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Adult-onset epilepsy associated with dysembryoplastic neuroepithelial tumors

J.G. Burneo [a,*], J. Tellez-Zenteno [b], D.A. Steven [a], N. Niaz [c], W. Hader [c], N. Pillay [c], S. Wiebe [c]

[a] *Epilepsy Programme, University of Western Ontario, 339 Windermere Road, London, Ontario, Canada N6A5A5*
[b] *Division of Neurology, University of Saskatchewan, Saskatoon, SK, Canada*
[c] *Division of Neurology, University of Calgary, Alberta, Canada*

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Summary

Rationale: Dysembryoplastic neuroepithelial tumors (DNET) are benign, localized lesions that typically cause localization-related epilepsy of childhood onset. Although excellent seizure outcomes are expected following surgical resection of focal, benign lesions, reports in pediatric epilepsy series suggest that this may not be the case with DNETs, which may exhibit complex and often multifocal epileptogenesis. We report the characteristics and surgical outcome of an adult- and childhood-onset cohort with this condition.
Methods: Retrospective cohort of 23 patients seen at two major epilepsy centers, with localization-related epilepsy associated with histopathologically demonstrated DNETs. We assessed clinical, electrographic and surgical outcome features in patients with adult- and childhood-onset epilepsy. We were particularly interested in the level of congruence of EEG and MRI data and the need for intracranial recordings. We evaluated seizure outcomes at last follow-up.
Results: The mean age was 33.3 years (range: 5—56 years). Ten patients had adult-onset epilepsy. Thirteen patients (57%) had simple partial, 21 (91%) had complex partial, 16 (70%) had secondarily generalized seizures and 5 patients had only simple partial seizures. Status epilepticus did not occur. Non-enhancing lesions on MRI were located in the temporal lobe in 17 patients, the frontal lobe in 3 patients and the parietal/occipital region in 2 patients. One patient had a DNET that involved both frontal and temporal areas. Ictal scalp EEG and MRI were congruent in 17 patients (74%). Eleven patients (48%) underwent lesionectomies, while the rest required some resection of extralesional cortex as well. Five patients required intracranial EEG.

* Corresponding author. Tel.: +1 519 663 3464; fax: +1 519 663 3498.
E-mail address: Jburneo2@uwo.ca (J.G. Burneo).

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There was no association with cortical dysplasia. Seventeen patients (74%) had an Engel class 1 outcome, in a follow-up period that ranging from 5 to 98 months.
Conclusions: We found no difference in outcomes between adult- and childhood-onset cases. Although epileptogenicity was complex, congruence between electro-clinical and neuroimaging studies was high and allowed good surgical outcomes at 1 year of follow-up.

Introduction

Dysembryoplastic neuroepithelial tumors (DNETs), which are characterized by a heterogeneous population of neurons, astrocytes and oligodendroglia-like cells,[1] are a common cause of tumor-related chronic epilepsy. Together with other low-grade cerebral neoplasms, including ganglioglioma, oligodendroglioma, mixed glioma and astrocytoma; DNETs comprise the etiology in some 10—30% of patients with chronic epilepsy resistant to therapy.[2]

The clinical syndrome associated with DNETs specifically includes localization-related epilepsy starting during childhood and adolescence.[3] Only sporadic cases of adult-onset epilepsy have been reported,[4] but these have not been well characterized and merit further study.

Although excellent seizure outcome is commonly expected following surgical resection of focal benign lesions, it is increasingly recognized that DNETs may have complex epileptogenesis and suboptimal surgical outcomes.[5,6]

Our aim was to define more clearly the clinical, neurophysiological and neuroimaging features of DNET in adult- and childhood-onset epilepsy, and to assess their association to surgical outcomes.

Methods

Patient population and data collection

We interrogated the databases of the Department of Pathology at two major Epilepsy Centers in Canada: London Health Sciences Centre (University of Western Ontario) and Foothills Medical Centre (University of Calgary) for all cases mostly adult, pathologically proven cases of DNET between 1997 and 2006, regardless of their clinical presentation. Subsequently, clinical charts were systematically reviewed to study the variables of interest. In addition to demographic aspects, we also included clinical presentation, age at epilepsy onset and at surgery, type, semiology and frequency of seizures, antiepileptic drugs (AEDs) used before and after surgery, electroencephalographic (EEG) findings, MRI findings, topography of the lesion, type of surgery (lesionectomy versus lesionectomy plus corticectomy) and seizure outcome using Engel's criteria.[7]

Clinical and electroencephalographic evaluation

All patients had MRI of the brain, based on protocols routinely used for patients with partial epilepsy in each institution, including axial T2-weighted and coronal FLAIR images, as well as a coronal 3D sequence with contiguous slices, with and without administration of gadolinium.

Seizures were classified as recommended by the International League Against Epilepsy.[8] Presurgical interictal routine awake and sleep EEGs were reviewed in each subject. Information on interictal slowing (theta or delta) and on epileptiform discharges (spikes and sharp slow-waves) was abstracted and analyzed. Findings of video EEG monitoring including ictal EEG were also assessed. The international 10/20 system was used to determine the localization of these EEG abnormalities. The distribution of EEG abnormalities was compared with the radiological information on the DNET localization. All EEG abnormalities (slowing, spikes and sharp slow-waves) were classified as concordant or discordant with the tumor localization. Concordant EEG abnormalities were defined as co-localized with the region of DNET location by MRI. Corticectomy was defined as cortical resection extending 1 cm or more beyond the lesional margin.

Cognitive dysfunction and psychiatric abnormalities were systematically assessed and recorded. Cognitive dysfunction was operationally defined as subnormal intelligence or as specific deficits documented on neuropsychological testing. Psychiatric abnormalities were defined as current or past psychiatric diagnoses or behavioral abnormalities.

Student's *t*-test was used to evaluate differences in continuous variables and Fisher's exact test assessed dichotomous or categorical outcomes.

Results

Twenty-three patients were identified and included in the analysis (Table 1). All patients presented with

Table 1 Demographic and clinical characteristics

Characteristics	
Number of patients	23
Demographics	
Mean age (range)	33.4 (5—56)
Male:female ratio	1.1
Age at seizure onset (range)	17.4 (1—43)
Seizure type, *n* (%)	
Simple partial	13 (57)
Complex partial	21 (91)
Secondary generalization	16 (70)
Tumor location (based on MRI), *n* (%)	
Temporal	18 (86)
Frontal	4 (17)[a]
Parietal	2 (9)
EEG, *n* (%)	
Congruent interictal EEG	13 (57)
Congruent ictal EEG	17 (85)
Intracranial EEG	5
Seizure free after surgery, *n* (%)	
Engel I	17 (85)
Engel II	2 (9)
Engel III/IV	2 (9)
Information not available	2 (9)

[a] One patient counted twice because of overlapping frontal—temporal location.

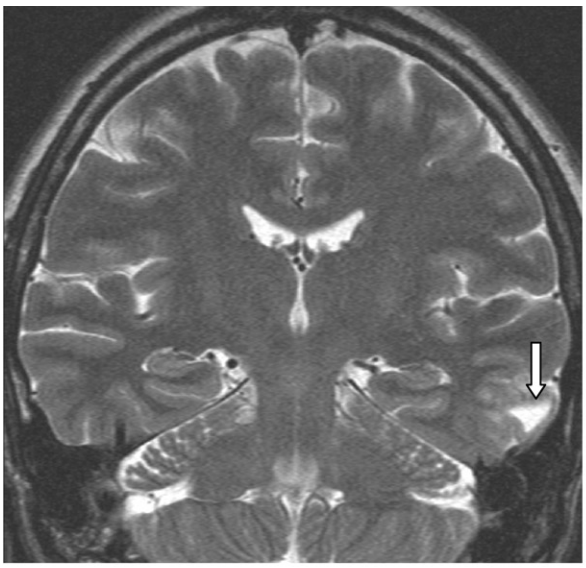
epilepsy and underwent resective epilepsy surgery. Twelve (52%) were male, and the mean age was 33.3 years (range: 5—56 years). The mean age at seizure onset was 17.4 years (range: 1—43 years). Seizure onset occurred before age 10 years in 2 patients (9%), before age 17 years in 13 patients (56%) and after age 17 years in 10 patients (43%). Therefore, 10 patients (43%) had adult-onset epilepsy. Thirteen patients (57%) had simple partial seizures, 21 (91%) had complex partial seizures and 16 (70%) had secondarily generalized seizures. Of the 13 patients with simple partial seizures, 8 had secondarily generalized tonic—clonic seizures and 12 also had complex partial seizures. In patients with partial seizures, the seizure frequency ranged from one every 4 months to daily events, while generalized seizures were rarely seen. Status epilepticus did not occur in any of the patients.

DNETs were located in the temporal lobe in 17 patients (74%), in the frontal lobe in 3 patients (13%), in the parieto-occipital region in 2 patients (7%) and in 1 patient the DNET overlapped frontal and temporal areas. No lesions demonstrated enhancement on MRI, and three had a cystic component. Concordant interictal spikes occurred in only 13 of 22 patients (59%). One patient did not have investigations with EEG and was operated on the basis of imaging alone. Ictal scalp EEG and MRI were congruent in 17 patients (74%). Five patients (22%) required investigations with intracranial EEG for further identification of the epileptogenic area. A prototypical case of discordant EEG and imaging is illustrated by a patient with adult-onset complex partial seizures who had a left neocortical anterior temporal DNET, but right anterior temporal scalp EEG ictal onset (Fig. 1). Intracranial EEG demonstrated seizures originating from the perilesional cortex and the mesial temporal region on the left, and independently from the mesial temporal area on the right. The decision was made to resect the left temporal lesion and adjacent mesial and neocortical epileptogenic cortex. There were no areas of cortical dysplasia in addition to the lesion proper. The patient remains seizure free 16 months after surgery.

Eleven patients (48%) underwent lesionectomies, while the rest required resection of extralesional cortex as well. None of the patients had significant abnormalities of cortical development in association with the DNETs. In terms of surgical planning there was not a specific pattern to the decision-making process. The resection was performed based on the analysis of the presurgical data obtained and the discussion between the medical and surgical team on an individual basis.

Follow-up was not available for three patients, because they live in remote areas. Postoperative follow-up for 20 patients ranged from 5 to 120 months, with a median of 27 months. Follow-up longer than 1 year was available in 16 patients (70%). Seventeen of 20 patients (85%) have had an Engel class I outcome. One patient was seizure free for 8 years before seizures recurred. Of those who are not seizure free, only one has more than two seizures per month. Despite the discordance on ictal scalp EEG in some patients, three became seizure free after surgery. There was no difference in seizure outcome with regard to mean duration of epilepsy ($p = 0.2$), mean age at surgery ($p = 0.2$) and mean age at seizure onset ($p = 0.4$). Only four patients (17%) are off AEDs and seizure free. Ten patients remain on more than one AED.

There was not a clear correlation between type of seizure and successful outcome following surgery. Of the patients with simple partial seizures who did not become seizure free, two had simple, but also complex partial and secondary generalized tonic—clonic seizures. One patient become free from complex partial seizures but continued to have simple partial seizures. Of the four patients who remained seizure free without AED, two of them had only complex partial seizures, one had simple partial and secondary generalized tonic—clonic seizures and one had complex partial with secondary generalized tonic—clonic seizures.



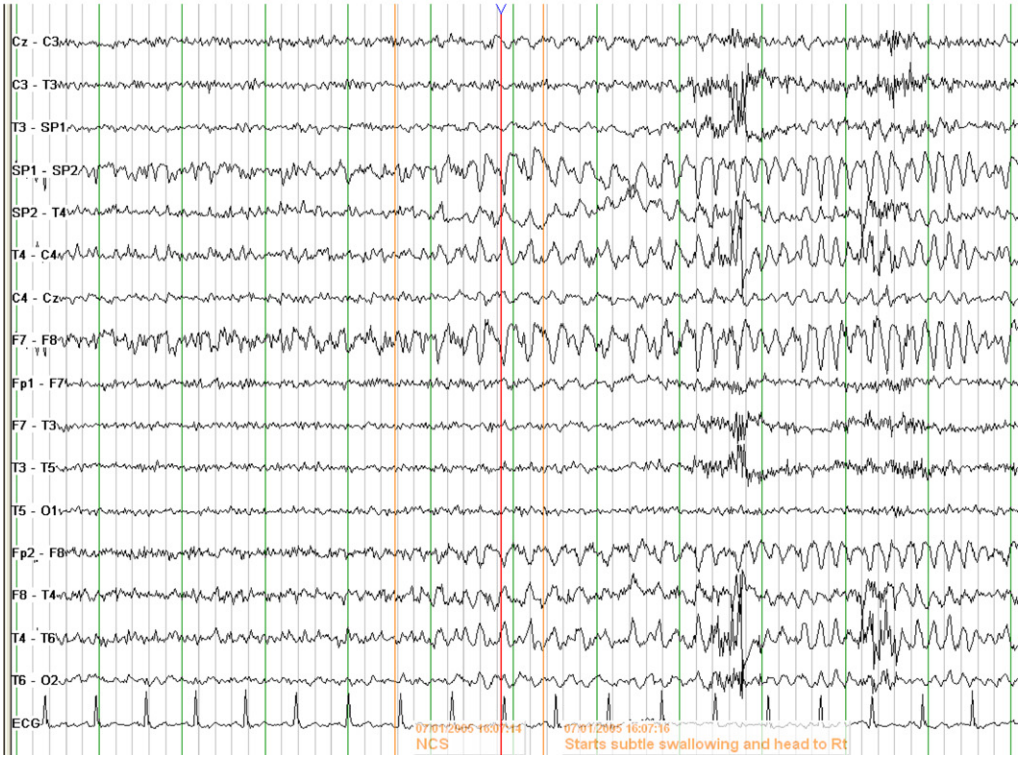


Figure 1 T2-weighted coronal MRI and ictal EEG demonstrating discordant MRI findings (left temporal neocortical DNET) and ictal EEG (right anterior temporal seizure onset) in an adult with late onset intractable complex partial seizures, successfully treated with resection of the lesion and adjacent epileptogenic cortex.

In the three patients with discordant EEG findings who became seizure free, only one had prolonged video-EEG monitoring, and despite the incongruence of the ictal and most of the interictal data, the decision was based on MR findings and semiology. The other two patients did not have long-term video EEG evaluation. In all three patients, the lack of congruence was not taken into account by the treating physicians, who decided to proceed with lesionectomy.

There was no difference in seizure outcome with regard to type of resection (lesionectomy alone versus lesionectomy plus corticectomy). Cognitive dysfunction did not occur in any of our patients, and only one patient had a psychiatric diagnosis, i.e. anxiety disorder after surgery.

Discussion

Since the term DNET was coined by Daumas-Duport et al.,[9] debate about their nature still continues. From malformation of cortical development to outright neoplasm,[10] DNETs are currently an important cause of medically intractable epilepsy.

Overall, we found that surgical treatment resulted in excellent seizure control (85% class I), without significant associations with the age at seizure onset, duration of epilepsy and age at surgery. However, several aspects deserve comment. First, our sample size was small and could have been insufficient to detect small but significant differences. Second, it is important to note, that despite a high rate of patients achieving Engel I outcomes, follow-up was longer than 2 years only in 13 patients. Nolan et al. have demonstrated that in children, seizure outcomes are excellent during the first postoperative year (85% class I), but decline after the second year (62% class I).[6] They also note that older age at seizure onset is associated with poorer long-term outcome. Plausibly, longer follow-up in our cohort would demonstrate similar findings, particularly because a substantial proportion of our patients have late (adult) onset epilepsy. In keeping with this finding, it is of note that only 17% of our sample were off AEDs and seizure free, whereas the corresponding figure for epilepsy surgery in general is almost twice as high (30%) in studies including studies with shorter follow-up, as ours,[11] and 20—25% in studies with long-term follow-up.[12,13]

On the other hand, younger populations have been reported to achieve better seizure outcomes following epilepsy surgery in some series.[6,14] Finally, poorer seizure outcomes in patients with DNET may also be associated with DNET recurrence, presence of cortical dysplasia,[6,15,16] incomplete resection of lesions or adjacent dysplastic tissue, and the presence of cognitive problems and developmental delay. The latter may reflect widespread dysplastic areas accompanying the DNET and causing disturbances in neuronal circuitry.[14,17] None of these features were present in our cohort. Arguably, the older age at presentation in our patients could reflect the fact that cortical dysplasia was not found.

The interictal (spikes and sharp slow-waves) findings were concordant in only half of the patients and they were not predictive of seizure outcome. Although substantial discordance can occur in individual patients (Fig. 1), the ictal recordings were congruent in most of the cases. However, they were not predictive of seizure outcome, as some cases did not become seizure free after surgery. The high congruency found in our study is at odds with some previous reports.[18] This is most likely related to the fact that we did not find areas of dysplasia surrounding the DNET. However, the small number does not permit us to draw firm conclusions.

Patients with DNETs usually present with focal seizures with or without generalization that become therapy resistant. Yet, despite high seizure frequencies and complex epileptogenicity, status epilepticus did not occur in this group. The cause for this is unknown, but it may relate to the circumscribed nature of the lesion and its lack of association with other epileptogenic pathologies in our sample (e.g. hippocampal sclerosis, cortical dysplasia), and to the adequacy of medical therapy. Detailed electrophysiological evaluation of the lesion, including patterns of seizure spread in EEG and functional neuroimaging in larger samples may shed light on the question of determinants of epileptogenicity.

The neuroimaging features of DNETs have previously been reported.[9,19,20] On MRI, lesions are usually intracortical and exhibit low signal on T1-weighted images and high signal on T2-weighted images, with occasional contrast enhancement. Our findings are in accordance with those in the literature. However, in some of our patients the lesions were not strictly intra-cortical, as is typically described, but rather subcortical, with minimal or no cortical involvement (Fig. 1).

DNETs are considered "benign" lesions because they do not require chemotherapy or radiotherapy, and because a complete or even incomplete resection generally results in favorable postoperative seizure outcomes. However, DNETs can recur, and are sometimes surrounded by areas of cortical dysplasia which may be responsible for surgical failure.[18] None of our patients had a recurrence or an obvious secondary abnormality; however, subtle foci of cortical dysplasia, not seen on MRI may explain failure of surgical treatment despite an "adequate" resection.

In general, patients with low-grade gliomas and intractable epilepsy, have a favorable seizure outcome following surgical treatment. In the case of a DNET, it appears that the appropriate treatment strategy would involve not only the complete surgical extirpation of the tumor, but of adjacent epileptogenic structures (e.g. hippocampus, cortical dysplasia) in some cases.

Patients with chronic intractable epilepsy have a higher incidence of psychiatric disorders than do the general population or epilepsy patients with good seizure control,[21] but causal directionality varies.[22] Andermann et al. described a case psychosis and

DNET.[23] We explored a possible relationship between DNETs and psychiatric and cognitive dysfunction in our cohort, but found none. One of our patients developed anxiety following surgery, which is not unusual in series of temporal lobe epilepsy surgery.[24]

In conclusion, DNETs remain an important cause of medically intractable epilepsy, and also produces adult-onset refractory epilepsy, which may be less frequently associated with cortical dysplasia than in childhood-onset epilepsy cases. The proposed clinical syndrome of DNET, includes early onset epilepsy, exclusive intracortical involvement and lack of mass effect. As experience increases, this syndrome requires expansion to also include the less common, but not rare occurrences that do not fit with these criteria, as described herein and in other reports. Outcomes of surgical resection in the adult-onset group appear to be as favorable as in childhood-onset series, despite complex epileptogenicity and the requirement for intracranial EEG.

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Conflict of interest

The authors do not have any conflict of interest to disclose.

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