

MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome

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Summary

Most patients with non-lesional temporal lobe epilepsy (NLTLE) will have the findings of hippocampal sclerosis (HS) on a high resolution MRI. However, a significant minority of patients with NLTLE and electroclinically well-lateralized temporal lobe seizures have no evidence of HS on MRI. Many of these patients have concordant hypometabolism on fluorodeoxyglucose-PET (¹⁸F]FDG-PET). The pathophysiological basis of this latter group remains uncertain. We aimed to determine whether NLTLE without HS on MRI represents a variant of or a different clinicopathological syndrome from that of NLTLE with HS on MRI. The clinical, EEG, [¹⁸F]FDG-PET, histopathological and surgical outcomes of 30 consecutive NLTLE patients with well-lateralized EEG but without HS on MRI (HS-ve TLE) were compared with 30 consecutive age- and sex-matched NLTLE patients with well-lateralized EEG with HS on MRI (HS+ve TLE). Both the HS+ve TLE group and the HS-ve TLE patients had a

high degree of [¹⁸F]FDG-PET concordant lateralization (26 out of 30 HS-ve TLE versus 27 out of 27 HS+ve TLE). HS-ve TLE patients had more widespread hypometabolism on [¹⁸F]FDG-PET by blinded visual analysis [odds ratio (OR = +∞ (2.51, -), *P* = 0.001]. The HS-ve TLE group less frequently had a history of febrile convulsions [OR = 0.077 (0.002–0.512), *P* = 0.002], more commonly had a delta rhythm at ictal onset [OR = 3.67 (0.97–20.47), *P* = 0.057], and less frequently had histopathological evidence of HS [OR = 0 (0–0.85), *P* = 0.031]. There was no significant difference in surgical outcome despite half of those without HS having a hippocampal-sparing procedure. Based on the findings outlined, HS-ve PET-positive TLE may be a surgically remediable syndrome distinct from HS+ve TLE, with a pathophysiological basis that primarily involves lateral temporal neocortical rather than mesial temporal structures.

Keywords: epilepsy; EEG; temporal lobe; hippocampal sclerosis; [¹⁸F]FDG-PET; surgery

Abbreviations: [¹⁸F]FDG-PET = fluorodeoxyglucose-PET; HS = hippocampal sclerosis; HS+ve TLE = NLTLE with HS on MRI; HS-ve TLE = NLTLE without HS on MRI; NLTLE = non-lesional temporal lobe epilepsy; OR = odds ratio; TLE = temporal lobe epilepsy

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Introduction

Temporal lobe epilepsy (TLE) represents the most common form of focal epilepsy that is refractory to medical treatment in adults. About 30% of TLE is due to foreign tissue lesions,

whilst 60–70% is designated 'non-lesional' (NLTLE). The most common pathological substrate for NLTLE is hippocampal sclerosis (HS), present in a majority of medically

refractory cases. Whilst it is difficult to give exact proportions, given that only patients with intractable seizures undergo full characterization, ~70% of these patients with NLTLE are thought to have HS (Cascino *et al.*, 1991). There is ongoing debate as to whether mesial TLE represents a distinct subtype of NLTLE, as proposed by the Commission on Classification and Terminology of the International League Against Epilepsy (1989).

It is estimated that at least 30% of patients with NLTLE have no evidence of HS on MRI (HS–ve TLE). It is possible that some of these may have HS without hippocampal atrophy or T2 signal changes detectable using current technologies, and some may have bilateral HS making detection through volume asymmetry difficult. Similarly, small or subtle cortical temporal pathologies may be undetected with current procedures. It is also possible that these HS–ve TLE patients represent a different group or groups from HS+ve TLE. The most important clinical issue with these patients relates to the definition of a subgroup that may benefit from surgery.

Many of these HS–ve TLE patients have prominent focal or regional hypometabolism on [¹⁸F]fluorodeoxyglucose-PET ([¹⁸F]FDG-PET) scans (O'Brien *et al.*, 2001). The underlying pathophysiological basis for the hypometabolism seen in patients with TLE is still unresolved. [¹⁸F]FDG-PET has shown a high correlation with MRI-identified HS for the lateralization of the epileptogenic zone. While some studies have found that the magnitude of the hypometabolism correlates weakly or not at all with either direct (Henry *et al.*, 1994) or indirect (Semah *et al.*, 1995; O'Brien *et al.*, 1997) (MRI hippocampal volumetry) measures of hippocampal neuronal loss, even in patients with HS, other groups have reported a correlation of hippocampal cell loss with hypometabolism in subcortical structures (Dlugos *et al.*, 1999) or in hippocampi (Knowlton *et al.*, 2001).

The current study aims to investigate whether HS–ve TLE is a different clinicopathological syndrome from HS+ve TLE by performing a retrospective matched case–control study comparing the clinical history, interictal and ictal EEG, [¹⁸F]FDG-PET, histopathology and surgical outcomes.

Subjects and methods

Case selection

Cases comprised 30 consecutive patients with clinically and video-EEG-defined NLTLE and well-lateralized ictal EEG changes, but without evidence of HS on MRI, including MR volumetry (HS–ve TLE). All patients had been admitted for a comprehensive in-patient assessment including video-EEG monitoring between 1996 and 2002 at one of three tertiary referral hospitals. Controls were 30 age- and sex-matched patients with either or both well-lateralized unilateral ictal and interictal epileptiform EEG discharges, and with concordant unequivocal evidence of HS on MRI, confirmed by MR volumetry (HS+ve TLE). Of both HS–ve TLE cases and HS+ve TLE controls, 14 were left- and 16 right-sided TLE. The controls were selected by starting with the most recent HS+ve TLE patient and moving consecutively retrospectively through the epilepsy monitoring

database, matching as appropriate for age and sex. To ensure that a potential effect of these variables was not missed, the age and sex distributions of the 60 most recent consecutive HS+ve patients were also compared with the HS–ve group. HS–ve TLE patients represented close to 20% of medically refractory partial epilepsy patients assessed at these institutions. The study was approved by the institutional ethics committees.

Historical data collection

Historical clinical data were obtained by retrospective review of the medical records from the time of admission for video telemetry, and of the attending neurologists' out-patient medical records. Clinical data included age at onset of afebrile seizures, duration of epilepsy, presence and types of auras, frequency of secondary generalization, history of febrile convulsions, family history of epilepsy, and history of CNS insult. Seizure frequency scores were classified according to a 12-point seizure frequency score (So *et al.*, 1997).

EEG methods

The scalp EEG was recorded with the international 10–20 system utilizing 21 electrodes. The interictal EEG was recorded during the period of in-patient video EEG monitoring, continuously in sleep and wake cycles and during routine activation procedures, i.e. hyperventilation and photic stimulation. The entire interictal EEG recording was reviewed for evidence of generalized or partial epileptiform discharges. Localization of the ictal EEG was based on the region of onset of rhythmic seizure activity. The frequency of ictal activity at onset of the ictal discharge was noted.

[¹⁸F]FDG-PET methods

[¹⁸F]FDG-PET scans were performed in all HS–ve TLE patients and all but three HS+ve TLE patients. Patients were imaged as out-patients in the interictal state on a PENN PET 300H Tomograph scanner with sodium iodide crystals, using a 25 cm field of view and 3D whole-head acquisition. For the 2 mm slice thickness used for whole-body imaging, the measured resolution was 4.2 mm at full width at half-maximum (FWHM) transaxially and 5.4 mm at FWHM out of plane (based on National Electrical Manufacturers Association-specified testing at the time of installation). Patients prepared by fasting for 4 h before the scan and resting in a quiet, darkened room for 30 min before [¹⁸F]FDG administration and for at least 30 min afterward. Scanning commenced 5–60 min after radiotracer administration. Routine EEG monitoring was not performed during the scan. Patients were, however, asked to report any seizures experienced on the day of the scan, whether before or after the [¹⁸F]FDG injection; a second examination was considered for patients with such seizures if the images were inconclusive.

The dose of [¹⁸F]FDG administered was 37–111 MBq (1–3 mCi). One bed position was used. The acquisition time was 30–40 min, achieving total counts of >40 million. An empiric attenuation correction (ellipse) was applied. The data were processed using a Wiener pre-filter (scaling value = 0.5) and ordered subsets expectation maximization iterative reconstruction. Wiener filtering attempts to reduce blurring of an object by restoring the amplitude of the object's power spectrum in certain ranges. In particular, the filter identifies frequencies that define the resolving power of the spectrum. The images were reconstructed into a 256 × 250 mm cylindrical volume with a 2 mm slice thickness. The reconstruction process

created a standard series of contiguous images oriented in the transaxial, coronal, sagittal and transtemporal planes.

A blinded reviewer (R.J.H.) with extensive experience in [¹⁸F]FDG-PET interpretation (>15 000 studies in oncological and neurological PET, including >900 epilepsy cases) reviewed the [¹⁸F]FDG-PET images using a high-resolution computer monitor and a standard rainbow-colour lookup table. The scans were reviewed in random order according to a previously described protocol with high inter-rater reliability (O'Brien *et al.*, 2001). No background subtraction was used. This image display methodology was applied prospectively to the analysis of patients evaluated in this study. Results were classified by laterality of relative hypometabolism and by areas of subregional involvement: mesial, anterior, posterior and lateral temporal and extratemporal hypometabolism. The extent of metabolic abnormality was categorized as extensive if there was extension beyond the mesial and anterior pole of the temporal lobe to involve the lateral, posterior or superior regions of the temporal lobe. MRI-co-registered images were not used for PET reporting but were considered by the neurosurgical team in planning surgery when any abnormality was reported by the PET team.

MRI methods

MRI scans were obtained using a three-dimensional volume acquisition sequence in addition to standard sequences in all subjects. Images were transferred to a UNIX workstation running Analyze 7.55 (Mayo Foundation). Raw 16-bit data were scaled to 8 bits before further analysis. Hippocampal volumes were measured using an established protocol (Cook *et al.*, 1992). One observer who was blinded to all clinical information, including group status, made all measurements. Hippocampal volumes were measured and side to side ratios of hippocampal volumes were calculated. Mean and SD of the side to side lesser ratios were 0.97, SD 0.17 in the HS-ve group, and 0.69, SD 0.08 in the HS+ve group, $P < 0.001$.

Epilepsy surgery

Surgery was performed in patients with intractable seizures who had failed three or more optimal trials of antiepileptic drugs and had a seizure frequency of at least one per month. This included 23 HS+ve TLE patients and 20 HS-ve TLE patients. In the HS+ve TLE group, surgery entailed anterior temporal lobectomy and amygdalohippocampectomy. Selection in the HS-ve TLE group required well-lateralized ictal events with concordant lateralization on inter-ictal [¹⁸F]FDG-PET, and no discordant information from other modalities, such as single photon emission computed tomography (SPECT) or neuropsychological assessment. In the HS-ve TLE group, 10 patients had a standard anterior temporal lobectomy and amygdalohippocampectomy (as for the HS+ve TLE group), whilst the other 10 had selective anterior temporal lobectomies sparing the hippocampus. At the time, there was little available evidence to direct towards either hippocampal resection or hippocampal-sparing procedures in these patients with apparently structurally normal hippocampi. The decision to include or spare hippocampus depended largely on the preference of the individual treating neurologist, and evolved over the course of the study. Overall, there was almost an even spread, not only in whether hippocampus was resected or spared in HS-ve TLE patients, but also in whether dominant or non-dominant hemispheres were involved in those proceeding to either procedure. Of the 20 procedures in HS-ve TLE patients, 12 were right sided and eight left. Of the right-sided procedures,

eight were hippocampal sparing and four were hippocampal resection. Of the left-sided procedures, two were hippocampal sparing and six were hippocampal resection. The posterosuperior limit of the neocortical resection in the HS-ve TLE group was determined by the extent of PET hypometabolism after the preoperative PET scan had been co-registered to the intraoperative MRI (Murphy *et al.*, 2001). In patients with dominant hemisphere lesions, the surgery was performed awake for language mapping. Subjects were compared for age at surgery, duration of epilepsy at surgery, seizure outcome following surgery according to Engel's classification, and length of postsurgical follow-up.

Pre- and postoperative neuropsychological assessments based on the Wechsler Adult Intelligence Scale-III were evaluated in those patients having surgery. Comparisons of verbal, performance and full-scale intelligence quotient (IQ) as well as memory assessment were made between HS-ve TLE ($n = 18$) and HS+ve TLE ($n = 14$) patients, and within the HS-ve TLE group according to whether mesial structures were resected or spared.

Histopathological reports were reviewed from patients in whom surgery had been performed. The reports were compared between the patient groups for the presence of HS, and for features of microdysgenesis such as scattered aberrant neurons, changes in the columnar arrangement of neurons, neuronal cytomegaly or heterotopias, and the presence of Purkinje cells in the granular and molecular layers and in the white matter (Kim, 1995).

Statistical analysis

Univariate analysis of categorical variables was based upon McNemar's test for matched case-control data. Exact significance levels are given. Most continuous variables were assessed using conditional logistic regression. Where appropriate, non-normally distributed continuous variables were transformed, or compared using non-parametric tests. Detailed multivariate regression modelling was limited by the small sample size.

Odds ratios (ORs) are expressed with 95% confidence intervals. Statistical analysis was performed with Stata 7.0 (Stata Statistical Software, 2001).

Results

Historical data

Each group consisted of 16 men and 14 women. Historical data are presented in Table 1. The age range was 21–59, median 35 years in the HS-ve TLE group, and 19–59, median 33 years in the HS+ve TLE group. When compared with the 60 most recent consecutive HS+ve patients, there was no difference from the HS-ve TLE group in either age (range 16–72 years, median 36, $P = 0.71$) or sex distribution (26 men, 34 women, $P = 0.37$).

Seizure history and characteristics

Age of onset of seizures was similar for each group (median 13.5 versus 13 years). There was no significant difference between the groups in duration of habitual seizures or frequency of seizures (Table 1). There was also no detectable difference in family history of seizures: in the HS-ve TLE group, two patients had a history of seizures in paternal first

Table 1 Demographic and clinical details of patients without (HS-ve) and with (HS+ve) evidence of hippocampal sclerosis on MRI

	HS-ve TLE (n = 30)	HS+ve TLE (n = 30)	OR	95% CI	P*
Sex (M/F)	16/14	16/14	–	–	–
Age (years): median, range	36 (20–58)	36 (18–58)	–	–	–
Lateralization (left/right)	14/16	14/16	–	–	–
Febrile convulsions	1 (3%)	13 (43%)	0.077	0.002–0.512	0.002
Head injury/CNS insult	3 (10%)	3 (10%)	1.00	0.13–7.47	1.000
Epilepsy onset [†] (years)	13 (1–42)	13.5 (1–35)	1.14	0.69–1.91	0.604
Epilepsy duration	18 (3–52)	19 (1–52)	1.00	0.96–1.05	0.928
Family history	2 (7%)	3 (10%)	0.67	0.06–5.82	1.000
Auras	20 (67%)	26 (87%)	0.33	0.06, 1.34	0.146
Secondary generalised seizures	See Table 2	–	0.83	0.20–3.28	1.000
Seizure frequency score	–	–	–	–	0.901 [†]
Incidence of interictal epileptiform transients	22 (73%)	20 (67%)	1.4	0.38–5.59	0.774
Delta waves at ictal EEG onset	20/30 (67%)	9/25 (36%)	3.67	0.97–20.47	0.057
Widespread [¹⁸ F]FDG-PET hypometabolism ^{‡,¶}	See Table 3	–	+∞	2.51, –	0.001

*Categorical variables were compared using McNemar's exact test and continuous variables were compared using conditional logistic regression based upon the Wald test; [†]age at epilepsy onset log-transformed; [†]Wilcoxon signed rank test; [‡]no matched pairs had unexposed cases, hence the OR denominator is zero; [¶]PET abnormality coded as 'widespread' if either or both mesial and anterior regions, plus at least one of any combination of lateral or posterior or superior regions; 'localized' if either or both mesial and anterior regions alone (see Table 3).

Table 2 Frequency of secondary generalization of seizures

	HS-ve TLE	HS+ve TLE
Frequent (>1/month)	5	6
Occasional (>1/year)	13	10
Rare (<1/year)	5	8
Never	7	6

cousins; in the HS+ve TLE group, one patient had a family history of seizures in mother, three siblings, maternal grandmother and uncle, one patient in two daughters and a third patient in both paternal and maternal first cousins.

Febrile convulsions were rare in the HS-ve TLE group [OR = 0.077 (0.002–0.512), $P = 0.002$]. The HS-ve TLE group less frequently reported a history of remote neurological insult, including febrile convulsions ($P = 0.008$). The probability of remote neurological insults apart from febrile convulsions was, however, similar between groups, and this difference is explained largely by the differing frequencies of febrile convulsions.

There was no significant difference in seizure frequency scores (Wilcoxon signed rank test, $P = 0.901$). There was no significant difference in the number of patients experiencing auras, in the type of auras or in the frequency of secondary generalization of seizures (Tables 1 and 2).

EEG findings

There was no significant difference between groups in the location of interictal epileptiform transients with the international 10–20 system, with a similar incidence of interictal sharp waves involving T3/4 or F7/8 between groups. The ictal EEG pattern in the HS-ve TLE group more frequently showed focal delta rhythm at onset of seizures, a finding that

approached significance (20 out of 30 versus nine out of 25, $P = 0.057$). Five out of 30 in the HS+ve group had lateralized interictal epileptiform discharges but did not have seizures recorded on video EEG monitoring.

[¹⁸F]FDG-PET results

Blinded review of the [¹⁸F]FDG-PET images revealed well-lateralized hypometabolism in 27 of 30 HS-ve TLE patients and 100% of HS+ve TLE patients in whom PET was performed (27 of 27). Where lateralized, the side of the PET hypometabolism concurred with that of the ictal EEG in 26 out of 27 HS-ve TLE and with ictal EEG and MRI in all HS+ve TLE patients. With blinded subclassification by region of temporal hypometabolism, 18 of 27 HS-ve TLE patients and seven of 27 HS+ve TLE patients had 'widespread' PET abnormalities, extending beyond anterior and mesial regions alone or in combination, to involve any combination of lateral, posterior and superior temporal regions, versus 'localized' abnormalities, involving either or both the anterior and mesial regions [OR = +∞ (2.51, –), $P = 0.001$] (Table 3).

Surgery

Twenty of 30 HS-ve TLE patients underwent surgery, compared with 23 of 30 HS+ve TLE patients (two HS-ve TLE and three HS+ve TLE are still awaiting surgery, the remainder have been offered but declined surgery). Mean duration of postsurgical follow-up was 38 months: range 25–73 months for HS-ve TLE and 24–125 months for HS+ve TLE. Follow-up was less for cases than controls [OR per month: 0.93 (0.86–1.01), $P = 0.088$], although the difference was not significant. This was most probably a result of the matching process.

Table 3 [¹⁸F]FDG-PET lateralized hypometabolism by subregional involvement

	HS–ve TLE (n = 30 scans)	HS+ve TLE (n = 27 scans)
Temporal		
Mesial	22	21
Anterior	23	18
Lateral	14	4
Posterior	5	0
Superior	7	1
Extratemporal		
Parietal	1	1
Non-lateralizing	3	0

PET abnormality coded as ‘widespread’ if either or both mesial and anterior regions, plus at least one of any combination of lateral or posterior or superior regions; ‘localized’ if either or both mesial and anterior regions alone.

Table 4 Surgical outcome in operated patients

	HS–ve TLE (n = 20)	HS+ve TLE (n = 23)
Seizure free	16 (80%)	17 (74%)
>80% fewer seizures	2 (10%)	2 (10%)
<80% fewer seizures	2 (10%)	2 (9%)
Unchanged	–	2 (9%)

There was no difference between groups in terms of post-operative Engel outcome classification (80% HS–ve TLE versus 74% HS+ve TLE class 1a or 1b outcome, Wilcoxon signed rank test: $P = 0.944$), despite half (10 of 20) of the HS–ve TLE patients having a hippocampal-sparing procedure (Table 4). Of the 20 HS–ve TLE patients having surgery, there was no difference in outcome between those with hippocampus either resected or spared: eight of 10 in both subgroups had a class 1a or 1b outcome.

Neuropsychological evaluation showed no difference in baseline scores between HS–ve TLE and HS+ve TLE groups. Patient numbers were too small to allow meaningful comparisons with subclassification by side of resection and type of surgery. Although the groups did not differ in the response of the neuropsychological scores to surgery, taken together both groups showed an improvement compared with the null hypothesis of no change, most notable with performance ($P = 0.027$) and full-scale IQ ($P = 0.070$), but not with verbal IQ ($P = 0.752$, Wilcoxon signed rank). There was no detectable postoperative change in memory performance between groups, irrespective of the side operated.

Histopathological examination of the resected surgical specimen detected HS in all 23 HS+ve TLE patients and one of the 10 HS–ve TLE patient in whom the hippocampus had been resected. There was no significant difference in the frequencies of findings of histopathological features of microdysgenesis, such as clustering of cortical neurons, molecular layer or white matter neurons, or of frank

Table 5 Histopathological features

	HS–ve TLE (n = 20)	HS+ve TLE (n = 23)
Focal cortical dysplasia	2 (10%)	2 (10%)
Microdysgenesis	8 (40%)	6 (26%)
Hippocampal sclerosis	1/10 (10%)	23/23 (100%)

dysplastic features (Table 5). The 41-year-old MRI-negative patient with histopathological HS had the shortest duration of preoperative seizures of the HS–ve TLE group at 5 years, had a theta rhythm at ictal onset, but had had no childhood febrile convulsions. She had concordant [¹⁸F]FDG-PET hypometabolism involving mesial, anterior and lateral right temporal lobe and has been seizure free for 25 months following surgery.

One HS–ve TLE patient had discordant left [¹⁸F]FDG-PET and right temporal ictal EEG: she had a right-sided hippocampal-sparing anterior temporal lobectomy with two early seizures before remaining seizure free to 54 months. Three HS–ve patients had non-lateralizing [¹⁸F]FDG-PETs: one had a right-sided temporal lobectomy and amygdalohippocampectomy after intracranial monitoring recorded six right and one left temporal lobe seizure, and has remained seizure free through 48 months follow-up; one had a left-sided temporal lobectomy and amygdalohippocampectomy after scalp ictal EEG recorded eight left-sided temporal lobe seizures and is seizure free at 60 months; the third has declined surgery. Two HS+ve TLE patients with confirmed histopathological HS had poor seizure outcome from surgery: one had not had preoperative PET performed; the other had localized mesial hypometabolism on [¹⁸F]FDG-PET preoperatively.

Discussion

Up to 60–70% of medically refractory NLTLE patients have evidence of HS on MRI examination (Cascino *et al.*, 1991). This still leaves a significant proportion of NLTLE patients without HS. Past studies have found that even in this HS–ve TLE group of patients, well-lateralized discharges on interictal or ictal EEG, and also lateralized hypometabolism on PET are often seen (Salanova *et al.*, 1998; Lamusuo *et al.*, 2001). The pathophysiological basis of seizures in this HS–ve TLE group remains unclear. In particular, the question as to whether it is a variant of HS+ve TLE with less marked hippocampal damage or an entirely different clinicopathological syndrome remains open.

This study provides evidence that this group without radiological criteria of HS and with well-lateralized and defined TLE is not a subgroup of HS+ve TLE. The striking difference in histopathological confirmation of HS between the groups (one of 10 HS–ve TLE versus 23 of 23 HS+ve TLE confirmed as histopathological HS+ve) confirmed both that volumetric MRI is an excellent predictor of histopathological HS (Berkovic *et al.*, 1991), and the corollary that if volumetric

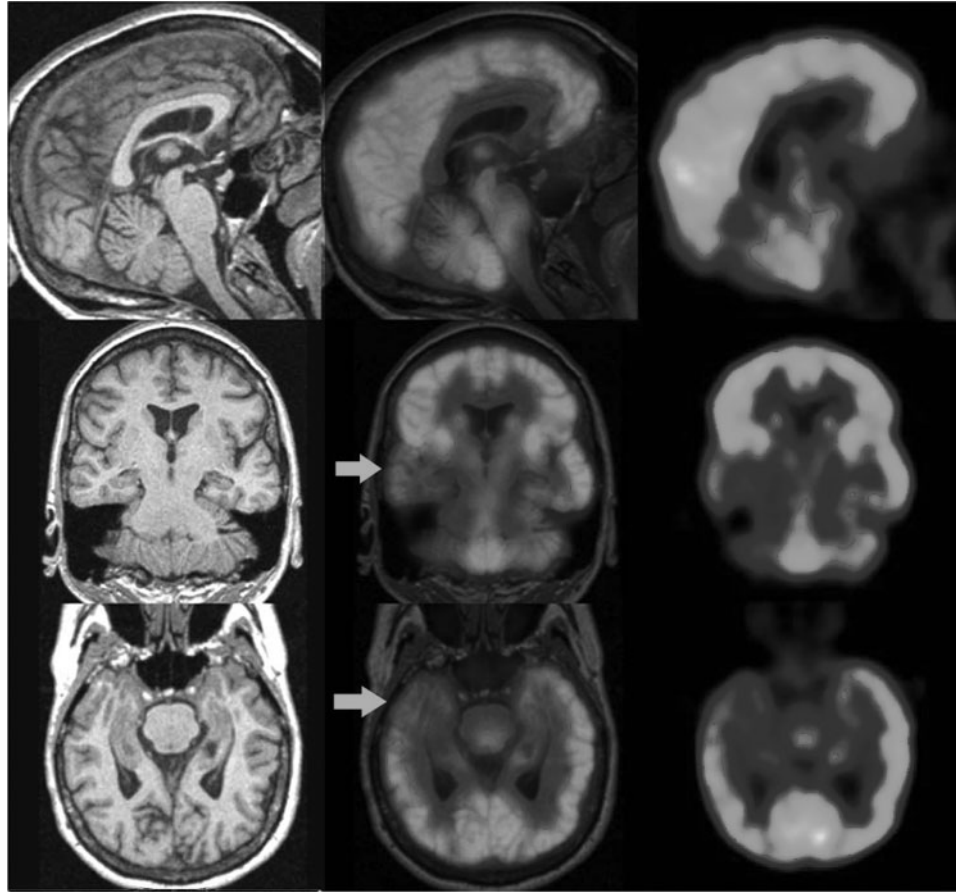


Fig. 1 MRI negative PET TLE. T1MR1 (left), [^{18}F] FDG-PET (right) and co-registered MR1 and [^{18}F]FDG-PET images (centre) from right sided HS-ve TLE patient show normal MRI and right temporal hypometabolism (arrows). This figure can be viewed in colour as supplementary data online.

MRI does not suggest HS, it is unlikely to be present. This finding disproves the suggestion that MRI-negative NLTLE patients generally represent a masked form of HS or bilateral HS.

Febrile convulsions are known to be a risk factor for HS (French *et al.*, 1993; Harvey *et al.*, 1995). The striking finding of differences in rates of febrile convulsions between the two groups suggests that they are different entities.

There were no other significant historical differences between the patient groups. Febrile convulsions were the only CNS insult that differed between the groups, and the fact that febrile convulsions occur at a young age accounted for the difference in age of any CNS insult seen. There was no significant difference in type or frequency of auras, or of positive family history. There was also no significant difference in duration or frequency of seizures, although this is probably biased by the tertiary referral centre sample, which would tend to select intractable patients regardless of the aetiology. The finding of no significant difference in the frequency of secondary generalization is more interesting, particularly in light of speculation that recurrent convulsions may contribute to hippocampal neuronal loss.

Location of interictal EEG transients did not differ between the two groups. Ictal EEG showed a tendency towards slower

rhythms at onset of seizures in the HS-ve TLE group. Past studies have shown slower rhythms at onset in temporal neocortical focal seizures compared with seizures of mesial temporal origin (O'Brien *et al.*, 1996; Ebersole and Pacia, 1996; Pacia and Ebersole 1997), which may favour a neocortical origin in the HS-ve TLE group.

We found that [^{18}F]FDG-PET was lateralizing correctly, concordant with EEG findings in both groups and also with MRI-detected HS in the HS+ve TLE group, i.e. in 26 of 27 (96.3%) of lateralized HS-ve TLE [^{18}F]FDG-PET scans and in 27 of 27 (100%) HS+ve TLE patients in whom [^{18}F]FDG-PET was performed. While not chosen on the basis of [^{18}F]FDG-PET positivity, it is of interest in considering our results that the majority of the HS-ve TLE group nevertheless had lateralizing [^{18}F]FDG-PET scans (Fig.1). This concurs with past studies: [^{18}F]FDG-PET is the most sensitive interictal imaging technique for identifying the focal functional deficit associated with HS, and is also known to be abnormal when MRI is negative (Knowlton *et al.*, 1997; Lamusuo *et al.*, 2001). Unilateral hypometabolism is seen in >70% of refractory TLE patients, increasing to 90% with quantitative techniques. The extent of hypometabolism in NLTLE is known to be often extensive, involving mesial and lateral structures and extending beyond the epileptogenic

temporal lobe to include ipsilateral thalamus, basal ganglia and contiguous frontal or parietal neocortex. The reasons for the hypometabolism seen on [^{18}F]FDG-PET scans remain elusive. One hypothesis is that the area of hypometabolism is a manifestation of neuronal diaschisis, with hypometabolism representing the remote effects of a distant insult on regions receiving projections from the epileptogenic area. However, given that the HS-ve TLE group has very little histologically identifiable neuronal loss, while the focal [^{18}F]FDG hypometabolism is often marked, it appears that the hypometabolism is not due primarily to neuronal loss, and must be at least in part reflective of some other process related to the epileptogenic zone. This may be a structural process not involving neuronal loss, such as changes in neuronal arborization. Another possibility is that hypometabolism develops because of functional changes in temporal lobe neurons as a result of the effects of repeated focal seizures. In support of this, patients with intractable TLE show hypometabolism more frequently than do those in whom seizures are well controlled, and the regional hypometabolism may decrease after successful epilepsy surgery (Hajek *et al.*, 1994). Studies have not found a clear relationship between the frequency of reported seizures, the time from the last seizure to acquiring [^{18}F]FDG-PET scans (Theodore *et al.*, 1992; Leiderman *et al.*, 1994) or the frequency of interictal epileptiform discharges (Engel *et al.*, 1982). Whilst there is evidence that hypometabolism may not be an acute post-ictal change, no conclusions can be drawn from cross-sectional studies about whether repeated seizures may induce a long-term functional change in the neurons that results in the hypometabolism seen on [^{18}F]FDG-PET.

The results of this study demonstrate that the extent of the hypometabolic changes differs between HS-ve TLE and HS+ve TLE groups, and suggest that the epileptogenic zone in the former group may primarily involve the lateral temporal region. One recent study has compared the patterns of hypometabolism in patients with confirmed mesial versus lateral TLE seen using statistical parametric mapping techniques (Kim *et al.*, 2003): 24 of 35 patients in the lateral TLE group in that study had identifiable structural lesions. That study found that the two groups differed in the pattern of hypometabolism, being most prominent in the lateral TLE group in the lateral temporal neocortex. This correlates well with the findings from our study where the non-lesional HS-ve TLE patients more often had extension of hypometabolism to involve regions beyond the mesial or anterior temporal lobes. One other past study involving smaller patient numbers found that mesiobasal TLE showed more extensive hypometabolism than neocortical TLE (Hajek *et al.*, 1993). In another study, more extensive hypometabolism was seen where HS was associated with temporal neocortical microscopic cortical dysplasia (Diehl *et al.*, 2003). Patients with intractable TLE more often have hypometabolism on PET than well-controlled patients, and hypometabolism may decrease after successful surgery (Spanaki *et al.*, 2000). However, in our study, there was no significant difference

in seizure frequency or duration between the groups, so intractability cannot be invoked as a factor in the more extensive hypometabolism. Hypometabolism has been shown to correlate with interictal slowing on EEG (Koutroumanidis *et al.*, 1998), which may reflect our finding that frequencies at ictal onset were slower in the HS-ve TLE group.

Past studies have given conflicting data on the association between the magnitude of PET hypometabolism and the extent of hippocampal cell loss (Henry *et al.*, 1994; Semah *et al.*, 1995; O'Brien *et al.*, 1997). The finding of more extensive hypometabolism in the HS-ve TLE group confirms that the extent of [^{18}F]FDG-PET hypometabolism does not correlate with the degree of hippocampal atrophy or neuronal loss alone.

Our finding of more extensive changes in the HS-ve TLE group may well bear on the relatively good surgical outcomes achieved (Wong *et al.*, 1996): greater severity of preoperative hypometabolism of the resected temporal lobe is known to be associated with significantly better postoperative seizure control, independent of the pathological diagnosis (Delbeke *et al.*, 1996). The pattern of hypometabolism also predicts postsurgical outcome, with anterior temporal polar hypometabolism most predictive of good outcome (Radtke *et al.*, 1993; Dupont *et al.*, 2000). In this study, both groups had a similar incidence of anterior temporal hypometabolism.

Our results are based on qualitative analysis of the [^{18}F]FDG-PET, and both qualitative and quantitative MRI analysis. The results with qualitative PET reporting are robust, and complement the MRI analysis. Comparison with quantitative PET analysis methods in these groups, such as statistical parametric mapping against control subjects, will be of great interest and is an intended area of further study.

HS on histopathological examination is thought to be predictive of a good postsurgical outcome. In past studies, HS on MRI has also been predictive of good surgical outcome, with worse outcome if the MRI is normal (Garcia *et al.*, 1994; Berkovic *et al.*, 1995). The reasons our cohort of HS-ve TLE patients have had better outcomes than similar groups in the past are unclear, but several factors may have contributed. MRI quality has improved, and modern imaging in some of these past 'MRI normal' series may have revealed subtle lesions, with likely seizure recurrence if unresected lesions remained. Detection of lesions on targeted high resolution volumetric sequences and FLAIR (fluid-attenuated inversion recovery) studies, for example, is a common basis for reclassification of scans referred to our institution as 'normal'. In particular, caution is required in accepting incidence data from studies spanning the early MRI era and, as resolution and reporting universally improve, the outcomes in this group—defined largely by exclusion—need to be critically reassessed. The earlier practice of suction removal of hippocampal structures, which may have resulted in some cases with undetectable HS on older MRI scanners also being classified as histopathologically 'normal', also complicates comparison with past studies. The proportion of patients in our HS-ve TLE group showing concordantly lateralized

hypometabolism at 96% is also higher than the typical rates (in the order of 70%) reported in the literature. This may again relate to MRI screening, with exclusion of subtle contralateral or extratemporal abnormalities, or it may be a chance finding: either way, this may have influenced the surgical outcomes. Although our HS-ve TLE patients were not selected by [^{18}F]FDG-PET positivity, the vast majority of these patients did have concordant lateralized PETs: rather than being simply defined by exclusion criteria on the MRI, perhaps this group should be regarded as 'MRI-negative PET-positive', and it may be this group who do relatively well with surgery. There were insufficient discordant or non-lateralizing [^{18}F]FDG-PETs for comparison in this study to address this question adequately, which merits further study. The use of co-registered [^{18}F]FDG-PET in the multimodality surgery may also have contributed to the better than expected surgical results.

Histopathological examination of resection specimens reveals no specific lesions in ~10–30% of NLTLE patients from most large surgical series (Falconer, 1971). Nevertheless, these specimens are rarely totally normal, often showing changes such as astrocyte proliferation, myelin loss and scattered neuronal loss (Taylor *et al.*, 1971). 'Microdysgenesis' refers to histological changes in the brain found in a number of patients with epilepsy that are relatively minor and are usually not associated with any change in the macroscopic appearance of the brain. These changes include the finding of scattered aberrant neurons within the molecular layer, the pia and the white matter, changes in the columnar arrangement of neurons in the cortex, and the presence of Purkinje cells in the granular and molecular layers and white matter (Kim, 1995). The significance of these findings is uncertain, as is whether they represent the cause or an effect of the seizures. Some studies suggest that such findings represent the pathological substrate for generalized or partial epilepsy (Meencke and Janz, 1984; Hardiman *et al.*, 1988). Other authors have pointed out that these changes are non-specific and are also often found in routine neuropathological specimens from patients with no history of epilepsy (Lyon and Gastaut, 1985; Kim, 1995). Our study found no difference in incidence of 'microscopic dysplasia' between the two groups. This suggests at least that these changes occur independently of the presence of HS, and also that they are probably not the pathological substrate for seizures in the HS-ve TLE patients. It is also of interest that there was no difference in prevalence of such findings despite the difference in extent of [^{18}F]FDG-PET changes. This does not necessarily contradict the past finding that [^{18}F]FDG-PET hypometabolism is more extensive in HS+ve TLE patients with associated microscopic dysplasia (Diehl *et al.*, 2003), but does suggest that dysplastic changes alone are not the only factor determining the extent of hypometabolic change.

A recent study (de Lanerolle *et al.*, 2003) reported detailed hippocampal histopathological findings in a series of TLE resections. This study found that the subgroup with 'no visual evidence of a lesion', termed 'paradoxical TLE',

had histopathological findings of mild (<25%) generalized hippocampal neuronal loss without immunohistochemical changes, distinguishing this group from both mesial TLE and from TLE associated with a mass lesion. Surgical outcome in the 'paradoxical TLE' subgroup was worse; however, the exact surgical approach in this group was not detailed.

The seizure-free outcome in our two groups was not significantly different, including HS-ve TLE patients where hippocampus was not resected. The rationale behind performing hippocampal-sparing procedures in HS-ve patients was the presumption that sparing mesial temporal structures might improve the functional outcome in these patients, presuming that the hippocampus was histologically, and consequently functionally, normal at the outset. The obvious reservation was that hippocampal-sparing resections might overlook instances of masked HS.

Past studies examining the effects of hippocampal resection on functional outcome have given variable results (Graydon *et al.*, 2001; Martin *et al.*, 2002). Although substantial individual variability exists with regard to postoperative functional outcome, in general, studies in patients with dominant hemisphere HS have found a postoperative decline in verbal memory function with left temporal lobectomy (Helmstaedter *et al.*, 1997), more marked in those with less severe preoperative HS (Martin *et al.*, 2002). With non-dominant resections, visuospatial deficits are more marked postoperatively (Graydon *et al.*, 2001). One study found that right HS+ve TLE patients had impaired visuospatial memory preoperatively, with postoperative improvement following amygdalo-hippocampectomy, while right HS-ve TLE patients had normal pre- and postoperative scores, with minor postoperative improvement after temporal resection sparing the hippocampus (Gleissner *et al.*, 1998). In general, the concept that the more normal the appearance of the hippocampus, the greater the risk of postoperative decline following mesial resection, especially with verbal memory function in dominant resections, is supported. The analysis of our neuropsychological data was limited by small numbers in the subgroups. There was no difference between HS-ve and HS+ve TLE in gross baseline scores or in change following surgery; however, taken as a whole, all patients showed improvement in performance and full-scale IQ. Superficially there were no obvious neuropsychological differences within the HS-ve group between those with hippocampus spared or resected; however, this comparison was severely underpowered. There was no obvious clinical deterioration in memory function in the HS-ve group, and specifically no detectable difference between verbal memory performance in those who had dominant temporal lobectomies, or between those in whom the hippocampus was resected or spared. This area is of great interest and warrants further prospective study.

Although this study was not designed to test the effect of extent of resection on seizure-free outcome, the comparable outcomes are nevertheless an interesting finding that warrants further investigation. Historically, the literature suggests

that seizure recurrence is more likely if an anteromesial epileptogenic focus is left partially or totally unresected. A randomized prospective trial of 70 such patients receiving total or partial hippocampectomy showed that 69% of patients with total hippocampal resections were seizure free at 1 year, compared with 39% with partial resections ($P = 0.009$) (Wyler *et al.*, 1995). In another study, postoperative MRI quantification of the extent of resection of lateral and mesiobasal structures showed significant correlation of seizure-free outcome with the extent of mesiobasal resection, regardless of the extent of lateral resection (Nayel *et al.*, 1991). The good outcome in our HS-ve TLE group, even with hippocampal-sparing procedures, may therefore be further evidence, along with the findings of more extensive hypometabolism on [^{18}F]FDG-PET and slower rhythms at ictal onset, that the epileptogenic region in this group is in fact neocortical rather than hippocampal. It is an important finding, given that the usual surgical approach in HS-ve TLE, if surgery is offered at all, is resection including the hippocampus. If the hippocampus could be spared in some NLTLE patients with the same rate of seizure freedom, their long-term functional outcome may well improve.

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