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Electro-clinical criteria and surgical outcome: is there a difference between mesial and lesional temporal lobe epilepsy?

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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 study has been approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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The study was conceptualized and designed by MW, FSL, GJdH, SGU and JWS. Data was collected and analyzed by MW, who also drafted the manuscript. All authors were involved in data interpretation and FSL, GJdH, SGU and JWS revised the manuscript for intellectual content. All authors had full access to the data and take responsibility for the integrity of the data, the accuracy of the data analysis and the conduct of the research. All authors approved the submitted version of the manuscript.

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Abstract

Objectives: Mesial temporal lobe epilepsy syndrome (MTLE) with specific electrophysiological and clinical characteristics and hippocampal sclerosis (HS) on MRI is considered the prototype of a syndrome with good surgical prognosis. Ictal onset zones in MTLE have been found to extend outside the hippocampus and neocortical seizures often involving mesial structures. It can, thus, be questioned whether MTLE with HS is different from lesional temporal epilepsies regarding electro-clinical characteristics and surgical prognosis. We assessed whether MTLE with HS is distinguishable from lesional TLE and which criteria determine surgical outcome.

Methods: People with MRI abnormalities in in a retrospective cohort of individuals who underwent temporal-lobectomy, were divided into 'HS only' or 'lesional' TLEs. We excluded from analysis those with dual pathology. Clinical data was extracted and we compared surgical outcome and electro-clinical characteristics using chi-squared, student's T or Mann-Whitney tests.

Results: Of 389 individuals, over half (61%) had 'HS only'. Four electro-clinical characteristics (age at epilepsy onset, febrile seizures, memory dysfunction and contralateral dystonic posturing) distinguished 'HS only' from 'lesional' TLE, but there was considerable overlap. Seizure freedom 2 years after surgery (Engel class 1) was similar: 67% ('HS only') versus 69% ('lesional' TLE). Neither presence of HS nor electro-clinical criteria was associated with surgical outcome.

Conclusions: Despite small differences in electrophysiological and clinical characteristics between MTLE with HS and lesional TLE, surgical outcomes are similar, indicating that aetiology seems irrelevant in the referral for temporal surgery.

Introduction

Early recognition of mesial temporal lobe epilepsy (MTLE) is important as it is considered the prototype of an epileptic syndrome suited for surgical referral and treatment. (1-3) MTLE is usually diagnosed based on the presence of several electrophysiological and clinical (electro-clinical) signs and symptoms (seizure semiology), accompanied by the presence of hippocampal sclerosis (HS) on MRI. (4, 5) Diagnosing MTLE, however, can be difficult with no diagnostic rule to define the electro-clinical syndrome. (5) Evidence is missing on how many, and which specific, electro-clinical criteria are needed for its diagnosis and whether HS is a prerequisite. Structural lesions, such as a tumour, cortical dysplasia, vascular or ischemic lesion, near the mesial temporal structures may exist or co-occur with HS, i.e. 'dual pathology', and give rise to similar electro-clinical signs and symptoms. (3) This may be explained by the fact that complex temporo-insular and temporo-opercular networks may be involved in seizure generation and ictal onset zones may extend outside the hippocampus, (6, 7) as shown by intracerebral EEG recordings (8, 9) and neuroimaging studies. (10, 11) Lesional TLEs may thus resemble MTLE due to HS and may have similar prospects regarding surgical outcome. (12) Yet, as a whole people, with MTLE with HS still form the largest group being surgically treated. (13)

We aimed to assess whether MTLE due to HS was different from lesional causes of TLE with respect to electro-clinical criteria and surgical outcome. We also assessed if the underlying aetiology or electro-clinical criteria could predict of surgical outcome.

Methods

Population and setting

People with medically intractable epilepsy (being unresponsive to at least two adequate and appropriate trials of anti-epileptic drugs) referred to the Dutch Collaborative Epilepsy Surgery Program undergo a standard stepwise pre-surgical screening. This includes evaluation by a multidisciplinary team of the clinical history, video-EEG (electrode placement according to the 10-20 system) with seizure monitoring, MRI with coronal FLAIR images, neuropsychological tests and, if applicable, further investigations (PET, SPECT, MEG, functional MRI or intracranial EEG monitoring). This study comprises a complete, nationwide, cohort of all people who underwent temporal lobectomy with or without (partial) amygdalohippocampectomy or a tailored lesionectomy between 1987 and 2004. In this period 651 people were referred as potential candidates for temporal lobectomy. (14) People without radiological temporal abnormalities ('negative' MRI or purely extratemporal abnormalities) and people rejected for temporal lobectomy, were excluded; with similar percentages rejected for HS and for lesions, with no differences in reasons for being rejected between these groups (chi-square test: p-value 0.276). Lastly, 389 people, who had temporal abnormalities on MRI and underwent temporal lobectomy (tailored lesionectomy, tailored or standard amygdalohippocampectomy with anterior lobectomy) were included. (Figure 1). The study was approved by the local ethics committee.

Data collection

Pre-surgical screening results were collected from program records, including data on: clinical history (gender, age, age at onset of non-febrile seizures and a history of febrile seizures),

video-EEG, MRI, neuropsychology (visual and verbal memory dysfunction and IQ) and, if applicable, other investigations (FDG-PET, SPECT or electrocorticography). Video-EEGs included data on lateralized interictal abnormalities (defined as spikes or sharp waves), ictal patterns of temporal seizure onset, extratemporal interictal abnormalities and seizure semiology; i.e. auras, automatisms, positive motor symptoms (dystonic posturing), postictal confusion or memory deficits including amnesia and aphasia. MRI images (1.5T until 1996 or 3.0T from 1996 onwards) according to a standardized epilepsy protocol with coronal FLAIR images. (14) After surgery, data were collected on lateralization of resection, completeness of amygdalohippocampectomy, results from histopathology and surgical outcome. The latter was assessed according to the Engel outcome classification (2) from postoperative follow-up visits at 2 years.

Data analysis

People with HS without other lesions on MRI ('HS only') were compared with those with a temporal lesion (lesional TLE). Patients with a dual pathology (structural lesion that may co-occur with HS) were considered a different group. This group was not included in our quantitative comparative analysis due to its relative small size. Differences in clinical, test (EEG, neuropsychology and additional tests) and surgical characteristics were compared between the HS only and lesional TLE groups, and differences in surgical outcomes after 2 years (Engel class 1: free from disabling seizures or Engel class 1A; complete seizure freedom since surgery) were assessed using chi-squared, student's T or Mann-Whitney tests. We determined the accuracy of MRI in detecting HS or a lesion (number of true positives and true negatives divided by the total number) compared to histopathology.

Nine electrophysiological and clinical characteristics from the original publication on the MTLE syndrome (2, 3) were evaluated as potential predictors of 'HS only' to distinguish HS from lesional TLEs. These were: 1) a history of febrile seizures in the first 5 years of life, 2) seizure onset between 6 and 14 years of age, 3) epigastric or experiential (fear/ déjà vu) aura, 4) complex partial seizures with automatisms (excluding hypermotor automatisms), 5) dystonic posturing of one arm contralateral to the ictal EEG discharge, 6) altered consciousness including a postictal phase with disorientation, recent-memory deficit, amnesia for the event or dysphasia, 7) interictal unilateral or bilateral independent anterior temporal EEG spikes, 8) temporal seizure onset i.e. focal rhythmic onset patterns on extracranial ictal EEG, 9) visual or verbal memory dysfunction at neuropsychology. These characteristics are commonly used and considered important from a clinical diagnostic perspective. (5, 15, 16) Their prognostic value was assessed by multivariable logistic regression analysis with backward selection using a p-value of <0.10, which was chosen to maximize the proportion of authentic independent variables. (17) The model fit was calculated by the Hosmer-Lemeshow test. Results from FDG-PET and SPECT were excluded from analysis to avoid selection bias as they were not performed in all individuals.

We estimated how many people fulfilled all nine electro-clinical criteria, and whether the corresponding proportion with seizure freedom 2 years post-surgery depended on the number of MTLE criteria fulfilled. We then assessed which electro-clinical and radiological criteria were predictive of seizure freedom 2 years post-surgery using multivariable logistic regression analysis with backward selection using a p-value of <0.10. Missing values were imputed by multiple imputation techniques to prevent biased estimates of results. Statistical analyses were performed using IBM SPSS statistics for Windows, version 20.0 (Armonk, NY: IBM Corp).

Results

Of the 389 people included, 57% (221) had ’HS only’ on MRI, 37% (142) presented with a temporal lesion and dual pathology was present in 7% (26) (Figure 1). Compared with histological findings, available for analysis in 93% (361), the accuracy of MRI in detecting HS was 82%. The accuracy of the 3.0T MRI (≥ 1996) was slightly higher (86%) than the 1.5T MRI (< 1996) (77%), although this was not statistically significant (p=0.09). The accuracy of MRI in detecting a lesion was 73%; 75% for 3.0T and 71% for 1.5T MRI (p=0.43).

Baseline characteristics are presented in Table 1. The median duration between epilepsy onset and surgery was 21 years. Most people (69%) had their first non-febrile seizure before the age of 14 years (median10; IQR 4 - 17), presented with temporal seizure semiology with automatisms (83%), postictal memory deficits or confusion (89%), and interictal (70%) and ictal (85%) temporal abnormalities on EEG. People with ‘HS only’ were younger at seizure onset (median 8 vs. 13 years) but older at surgery (median 34 vs. 31.5 years) than people with ‘lesional’ TLE. They more frequently had a history of febrile seizures, memory dysfunction and presented with automatisms and contralateral dystonic posturing; additionally FDG-PET and complete amygdalo-hippocampectomy were more frequently performed in those with ‘HS only’ (Table 1). A younger age at seizure onset, a history of febrile seizures, contralateral dystonic posturing and memory dysfunction were independently predictive of the presence of ‘HS only’ and may distinguish it from lesional TLE. (Table 2). The model fit indicated reasonable calibration (p= 0.18).

In both groups, about two-thirds (67% HS only) and (69% lesional TLE) was seizure free (Engel class 1) 2 years post-surgery. Percentages for those who became seizure free differed per

lesion type: 42% for gliosis/ trauma, 60% for lesions not further specified with respect to its pathology, 64% for a vascular or ischaemic lesion, 74% for those with a tumour and 100% for a cortical dysplasia; though absolute numbers for different types of lesions were small and may vary according to thetype of resection.

Complete seizure freedom (Engel class 1A) was achieved in about half, with no difference between 'HS only' (49%) and 'lesional' TLE (52%) (Table 3). Rates of seizure freedom for those with dual pathology were somewhat lower; 58% had an Engel class 1 score 2 years post-surgery and only 27% was completely seizure free (Engel class 1A), indicating more complex pathology.

Few people presented with more than 6 electro-clinical MTLE criteria. Automatisms, impaired consciousness or postictal signs were present in almost all people with HS (83% and 89% respectively), but only 14% presented with all of the four characteristic seizure semiology criteria for MTLE: epigastric or experiential aura, automatisms, positive motor sings and impaired consciousness or postictal signs. Only four (all 'HS only') fulfilled all nine criteria. Those with 'HS only' fulfilled slightly more electro-clinical criteria (median 6) than those with lesional TLE (median 5). People fulfilling more electro-clinical MTLE criteria were not more likely to become seizure free, with 67% of those fulfilling up to 4 criteria being seizure free and 64% of those fulfilling more than 8 criteria. This was irrespective of radiological findings (data not shown).

Table 4 shows the univariable association of the electro-clinical criteria related to surgical outcome, demonstrating that none of these criteria, nor the underlying aetiology ('HS only' or lesional), is independently associated with surgical outcome ($p<0.10$ in multivariable analysis).

Discussion

Principal findings

Fifty-seven percent of our sample fulfilled a diagnosis of MTLE when defined by the single criterion of the presence of HS without other lesions. People with 'HS only' can be distinguished from people with lesional TLE based on criteria such as a younger age at seizure onset, a history of febrile seizures, memory dysfunction and a 'temporal' seizure semiology including contralateral dystonic posturing. These have frequently been associated with MTLE with HS, (4) although, unlike earlier reports, interictal temporal epileptiform EEG discharges did not differ between our groups. (15) These criteria are certainly not exclusive for 'HS only'. (18) About 30-60% of individuals with 'lesional' TLE in our population also fulfilled these criteria. Diagnostically, the MTLE syndrome cannot be regarded as unitary syndrome and is thus not easy to define, unless reduced to its radiological or etiological features.

Even if MTLE with HS may be distinguished from lesional TLE, it does not seem to have a more favourable surgical prognosis. Due to the small numbers of the different types of lesional TLEs we didn't differentiate into subgroups. We acknowledge that there may be differences in surgical outcome between the various lesion types, due to differences in etiology or differences in type or location of resection. We found no difference between the lesional TLEs, when grouped together, and MTLE with HS. This result, as well as those from other studies (19, 20), challenge the classical view that HS is associated with a greater chance of postoperative seizure freedom compared with other aetiologies. Differences in surgical outcomes may be explained by differences in epilepsy duration from onset to definitive surgery as a longer duration has been found associated with worse postoperative seizure freedom rates. (20, 21) In our cohort, people with HS had a longer duration than those with

lesional TLE (24 years versus 14 years), which may have decreased the surgical success rates in those with HS, resulting in more similar rates of seizure freedom compared with lesional TLEs. This was, however, not assessed.

Two thirds were free of disabling seizures 2 years after surgery, which is in line with earlier reports. (22-24) Several electro-clinical criteria have been hypothesized to predict surgical outcome. (25-27) Recently, a nomogram was developed that included 4 to 6 criteria (depending on the outcome) to predict seizure freedom (complete or Engel class I) after surgery. (26) This study demonstrated, amongst others, differences in surgical outcome between patients with Mesial Temporal Sclerosis and other lesions as pathological cause and also temporal interictal EEG discharges to predict surgical outcome. (26) These criteria have been reported earlier (12, 25, 27) but could not be confirmed in other studies (28, 29), nor in our study. Other potential predictors, such as generalized tonic-clonic seizures, (25-27) were not assessed in our review as we specifically studied those criteria associated with the MTLE syndrome. Conflicting findings may reflect differences in design, selection criteria, sample size and outcome definitions. (27) These differences in methodology thus largely impede direct comparison of results.

We did not find any electro-clinical criteria nor aetiology being predictive of surgical outcome. Rates of postsurgical seizure freedom were also not worse in people presenting with extratemporal or atypical electroclinical features. (16) This suggests that, although electro-clinical criteria are important in the diagnosis of TLE and may be used to distinguish MTLE from lesional TLE, they don't seem relevant at referral for surgery. Our findings support the idea that MTLE with HS is part of the broad spectrum of TLEs with related signs and symptoms, (6) rather than a sharply delineated and distinguishable syndrome with a particularly favourable surgical prognosis.

Strengths and weaknesses

Our data comprise a complete, nationwide cohort of people who underwent epilepsy surgery between 1987 and 2004. This is a retrospective analysis of surgical outcomes, which may be prone to deficiencies in documentation that are difficult to solve. Throughout the years the diagnostic workup has largely remained unchanged thus a large bias could not be expected. Recent advances in imaging and source localization techniques may have led to improved detection, (30) but this has not dramatically changed postsurgical seizure freedom rates nor is it likely to have influenced the direct relation between electro-clinical characteristics and surgical outcome. In our series, all individuals underwent the same diagnostic workup, though in 1996 3T MRI became the norm. The added benefit of 3T over 1.5T MRI scans in the detection of MRI abnormalities remains controversial for use in clinical practice, as detection of abnormalities seem to rely more on the experience of the reviewers than on the scanning technique itself. (31, 32) In our series, we found the accuracy of MRIs before 1996 (1.5T) was lower than after 1996 (3T), but this difference failed to reach statistical significance and thus would not have greatly influenced our classification.

A potential limitation was that we grouped people into 'HS only' or 'lesional' TLE based on preoperative MRI reports and did not rely on histopathology, which is the gold standard. A 'negative MRI' may be misleading as abnormalities can be missed. (33) Conversely, a diagnosis of HS can also be missed if *en bloc* resection fails and only tissue fragments are available for histopathological examination. The accuracy of MRI compared with histopathology was quite good (82% for HS and 73% for other structural lesions). When results were based on histopathological diagnosis, 2-years postsurgical seizure freedom rates were in line (66% for

HS and 69% for lesional TLE) with those based on MRI diagnosis. As prediction of surgical outcome is only clinically relevant pre-surgically, when histopathology is not yet available, we presented the results based on a MRI diagnosis to reflect clinical practice.

The minimal difference (2%) in surgical outcome between the groups suggests that even a larger study sample is unlikely to show a clinically relevant difference. The ultimate outcome in epilepsy surgery, however, is complete seizure freedom including AED withdrawal, as continued drug use might mask surgical cure. (34) There may be differences between our groups with respect to AED continuation after surgery. AEDs are usually continued for at least 2 years post-surgery due to fear of seizure recurrence that may be difficult to control. (35) This prevented analysis of surgical cure rates at 2 years follow-up and requires further assessment over a longer time period. We limited our analysis to a 2 years follow-up. Longer follow-up for example for 5 or 10 years was only available for a small subset of less than half of the subjects. This may be due to the fact that subjects return to their referring physician. A further difficulty is that there is no consensus on AED (dis-) continuation hampering the assessment of complete seizure freedom.

It is possible that people with electro-clinical features suggestive of MTLE were more likely to be referred for pre-surgical evaluation and diagnosed with temporal abnormalities on MRI. This may have resulted in referral bias in which people with a lesion are more similar to people with ‘HS only’ and would explain our inability to find electro-clinical differences between groups. As this is the standard diagnostic work-up, this will hold for any surgical series and such a bias will be difficult to avoid. What mitigate against such bias is that none of the electro-clinical criteria for MTLE was, even cumulatively, associated with surgical outcome. This suggests that even if those with ‘lesional’ epilepsy in our cohort are more similar to those with ‘HS only’, this would not have influenced their probability of surgical success.

Conclusion

MTLE with HS can be distinguished from lesional TLEs based on electro-clinical criteria (age at onset, history of febrile seizures, memory dysfunction and contralateral dystonic posturing), but there is considerable overlap in characteristics. None of the electro-clinical criteria, nor a finding of 'HS only' is predictive of seizure freedom after temporal lobectomy. MTLE with HS and lesional TLEs have an overall similar prognosis indicating that aetiology is not relevant as predictor of success in the referral for epilepsy surgery in people with electro-clinical criteria associated with MTLE.

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Conflict of interests:

No author has any conflict of interest in respect to this work. MW, FSL, GJH and SGU have no disclosures to make. JWS has received research grants and honoraria from UCB, Eisai, Teva, Lundbeck and GSK which are involved in the manufacturing of AEDs.

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Table 1 Baseline characteristics

	Total population (n = 363)	**'HS only' (n = 221)**	**'Lesional' TLE (n = 142)**	**P value**
Male gender (n, %)	174 47.9	101 45.7	73 51.4	0.288
Age at onset (years), median (IQR)	10 (4-17.0)	8 (2-13)	13 (8-20)	<0.001
Age at surgery (years), median (IQR)	34 (25-40)	34 (27-41)	31.5 (22-39.25)	0.002
Epilepsy duration (years), median (IQR)	21 (13-29)	24 (16-31)	14 (7-23.25)	< 0.001
IQ neuropsychology, median (IQR)	104 (100-109)	104 (100-108)	105 (99-112)	0.199
Interictal extratemporal abnormalities on video-EEG (n, %)	133 36.6	78 35.3	55 38.7	0.614
Additional extratemporal MRI abnormalities (n, %) (white matter abn./ vascular lesions/ tumors/ dysplasia)	60 16.5	43 19.5	17 12.0	0.070
Ancillary tests performed (FDG-PET, interictal SPECT ECoG) (n, %)	124 34.2	88 39.8	36 25.4	0.005
Lateralization of epileptic focus (side of surgery) (n, % right)	188 51.8	113 51.1	75 52.8	0.754
Complete amygdalohippocampectomy (n, %)	310 85.4	198 89.6	112 78.9	0.006
MTLE criteria:				
History of febrile seizures (n, %)	151 41.6	111 50.2	40 28.2	0.002
Onset between 6 and 14 years (n, %)	136 37.5	86 38.9	50 35.2	0.477
Epigastric/ experiential aura (n, %)	135 37.2	89 40.3	46 32.4	0.154
Automatisms (n, %)	300 82.6	193 87.3	107 75.4	0.012
Positive motor signs (contralateral dystonic posturing) (n, %)	137 37.8	101 45.7	36 25.4	0.004
Impaired consciousness/ postictal signs (memory deficits/ postictal confusion) (n, %)	324 89.3	203 91.9	121 85.2	0.158
Interictal temporal spikes on video-EEG (n, %)	255 70.2	160 72.4	95 66.9	0.340
Ictal temporal onset on video-EEG (n, %)	310 85.4	189 85.5	121 85.2	0.957
Visual or verbal memory dysfunction on neuropsychology (n, %)	242 66.7	163 73.8	79 55.6	0.001

Table 2 Independent predictors of 'HS only'; results from multivariable analysis

	OR	95% CI	P value
Age at onset (years)	0.94	0.92 - 0.97	< 0.001
History of febrile seizures	2.24	1.28-3.92	0.005
Positive motor signs (contralateral dystonic posturing)	1.91	0.99-3.69	0.055
Visual or verbal memory dysfunction	2.27	1.36-3.78	0.002

Table 3 Surgical outcome at 2 years post surgery

	Total population (n = 363)	**'HS only' (n = 221)**	**'Lesional' TLE (n = 142)**	**P value**
Free of disabling seizures (ENGEL 1) at 2y follow up (n, %)	245 67.5	147 66.5	98 69.0	0.632
Complete seizure freedom (ENGEL 1A) at 2y follow up (n, %)	183 50.4	109 49.3	74 52.1	0.607

Table 4 Determinants of surgical outcome (Engel 1) 2 years after surgery*

	OR	95% CI	P value
'HS only' on MRI (%)	0.88	0.53 - 1.47	0.632
History of febrile seizures (%)	0.88	0.52 - 1.49	0.622
Age at onset between 6 and 14 years (%)	1.16	0.72 - 1.86	0.535
Epigastric or experiential aura (%)	1.31	0.77 - 2.22	0.318
Automatisms (%)	1.23	0.67 - 2.25	0.510
Contralateral dystonic posturing (%)	0.77	0.47 - 1.26	0.293
Impaired consciousness/ postictal signs (memory deficits/ postictal confusion) (%)	0.75	0.34- 1.66	0.479
Visual or verbal memory dysfunction (%)	0.99	0.59 - 1.65	0.956
Interictal anterio-temporal spikes on video-EEG (%)	1.02	0.62 - 1.67	0.937
Ictal temporal onset on video-EEG (%)	1.17	0.62 - 2.20	0.630

* Results from univariable analysis