RESEARCH ARTICLE

Angiocentric Neuroepithelial Tumor (ANET): A New Epilepsy-Related Clinicopathological Entity with Distinctive MRI

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Several types of glioneuronal tumors are known to induce intractable partial seizures in children and adults. The most frequent are dysembryoplastic neuroepithelial tumors (DNETs) and gangliogliomas. We report here a new clinicopathological entity within the spectrum of glioneuronal tumors observed in 10 children who underwent surgery for refractory epilepsy. These tumors demonstrate a unique, pathognomonic histological pattern and a specific appearance at magnetic resonance imaging (MRI). The most striking neuropathological feature is an angiocentric polarity of the tumor with gliofibrillary acidic protein (GFAP) positive fusiform and bipolar astrocytic cells arranged around blood vessels (perivascular cuffing with tumoral astrocytes). Characteristic MRI findings include involvement of cortical gray and white matter, intrinsically high signal on T1-weighted images, as well as a stalk like extension to the ventricle. Immunohistochemical neuronal markers (neurofilament protein, synaptophysin and chromogranin) confirm the presence of a neuronal cell component. Therefore, the term angiocentric neuroepithelial tumor (ANET) is proposed.

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INTRODUCTION

The development of neurosurgical treatment for medically intractable partial epilepsy in children has given neuropathologists the opportunity to examine resected specimens histologically. Three kinds of lesions are frequently observed in histological samples of surgically removed tissue in the pediatric epilepsy population: dysplasia, tumors and destructive lesions. Dysplastic lesions are the most frequent and consist of various types of focal cortical dysplasias with several classification schemes (2, 12) proposed since the first description by Taylor (19). Glioneuronal tumors also represent a common etiology (7, 10). Among the glioneuronal tumors, gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs) are the best known. However, we have observed other types of complex glioneuronal lesions which are not easily classified using the World Health Organization Classification of Central Nervous System (CNS) tumors (11). In our series of 204 cases of epilepsy surgery specimens, we identified glioneuronal tumors in approximately 20% of patients.

A previously undescribed, apparently unique pattern of glioneuronal tumor was identified in 10 cases from this series. The striking microscopic feature was their vascular polarity with a fusiform and bipolar GFAP-positive astrocytic component forming perivascular cuffs. An associated morphologically evident neuronal component, was confirmed by immunohistochemistry. Neuroradiological review revealed a surprisingly specific appearance at MRI: an intrinsic cortical rim like hyperintensity on T1-weighted spin echo (SE) sequences and a clear subcortical hyperintensity with a stalk like extension to the ventricle on T2-weighted and FLAIR sequences.

Based on the histopathological characteristics, we propose to refer to this new entity as "angiocentric neuroepithelial tumor" (ANET). We describe here the clinical, radiological and neuropathological features in 10 patients with this new entity in order to increase awareness among pathologists and promote a better understanding of glioneuronal tumors.

MATERIALS AND METHODS

Patients. The patients were selected from a population of 204 children aged 2 to 14 years whose specimens were referred for neuropathological diagnosis from 3 pediatric neurosurgical centers (Necker-Enfants malades, Fondation Rothschild and Hôpital neurologique de Lyon). Ten patients (5 boys, mean age at surgery 9.2 ± 4.5 [range 2.3 -14.5]) years were studied. The age at epilepsy onset ranged from 2 to 13 years mean age 6.9 ± 3.9 years. Inclusion criteria were: partial seizures refractory to medical treatment, indication for neurosurgery, and the characteristic neuropathological findings of ANET.

All patients were evaluated for intractable partial epilepsy and subsequently underwent surgery. Extensive clinical evaluation included detailed epilepsy history and neurological in addition to general medical examination. All patients had routine EEG studies using the international 10 to 20 system with supplemental temporal anterior electrodes (FT9 FT10). The majority also had long-term video EEG monitoring with scalp electrodes. Some of the patients underwent Intracranial Video-EEG monitoring using either subdural electrodes or intracerebral depth electrodes. The follow-up of epilepsy was assessed using the Engel four category classification of outcome of seizures (6).

Examinations were performed by experienced neurologists. Other than epilepsy

Patient/Sex	Age at epilepsy onset (yrs)	Surgery age Result	Seizure semiology and frequency	Seizure origin	Follow up Engel class Duration
1/F	4	5 GTR	Behavioral arrest, unresponsive, mouth deviation rightward, dystonic right arm posturing 1/ week	Left anterior temporal	lost 13.7 years
2/M	6.5	7 GTR	Right hemiplegia, vomiting, headache, postictal coma	Left fronto/temporal	1A 13.8 years
3/M	2	2.3 IR	left arm and leg clonic motion 5/day	Right frontal/parietal	2 3 years MRI residual tumor stable
4/F	4	10.5 GTR	Loss of contact, incoherent speech, strolling, drooling, mouth deviation leftward 1/week	Left mesial temporal	1A 6 years
5/M	4.5	6.5 GTR	Prickling sensation left palm, left arm extension, anteflexion of the head 1/day	Right parietal	1A 5 years
6/F	9.5	12 GTR	Cephalic sensation, staring, trunk flexion, stiffness, clonic motion four limbs 10-15/months	Left frontal lobe	1A 2.3 month
7/F	13	14.5 IR	Loss of contact, pupillary dilatation automatism: jumping, singing, complex vocalizations. Post ictal confusion 20-30/day	Right orbitofrontal Gyrus Rectus and insula	2 2 years MRI residual tumor stable
8/M	12	13.5 GTR	Left deviation of eyes and head. Difficulties to orient left arm. No loss of contact 3/ week	Right parietal	1A 2 years
9/F	3	6.4 IR	Heavy feeling right leg, followed by clonic motion, right limbs; post ictal hemiparesis 1/month	Left frontal lobe	2 14 month MRI residual tumor stable
10/M	10	15.5 IR	Staring, spasm right face , speech arrest 4/day	left frontolateral and premotor	2 1 year MRI residual tumor stable

Table 1. Main clinical findings of the 10 patients. Abbreviations: GTR = gross total removal; IR = incomplete resection.

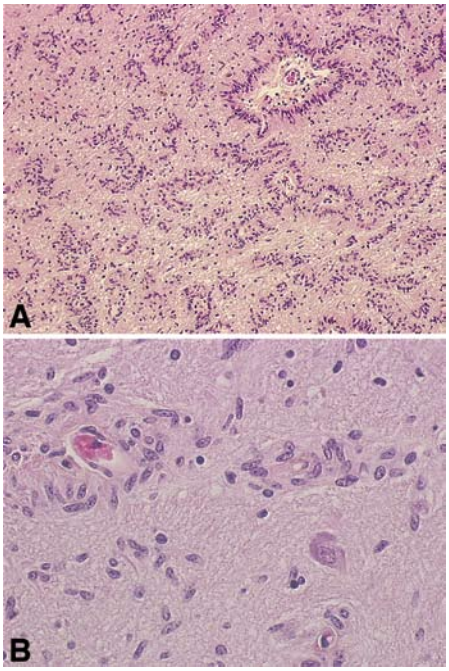

Figure 1. *Light microscopic features of ANET.* **A.** Angiocentric pattern, with elongated cells arranged around vessels walls. Hematoxylin phloxin staining, ×100. **B.** Tumoral cells are elongated, bipolar. Note the presence of neurons. Hematoxylin phloxin staining, ×400.

history, neurological evaluation was normal. The principal clinical findings are described in Table 1; age at epilepsy onset, age at surgery, seizure semiology, seizure frequency, seizure origin, surgical outcome and epilepsy follow-up.

Light microscopy and immunohistochemistry. The samples obtained at surgery were fixed in 10% buffered formalin and embedded in paraffin for histopathological and immunohistochemical study. Sections were stained by Hematoxylin-Phloxin, Masson trichrome and Klüver-Barrera methods. Immunohistochemical staining was performed using the peroxidase-antiperoxydase technique.

The following monoclonal (M) and polyclonal (P) primary antibodies were utilized: glial fibrillary acidic protein (GFAP; Dako, dilution 1:50), S100 protein (S100; Dako, dilution 1:100), vimentin (Dako, dilution 1:100), neuron-specific enolase (NSE; Dako, dilution 1:100), neurofilament (NF) protein (70K monoclonal; Dako, dilution 1:20), synaptophysin (Bohringer, dilution 1:10), Neu-N (Euromedex, dilution 1:100), chromogranin (Dako, dilution 1:200), Epithelial membrane antigen (EMA; Dako, dilution 1:50), CD34 (Immunotech, dilution 1:800), lymphocytic common antigen (LCA; Dako, dilution 1:25), Mib1 (Immunotech, dilution 1:10) and P53 (Dako, dilution 1:50). Microwave pre-treatment was performed with all antibodies.

Brain imaging. We retrospectively reviewed the brain MRI studies of 9 patients with the neuropathological diagnosis of ANET. MRI of one patient (case 10) was not available. MR images were obtained using a 0.5-T (1 patient) or 1.5-T (8 patients) imaging unit. MRI was performed using T2-weighted spin-echo (SE) or FLAIR sequences and with sagittal T1-weighted SE sequences without gadolinium and axial and/or coronal T1-weighted sequences with gadolinium. The T2 sequences were acquired in the axial or coronal plane. Neuroradiological examinations were analyzed by 3 pediatric neuroradiologists. Three CT

scans were performed both without and with contrast.

RESULTS

Ten patients were found to have the same pathological appearance (ANET) on the examined surgical samples.

Neuropathology. In all cases, the lesion consisted of an angiocentric tumor located in the cortex and the subcortical white matter. This was predominantly composed of elongated astrocytes forming rings around blood vessels. The lesions exhibited marked vascular polarity or orientation (Figure 1A). The astrocytic cells within the tumor had an elongated bipolar shape (Figure 1B) and resembled tanycytes of the third ventricular wall or radial glia in the developing brain. In addition, a neuronal component, consisting of large neurons, was present in each tumor.

The cellular density was variable. There was minimal cytological atypia. No mitotic activity was present and no endotheliovascular proliferation, nor necrosis were identified. White matter infiltration by tumor was accompanied by demyelination (Figure 2A). Quite strikingly, in 2 cases tumor cells were seen extending into the subpial spaces and infiltrating Virchow-Robin spaces in the brain parenchyma (Figure 2B). In 2 other cases, a highly fibrillary pattern was present, in one case, this exhibited a fascicular and shwannoid pattern (Figure 2C). In 3 cases, a microcystic pattern was present (Figure 2D), in one of these cases large cystic cavities were formed. A large microcalcification was present in one case.

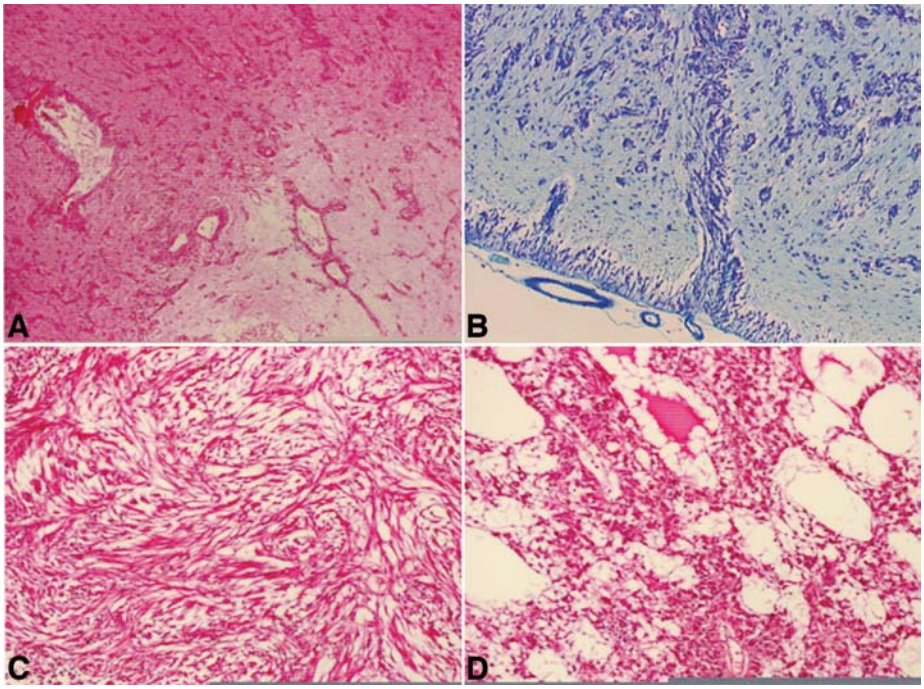

Figure 2. *Light microscopic features.* **A.** The tumor infiltrates the cortex and the white matter, which appears demyelinated. Hematoxylin phloxin staining, ×25. **B.** Subpial infiltration of the tumor was seen in two cases. Tumoral cells also infiltrate Virchow-Robin spaces. Luxol-Cresyl Violet staining, ×25. **C.** A fibrillar component of the tumour showing a schwannoid pattern. Hematoxylin phloxin staining, ×250. **D.** A microcystic pattern was also observed in several cases. Hematoxylin phloxin staining, ×100.

Immunohistochemical findings (Table 2). The bipolar and elongated tumoral cells, are strongly immunoreactive for NSE, GFAP (Figure 3A) and S100 protein, suggesting a glial origin. Some neuronal cells were present, exhibiting immunoreactivity for neuronal markers (neurofilament protein, Neu-N and synaptophysin)(Figure 3B). Tumoral cells expressed EMA in a dot-blot manner (Figure 3C) in 100% of cases. CD34 is expressed only in vessels walls.

In all cases, the proliferative rate, measured by Mib1 immunoreactivity, was very low, with 1% to 3% of the cells expressing the antibody (Figure 3D).

Neuroradiological features. ANET lesions are homogeneous but not well demarcated. The tumor involved cortical gray matter and white matter with a "stalk like" extension to the ventricle. No calcification or contrast enhancement was observed in our series.

Cortical abnormalities. Cortical abnormalities were not visible on CT. At MRI, a significant enlargement of cortical gyri with local mass effect and effacement of adjacent cortical sulci was always present. OnT1-weighted SE sequences the involved cortical gyri were isointense with an intrinsic "rim like" hyperintensity. On T2-weighted

Antibodies	case 1	case 2	case 3	case 4	case 5	case 6	case 7	case 8	case 9	case 10
GFAP	++	++	++	++	++	++	++	++	++	++
S100	+	++	++	+	++	++	+	++	++	++
Vimentine	++	++	++	++	++	+	++	++	++	++
EMA	++	++	+	++	++	++	++	++	++	++
Synaptophysine	+	+	+	+	+	+	+	+	+	+
NF	+	+	+	+	+	+	+	+	+	+
NeuN	++	+	+	++	+	+	++	+	++	+
Chromogranine	+	+	+	+	+	+	+	+	+	-
NSE	+	+	++	++	++	+	+	++	+	++
CD34	++	+	+	+	+	+	+	+	++	+
Mib1	1% to 2%	<1%	2% to 3%	<1%	<1%	<1%	<1%	1%	1% to 2%	1% to 2%
P53	-	-	-	-	-	-	-	-	-	-

Table 2. Immunohistochemical findings.

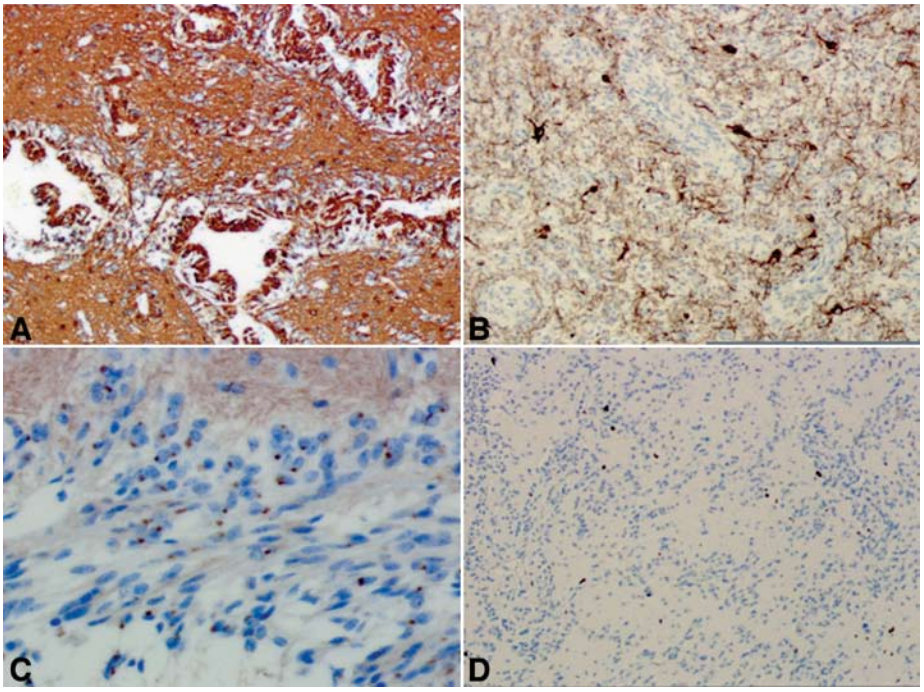

Figure 3. *Immunohistochemical staining.***A.** Intense GFAP labeling of tumor cells was observed in all cases, ×100. **B.** Cytoplasmic NF immunoreactivity was observed in the neuronal component of the tumor, ×100. **C.** Dot blot staining for EMA was seen in the tumoral cells, ×400. **D.** Mib1 immunoreactivity of the tumoral cells was very week, sparse cellular labeling, ×100.

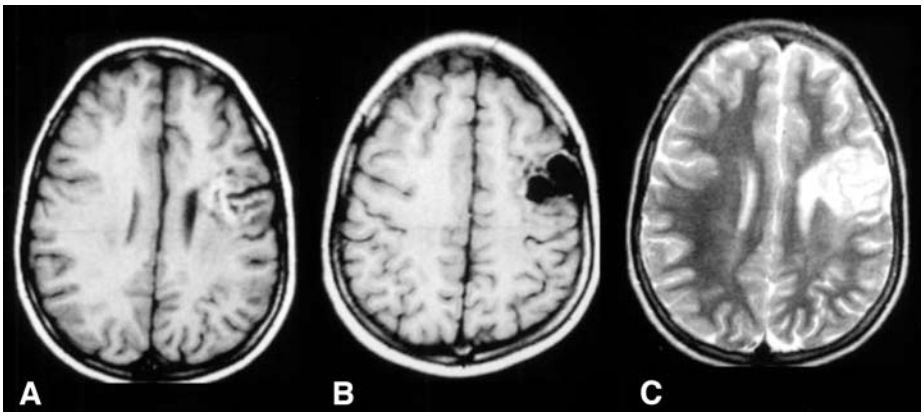

Figure 4. (case 1) Intrinsic cortical rim of hyperintensity on T1 SE-weighted sequences (**A, B**) and clear subcortical hyperintensity with extension to the ventricle on T2-weighted sequences (**C**) are observed.

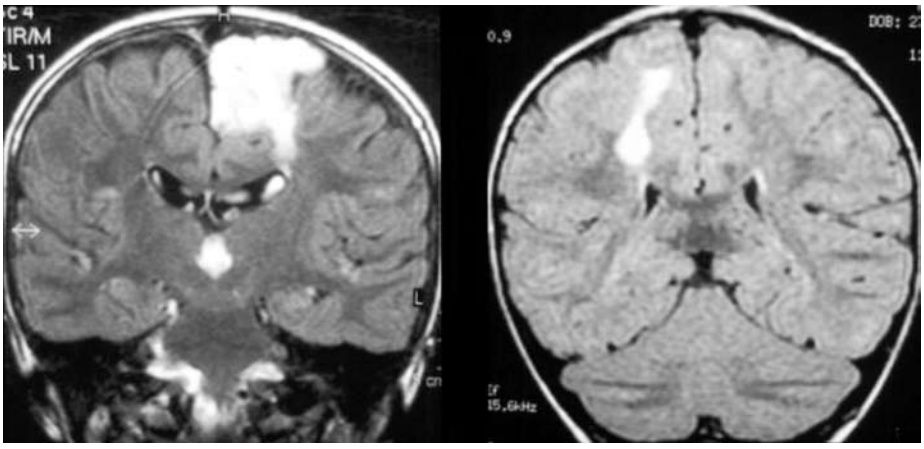

Figure 5. Two different cases: hyperintensity on FLAIR sequences in the subcortical white matter. Hyperintensity extends to the nearest lateral ventricle in all cases.

or FLAIR sequences, the lesions appeared hyperintense (Figure 4).

Subcortical abnormalities. The cortical lesion was associated with a narrow strip of white matter abnormality, similar in signal pattern to the body of the lesion, extending toward the nearest ventricular wall in each case (Figure 5). The stalk like white matter abnormality perpendicular to the ventricular wall appeared hypodense on CT, hypointense onT1-weighted MRI scan and hyperintense on T2 as well as FLAIR sequences.

Clinical features . The age at onset of epilepsy ranged from 2 to 13 years (6.9 ± 3.9); the age at surgery ranged from 2.3 to 14.5 years (9.2 ± 4.5). All patients had a history of partial seizures originating supratentorially. Seven of the 10 specimens were received "en bloc."

Preoperative evaluation, other than MRI scans, did not distinguish these patients from other patients in our epilepsy surgery experience. We did not find any characteristic pattern of patient age at epilepsy onset, lesion location or seizure characteristics in association with this histopathological pattern. Clinical follow up revealed a favorable prognosis. No tumor recurrence has been observed during the period of follow-up ranging from 1 to 13 years, mean 4 years ± 3.5.

DISCUSSION

Tumors are one recognized cause of pharmacoresistant partial epilepsy in children and young adults (3, 21). Other causes include destructive and developmental lesions. Most tumors causing medically refractory epilepsy are glioneuronal, consisting of a mixture of glial and neuronal elements (3). The most frequent is DNET (55% in our series). Gangliogliomas (33% in our series) are also widely known to cause epilepsy. These glioneuronal tumors are usually benign and their maldevelopmental origin is a matter of debate (10, 15). In our series of patients who underwent epilepsy surgery, tumors represent approximately 20% of the lesions. These findings are consistent with the literature (7, 14).

We have identified a new entity, that we have named ANET (angiocentric neuroepithelial tumors). These 10 cases represent 8% of tumors discovered at epilepsy surgery in our series. We think that 3 cases

corresponding to this entity were presented to the American Association of Neuropathologists in 2002 by Wang et al and published in an abstract form (20). Morphologic features distinguish these tumors from DNET and gangliogliomas, which do not have the characteristic angiocentric pattern of ANET. Whereas DNET essentially consist of oligodendrocytes in their glial component (5), ANET is composed of astrocytes. These astrocytes appear peculiarly elongated and bipolar in shape and are characteristically arranged around blood vessels. They resemble radial glia and tanycytes morphologically. The ANET is also easily distinguished from ganglioglioma which manifests an entirely different architectural pattern without an angiocentric pattern. Furthermore, in ganglioglioma there is usually perivascular lymphocytic cuffing which is not present in ANET. Another feature which distinguishes ANET from ganglioglioma is the presence of calcifications in the vast majority of ganglioglioma cases. We observed calcification in only one of our ANET cases.

A neuronal component was present in all of the ANET tumors. The neurons nearly always have a normal cytological appearance, with only rare dysplastic features. This is similar to other epileptogenic tumors, such as DNET in which the neuronal component is widely considered to be tumoral. In our cases, the neurons are not clearly neoplastic. If these neurons are interpreted as resident neurons, the tumor might be considered infiltrative. However, it remains possible that these neurons are a tumoral cell component, accounting for epileptogenicity of the tumor.

The radiological appearance of ANET is different from that of DNET, particularly because of the intrinsic hyperintensity of the margins of the cortical gyri on T1-weighted SE images. This may be pathognomomic of this new entity, because this appearance has not been described previously. However, further experience may fail to confirm this observation. Marked hyperintensity onT2-weighted and FLAIR images, and the hypointensity T1 of the subcortical white matter was seen in all of the ANETs studied by MRI, but this signal pattern is not specific to this lesion. Neither DNET nor ANET exhibit calcifications, but these are seen frequently in gangliogliomas. We observed no contrast enhancement in this series, further distinguishing ANET from ganglioglioma radiologically. Neither ANET nor DNET enhance with paramagnetic or iodinated contrast material in most cases, though a small minority of DNETs are reported to enhance.

Another unusual radiological feature is the band of T2 signal abnormality which extends as a stalk-like projection from the deep surface of the tumor to the ventricular wall. This can also be seen in DNET and dysplasias suggesting a link between these entities. This feature may shed light on the etiology of these lesions perhaps suggesting that they share both dysplasic and neoplastic origins. Because of the unique radiological appearance of ANET, the diagnosis can be strongly suggested prior to surgery in this setting if peripheral T1 high signal and a band of T2 abnormality extends to the ventricle.

The abnormal glial cells in ANET may arise from the radial glia during embryogenesis. Several types of glial cells are distinguished in the brains of vertebrates: tanycytes that are found along the inferolateral walls of the third ventricle and its floor; radial glia, which constitute a major cell type in the developing brain; and astrocytes. Tanycytes are specialized ependymal cells that possess morphological and biochemical characteristics of immature radial glia, from which they are probably derived (8). These 2 cell types, tanycytes and radial glia, are defined as ependymoglia. They are bipolar and extend one of their processes to the lumen of the ventricular system (17). In the case of radial glia, the processes span the entire width of the neural epithelium. It has been proposed by Reichenbach et al (17) that vertebrate radial glia and ependymocytes share a common evolutionary origin, and that they are functionally and structurally homologous. Sundholm-Peters et al (16), however, state that it is more likely that radial glia give rise to the ependymal cells that line the ventricles in the adult, and that the evolutionary lineage relationship between them is unclear. Interestingly, in our cases, on immunohistochemistry, tumoral cells express EMA "in a dot-blot manner " just as ependymocytes do (Figure 3C), which corroborates the view of Reichenbach et al (16). At MRI, the lesions extend to the ventricle, suggesting an origin during the period of neuronal migration. Histologically, the tumoral cells are elongated and bipolar, resembling radial glia which constitute a major cell type within the developing brain in mammals (1). Glial differentiation has long been associated with the process of neuronal migration (9). During cortical development, radial glia are known to precede and stimulate neurogenesis and migration (2, 16). Our epileptogenic tumors present as a proliferation of cells resembling immature radial glial cells, and this suggests a dysembryoplastic origin of these tumors from radial glia. Perhaps the ANET arises from neoplasic transformation of radial glial cells during the period of neuronal migration. A possible ependymal origin of this lesion must also be considered, as rare cases of cortical ependymomas with epilepsy have been reported (12). Further studies by electron microscopy would be required to resolve this question more definitively.

The prognosis for this tumor appears to be excellent if the surgical goal of gross total removal can be achieved safely. In each case in which the tumor was completely removed the seizures were cured. In 4 cases residual tumor remained and the seizures recurred. In this respect, ANET is similar to DNET in our experience. MRI follow-up in these 4 cases confirmed stable residual tumor volume.

ANET shares common clinical features with DNET, but differs in its histological appearance and cellular components. For this reason, we propose the term angiocentric neuroepithelial tumor (ANET) for this new histopathological and neuroradiological entity which apparently belongs to the group of benign glioneuronal tumors of epilepsy surgery.

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