Original article

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Low-grade epilepsy-associated tumour management with or without presurgical evaluation: a multicentre, retrospective, observational study of postsurgical epilepsy outcome

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ABSTRACT – *Aims*. Low-grade epilepsy-associated neuroepithelial tumours (LEATs) encompass the broad spectrum of tumours associated with epilepsy. Since the postsurgical seizure outcome in LEATs is favourable, it is speculated that epileptological presurgical evaluation (EPE) might not be required for patients with LEATs.
Methods. A multicentre study involving referring epilepsy and neurosurgery centres was performed, aimed at evaluating postsurgical epilepsy outcome in patients with LEATs, with and without EPE, including long-term video-EEG monitoring (vEEGM). In total, 149 surgically treated patients were enrolled (age: 31±14 years; age at surgery: 26.4±13.1 years; males; 55.7%) with histopathological confirmation of LEATs and follow-up of more than six months. All patients had undergone standard assessment: clinical, routine EEG and brain MRI. In addition to vEEGM, EPE included other additional investigations. Epileptologists did not assess patients treated in neurosurgical centres. The EPE was performed in 51% of patients.
Results. Histopathological diagnosis revealed ganglioglioma in 43.6%, DNET in 32.9%, pilocytic astrocytoma in 17.4%, and others in 6.1% of patients. The majority of patients were seizure-free (ILAE epilepsy

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surgery outcome Class 1; 71.1%). The median follow-up period was 36 months. Patients who were rendered seizure-free were younger (mean age: 24.2±12.2) than those who were not seizure-free (31.8±14.0) (p=0.001). No difference was identified between evaluated and non-evaluated patients with respect to seizure freedom (p=0.45). EPE patients had a longer epilepsy duration (median: 10 years) and a higher proportion of drug resistance (73.6%) compared to non-evaluated patients (median: two years; 26.4%) (p<0.001). Based on a significant difference in major clinical variables, that may well affect postoperative results, the similar postsurgical seizure outcome in groups with and without EPE observed in our study should be considered with caution, and conclusions as to whether there is value in formal presurgical evaluation in LEAT patients cannot be drawn.
Conclusions. Our data strongly encourage the clear need for continued discussion around such patients at epilepsy management conferences.

Key words: low-grade epilepsy associated neuroepithelial tumours, LEAT, epilepsy surgery, outcome, presurgical evaluation

Low-grade epilepsy-associated neuroepithelial tumours (LEATs) comprise the broad spectrum of different tumours typically associated with epilepsy (Luyken *et al*., 2003). Although not systematically studied, the most common clinical impression is that focal epilepsy associated with LEATs is drug resistance in a large proportion of patients. Nevertheless, focal epilepsy associated with LEATs is exceptionally responsive to surgical treatment, especially in glioneural subtypes, when the surgery is performed in the paediatric population (Pelliccia *et al*., 2017). Based on a meta-analysis on seizure outcome after LEAT resection, 910 patients were investigated from 39 studies, with stratified outcomes according to several potential prognostic variables. Rates of complete seizure freedom postoperatively ranged from 45 to 100% across individual data sets. Overall, 80% of patients were completely seizure-free after surgery (Engel Class I), whereas 20% continued to have seizures (Engel Class II-IV) (Englot *et al*., 2012). Accordingly, it is advocated that timely surgery should be warranted in patients with LEAT regardless of drug resistance, and oriented to optimize epilepsy, neuropsychological, and oncologic outcomes (Giulioni *et al*., 2017).

Presurgical evaluation typically performed by epileptologists usually precedes epilepsy surgery. It inevitably encompasses long-term video-EEG monitoring (vEEGM), defined as a critical tool to identify the epileptogenic locus. The extent of resection largely depends on the area of the epileptogenic zone and proximity to the eloquent cortex and white matter tracts (Gil-Robles and Duffau, 2010). In cases of overlapping functional tissue, invasive recordings and intraoperative mapping are needed to avoid possible resulting neurological deficit and limit resection. However, vEEGM may not be required for all patients with tumour-related epilepsy, since the postsurgical seizure outcome in these patients is better than that in most general epilepsy surgery series, before and after vEEGM became accessible (Kennedy and Schuele, 2013). Indeed, a multicentre trial studying attitude and data on surgical treatment of LEATs in Italian epilepsy surgery centres revealed that post-surgical outcome was equally successful for patients who underwent vEEGM and those who did not (Giulioni *et al*., 2017).

The primary belief is that cortical lesions (irrespective of aetiology) in people with focal epilepsy are almost always the cause of seizures (Asadi-Pooya and Sperling, 2008) and this may directly reflect common neurosurgical practice. Therefore, patients with LEATs could be surgically treated by neurosurgeons without expertise in epilepsy surgery, especially in public health systems that lack resources and technologies related to epilepsy surgery. Thus, the management of patients with LEATs in countries with restricted funds may be heterogeneous and driven by current and available settings. We therefore set out to evaluate seizure freedom rates in patients with LEATs who received management in different settings with various approaches. This multicentre, retrospective, observational study, based in referring epilepsy and neurosurgery centres (Serbia, Romania, Bulgaria, and Hungary), was aimed at evaluating postsurgical epilepsy outcome in patients with LEATs.

Materials and methods

Consecutive patients with LEATs were surgically treated at four centres, either epilepsy or neurosurgery centres, in south-east European neighbouring countries (Serbia, Romania, Bulgaria and Hungary). Patients were enrolled in this multicentre, retrospective, observational study between January 2009 and August 2016. The following inclusion criteria were applied: histopathological confirmation of LEATs and

Table 1. Routine investigations in the presurgical evaluation across the countries.

Serbia	Romania	Bulgaria	Hungary
vEEGM (100 hours) Epilepsy protocol high-resolution brain MRI (1.5T and 3T) Neuropsychological battery test Interictal brain FDG-PET (performed in 100%) Electrocorticography (intraoperative) according to PMC decision in selected cases)	vEEGM (24-72 hours) Epilepsy protocol high-resolution brain MRI (1.5T and 3T) Neuropsychological battery test	vEEGM (72-120 hours) Epilepsy protocol high-resolution brain MRI (1.5T and 3T) Neuropsychological battery test Interictal brain FDG-PET (performed in 50%) Electrocorticography (intraoperative) according to PMC decision in selected cases)	vEEGM (100 hours) Epilepsy protocol high-resolution brain MRI (1.5T and 3T) Neuropsychological battery test Interictal brain FDG-PET (performed in 30%) Electrocorticography (intraoperative) according to PMC decision in selected cases

vEEGM: long term video-EEG monitoring; PMC patient management conference; two patients from Romania underwent invasive recordings (stereo EEG) to investigate the possible impact on visual tracts in the right TPO junction in one case and language network in a left temporobasal region in the second case.

postoperative outcome >six months. Patients with missing data (nine patients were lost to follow-up; two from the Serbian centre, one from the Romanian centre, two from the Bulgarian centre, and one from the Hungarian centre) and multiple pathologies were excluded from the study.

All analysed patients had undergone an assessment which included detailed history, clinical examination, routine EEG (interictal EEG localization data) and high-resolution brain MRI (1.5 and 3T). Epileptological presurgical evaluation (EPE) consisted of vEEGM and other investigations (*table 1*). Epileptologists did not assess patients treated in neurosurgical centres before surgery. Therefore, data on semiology and precise seizure frequency and classification were not obtained. In the neurosurgical workup, only EEG interpretation by available neurophysiologists was used for further management consideration. Tumour location was defined as temporal, extra-temporal and temporal plus surrounding lobe tissue.

Histological diagnosis according to the World Health Organization classification systems of tumours of the central nervous system (Louis *et al.*, 2016) was established in all cases. We differentiated tumours in four groups: dysembryoplastic neuroepithelial tumour (DNET), ganglioglioma, other glioneural tumours, and other low-grade gliomas.

Seizure outcome was assessed based on neurosurgical or neurological follow-up visits in outpatient settings and reconfirmed by telephone contact. The postsurgical outcome was graded according to ILAE classification (Wieser *et al.*, 2001).

Research ethics boards of the affiliated institutions approved the study.

Results

In total, 149 consecutive patients with LEATs were surgically treated at four epilepsy or neurosurgery centres in Serbia (*n*=30; EPE not performed in 43.3%/ performed in 56.7%), Romania (*n*=22; EPE not performed in 27.2%/ performed in 72.8%), Bulgaria (*n*=39; EPE not performed in 56.4%/ performed in 43.6%) and Hungary (*n*=58; EPE not performed in 55.1%/ performed in 44.9%) (p=0.09). The mean age of analysed patients was 31±14 years (median: 29; range: 2-69), and mean age at surgery was 26.4±13.1 years (median: 25; range: 1-59). The majority of patients were males (*n*=88; 59.1%). Right-side tumour location was slightly more frequent (*n*=76; 51%). Median epilepsy duration was five years (range: 0-46 years). Presurgical evaluation by epileptologists was performed for the majority of patients (*n*=76; 51.0%); in 5.2%, no seizures were recorded (median vEEGM duration was four days). A non-epileptic event was recorded in one patient. Interictal ipsilateral discharges were seen in less than half of patients in the non-evaluated group recorded by routine EEG (*n*=25; 34.7%). Distribution of the histopathological diagnosis was as follows: ganglioglioma (*n*=64; 43.6%), DNET (*n*=49; 32.9%), pylocitic astrocytoma (*n*=26; 17.4%), angiocentric neuroepithelial tumour (*n*=3; 2%), pleomorphic xanthoastrocytoma (*n*=2; 1.3%), papillar glioneuronal tumour (*n*=2; 1.3%), gangliocytoma, infantile desmoplastic astrocytoma and multinodular and vacuolating neural tumour in single patient (0.7%). Location of the tumour was most frequent in the temporal lobe (*n*=101; 67.8%) or temporal lobe plus surrounding lobes (*n*=11; 7.4%), and less frequent in extratemporal lobes (*n*=37; 24.8%). Febrile convulsions were reported

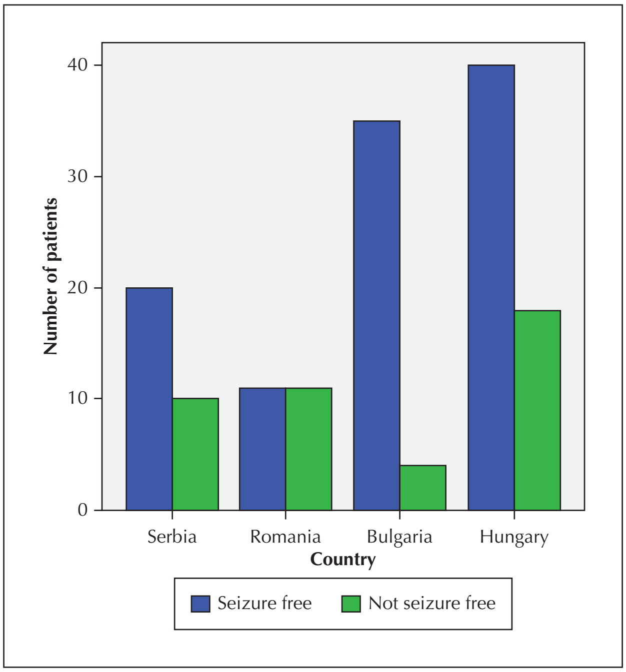

Figure 1. Distribution of postsurgical outcome across countries.

by 33 patients (22.8%). The majority of patients had a history of secondary GTCS (*n*=86; 62.8%). The majority of patients fulfilled the criteria for drug resistance according to the ILAE (*n*=95; 63.8%) (Kwan *et al.*, 2010). Psychiatric comorbidity was detected in 11 patients (psychosis in two patients, and depression in nine).

The majority of patients were seizure-free (ILAE epilepsy surgery seizure outcome Class 1: *n*=106, 71.1%; Class 2: *n*=7, 4.7%; Class 3: *n*=18, 12.1%; Class 4: *n*=11, 7.4%; Class 5: *n*=6, 4.0%; and Class 6: *n*=1, 0.7%). Median follow-up was 36 months (range: 6-205). Median time from surgery to relapse in the non-seizure-free group was seven months (range: 1-70). Postsurgical outcome was significantly different between countries (dF=3 *p*=0.008) (*figure 1*). One patient in the non-evaluated group underwent surgery a second time (again without EPE) without achieving seizure freedom, and two patients in the evaluated group also received surgery again and seizures were stopped. *Table 2* presents the distribution of the clinical characteristics among the patients regarding postsurgical outcome. Same variables stratified to countries did not show a significant difference relative to postsurgical outcome except that seizure-free patients were younger at the time of surgery (median: 26 years) compared to those who were not rendered seizure-free in Hungary (median: 35.5 years) (*p*=0.032). A small portion of the analysed patients was ≤21 years old (*n*= 36; 24.1%) and this subset had significantly better seizure-free postsurgical outcome compared to older patients (86.1% vs. 66.3%; *p*=0.023). Postsurgical seizure outcome in this subset was not significantly related to gender (*p*=0.58), tumour side (*p*=0.12), tumour location (*p*=0.22), or confirmed drug resistance (*p*=0.53).

No difference in postsurgical seizure outcome was determined between patients who underwent EPE and those who did not (52/106 [49.1%] seizure-free patients vs. 24/43 [55.8%] non-seizure-free patients; *p*=0.45). The main clinical features in the groups with and without EPE are presented in *table 3*. Since we found several important clinical differences between patients with and without EPE, we performed additional analyses in a subset of patients (age at surgery ≥26 years, epilepsy duration ≥five years, confirmed drug resistance and LEAT location in temporal and temporal plus regions). There was no significant difference in postsurgical seizure outcome between presurgically evaluated and non-evaluated groups (*n*=34; *p*=0.51).

Discussion

We performed an analysis of postsurgical seizure outcome after LEAT surgery at different referring epilepsy or neurosurgery centres in four neighbouring south-east European countries. Although on the low side, our results are still consistent with well-established knowledge that the rate of seizure freedom in patients undergoing LEAT resection is significantly higher (70-90%) than that in most epilepsy surgery series (Kennedy and Schuele, 2013; Giulioni *et al.*, 2017). More precisely, apart from several studies that reported a lower seizure freedom rate after LEAT surgery (Jooma *et al.*, 1995; Lombardi *et al.*, 1997), the majority of the data indicate good outcome, even when the surgery is performed in the eloquent areas (Devaux *et al.*, 2017). We found that age at surgery was the only variable significantly associated with postsurgical outcome. This was a constant finding even when stratified analysis was performed for all centres. This is pursuant to recently published series which emphatically proved that younger patients with LEAT have a higher chance of seizure freedom following epilepsy surgery (Ramantani *et al.*, 2014; Pelliccia *et al.*, 2017; Giulioni *et al.*, 2017; Faramand *et al.*, 2018). This favourable outcome was not related to different variables, including drug responsiveness, which is in agreement with meta-analysis of potential prognosticators of seizure freedom based on a cohort of 910 patients with tumour-related epilepsies after LEAT resection (Englot *et al.*, 2012). Finally, our data further support epilepsy surgery as an early therapeutic strategy. In line with previous results, a higher rate of complete seizure freedom was achieved in paediatric patients in our study (≤ 21 years old).

Table 2. Distribution of clinical characteristics between patients relevant to postsurgical outcome.

Variable	Seizure-free (Class 1) *n*=106	Non-seizure-free (Class 2-6) *n*=43	*p*
Male gender	59 (55.7%)	29 (67.4%)	0.18
Epilepsy duration (median years)	5 (range 0-44)	8.5 (range 0-46)	0.25
Presurgical evaluation performed by epileptologists	52 (49.1%)	24 (55.8%)	0.45
Serbia (presurgical evaluation/not evaluated) *n*=30	11/9	6/4	0.79
Romania (presurgical evaluation/not evaluated) *n*=22	7/4	9/2	0.33
Bulgaria (presurgical evaluation/not evaluated) *n*=39	14/21	3/1	0.18
Hungary (presurgical evaluation/not evaluated) *n*=58	20/20	6/12	0.23
Drug resistance	65 (61.3%)	30 (69.8%)	0.33
Age at surgery	24.2±12.2	31.8±14.0	0.001
Tumour type			0.82
DNET	35 (33.0%)	14 (32.6%)	
Ganglioglioma	48 (45.3%)	17 (39.5%)	
Other GNT	2 (1.9%)	1 (2.3%)	
Other LGG	21 (19.8%)	11 (25.6%)	
Right-sided tumour	54 (50.9%)	22 (51.1%)	0.81
Tumour location			0.83
Temporal	72 (67.9%)	29 (67.4%)	
Mesiotemporal	50 (69.4%)	13 (44.8%)	0.19
Neocortical temporal	23 (30.6%)	15 (55.2%)	
Extratemporal	27 (25.5%)	10 (23.3%)	
Temporal plus	7 (6.6%)	4 (9.3%)	
History of febrile convulsions (unknown: *n*=4; 2.7%)	23 (22.1%)	10 (24.4%)	0.76
History of sGTCS (unknown: *n*=12; 8.1%)	61 (61.6%)	25 (65.8%)	0.65
Follow-up (median [months])	36 (range: 6-205)	24 (range: 6-127)	0.44

DNET: dysembryoplastic neuroepithelial tumour; GNT: glioneural tumours; LGG: low-grade glioma; sGTCS: secondary generalized tonic-clonic seizure.

Studies of seizure outcome aiming to investigate whether a preoperative electrophysiological study should be mandatory to guide the extent of resection in tumour-related epilepsy are scarce. So far, only one study on LEAT and postsurgical seizure outcome (Giulioni *et al.*, 2017) addressed this issue based on a smaller proportion of patients, who were not preoperatively evaluated in a standard fashion, including vEEGM. The authors did not find a significant difference in postsurgical seizure outcome between patients with and without presurgical evaluation. In this study, we replicated previously published data. However, there are several important differences between the two studies. In our sample, almost half of the analysed patients were referred for surgery by neurosurgeons without being preoperatively evaluated by epileptologists. This fact most likely represents current medical practice in all countries included in this analysis. The profile of patients who were immediately treated by neurosurgeons (young patients at the time of surgery with a short duration of epilepsy who were still drug-sensitive) further delineates the present form of management of LEAT patients in regions investigated in this study. Significant variation in presurgical protocols, as well as surgical methods and strategies which reflect the multicentric design of this study, are most likely responsible for the difference in postsurgical seizure outcome in different centres. For example, nine out of 22 patients in the Romanian group (which had the lowest seizure

Table 3. Clinical features in patients with and without presurgical evaluation performed by epileptologists.

Variable	Presurgical evaluation performed *n*=76	Presurgical evaluation not performed *n*=73	*p*
Age (years)	32.8±13.2	29.0±14.6	0.7
Age at surgery (years)	28.7±12.1	24.0±13.8	0.026
Epilepsy duration (median years)	10 (range 0.5-44)	2 (range 0-46)	<0.001
Country			0.099
Serbia	17 (22.3%)	13 (17.8%)	
Romania	16 (21.0%)	6 (8.2%)	
Bulgaria	17 (22.3%)	22 (30.1%)	
Hungary	26 (34.2%)	32 (43.8%)	
Right-sided tumour	39 (51.3%)	37 (48.7%)	0.59
Tumour location			<0.001
Temporal	64 (63.3)	37 (36.7%)	
Mesiotemporal	42 (65.0%)	21 (56.7%)	0.22
Neocortical temporal	22 (35.0%)	16 (43.3%)	
Extratemporal	7 (18.9%)	30 (81.1%)	
Temporal plus	5 (45.4%)	6 (54.6%)	
Tumour type			0.22
DNET	26 (53.0%)	23 (47.0%)	
Ganglioglioma	36 (55.3%)	29 (45.7%)	
Other GNT	0 (0%)	3 (100%)	
Other LGG	14 (43.7%)	18 (56.3%)	
FCD presence	9 (11.8%)	5 (6.8%)	0.26
History of febrile seizures (unknown: *n*=4; 2.7%)	16 (48.4%)	17 (51.6%)	0.73
History of sGTCS (unknown: *n*=12; 8.1%)	39 (45.3%)	47 (54.7%)	0.19
Seizure frequency			0.10
< Monthly	-	13.7%	
Monthly	25%	23.3%	
Weekly	48.7%	32.9%	
Daily	25%	23.3%	
Missing data	1.3%	6.8%	
Number of AEDs before surgery	1.58±1.51	3.3±2.71	<0.001
Drug resistance	70 (73.6%)	25 (26.4%)	<0.001
Median follow-up (months)	24 (6-89)	48 (6-208)	<0.001
Median time to first seizure with ILAE Class 2-6 (months)	6.5 (1-70)	12 (1-60)	0.81

DNET: dysembryoplastic neuroepithelial tumour; GNT: glioneural tumours; LGG: low-grade glioma; FCD: focal cortical dysplasia; sGTCS: secondary generalized tonic-clonic seizure; AED: antiepileptic drug.

freedom rate) had an epileptogenic zone overlap with the functional cortex or white matter tracts. Moreover, in this group, the population was older. Nevertheless, these observations are compatible with the results from previous multicentric studies (Téllez-Zenteno *et al.*, 2005; Giulioni *et al.*, 2017). However, in contrast to our study, the majority of surgeries in the Italian multicentre study were carried out at epilepsy surgery centres or centres with significant expertise in epilepsy. This may make the comparison between studies somewhat unclear. The primary aim of the presurgical evaluation is to identify the epileptogenic zone, *i.e.*, the minimum amount of brain tissue that should be resected in order to render the patient seizure-free. However, analysis of the presurgical data is often performed with considerable heterogeneity (Ryvlin and Rheimes, 2008). This multicentric trial (*i.e.*, heterogeneous patient management for presurgical evaluation in different centres), in addition to a previous study (Giulioni *et al.*, 2017), further supports the discussion on the role of presurgical evaluation and vEEGM in LEAT-related epilepsy surgery management. Indeed, our study contributes to the perception that, despite limited workup without an epileptologist or long-term video-EEG availability, individual centres may still perform resection of the lesion, which would allow seizure freedom in a significant number of patients. In these circumstances, surgical failure following the first operation should be inevitably evaluated by an epilepsy expert and then considered for further testing.

The major limitation of our study is that groups with and without presurgical evaluation were fairly non-homogeneous, and this may explain the equality in seizure outcome. Namely, patients treated by neurosurgeons without presurgical evaluation were of significantly younger age and had shorter epilepsy duration and a lower rate of drug resistance. These variables are known to be associated with poor outcome. Consequently, one would have suspected a better outcome in patients who did not undergo epilepsy evaluation. Additionally, a higher rate of temporal lobe tumours in presurgically evaluated LEAT patients and restrictive resections aimed at preventing memory deficit may potentially reveal no difference in postsurgical outcome. However, in a subset of 34 patients with comparable variables, we did not find any difference in postsurgical seizure outcome. This might imply that further prospective research with sufficient statistical power could reveal the subset of patients which might directly benefit from presurgical evaluation. The second significant limitation to our study is that neuropsychological postoperative data were not available for the majority of non-evaluated patients. Therefore, we could not compare this with evaluated patients in whom neuropsychological deficit followed a previously described pattern (data not shown) (Vogt *et al.*, 2018). Thus, whether presurgical evaluation and direct epileptologist input into treatment prevent major neuropsychological deficits cannot be addressed in our study and remains to be elucidated in further work. Finally, data on several important variables could not be consistently gathered due to the retrospective method of the study. Relevant clinical data obtained by history taking such as aura types, focal features, and possible lateralizing signs were not regularly recorded in the group of patients managed by neurosurgeons. The same is true for the maximum voltage field regarding interictal findings in patients without EPE. Therefore, whether the variables presented here have a potential influence on postsurgical seizure outcome remains unknown. Due to the numerous limitations, it is not possible to draw any definitive conclusion regarding whether there is value in formal presurgical evaluation in LEAT patients. However, we argue that a prospective, well-designed study addressing the value of epileptological evaluation for LEATs should be performed. Finally, our findings strongly support the clear need for continued discussion around such patients at epilepsy management conferences in centres with significant experience in epilepsy surgery. □

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Is long-term video-EEG monitoring required for all patients with LEAT-related epilepsy?

(2) Is there a difference between presurgically evaluated and non-evaluated patients with LEAT with respect to postoperative seizure freedom?

(3) What is the role of presurgical evaluation in LEAT-associated epilepsy surgery management?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".