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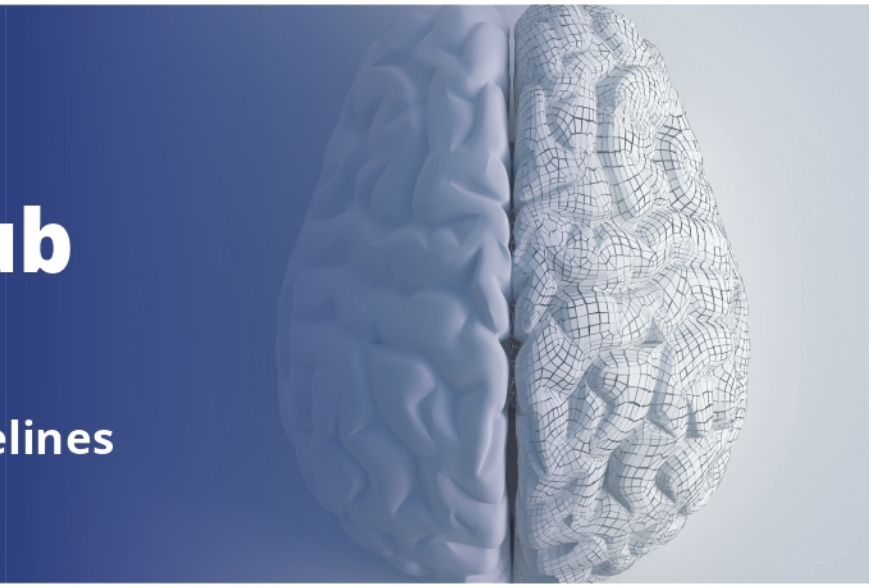

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Castro Felipe Andres (Orcid ID: 0000-0002-8569-6160)

D'Arco Felice (Orcid ID: 0000-0001-7396-591X)

Scott Rodney C. (Orcid ID: 0000-0002-8944-928X)

Cross J.Helen (Orcid ID: 0000-0001-7345-4829)

Eltze Christin (Orcid ID: 0000-0003-4411-2939)

Corresponding author mail id- c.eltze@ucl.ac.uk

Seizure outcome determinants in children after surgery for single unilateral lesions on MRI: role of preoperative ictal and interictal EEG

Felipe Castro-Villablanca[1,7], Friederike Moeller [2,5], Suresh Pujar[1,5], Felice D'Arco[3,5], Rod C. Scott[1,5,6], M Zubair Tahir[4] ,Martin Tisdall[4,5], J Helen Cross[1,5], Christin Eltze[1,5]

Affiliations:

[1]Epilepsy Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
[2]Clinical Neurophysiology Department, Great Ormond Street Hospital for Children NHS Foundation Trust,
[3]Neuroradiology Department, Great Ormond Street Hospital for Children NHS Foundation Trust,
[4]Neurosurgery Department, Great Ormond Street Hospital for Children NHS Foundation Trust,
[5] Developmental Neurosciences Unit, UCL Great Ormond Street Institute of Child Health, London, UK
[6]Divsion of Neurology, AI DuPont Hospital for Children, Wilmington, Delaware, USA
[7] Paediatrics Department, University of Chile, Santiago, Chile

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID IDs:

Felipe Castro-Villablanca 0000-0002-8569-6160

Christin Eltze 0000-0003-4411-2939

Corresponding author:

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Dr Christin Eltze
Neurology Department
Great Ormond Street Hospital for Children
Great Ormond Street
WC1N3JH
Tel: ++442074059200 ext 4411
https://orcid.org/0000-0003-4411-2939

ABSTRACT (300 words):

Objective: To determine if an ictal EEG recording as part of pre-surgical evaluation of children with a demarcated single unilateral MRI lesion is indispensable for surgical decision making, we investigated the relationship between interictal/ ictal EEG and seizure semiology with seizure-free outcome.

Methods: Data were obtained retrospectively from consecutive patients (≤ 18 years) undergoing epilepsy surgery with a single unilateral MRI lesion at our institution over a 6-year period. Video-telemetry EEG (VT-EEG) was classified as concordant or non-concordant/non-informative in relation to the MRI lesion location. The odds of seizure-free outcome associated with non-concordant versus concordant for 'semiology', 'interictal' and 'ictal' EEG were compared separately. Multivariable logistic regression was conducted to correct for confounding variables.

Results: After a median follow-up of 26 months (IQR 17-37.5) 73 (69%) of 117 children enrolled were seizure free. Histopathological diagnoses included: low-grade epilepsy associated tumours 46 (39%), Focal Cortical Dysplasia (FCD) 33 (28%), mesial temporal sclerosis (MTS) 23 (20%), polymicrogyria 3, 3%) and non-diagnostic findings/gliosis 12 (10%). The odds of seizure freedom was lower with a non-concordant interictal EEG (OR=0.227, 95% CI 0.079 to 0.646, p=0.006) and non-concordant ictal EEG (OR=0.359, 95%CI 0.15 - 0.878, p=0.035). In the multivariable logistic regression model, factors predicting lower odds for seizure free outcome were developmental delay/intellectual disability, higher number of anti-seizure medications tried and a non-significant trend for 'non-concordant interictal EEG'.
In the combined subgroup of patients with FCD and tumours (n=79) there was no significant relationship of VT-EEG factors and seizure outcomes, whilst in children with MTS and acquired lesions (n=25) a non- concordant EEG was associated with poorer seizure outcomes) p =0.003).

Significance: An ictal EEG may not be mandatory for pre-surgical evaluation, particularly when a well-defined single unilateral MRI lesion has been identified and

the interictal EEG is concordant.

Key points:

- 68.4% of children with a single unilateral lesion on MRI become seizure free following epilepsy surgery
- A pre-surgical interictal scalp EEG non-concordant with the MRI lesion shows a trend towards a lower chance of seizure free outcome after adjustment for confounding variables
- A pre-surgical ictal scalp EEG is not independently associated with seizure free outcome after adjustment ion for confounding variables in this group
- In the FCD and tumour subgroup there was no significant relationship of presurgical interictal or ictal EEG with seizure outcomes
- The mandatory requirement of an ictal EEG recording in presurgical evaluation for all patients requires review

Introduction:

Epilepsy surgery has a higher chance of achieving seizure free outcome in well-selected patients with pharmacoresistant focal epilepsy compared to continued treatment with antiseizure medications (ASM) [1]. Amongst the different epilepsy surgery procedures, focal resections, account for the largest proportion of epilepsy surgery procedures and have the best seizure free outcome rates [2, 3]. Relevant predictive factors for seizure free outcomes identified for these types of surgical procedures include 'age at epilepsy onset' [4], 'shorter duration of epilepsy' [5], 'anatomical location of surgery (temporal lobe has better outcomes compared to extratemporal surgery)', and 'completeness of neuroradiological lesion resection' [6, 7].

The most common histopathologies identified in paediatric surgical specimens in order of highest prevalence are Focal Cortical Dysplasia (FCD), low-grade tumours and Mesial Temporal sclerosis (MTS)[8].

Presurgical evaluation (PSE) is a comprehensive multimodal assessment, providing information on whether epilepsy surgery can be offered along with the surgical outcome-goals, risks and benefits. Standard practice of most surgical centres is to perform core presurgical investigations and assessments consisting of brain magnetic resonance imaging (MRI) applying high resolution protocols, neurological clinical evaluation, neuropsychological / neuropsychiatry assessments and scalp video-telemetry -EEG (VT-EEG) to obtain interictal and ictal recording [9]. Although the aim of the VT-EEG is to ascertain information about localisation and extent of the seizure onset zone [10] , there are limitations including reduced ability to identify epileptic foci in deeper structures (i.e. interhemispheric or mesial temporal cortex) and poor spatial resolution. VT-EEG to record the habitual seizure type, can be time and cost intensive and may not be successful (despite ASM reduction) in individuals with infrequent seizures [11]. Recently, the value of the ictal EEG recording, especially for patients with MRI- lesion positive focal epilepsy, in the surgical decision-making process has been questioned by some studies [12, 13] . In a previous study at our institution pre-operative VT-EEG recordings in 353 patients with unilateral structural MRI abnormality did not influence the decision to offer epilepsy surgery [12]. The relationship of VT-EEG to post-surgical seizure outcomes, however, was not investigated in that study. Another study found no difference in seizure outcomes of patients undergoing a focal resection due to a MRI positive lesion with ´positive ictal EEG´ and those with a ´negative ictal EEG´-defined as no available ictal recording or ictal EEG discordant with the MRI lesion [14].

However, this study did not distinguish between interictal EEG, ictal EEG and semiology in relation to post-surgical seizure outcomes.

The primary aim of this study was to investigate the relationship between pre surgical semiology, interictal EEG, ictal EEG, and postsurgical seizure outcome in children undergoing epilepsy surgery for pharmaco-resistant focal epilepsy for well demarcated, single, unilateral MRI lesions. We also describe the spectrum of pathologies and association of other relevant clinical variables with seizure free outcome in this particular patient group.

Methods:

We retrospectively reviewed data from a cohort of consecutive paediatric patients undergoing epilepsy surgery at our institution. Our institution (Great Ormond Street Hospital for Children) is one of the largest providers for the nationalised specialist service for childhood epilepsy surgery in the UK, with main catchment area of the East and South-East of England. From our institutional electronic database, we selected all patients who underwent focal resections for epilepsy in the period from 1st January 2012 to 31st December 2017. Patients meeting the following criteria were included: a) age ≤ 18 years at surgery b) lobar or sublobar structural lesions on MRI c) sublobectomy or lobectomy performed d) at least 1-year post-surgical follow up. We excluded children: a) who underwent surgery for hypothalamic hamartoma b) with bilateral, and/or diffuse MRI abnormalities, including Tuberous Sclerosis Complex (TSC) c) who underwent corpus callosotomy or multi-lobar disconnection-surgery (hemispherectomy, temporo-parieto-occipital disconnection, and multilobar resection surgery, d) who had previous epilepsy surgery, e) with incomplete information, i.e.

absent record of epilepsy surgery meeting (ESM) discussion and/or no pre-surgical VT-EEG data

All patients included in this study underwent 1.5T or 3T (from 2014 onwards) MRI using dedicated epilepsy protocols (including 3D T1 weighted and FLAIR sequences).

Clinical and presurgical investigation information was obtained from the case notes, including neuropsychological assessment, neuroimaging, surgical and follow-up data. Seizure outcomes were categorised according to the Engel classification [15]. We applied the simplified classification with the 4 main categories: Engel class I (seizure free), Class II (rare disabling seizures, 1-4 seizure days/year), Class III (worthwhile improvement) and Engel Class IV (no worthwhile improvement).

Psychomotor Development was categorised as normal or developmental delay/intellectual disability (DD/ID) using DSM V criteria (with IQ cut off at 70 points or DQ equivalent) according to the conclusions of standardised assessments performed as part of the pre-surgical evaluation (instruments used according to age and cognitive ability: Wechsler Preschool intelligence Scale (WPPSI) Wechsler Intelligence Scale (WISC), Bayley scales for infant and toddler assessment, Griffiths Developmental Scales)[16-18]. Children with normal cognition, but with another developmental disorder diagnosis, such as autism spectrum disorder or specific language disorder, were categorised as cognitively normal (i.e. not having an intellectual disability).

The VT-EEG recordings at our institution are reviewed by expert clinical neurophysiologists, who generate a detailed report of interictal, ictal EEG and semiology findings according to their qualitative judgement of the distribution of EEG

abnormalities (interictal epileptiform discharges, focal slow activities, ictal rhythms). This study was carried out with data obtained from a clinical service delivery setting and therefore the clinical neurophysiologists were not blinded to MRI findings.

Based on the VT-EEG reports and the epilepsy surgery meeting discussion records we classified interictal and ictal EEG as well as semiology separately as either a 'localising', 'lateralizing' or 'non-concordant' in relation to the anatomical location of the MRI lesion. 'Localising' was allocated for 'ictal' or 'interictal VT-EEG' if features were in keeping with the same lobe or quadrant of the MRI location and 'lateralized' if features were in keeping with the hemispheric lateralisation of the MRI lesion but not permitting further localisation within the hemisphere. Semiology was categorised as 'localising' if features were in keeping with same lobe of the MRI lesion location, even if lateralisation was not possible or 'lateraling' if manifestations were in accordance with onset in the hemisphere of the MRI lesion location. 'Non-concordant' was used when VT-EEG features were neither in keeping with cortical area nor hemisphere of the anatomical MRI lesion location. We also categorised as non-concordant ictal VT-EEGs with bilateral ictal discharge at seizure onset, that did not permit a judgement with regards to lateralisation, and interictal VT-EEGs with multifocal epileptiform discharges without a clear predominant focus.

Neuroimaging information and diagnosis was obtained from the MRI reports generated by paediatric neuroradiologists as part of our epilepsy surgery program in conjunction with the record of the epilepsy surgery MDT discussion. As this is part of our routine post-surgical evaluation, determination of completeness of radiological lesion resection was also based on our institutional post-surgical MRI reports.

Seizure outcomes of patients with 'concordant' (i.e. localising and lateralizing groups combined) semiology, interictal or ictal EEG (i.e. MRI lesion concordant) were compared with those who had 'non-concordant' semiology, interictal or ictal EEG for each of these variables separately.

Statistical analysis

Data were analysed using SPSS 28. We compared group differences between seizure free outcome (Engel class I) versus ongoing seizures (i.e. categorised Engel class II/II/IV combined) using either chi-square or Fisher's exact test for categorical data, and Student's T test or Mann-Whitney U test for numeric data. Factors investigated in this comparison included 'non-concordant' versus 'concordant' for each VT-EEG components (interictal, ictal and semiology) and other relevant predictors reported in the literature (see table 3). The Odds ratios (OR) with 95% confidence interval (CI) predicting seizure free outcomes were calculated. (p values and 95% CI were obtained for both numeric (mean/median) and categorical data (proportions).

A multivariable logistic regression model (stepwise backwards method) was applied including the factors that were significant in the univariable analysis to determine factors related to seizure free outcome at last follow up (elimination threshold for variable selection in the final was a p value of 0.1).

We used the same approach for a subgroup analysis of the developmental lesions as determined by the histopathology report: Tumours and FCD combined (n=79). The number of the patients in the subgroup with acquired lesions (hippocampal sclerosis

and porencephalic cyst) was in comparison too small (n=25) for further subgroup analysis.

Only cases with available data for the variables were included in the analysis.

Institutional Approval:

This project was approved by Great Ormond Street Hospital for Children as a service evaluation project.

Results:

A total of 466 children underwent epilepsy surgery during the reviewed period, of which 168 (36%) underwent a focal resection. 21 cases (23%) were excluded because of insufficient information; 117/169 (69%) met inclusion criteria and were therefore included in the analysis (see Figure 1). Of these 59 (50.4%) were female. The median age of seizure onset was 2 years (IQR 0.7-5), and mean age at epilepsy surgery 9.3 years SD 4.8 years. Sixty-five children (55.6% had daily seizures at the time of epilepsy surgery evaluation. 39 of 114 with available data (34%) had developmental delay / Intellectual disability (DD/ID) at the time of evaluation. The distribution of the MRI lesion diagnosis and location in relation to lobe is summarised in table 1.

The median time of follow-up after surgery was 25.5 months (IQR 17-36.5, range 12 - 67 months); in 69 (59% of 117) patients this was longer than two years.

Insert Figure 1

Insert Table 1

Post-surgical-seizure outcome and histopathology findings:

Eighty children (68.4%) were seizure free at last follow up (median 26 months; IQR 17-37.5). Low grade epilepsy associated tumours (LEAT: gangliogliomas and dysembryoplastic neuroepithelial tumours, DNTs) were the most frequent pathology (n=46, 39%), followed by FCD (n=33, 28%, mostly FCD type II), MTS (n=23, 20%), other cortical malformations with polymicrogyria (3, 3%) and others (Cyst, nonspecific gliosis and non-diagnostic findings, n=12, 10%). Tumours and FCD had the best outcome, with seizure freedom rates of 74%, and 76% respectively. Surgery for MTS presented the poorest surgical outcome, with a seizure freedom rate of only 52%. The details of histopathology findings in relation to seizure outcomes are listed in the supplementary table e5.

VT-EEG as seizure outcome predictor:

VT-EEG recordings as part of the presurgical evaluation were obtained at our institution for 102/117 (87%) and for 15 (13%) children at other institutions (external). All 'external' VT-EEG recordings were reported and discussed by expert clinical neurophysiologists from our institution in the epilepsy surgery meeting. Long-term VT-EEG, of at least 24 hours, was performed in 105/117 (89%) patients with a median duration of 3 nights (range 1-4). Short VT-EEG recordings (< 24 hours) were performed in 4/117 (3.4%, mean duration 2.9 hours, SE+/- 1.1), whilst the total VT-EEG duration was unknown for 5/117 (4.3%) patients (all performed 'externally'). Ictal

EEG recordings were obtained for 115/117 (98%) patients (1 seizure for 9 (8%), 2-5 for 51 [45%], 6-10 for 27 [23%], and > 10 for 28 [24%] patients).

The children with VT-EEG components scored as either MRI lesion 'localising' or 'lateralising' were pooled in one group (MRI lesion concordant or 'localising/lateraling interictal, ictal VT-EEG or semiology) because on exploratory univariable analysis using Chi square / Fisher exact statistics there was no significant difference between seizure free outcome (Engel I) versus ongoing seizures (Engel II/II/IV) for each of these components.

The majority of *ictal VT-EEG* categorised as non-concordant were non-informative with bilateral ictal patterns at onset (19/28). Similarly, the majority of *interictal VT EEG* scored as non-concordant were multifocal, non-informative (13/17).

In 26 (23%) of 115 patients the pre-surgical interictal *and* ictal VT-EEG data were discordant with each other, i.e. 8 patients with non-concordant interictal VT-EEG had a concordant ictal VT-EEG (7 achieved Engel I or II seizure outcomes at last follow up) and 18 patients had a concordant interictal VT-EEG and a non-con-concordant ictal VT EEGs (14 achieved Engel I or II seizure outcomes at last follow up).

Table 2a shows univariable (unadjusted) group comparisons (ORs) between seizure free (Engel I) outcome versus ongoing seizures (Engel II/III/IV) and MRI lesion concordance categories ('non-concordant' versus 'concordant') for each VT component: interictal EEG (117), ictal EEG (115) and semiology (113).

Insert Tables 2 a and b

Both a non-concordant interictal and non-concordant ictal EEG were associated with significantly lower odds of becoming seizure free (Engel I category) post-surgery, whilst there was no significant association of a non-concordant semiology with seizure free outcome.

The following factors, including those significant in the univariable analysis, were entered in a multivariable logistic regression model: 'Non-concordant interictal EEG', 'Non-concordant ictal EEG', 'Latency to surgery (years)', 'Complete radiological lesion resection', 'Developmental delay / Intellectual Disability (DD/DI)'. A stepwise backwards method for factor selection was applied. Table 3b lists the factors remaining in the final model: 'DD/ID', 'total number of ASMs tried' and 'non-concordant interictal EEG'. A non-concordant interictal EEG showed weak non-significant (p=0.058) association with lower odds of seizure freedom.

Insert table 3a and b

Insert table 4

In the subgroup analysis of patients with developmental lesions (combined FCD and tumour group (n=79) there was no significant association between the VT-EEG components (non-concordant interictal, ictal EEG and semiology) and seizure free outcome after surgery (table 3a, while int the subgroup analysis of patients with acquired lesions (MTS, Chaslin gliosis and cyst (n=25) there was an association between non-concordant interictal EEG and seizure free outcome only (Table 4).

Other factors associated with seizure outcome:

Previously reported variables associated with poor surgical outcome, namely 'age at epilepsy onset', 'latency to surgery (duration of epilepsy before surgery)', 'age at surgery', ´total number of ASMs tried (from epilepsy onset to the time of surgery)', 'Developmental Delay/ Intellectual disability (DD/ID)', 'temporal versus extratemporal lobe surgery' and 'complete radiological lesion resection', were compared between seizure free and non-seizure free patients for the entire cohort (table 2a) and the subgroups of patients with developmental lesions (table 3a).

Total number of ASMs and presence of DD/ID were significantly associated with lower odds of seizure free outcomes in the entire cohort in the univariate comparisons. In the multivariable logistic regression model, mentioned in the previous paragraph both factors remained significantly associated with lower odds for seizure free outcomes (table 2b).

In the subgroup of children with developmental lesions (combined FCD/ tumour group) in the univariate analysis shorter 'Latency to surgery (duration of epilepsy before surgery') and 'complete radiological lesion resection' were significantly associated with seizure free outcome, whilst 'total number of ASMs tried' and 'DD/ID' were significantly associated with persisting seizures. In the multivariate logistic regression model entering all four factors ' total number of ASMs tried' remained the only significant factor associated with persisting seizures with a non-significant trend of complete MRI lesion resection suggesting higher odds for seizure free outcomes (table 2b).

There were differences between children with ID/DD (n=39) and those with normal intellect: 80% (60/75) of children with normal intellect were seizure free, compared

with only 43.6% (17/39) with DD/ID. These two groups were different in respect to other clinical variables: patients with DD/ID were younger at epilepsy onset (median 1 years vs 3 years, p=0.001), had been trialled on a higher number of ASMs (mean ASM 5.15 vs 3.72, p=0.001), had a higher proportion with non-concordant interictal EEG (25.7% vs 10.7% p=0.038) and non-concordant ictal EEG (46.4% vs 17.6% p=0.011).

Discussion:

VT-EEG as seizure outcome predictor

We have shown in a cohort of paediatric epilepsy patients, with a single unilateral MR lesion, that the pre-surgical ictal EEG recording is not an independent predictor of seizure free outcome after adjustment for other relevant clinical variables. In the same logistic regression model an interictal EEG non-concordant with the MRI lesion was associated with a non-significant trend, towards lower odds of achieving seizure free outcome.

Subgroup analysis indicates differences between histopathological groups. In the subgroup of children with discrete developmental lesions (FCD and Tumours combined) no association of VT- EEG factors (ictal, interictal VT-EEG, semiology) to seizure outcome was observed, whilst in those with acquired lesions, mainly MTS, univariable comparison demonstrate a significant relationship of a non-concordant interictal VT-EEG with lower odds of seizure free outcome. In MTS/acquired lesion subgroup there was no significant relationship between the ictal VT-EEG and seizure outcome. The interpretation of this result is, however, limited by the small number in the MTS group.

In paediatric and adult patients with FCD undergoing epilepsy surgery the interictal as well as ictal scalp EEG patterns and especially co-localisation with the structural MRI lesion is variable as shown in a large cohort consisting of pooled data of several surgical series with little apparent correlation to the lesion extent [19]. This paper provided no information about MRI lesion concordance of interictal / ictal scalp EEG abnormalities and their relations to post-surgical seizure outcomes.

Similar to our findings in the combined FCD and tumour group, previous studies found for patients with low grade epilepsy associated tumours that the pre-operative scalp EEG was not a significant factor associated with seizure outcome, whilst significant outcome predictors were other factors including completeness of lesion resection and duration of epilepsy [20-22].

A recent systematic literature review found that the pre-surgical VT-EEG (long-term video EEG monitoring) was associated with moderate sensitivity (0.7; 44 studies included) to localize the epileptic zone in patients, who became seizure free, and low specificity (0.4; 34 studies included), defined as proportion of patients with non-localising VT-EEG , who failed to become seizure free [23]. The sensitivity was higher in lesional temporal compared to extratemporal epilepsy. Studies were assessed to have a high risk of bias and the quality of the evidence was evaluated as 'very low'. The prognostic value of ictal and interictal EEG were not investigated separately in this review.

In adult patients undergoing surgery with MRI positive mesial temporal sclerosis several studies report such data. In a retrospective study, lesion concordant interictal discharge lateralisation / localisation was highly correlated with ipsilateral ictal EEG

onset, but the ictal EEG pattern was not related with seizure outcome and judged as non-contributory to surgical decision making [24]. It remains uncertain whether the interictal changes were predictive of outcome. A more recent prospective study enrolling patients with MRI lesion positive MTS and > 80 % ipsilateral interictal epileptiform discharges found no statistical difference in seizure free outcomes between those patients with and without pre-operative ictal EEG recordings [25].

Similar observations have also been reported in children undergoing temporal lobe surgery. Smyth et al found no significant difference in post-surgical seizure outcomes in patients with pre-operative ipsilateral temporal EEG abnormalities (ictal and/or interictal) compared to those with bilateral abnormalities, although, bilateral EEG findings were associated with a trend towards worse outcome [26].

The pre-operative scalp -EEG was not related to seizure outcomes in children with early acquired or developmental, mostly multi-lobar and hemispheric brain lesions presenting with refractory epilepsy and developmental impairment. Seizure free outcomes in those with pre-operative bilateral or contralateral interictal / ictal epileptiform activity were similar to a comparison group of patients with predominantly ipsilateral epileptiform discharges [27]. This was confirmed again in a more recent study. The authors report their experience using a 'lesion-orientated' presurgical evaluation algorithm with limited VT-EEG in a series of 54 children with MRI visible lesions, in the majority cortical malformations and infarctions (60%), Fifty seven percent of patients underwent hemispherectomy and overall 86% of patients were reported seizure free after a median follow up of 20.45 months. Surgery was performed without preoperative ictal EEG recording in 35% of children, whose seizure outcome was not significantly

different compared to those with ictal EEG. An ipsilateral ictal EEG, bilateral or contralateral interictal EEG abnormalities were not related to surgical outcome [28].

Statistical modelling of post surgical seizure outcome prediction using clinical and presurgical scalp EEG data in a large surgical series of mainly adult patients (n=470, MRI negative and positive focal epilepsy), in the majority temporal lobe epilepsy due to MTS, showed that inclusion of presurgical EEG resulted in only a modest improvement of the prediction. Including Scalp EEG data improved the model from 59% to 65% correct seizure outcome prediction [29]. Interestingly in the final model used to create a 'nomogram' to predict seizure freedom at 2 years after surgery included only the interictal EEG together with other clinical and neuroimaging factors.

Although we observed concordance between MRI lesion and semiology as described in VT-EEG in a relative high proportion of children (in 89% seizures were categorised as localising/lateralising), similar to previous reports from adults, there was no significant association with seizure free postoperative outcome [OR=0.819, 95% CI 0.22-3.0, P=0.744] [30]. This could not be explained by the age of children in our cohort. There was no difference in separate analysis of non-concordant/concordant semiology versus seizure free post surgical outcome) in the group of children undergoing surgery younger or older than 5 years. Although seizure semiology may give important clues to the localisation of the seizure onset zone it does not reliably distinguish areas of onset and cortical areas, which generate manifestations after propagation of ictal activity .

Our findings as well as previous studies support that ictal EEG recordings as part of the pre-surgical evaluation are not imperative to decide whether surgery can be offered, when patients have well defined MRI lesions. A lesion concordant interictal EEG provides useful information, of some prognostic relevance, although this may be less relevant for discrete developmental lesions (FCD and low grade epilepsy associated tumours).

An ictal EEG as part of presurgical evaluation in this group of patients may have a role in specific circumstances, for example if a diagnosis of non-epileptic events are suspected, to provide additional information for patients and family during the surgical counselling session, or if an additional diagnosis of a generalised electroclinical epilepsy syndrome diagnosis is considered.

In this selected cohort a discordant interictal EEG should not lead to exclusion of a patient from epilepsy surgery, especially those children and young people with high seizure burden and poor quality of life. The pre-surgical evaluation and decision making using limited VT-EEG (interictal EEG data only) for specified subgroups of patients, however, should be undertaken by an experienced multidisciplinary team.

This study was not designed to provide evidence to recommend a minimum duration of an interictal EEG recording to sample sufficient interictal abnormalities. A pragmatic approach, however, in the paediatric population with a compatible seizure history would be to obtain an EEG recording in wakefulness and sleep, aiming to record all sleep stages [31].

Other factors predicting seizure outcome.

Developmental delay/ID in our cohort was an important predictor of ongoing seizures at last follow-up in our cohort (0R=0.193, 95%CI 0.083 to 0.451, p= 0.001, see table 2 a). Previous studies have demonstrated that patients with intellectual disability and focal lesional epilepsy show a less favourable outcome both for pharmacological as well as surgical treatments [32, 33 34]. However, the causes for poorer seizure outcomes, particularly in patients with DD/ID in our cohort with MTS, are not completely understood. Persisting seizures in focal epilepsy are associated with changes in white matter connectivity, abnormal functional and structural brain network topology, and hippocampal volume and structural changes, sometimes associated with adverse cognitive outcomes[35]. The presentation of developmental delay and intellectual impairment could indicate a more widespread and diffuse network dysfunction beyond that relating to the focal lesion. Genetic factors could well have contributed to this finding. However, investigating such factors was beyond the scope of our study, given the retrospective design and the fact that genetic investigations applying modern technology were carried out in only a small and selected proportion of patients in this cohort.

Limitations:

Due to the retrospective nature of this study, inconsistencies in documentation of seizure outcomes in patient's records may have occurred, which limits the accuracy of seizure outcome classification, especially when deciding between Engel categories. The numbers of patients in each pathology group were too small to perform statistical analysis of each subgroup separately . In addition, we cannot exclude reduction of seizure freedom rate after a longer follow-up period than in our cohort. Our analysis was also based on a cohort of patients, who underwent surgical resection with

available outcome data. We can therefore not comment on outcomes of potential patients with single unilateral MRI lesions, who did not undergo surgery.

Although we investigated cognitive impairment as a factor relating to seizure free outcome, we did not include presence of behavioural / psychiatric disturbances as a separate category.

The classification of VT-EEG data was based on the reports by consultant clinical neurophysiologist, who were not blinded to the neuroimaging diagnosis, which may have potentially influenced their judgement. Likewise, as the neuroimaging information was derived from MRI reports, we cannot exclude that the paediatric neuroradiologists were blinded to clinical information including EEG findings. However, the aim of this study was to investigate information derived from a real-world setting. International standards for presurgical evaluation, including multidisciplinary team discussions have been published[9]. We therefore feel that our findings are applicable to the practice in other epilepsy surgery centres.

Although temporal (69%) compared to extratemporal lesion location was more frequent in children enrolled in our cohort, we feel that our findings with respect to the predictive value of the interictal EEG is independent from the anatomical lesion location.

Conclusions:

Almost 70% of children with a single unilateral lesion on MRI become seizure free following epilepsy surgery. Within the confines of these data originating from a single paediatric surgical centre, we found that the association of the presurgical VT-EEG in this particular group of children with post-surgical seizure outcomes were weak. In

the overall cohort a non-concordant pre-surgical ictal EEG was not associated with seizure outcome after adjustment for relevant confounding variables, whilst there was a non-significant trend for a non-concordant interictal EEG to be associated with a lower odds for seizure freedom.

The underlying histopathology appears to impact on the relationship between pre-surgical interictal / ictal EEG and seizure outcomes. The ictal and interictal VT -EEG data were not related to seizure outcomes in patients with developmental lesions (low grade epilepsy associated tumours and FCDs), whereas in those with MTS/acquired lesions only a non-concordant *interictal* EEG was significantly associated with lower odds of seizure free outcome, with the caveat that especially in the latter subgroup the numbers were small. Further validation of our observations in a larger patient cohort in a multicentre setting would be desirable.

Nevertheless, the current practice that requires an ictal VT-EEG for all patients considered for epilepsy surgery indiscriminately should be reviewed. Limiting ictal VT-EEG in children with clear single focal unilateral lesions, especially in those with lesion concordant interictal EEG, would allow increased resources to investigate those with unclear or negative MRI findings or bilateral lesions, where an ictal recording continues to have an important role, as well as in the documentation of no non-epileptic episodes that may persist after surgery.

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Author's statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines
The corresponding and senior author (Christin Eltze) had full access to all data and takes responsibility for the statistical analysis and results.

The study was registered by our institutional audit department as service evaluation. As the data analysis was retrospective and no additional data were collected beyond that required for standard medical care of the patient, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was deemed not necessary by the study team.

Author's contribution:

Felipe Castro-Villablanca: study design, data collection, statistical analysis , drafting of manuscript

Friederike Moeller: study design, data collection, commenting on manuscript
Suresh Pujar: commenting on manuscript
Felice D'Arco: commenting on manuscript
Rod C. Scott: commenting on manuscript
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References:

1. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for Drug-Resistant Epilepsy in Children. N Engl J Med 2017;377:1639-1647.
2. Barba C, Cross JH, Braun K, et al. Trends in pediatric epilepsy surgery in Europe between 2008 and 2015: Country-, center-, and age-specific variation. Epilepsia 2020;61:216-227.
3. Harvey AS, Cross JH, Shinnar S, Mathern GW. Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia 2008;49:146-155.
4. Cossu M, Lo Russo G, Francione S, et al. Epilepsy surgery in children: results and predictors of outcome on seizures. Epilepsia 2008;49:65-72.
5. Bjellvi J, Olsson I, Malmgren K, Wilbe Ramsay K. Epilepsy duration and seizure outcome in epilepsy surgery. A systematic review and meta-analysis 2019;93:e159-e166.
6. Jenny B, Smoll N, El Hassani Y, et al. Pediatric epilepsy surgery: could age be a predictor of outcomes? J Neurosurg Pediatr 2016;18:235-241.
7. Paolicchi JM, Jayakar P, Dean P, et al. Predictors of outcome in pediatric epilepsy surgery. Neurology 2000;54:642-647.
8. Blumcke I, Spreafico R, Haaker G, et al. Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery. New England Journal of Medicine 2017;377:1648-1656.
9. Jayakar P, Gaillard WD, Tripathi M, Libenson MH, Mathern GW, Cross JH. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia 2014;55:507-518.
10. Pressler RM, Seri S, Kane N, et al. Consensus-based guidelines for Video EEG monitoring in the pre-surgical evaluation of children with epilepsy in the UK. Seizure 2017;50:6-11.
11. Kobulashvili T, Hofler J, Dobesberger J, et al. Current practices in long-term video-EEG monitoring services: A survey among partners of the E-PILEPSY pilot network of reference for refractory epilepsy and epilepsy surgery. Seizure 2016;38:38-45.
12. Patil SG, Cross JH, Kling Chong W, et al. Is streamlined evaluation of children for epilepsy surgery possible? Epilepsia 2008;49:1340-1347.
13. Tanaka H, Gotman J, Khoo HM, Olivier A, Hall J, Dubeau F. Neurophysiological seizure-onset predictors of epilepsy surgery outcome: a multivariable analysis. J Neurosurg 2019:1-10.
14. Hur YJ, Kim AJ, Nordli DR, Jr. MRI supersedes ictal EEG when other presurgical data are concordant. Seizure 2017;53:18-22.
15. Wieser HG, Blume WT, Fish D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia 2001;42:282-286.
16. Diagnostic and statistical manual of mental disorders : DSM-5. Arlington, VA: American Psychiatric Association, 2013.
17. WISC-IV. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of Clinical Neuropsychology. New York, NY: Springer New York, 2011: 2719-2719.

18. Warschausky S. Wechsler Preschool and Primary Scale of Intelligence. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of Clinical Neuropsychology. New York, NY: Springer New York, 2011: 2690-2693.
19. Lerner JT, Salamon N, Hauptman JS, et al. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: A critical review and the UCLA experience. Epilepsia 2009;50:1310-1335.
20. Radhakrishnan A, Abraham M, Vilanilam G, et al. Surgery for "Long-term epilepsy associated tumors (LEATs)": Seizure outcome and its predictors. Clinical neurology and neurosurgery 2016;141:98-105.
21. Bonney PA, Glenn CA, Ebeling PA, et al. Seizure Freedom Rates and Prognostic Indicators After Resection of Gangliogliomas: A Review. World neurosurgery 2015;84:1988-1996.
22. Bonney PA, Boettcher LB, Conner AK, et al. Review of seizure outcomes after surgical resection of dysembryoplastic neuroepithelial tumors. Journal of neuro-oncology 2016;126:1-10.
23. Kobulashvili T, Kuchukhidze G, Brigo F, et al. Diagnostic and prognostic value of noninvasive long-term video-electroencephalographic monitoring in epilepsy surgery: A systematic review and meta-analysis from the E-PILEPSY consortium. Epilepsia 2018;59:2272-2283.
24. Pataraia E, Lurger S, Serles W, et al. Ictal scalp EEG in unilateral mesial temporal lobe epilepsy. Epilepsia 1998;39:608-614.
25. Alvim MKM, Morita ME, Yasuda CL, et al. Is inpatient ictal video-electroencephalographic monitoring mandatory in mesial temporal lobe epilepsy with unilateral hippocampal sclerosis? A prospective study. Epilepsia 2018;59:410-419.
26. Smyth MD, Limbrick DD, Jr., Ojemann JG, et al. Outcome following surgery for temporal lobe epilepsy with hippocampal involvement in preadolescent children: emphasis on mesial temporal sclerosis. J Neurosurg 2007;106:205-210.
27. Wyllie E, Lachhwani DK, Gupta A, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. Neurology 2007;69:389-397.
28. Makridis KL, Prager C, Atalay DA, et al. Ictal EEG recording is not mandatory in all candidates for paediatric epilepsy surgery with clear MRI lesions and corresponding seizure semiology. Epileptic disorders : international epilepsy journal with videotape 2022;24:1-10.
29. Fitzgerald Z, Morita-Sherman M, Hogue O, et al. Improving the prediction of epilepsy surgery outcomes using basic scalp EEG findings. Epilepsia 2021;62:2439-2450.
30. Elwan S, Alexopoulos A, Silveira DC, Kotagal P. Lateralizing and localizing value of seizure semiology: Comparison with scalp EEG, MRI and PET in patients successfully treated with resective epilepsy surgery. Seizure 2018;61:203-208.
31. Burkholder DB, Britton JW, Rajasekaran V, et al. Routine vs extended outpatient EEG for the detection of interictal epileptiform discharges. Neurology 2016;86:1524-1530.
32. Kimura N, Takahashi Y, Shigematsu H, et al. Risk factors of cognitive impairment in pediatric epilepsy patients with focal cortical dysplasia. Brain Dev 2019;41:77-84.
33. Pujar SS, Martinos MM, Cortina-Borja M, et al. Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study. Lancet Child Adolesc Health 2018;2:103-111.
34. Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: A systematic review. Seizure 2015;29:46-62.
35. Braun KP. Preventing cognitive impairment in children with epilepsy. Curr Opin Neurol 2017;30:140-147.

Figure 1: Focal resections and excluded cases

Table 1: MRI diagnosis and lobar lesion location of 117 patients included for analysis.

MRI Lesion location	MTS	FCD	Tumour	Cyst	Total
Frontal	0	27	3	0	30 (25.6%)
Temporal	23	25	28	2	78 (66.7%)
Parietal	0	1	3	1	5 (4.3%)
Occipital	0	2	2	0	4 (3.4 %)
Total	23 (19.7%)	55 (47%)	36 (30.8%)	3 (2.6%)	117 (100%)

MTS = Mesial Temporal sclerosis, FCD =Focal Cortical Sclerosis, Tumour (Low grade epilepsy associated Tumours)

Table 2 a) Univariable comparisons of VT-EEG components and other clinical factors for seizure free outcome (Engel I) at last follow-up at surgery (N=117, median 25 months, IQR 17-36.7).

	Engel I (N=80)	Engel II/III/IV (N=37)	p value	*CI 95%* (of mean difference)	
Age at epilepsyonset (median, years)	2.25	1	0.115		
Latency to surgery (median, years)	4.6	6.25	0.391		
Age at surgery (mean, years)	9.3	9.4	0.907	-1.8 to 2.02	
Total number of ASM (mean)	3.8	5.3	0.000	0.78 to 2.21	
	N	N		***OR for Engel I***	**CI 95%**
Non-Concordant Interictal VT-EEG (Total n=117)	7	11	**0.006**	**0.227**	**0.079-0.646**
Non-Concordant Ictal EEG (Total n=115)	14	14*	**0.035**	**0.359**	**0.15-0.878**
Non- concordant Semiology (Total n=113)	8	4	0.963	0.971	0.27-3.5
DD/ID (n=39)	17	22	< 0.001	0.19	0.08 - 0.45
Temporal (n=77)	52	25	0.84	0.89	0.4 - 2
Extra temporal (40)	28	12			
Complete radiological lesion resection (n=114)	67	26	0.117	2.34	0.89 - 6.2

DD/DI= developmental Delay/Intellectual Disability; ASM = Anti-seizure Medication

Table 2 b: Multivariable logistic regression model (stepwise backwards factor selection): predictors for seizure free (Engle 1) outcome versus on-going seizures (Engel II/III/IV), Entire cohort (n=117)

Variables entered in step 1: Non-concordant interictal EEG , Non-concordant ictal VT-EEG, Latency to surgery (years), Complete MRI lesion resection , Developmental delay/ Intellectual Disability, Total number ASMs tried

Factors left in final Model	P value	OR	95% CI.for EXP(B)	
			Lower	Upper
Non-concordant interictal EEG	0.058	0.309	0.092	1.043
Developmental delay / Intellectual Disability	**0.042**	**0.366**	**0.139**	**0.966**
Total Number of ASMs tried	**0.002**	**0.652**	**0.497**	**0.857**

ASM: Anti-seizure medication, OR: Odds ratio, CI confidence interval

Table 3a: Subgroup analysis: FCD and Tumours combined (n=79)

Unadjusted	Engel I (N=59)	Engel II/III/IV (N=20)	p value		
Age at epilepsyonset (median, years)	2	2.5	0.63		
Latency to surgery (median, years)	**3.5**	**5.5**	**0.039**		
Age at surgery(mean, years)	8.4	9.8	0.18		
Total number of ASM tried (mean)	**3.9**	**5.1**	**0.012**		
				OR for Engel I	**CI 95%**
Non-Concordant Interictal VT-EEG (n =79)	5	3	0.416	.525	0.1 – 2.4
Non-Concordant Ictal EEG (n=77)	9	7	0.11	0.35	0.1-1.1
Non-concordant Semiology(=76)	6	1	0.67	2.3	0.26-20.2
DD/ID (n=22)	**13**	**11**	**0.016**	**0.273**	**0.09 - 0.81**
Temporal	36	11	0.63	1.3	0.46 - 3.6
Extra temporal	23	9			
Complete radiological lesion resection (n=76)	**10**	**46**	**0.016**	**3.8**	**1.2 - 11.5**

ASM: anti-seizure medication, DD/ID: Developmental Delay/ Intellectual Disability

Table 3 b Multivariable logistic regression subgroup FCD and Tumour combined n=79
Predictors for seizure free outcome (Engle 1) versus ongoing seizures (Engel II/II/IV)

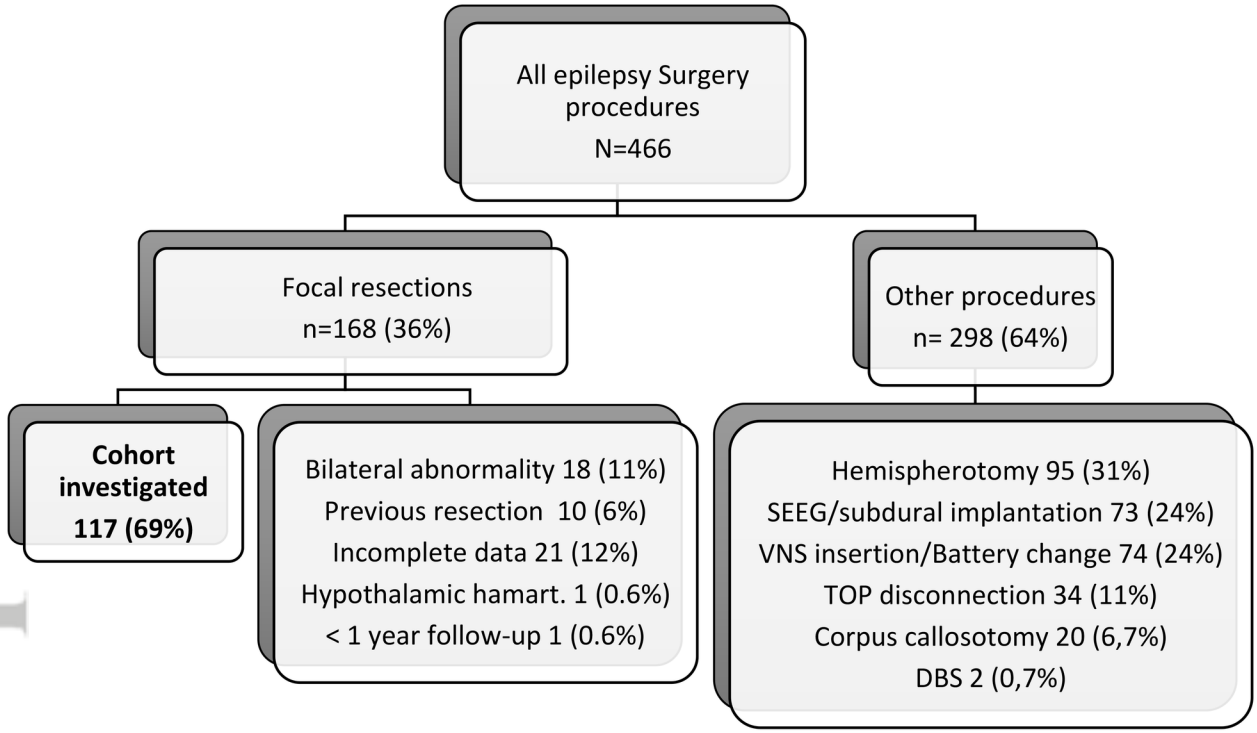
			95% C.I.for OR	
	Sig.	OR	Lower	Upper
Latency to surgery (years)	0.283	0.921	0.792	1.070
Total Number of ASMs tried	**0.042**	**0.667**	**0.452**	**0.985**
DD/ ID	0.375	0.560	0.155	2.017
Complete radiological lesion resection	**0.053**	**3.480**	**0.986**	**12.275**

Variable entered on: Latency to surgery (years), Total Number of ASMs tried , DD / ID , Complete MRI lesion resection .ASM: anti-seizure medication, Developmental delay / Intellectual Disability

Table 4 Subgroup analysis MTS, chaslin gliosis and cyst combined group (n=25)

	Engel I (N=14)	Engel II/III/IV (N=11)	p value		
Age at epilepsyonset (median, years)	2.7	1	0.099		
Latency to surgery (median, years)	8.9	8.2	0.428		
Age at surgery(median, years)	12.2	9.2	0.222		
Total number of ASM (mean)	3.6	4.27			
				OR for Engel I	**CI 95%**
Non-Concordant Interictal VT-EEG	**0**	**6**	**0.003**		
Non-Concordant Ictal EEG	2	5	0.177	0.2	0.03 to 1.35
Non- concordant Semiology	0	3	0.072		
DD/ID (n=24)	4	7	**0.116**	0.229	0.04 to 1.23
Temporal	14	10	0.44		
Extra temporal	0	1			
Complete radiological lesion resection n=79)	14	10	0.44		

DD/DI= developmental Delay/Intellectual Disability; ASM = Anti-seizure Medication



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