complete resolution of seizures and withdrawal of antiepileptic medications.

Focal cortical dysplasia, a known cause of epileptic activity [2–10], is generally assumed to result from abnormal cortical neuronal migration. Neoplastic lesions, including those expressing neuronal phenotypes, are characterized by uncontrolled and continuous cell proliferation and mass enlargement. The appearance of neoplastic-like

growth has been described in association with cortical dysplasia in the recently described entity of dysembryoplastic neuroepithelial tumors (DNTs) [13–15]. The clinical importance of distinguishing between dysplastic and neoplastic lesion is the negligible risk of neoplastic progression in the former, but potential for recurrence in the latter.

Instances of concurrent dysplasia and neoplasia have been reported. Prayson and Estes [6] found a high incidence of a hypercellular molecular layer in cases of cortical dysplasia (31 of 52 cases reviewed), although specific evidence of proliferative changes was lacking in these cases. The observed hypercellularity was within the dysplastic cortex, as opposed to the sometimes distinct zones of hypercellularity seen in the cases reported here. A low incidence of specific tumor types, including ganglioglioma (8/52), DNT (3/52), or low-grade astrocytoma (2/52) were also noted. These specific tumor types will be discussed individually.

In a review of gangliogliomas, Prayson et al. [16] identified 38 of these tumors resected with adjacent nonneoplastic cortex, and found evidence of dysplastic architecture in 19 (50%) of the cases, emphasizing the high rate of dysplasia associated with this tumor type. Becker [17] noted that some tumors with neuronal phenotype may be difficult to distinguish from cortical dysplasia. Our cases

differ from the gangliogliomas quite clearly in lacking a neoplastic neuronal component. Absence of gadolinium enhancement also distinguished these cases from the typical gangliogliomas.

The cases reported here also differ from DNTs [13–15] in the absence of the complex multinodular, intracortical proliferation of cells with oligodendroglial-like appearance, and ‘floating neurons’. However, a glial proliferation which could be interpreted as glial neoplasm in some DNTs, and the adjacent cortical dysplasia, are similarities between DNTs and the lesions reported in this paper.

The difficult differential distinction in the cases presented here is between low-grade astrocytoma and proliferating reactive astrocytes. The hypercellularity and the presence of staining with markers of proliferation (MIB-1, Ki-67; expressed in active stages of the cell cycle) suggest that these cases represent slow but active glial proliferation.

Thus far, study of nonneoplastic tissue surrounding tumors of any type has depended on removal of ‘normal’ tissue around a mass, or additional resection intended to improve epilepsy control. With greater appreciation of the difficult distinction between neoplasia and developmental dysplasias with glial proliferation, more careful study of the tissue surrounding the mass may help better define the prognosis in these lesions.

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