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ORIGINAL COMMUNICATION

Prognostic factors of postoperative seizure outcome in patients with temporal lobe epilepsy and normal magnetic resonance imaging

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Abstract

Purpose To retrospectively analyse a single-centre consecutive surgical series of patients with temporal lobe epilepsy (TLE) and negative MRI. To identify factors associated with postoperative seizure outcome among several presurgical, surgical and postsurgical variables.

Methods Clinical records of 866 patients who received temporal lobe resections and with a minimum follow-up of 12 months were retrospectively searched for MRI-negative cases. Anamnestic, clinical, neurophysiological, surgical, histopathological and postsurgical data were collected. Seizure outcome was categorised as favourable (Engel's class I) and unfavourable (Engel's classes II–IV). Uni- and multivariate statistical analysis was performed to identify variables having a significant association with seizure outcome.

Results Forty-eight patients matched the inclusion criteria. 26 (54.1%) patients required invasive EEG evaluation with Stereo-electro-encephalography (SEEG) before surgery. Histological evaluation was unremarkable in 34 cases (70.8%), revealed focal cortical dysplasias in 13 cases and hippocampal sclerosis in 2. 28 (58.3%) patients were in Engel's class I after a mean follow-up of 82 months (SD ± 74; range 12–252). Multivariate analysis indicated auditory aura, contralateral diffusion of the discharge at Video-EEG monitoring and use of ^{18}F-FDG PET as variables independently associated with seizure outcome.

Conclusion Carefully selected patients with MRI-negative TLE can be good candidates for surgery. Surgery should be considered with caution in patients with clinical features of neocortical seizure onset and contralateral propagation of the discharge. Use of ^{18}F-FDG PET may be helpful to improve SEEG and surgical strategies. The presented data help in optimising the selection of patients with MRI-negative TLE with good chances to benefit from surgery.

Keywords Temporal lobe epilepsy · Epilepsy surgery · Negative magnetic resonance imaging · Results on seizures · Outcome predictors

Abbreviations

TLE	Temporal lobe epilepsy
VEEG	Video-electro-encephalography
EZ	Epileptogenic zone
FS	Febrile seizures
SEEG	STEREO-electro-encephalography
HS	Hippocampal sclerosis
APOS	Acute postoperative seizures
FCD	Focal cortical dysplasias

Valeria Mariani and Martina Revay contributed equally to the preparation of the paper.

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Introduction

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy [1] and surgery is the treatment of choice for medically intractable cases [2–4]. Hippocampal sclerosis (HS), associated or not with focal cortical dysplasia, is the most common histopathological diagnosis in patients with drug-resistant focal epilepsy requiring surgery; other frequent histopathological findings in TLE are low-grade epilepsy-associated tumours, vascular malformations, malformations of cortical development, scars [5]. Despite the great improvement of neuroradiological techniques, that allow detecting the great bulk of these lesions, 30% of pharmaco-resistant TLE is MRI negative [6].

The chances of being seizure-free after surgery are higher in patients with MRI-visible or histopathological-confirmed lesions than in non-lesional patients [7, 8], with the proportion of seizure-free patients in MRI-negative TLE being 51% compared with 75% in HS+ mesial TLE [6].

When MRI fails to detect a lesion, fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) may be useful to disclose a hypometabolism in the temporal lobe [9, 10] that can strengthen the surgical indication. The presence of temporal lobe hypometabolism ipsilateral to the EEG side of seizure onset is associated with Engel class I postoperative outcomes in 75–80% of MRI-negative TLE [11].

It is possible that, in some patients operated on for TLE, histopathological evaluation of surgical specimens reveals MRI-occult structural lesions. In fact, several surgical series [11–15] of MRI-negative TLE report variable, but substantial, percentages of cases with HS or cortical malformations as histopathological findings. On the other hand, there are also MRI-negative TLE series with prevailing unremarkable histological findings [16–18].

Surgical indications are clear in lesional TLE, while they are still undefined in patients with TLE and normal MRI. In these patients, the analysis of clinical history, electro-clinical data (video-electro-encephalography, VEEG) and other diagnostic non-invasive exams often fails to correctly define the epileptogenic zone (EZ), thus requiring invasive EEG. The question as to which patients are candidates to invasive EEG monitoring, and which patients can be offered surgery with only non-invasive presurgical work-up is still debated. Furthermore, it is not clear which prognostic factors are associated with postoperative seizure outcome [6].

In this retrospective study, we have evaluated a single-centre cohort of patients with normal MRI who underwent temporal lobe resections, with the aim to identify the prognostic factors for a favourable outcome and to optimise the selection of those patients that can really benefit from epilepsy surgery.

Material and methods

Out of a consecutive series of 866 patients who underwent temporal lobe resections for drug-resistant focal epilepsy between January 1996 and June 2017 at our Institution, we selected the patients with no structural lesions at preoperative MRI. Data were collected by retrospective review of patients' clinical records and of a prospectively filled database.

Presurgical evaluation

Demographic and anamnestic data

Clinical records were reviewed for age at seizure onset, age at surgery, epilepsy duration, family history of epilepsy, epileptologically relevant antecedents, febrile seizures (FS), comorbidities, and estimated seizure frequency.

Neuroimaging

In all patients, brain MRI studies were performed by an Achieva 1.5-T magnet (Philips Healthcare; Best, The Netherlands). During the presurgical evaluation, MRI studies were performed according to a standardised protocol including T1- and T2-weighted images with FLAIR sequences in several planes, and a volumetric T1-weighted sequence; additional sequences were acquired according to each patient's requirements for diagnostic purposes. Sequences, especially fluid-attenuated inversion recovery (FLAIR) and T1-IR, were constantly updated and set to obtain optimal visualisation of lesions. Acquisition and interpretation of each study were conducted and validated by neuroradiologists expert in epileptic disorders. The MRI studies were then reviewed by epileptologists and neurosurgeons, who agreed that images did not show any structural abnormality and were, therefore, indentified as normal.

From 2012, a ^{18}F-FDG PET scan was performed for most patients, to point out hypometabolic areas correlated with seizure onset on scalp EEG. Patterns of hypometabolism were defined as ispilateral temporal and ipsilateral temporal and extratemporal (modified from Yang et al. 2014) [19].

Scalp VEEG

All patients underwent VEEG long-term monitoring, with the aim to record habitual seizures. Both interictal EEG epileptiform abnormalities and ictal EEG modifications were classified as unilateral temporal, unilateral temporal-plus (temporal and extratemporal) and bilateral (independent bilateral epileptiform abnormalities or independent bilateral ictal onset). Possible contralateral diffusion was also considered, according to the definition previously provided by others [20, 21] (Fig. 1).

Stereo-electro-encephalography (SEEG)

SEEG was performed when non-invasive investigations failed to correctly localise the EZ. Number and arrangement of intracerebral electrodes were tailored for each patient according to the presumed localization of the EZ [22]. The

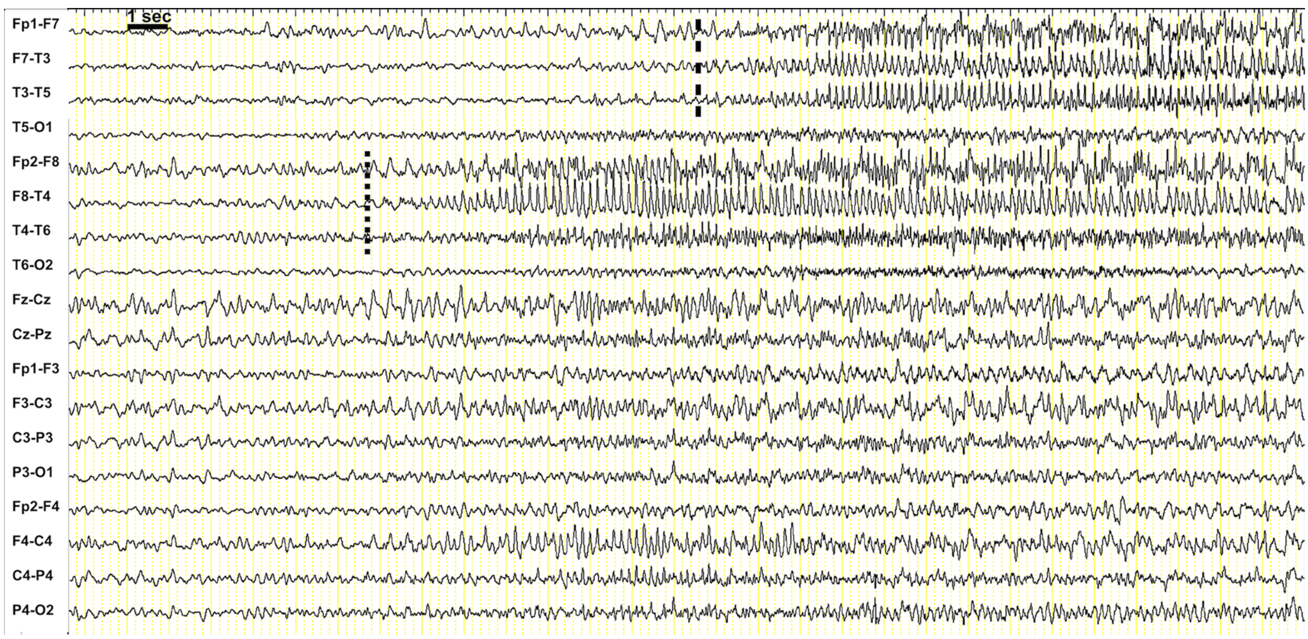

Fig. 1 Ictal EEG recording of a typical example of a discharge with contralateral diffusion. Dotted line indicates the onset of a right temporal discharge. After 8 s, the ictal electrical activity, with a comparable frequency, is clearly visible on the left temporal derivations (dashed line)

localization of the ictal discharge as recorded at SEEG was defined as temporal or temporal and extratemporal (temporal-plus). The seizure pattern was defined as predominantly “antero- mesial” (seizure onset in hippocampus, amygdala, parahippocampal gyrus and temporal pole) or “neocortical” (seizure onset in the temporal neocortex).

Ictal clinical semiology

Both scalp VEEG and SEEG monitoring allowed collecting data on type and chronology of ictal symptoms (auras) and signs. Supplemental ictal clinical information anamnestically reported by patients or by seizure witnesses were also considered.

Neuropsychology

Neuropsychological testing included the main areas of cognitive functions and mood. The complete neuropsychological test battery with the cognitive domains explored and administered tests are available in Online Resource 1, Table A.

The hemispheric dominance for language was defined in selected cases using intracarotid amytal test, and, more recently, by functional MRI. Further information about language localization was obtained in patients undergoing SEEG evaluation by intracerebral electrical stimulations.

Surgery and postsurgical evaluation

All patients underwent tailored resections within the anatomical limits of the temporal lobe. All surgeries were conducted using microsurgical techniques and neuronavigation.

Surgical specimens were routinely processed for histological and immunohistochemical investigations [23]. Pathology was defined according to the ILAE classification of focal cortical dysplasias (FCD) [24] and hippocampal sclerosis (HS) [25].

Clinical records were reviewed also for surgery-related complications and new, unexpected postoperative neurological deficits, as well as for seizures occurring in the first 7 days after surgery (acute postoperative seizures, APOS). Six months after surgery, all patients were re-evaluated by routine EEG and brain MRI. Subsequently, clinical follow-up was performed yearly by outpatient visits. Neuropsychological testing was repeated postoperatively at different time intervals.

Seizure outcome

Postoperative seizure outcome was assessed according to the Engel’s classification [26]; patients were assigned to two outcome groups: favourable (free from disabling seizures, corresponding to Engel’s class I) and unfavourable (corresponding to Engel’s classes II–IV).

Data analysis

Statistical analysis was performed to investigate which variables were associated with seizure outcome, as assessed at last available follow-up (favourable vs. Unfavourable). The following variables were analysed using a univariate logistic regression with the Wald's test (when the value of one category was equal to 0 a Fisher's test was used):

- Demographic and anamnestic data: gender, age at seizure onset, age at surgery, epilepsy duration, dominance for language, family history of epilepsy, antecedents/comorbidities, FS and estimated seizures frequency (daily [more than 30/month], weekly [5–30/month], monthly [1–4/month], sporadic [less than 1/month]).
- EEG findings: inter-ictal EEG, ictal EEG, contralateral diffusion of the discharge, SEEG (performed/not performed), SEEG ictal discharge (temporal vs. temporal-plus), SEEG seizure pattern (mesial vs. neocortical), ^{18}F-FDG PET (performed/not performed), ^{18}F-FDG PET site of hypometabolism (ipsilateral temporal/ipsilateral temporal and extratemporal).
- Ictal clinical semiology: aura (present/absent), different kinds of aura (epigastric, auditory, visual, olfactory, gustative, psychic, autonomic and sensitive), verbal or gestural warning of incoming seizure, oral automatisms, lateralizing signs (dystonia, limb automatisms, head deviation and postictal language disturbance), loss of contact, secondary generalisation, falls and awareness at the end of the seizures.
- Surgical and postsurgical data: side, surgery type, histology, APOS, postoperative EEG.

A multivariate logistic regression model was then built to identify variables independently associated with the odds of an unfavourable outcome, after exclusion of reciprocally correlated variables.

Statistical significance was assumed at $P < 0.05$. Statistical analysis was performed using the statistical software STATA (version 5.1, StataCorp, College Station, Texas, USA).

Results

Forty-eight patients fulfilled the selection criteria and were included in the analysis: they represent 5.5% of the total number of patients that underwent temporal lobe resections in our Institution in the considered period.

Demographic and anamnestic data

There were 19 (39.6%) females and 29 (60.4%) males. The mean age at seizure onset was 15.2 years (SD ± 9), the mean age at surgery was 31.7 years (SD ± 9) and the mean duration of epilepsy was 16.5 years (SD ± 8.4). Ten (20.8%) patients had a family history of epilepsy. The following epileptologically relevant antecedents were reported: 1 threatened abortion, 2 dystocic deliveries, 3 perinatal troubles, 3 infections of central nervous system, 1 radiosurgery for artero-venous malformation. Eight patients (16.7%) experienced FS (6 simple and 2 complex) in infancy.

Three patients had comorbidities: celiac disease, systemic lupus erythematosus, thyroiditis in 1 patient each.

Seizure frequency was daily in 8 (16.7%) patients, weekly in 18 (37.5%) patients, monthly in 18 (37.5%) patients and sporadic in 4 (8.3%) patients.

Neuroimaging

According to the selection criteria, none of the patients presented structural lesions at brain MRI.

Seventeen (35.4%) patients underwent ^{18}F-FDG PET. At the visual analysis all these patients had a definite, hypometabolic area in the presumably epileptogenic temporal lobe as indicated by the electro-clinical data. In 11 cases, hypometabolism involved also extratemporal areas (opercular–insular in 5 cases, frontal cortex in 4 cases, parieto-occipital in 2 cases). Ten out of these 11 patients were evaluated by SEEG monitoring before surgery.

Scalp VEEG and SEEG findings

Seizures were recorded in 46 (96%) patients during scalp VEEG monitoring and in all the 26 (100%) patients that underwent SEEG. Details about scalp VEEG and SEEG findings are summarised in Table 1.

After non-invasive evaluation, 22 patients whose data co-localised to one temporal lobe proceeded directly to surgery. In these cases, electroclinical data (corroborated in 4 cases by metabolic findings) were consistent with the involvement of mesial temporal structures in seizure onset. In the remaining 26 patients, with partially unconclusive non-invasive data suggesting a neocortical and/or extratemporal involvement, surgery was guided by a SEEG investigation.

Ictal clinical semiology

Details about ictal clinical signs and symptoms of the 48 patients are summarised in Table 2. No aura was reported by 8 (16.7%) patients. Among the other 40 (83.3%) patients, 30 reported more than 1 type of aura.

Table 1 Interictal and Ictal VEEG and SEEG findings

	N[c] (%)
VEEG[a]	
Interictal epileptiform abnormalities	
Unilateral temporal	14/48 (29.2%)
Unilateral temporal-plus	21/48 (43.7%)
Bilateral	13/48 (27.1%)
Ictal onset discharge	
Unilateral temporal	23/46 (50.0%)
Unilateral temporal-plus	23/46 (50.0%)
Bilateral	0/46 (0.0%)
Contralateral discharge diffusion	18/46 (39.1%)
SEEG[b]	
Ictal discharge	
Temporal	11/26 (42.3%)
Temporal-plus	15/26 (57.7%)
Seizures pattern	
Mesial	14/26 (53.8%)
Neocortical	12/26 (46.2%)

[a]Video-electroencephalography

[b]Stereo-electroencephalography

[c]Number of cases

Table 2 Ictal clinical semiology

Symptoms/signs	N[a] (%)
Aura	
Psychic	25 (52.1%)
Epigastric	21 (43.8%)
Autonomic	18 (37.5%)
Auditory	11 (22.9%)
Visual	9 (18.8%)
Somato-sensory	7 (14.6%)
Gustative	4 (8.3%)
Olfactory	3 (6.3%)
Warning	
Verbal	17 (35.4%)
Gestural	8 (16.7%)
Dystonia[b]	
Contralateral	17 (35.4%)
Ipsilateral	2 (4.2%)
Bilateral	4 (8.3%)
Head deviation[b]	
Ipsilateral	15 (31.3%)
Contralateral	4 (8.3%)
Oro-alimentary automatisms	36 (75.0%)
Gestural automatisms[b]	
Ipsilateral	19 (39.6%)
Contralateral	1 (2.1%)
Bilateral	10 (20.8%)
Loss of contact	44 (91.7%)
Secondary generalisation	18 (37.5%)
Falls	8 (16.7%)
Postictal speech impairment	25 (52.1%)
Awareness	36 (75.0%)

[a]Number of cases

[b]Lateralizing signs are referred to the side of surgery

Surgery and postsurgical evaluation

Although all resections were tailored according to each patient's specific requirements, as revealed by preoperative evaluation, three main patterns of resection could be ex post recognised: antero-mesial temporal lobectomy (34 patients, 70.8%); complete temporal lobectomy (10 patients, 20.8%); lateral cortectomy (4 patients, 8.3%). Twenty-one (43.7%) patients were operated on in the dominant hemisphere for language; in these cases, the posterior portion of the first temporal gyrus was spared irrespective of the type of resection.

Histology revealed type I FCD in 11 cases, type II FCD in 1 case and HS in 2 cases (1 type I and 1 type III). Histological evaluation was unremarkable (no lesion or unspecific gliosis) in 34 (71%) cases.

Mild surgical complications occurred in four patients, 1 with wound dehiscence and 3 with intracranial bleeding at the surgical site, none of which required surgical treatment. One patient suffering a postoperative bleeding developed mild permanent speech impairment.

Eight (16.7%) patients presented APOS. The postoperative EEG showed epileptiform abnormalities with variable localizations in 29 (60.4%) patients.

Neuropsychological data

Hemispheric dominance for language was left sided in 44 patients and right sided in 4.

Preoperative and last available postoperative results of neuropsychological evaluations have been analysed.

A preoperative evaluation was available in 41 patients. Eleven of them had a completely normal neuropsychological profile; 9 of them received an antero-mesial temporal lobectomy and 2 a complete temporal lobectomy. Only 8 of these 11 patients were re-tested postoperatively: 3 were completely normal, 1 showed a decline in episodic memory and 4, all operated on in the dominant hemisphere with an antero-mesial temporal lobectomy, exhibited a reduction in language and verbal memory skills (details about cognitive decline in these 5 patients and percentages of score reduction are available in Online Resource 1, Table B). Abnormal neuropsychological scores were recorded in 30 patients at preoperative test. A postoperative evaluation was available in 25 of these 30 cases: 6 patients (5 with an antero-mesial temporal lobectomy, 1 with a lateral cortectomy) had completely normalised scores and in 19 patients the pathological profile did not change significantly. As a whole, the percentages of patients with a pathological score at the preoperative and, respectively, at the last available postoperative evaluation did not significantly differ in any of the considered domains.

Seizure outcome

The mean postoperative follow-up was 82 months (SD ± 74; range 12–252); a total of 28 (58.3%) patients were in Engel's class I (17 patients Ia, 1 patient Ib, 7 patients Ic and 3 patients Id), 5 (10.4%) patients were in class II, 5 (10.4%) patients were in class III and 10 (20.8%) patients were in class IV. Patients in Engel's class I were 28/48 (58.3%), 26/44 (59.1%) and 14/26 (53.8%) 1, 2 and 5 years after surgery, respectively.

At the end of follow-up, antiepileptic drugs were withdrawn in 5 (10.4%) patients and tapered in 14 (29.2%) patients in Engel's class I.

Details on the association of the different variables with seizure outcome at univariate analysis are reported in Tables 3, 4, 5, 6. An unfavourable seizure outcome was significantly associated with auditory aura, falls, postictal speech impairment, bilateral or extra-temporal interictal EEG abnormalities, contralateral diffusion of the discharge and presence of epileptiform abnormalities at postoperative EEG. Patients who underwent ^{18}F-FDG PET had a significantly more favourable outcome. Age at seizure onset, age at surgery and duration of epilepsy were not significantly associated with seizure outcome.

A multivariate logistic regression model showed that auditory aura, contralateral diffusion of the ictal discharge at VEEG evaluation and use of ^{18}F-FDG PET were independently associated with seizure outcome (Table 7).

Discussion

This retrospective study provided evidence that, if carefully selected, patients with MRI-negative TLE may be good candidates to resective surgery, although the seizure outcome is less favourable than in patients with lesional TLE [6]. At the last available follow-up, 58.3% of our patients were in Engel's class I. A slight decrease of class I outcome to 53.8% was recorded 5 years postoperatively. Auditory aura and contralateral diffusion of the discharge at scalp VEEG were found to be independent predictors of an unfavourable outcome in this cohort; use of ^{18}F-FDG PET was independently associated with postoperative seizure freedom.

The frequency of auditory auras in TLE is low, ranging from 5 to 7% in largest series [27–31]. The rate of patients with auditory auras in our cohort is 22%, a figure which might reflect a specific feature of MRI-negative TLE [31]. Several studies have investigated the predictive value of single ictal symptoms and signs, including auditory auras, on seizure outcome after temporal lobe epilepsy surgery [27, 31–35]. While Dupont et al., in 305 surgical cases, found no association between any type of aura and seizure outcome, a number of studies reported auditory auras as predictors of seizure recurrence after TLE surgery. Asadi-Pooya et al., found a significantly worse postoperative outcome in

Table 3 Results of univariate statistical analysis of demographic and anamnestic features vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II–IV	*P* value
Gender	Binomial	Male	18 (62.1%)	11 (37.9%)	NS[a]
		Female	10 (52.6%)	9 (47.4%)	
Dominance for language	Binomial	Left	27 (61.4%)	17 (38.6%)	NS[a]
		Right	1 (25.0%)	3 (75.0%)	
Familiarity	Binomial	No	22 (57.9%)	16 (42.1%)	NS[a]
		Yes	6 (60.0%)	4 (40.0%)	
Antecedents/comorbidities	Binomial	No	21 (60.0%)	14 (40.0%)	NS[a]
		Yes	7 (53.8%)	6 (46.2%)	
Febrile seizures	Binomial	No	21 (52.5%)	19 (47.5%)	NS[a]
		Yes	7 (87.5%)	1 (12.5%)	
Seizure frequency	Multinomial	Daily[b]	3 (37.5%)	5 (62.5%)	
		Weekly	11 (61.1%)	7 (38.9%)	NS[a]
		Monthly	12 (66.7%)	6 (33.3%)	NS[a]
		Sporadic	2 (50.0%)	2 (50.0%)	NS[a]

[a]Not significant

[b]Reference category

Table 4 Results of univariate statistical analysis of VEEG, SEEG and ^{18}F-FDG PET findings vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II–IV	*P* value
Interictal EEG	Binomial	Unilateral temporal	13 (92.9%)	1 (7.1%)	**0.010**
		Other	15 (44.1%)	19 (55.9%)	
Ictal EEG	Binomial	Unilateral temporal	17 (73.9%)	6 (26.1%)	NS[a]
		Other	10 (43.5%)	13 (56.5%)	
Contralateral discharge diffusion	Binomial	No	23 (82.1%)	5 (17.9%)	**< 0.001**
		Yes	4 (22.2%)	14 (77.8%)	
SEEG	Binomial	No	13 (59.1%)	9 (40.9%)	NS[a]
		Yes	15 (57.7%)	11 (42.3%)	
SEEG Ictal discharge	Binomial	Temporal	5 (45.5%)	6 (54.5%)	NS[a]
		Temporal-plus	10 (66.7%)	5 (33.3%)	
SEEG seizure pattern	Binomial	Mesial	10 (71.4%)	4 (28.6%)	NS[a]
		Neocortical	5 (41.7%)	7 (58.3%)	
18F-FDG PET[b]	Binomial	No	14 (45.2%)	17 (54.8%)	**0.016**
		Yes	14 (82.4%)	3 (17.6%)	
18F-FDG PET[b]	Binomial	Temporal	6	0	NS[a]
		Temporal and extratemporal	8	3	

VEEG video-electroencephalography, *SEEG* stereo-electroencephalography

[a] Not significant

[b] Fluorine-18 fluorodeoxyglucose positron emission tomography

Bold values indicate $P < 0.05$

patients with auditory aura compared with those without. They concluded that these cases should be considered for a different approach when performing epilepsy surgery, including SEEG evaluation to study possibly involved networks [30]. Radhakrishnan et al., in a series of 344 patients who received anterior temporal lobectomy, reported that the presence of auditory and of vertiginous auras was significantly associated with an unfavourable seizure outcome. Their conclusion was that "auditory and vertiginous auras are red flags which need attention before ATL". Barba et al., while evaluating failures of TLE surgery, identified at single-symptoms analysis that a number of semeiological features, including auditory illusions, were more frequently associated with temporal-plus epilepsies, which showed a significantly worse outcome at surgery. In the same paper, cluster analysis identified a cluster including only auditory hallucinations and illusions as markers of temporal-plus epilepsy [36].

We may postulate different reasons to explain the association between auditory auras and unfavourable seizure outcome after surgery. First, assuming that auditory auras are localising symptoms consistent with the involvement of the superior temporal gyrus, in particular of its intermediate portion for illusions and of the Heschl's gyrus for hallucinations, resection in this area may have been insufficient for fear to damage the Wernicke's area in patients operated on in the dominant hemisphere. Nevertheless, this may be the case in only 4 of our 11 patients with auditory auras. Second, patients with ictal auditory illusions and hallucinations may have an extensive epileptogenic zone out-passing the limits of the temporal lobe ("temporal plus" epilepsy), a factor which, for this reason, may be associated with an unfavourable outcome if resection is limited to the temporal lobe [36, 37]. As a matter of fact, there is evidence, provided by neurophysiological testing during invasive EEG investigations, that acoustic phenomena may be elicited by electrical stimulations of extratemporal areas, including the frontal operculum [38] and of the insular cortex [39, 40]. Another study on frequency analysis and functional MRI supported the possible role of the insula in acoustic processing [41]. The hypothesis of an extratemporal origin of some auditory auras is also suggested by the reporting of opercular [38] and insulo-opercular [42] epilepsies associated with auditory auras, as well as the presence of 7% of patients with extratemporal epilepsy in a series of patients with auditory auras [30]. This does not necessarily imply the existence of extratemporal acoustic areas, considering that, given the wide connectivity of the primary acoustic cortex [43], this may be activated by an ictal discharge with an extratemporal origin.

A well-localised and lateralised ictal and interictal EEG is correlated with a favourable postoperative outcome in MRI-negative TLE [11, 18, 44]. Our analysis corroborates these data and, in addition, shows that contralateral diffusion of the discharge is an independent prognostic factor for seizure recurrence. The role of the contralateral propagation

Table 5 Results of univariate statistical analysis of ictal clinical semiology vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II–IV	*P* value
Aura	Binomial	No	3 (37.5%)	5 (62.5%)	NS[a]
		Yes	25 (62.5%)	15 (37.5%)	
Psychic aura	Binomial	No	11 (47.8%)	12 (52.2%)	NS[a]
		Yes	17 (68.0%)	8 (32.0%)	
Epigastric aura	Binomial	No	14 (51.9%)	13 (48.1%)	NS[a]
		Yes	14 (66.7%)	7 (33.3%)	
Autonomic aura	Binomial	No	17 (56.7%)	13 (43.3%)	NS[a]
		Yes	11 (61.1%)	7 (38.9%)	
Auditory aura[b]	Binomial	No	25 (67.6%)	12 (32.4%)	**0.025**
		Yes	3 (27.3%)	8 (72.7%)	
Visual aura	Binomial	No	22 (56.4%)	17 (43.6%)	NS[a]
		Yes	6 (66.7%)	3 (33.3%)	
Somato-sensory aura	Binomial	No	25 (61.0%)	16 (39.0%)	NS[a]
		Yes	3 (42.9%)	4 (57.1%)	
Gustative aura	Binomial	No	25 (56.8%)	19 (43.2%)	NS[a]
		Yes	3 (75.0%)	1 (25.0%)	
Olfactory aura	Binomial	No	25 (55.6%)	20 (44.4%)	NS[a]
		Yes	3 (100.0%)	0 (0.0%)	
Warning	Binomial	No	14 (60.9%)	9 (39.1%)	NS[a]
		Yes	14 (56.0%)	11 (44.0%)	
Dystonia	Binomial	Contralateral	8 (47.1%)	9 (52.9%)	NS[a]
		Other	20 (64.5%)	11 (35.5%)	
Head deviation	Binomial	Ipsilateral	6 (40.0%)	9 (60.0%)	NS[a]
		Other	22 (66.7%)	11 (33.3%)	
Oro-alimentary automatisms	Binomial	No	6 (50.0%)	6 (50.0%)	NS[a]
		Yes	22 (61.1%)	14 (38.9%)	
Gestural automatisms	Binomial	Ipsilateral	13 (68.4%)	6 (31.6%)	NS[a]
		Other	15 (51.7%)	14 (48.3%)	
Loss of contact	Binomial	No	4 (100.0%)	0 (0.0%)	NS[a]
		Yes	24 (54.5%)	20 (45.5%)	
Secondary generalisation	Binomial	No	20 (66.7%)	10 (33.3%)	NS[a]
		Yes	8 (44.4%)	10 (55.6%)	
Falls	Binomial	No	27 (67.5%)	13 (32.5%)	**0.017**
		Yes	1 (12.5%)	7 (87.5%)	
Post-ictal speech impairment	Binomial	No	18 (78.3%)	5 (21.7%)	**0.009**
		Yes	10 (40.0%)	15 (60.0%)	
Awareness	Binomial	No	5 (41.7%)	7 (58.3%)	NS[a]
		Yes	23 (63.9%)	13 (36.1%)	

[a]Not significant

[b]Auditory hallucinations in 8 cases, auditory illusions in 3 cases

Bold values indicate $P < 0.05$

of the ictal discharge at scalp EEG as a prognostic factor of postoperative seizure outcome in TLE is somewhat controversial. In some studies, this variable is scotomized [44, 45]; in others, no significant association, or only a trend towards association with poorer outcome, was found [46, 47]. Conversely, Schulz et al. [21] reported a negative significant association between contralateral propagation and postoperative seizure outcome, postulating that this may be an index of bilateral epileptogenicity. Another study on HS-related TLE found that the risk of long-term unfavourable postoperative outcome was higher in patients with contralateral diffusion of the ictal scalp EEG discharge [48]. Sirin et al. [49] provided further evidence of the negative predictive value of contralateral diffusion on postoperative outcome by analysing a cohort of HS patients; they concluded that this finding increases the risk of false lateralization. Seizure recurrence

Table 6 Results of univariate statistical analysis of surgical and postsurgical variables vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II–IV	*P* value
Side	Binomial	Dominant	9 (42.9%)	12 (57.1%)	NS[a]
		Non-dominant	19 (70.4%)	8 (29.6%)	
Surgery type	Multinomial	Antero-mesial temporal lobectomy[c]	19 (55.9%)	15 (44.1%)	
		Complete temporal lobectomy	7 (70.0%)	3 (30.0%)	NS[a]
		Neocortectomy	2 (50.0%)	2 (50.0%)	NS[a]
Hystology	Multinomial	Uninformative	19 (55.9%)	15 (44.1%)	NS[a]
		Type I FCD	6 (54.5%)	5 (45.5%)	
		Type II FCD	1 (100.0%)	0 (0.0%)	
		HS	2 (100.0%)	0 (0.0%)	
APOS[b]	Binomial	No	26 (65.0%)	14 (35.0%)	NS[a]
		Yes	2 (25.0%)	6 (75.0%)	
Postoperative EEG: epileptiform abnormalities	Binomial	No	16 (84.2%)	3 (15.8%)	**0.006**
		Yes	12 (41.4%)	17 (58.6%)	

[a]Not significant

[b]Acute postoperative seizures

[c]Reference category

Bold values indicate $P < 0.05$

Table 7 Multivariate logistic regression analysis for the risk of seizure recurrence

	OR[a]	95% OR[a] CI[b]	*P* value
Auditory aura	0.031	0.002–0.453	**0.011**
Contralateral discharge diffusion	0.027	0.003–0.214	**0.001**
Use of ^{18}F-FDG PET	9.43	1.189–74.693	**0.034**

[a]Odds ratio

[b]Confidence interval

Bold values indicate $P < 0.05$

after surgery in patients with contralateral involvement of the ictal discharge is possibly due to an epileptogenic network involving also the contralateral temporal lobe, even if a postsurgical VEEG monitoring would be necessary to support this hypothesis. The interpretation of electro-clinical correlations is essential and often challenging in MRI-negative TLE. Therefore, long-term VEEG evaluation is a crucial step in the presurgical work-up, as it provides key information about factors with prognostic relevance since the early phases of the selection procedure.

Use of ^{18}F-FDG PET has been suggested in MRI-negative patients, including those with TLE. In these patients, the presence of a hypometabolism co-localising with the electro-clinical findings may allow proceeding to surgery without further investigations [11]. The small number of patients of our cohort submitted to ^{18}F-FDG PET prevented a reliable analysis of the impact of ^{18}F-FDG PET findings on seizure outcome. Nevertheless, it was clear that the use of ^{18}F-FDG PET represented an independent predictor of a favourable seizure outcome. We postulate that ^{18}F-FDG PET strongly contributed to corroborate the surgical indication in patients with consistent electro-clinical findings, and to optimise the strategy of SEEG explorations in case of partial incoherence of non-invasive information. Notably, all but one of the patients with a temporal and extratemporal hypometabolism were evaluated by SEEG monitoring, indicating that metabolic findings were relevant to guide the presurgical work-up in this cohort of patients. Unfortunately, we could not investigate the metabolic pattern of patients with a contralateral diffusion of the ictal EEG discharge, because 14 out of 18 patients with this EEG pattern were evaluated before the introduction of PET scan in our hospital. We cannot, therefore, exclude the presence of bilateral hypometabolism in similar cases, with lower chances of postoperative seizure freedom.

Patients with seizure recurrence had more frequent secondary generalisations compared to seizure-free cases (44.4% and 66.7% of Engel's class I, respectively), although this difference did not reach statistical significance ($P=0.135$). As a matter of fact, secondary generalisation has been associated with a worse seizure outcome after TLE surgery in most series [50–52]. We may postulate that in our analysis statistical significance was not reached for the small size of our sample. Alternatively, a possible explanation is that in our data collection, we did not include secondary generalisations which occurred at seizure onset. Of note, some studies reported a significantly higher proportion of secondary generalisation in patients with HS-related TLE [35, 52], which are recognised as those with the best seizure outcome among TLE surgically treated.

The question of the selection criteria for surgery and, specifically, the need for invasive investigations in MRI-negative TLE is still open. Patients with clinical symptoms consistent with antero-mesial TLE, well-localised and lateralized ictal and interictal EEG abnormalities and no diffusion of the discharge are probably good candidates for surgery. On the other hand, our data suggest that, in patients with symptoms evocative of a neocortical seizure onset (auditory aura), or with contralateral diffusion of the discharge, surgery should be considered with caution. In similar cases, SEEG is likely to represent a useful tool to correctly identify the EZ, but the criteria for indications to this evaluation are still undefined. According to the results provided by other studies, the use of SEEG investigations with appropriately placed extra-temporal electrodes may be helpful in patients whose past history or electroclinical data suggest the possibility of temporal-plus and neocortical (especially in the dominant hemisphere) epilepsies [30, 53].

Analysis of the neuropsychological profile and outcome after surgery was not the main goal of this study. Indeed, the relatively small size of our cohort and the considerable number of the neuropsychological tests performed prevented a reliable stratification of data for statistical analysis. Furthermore, the available data were incomplete and not systematically collected. Nevertheless, in our sample, there is no evidence of gross cognitive deficits at the postsurgical clinical follow up. This finding corroborates recent evidence in large samples of patients submitted to surgery for TLE [54]. It should be underlined, however, that in our patients with intact cognitive profiles, a postoperative decline may be observed, especially in those operated on in the dominant hemisphere. On the other hand, in patients with preoperative neuropsychological impairments, no additional deterioration was recorded postoperatively, with a subset of patients experiencing normalisation of their cognitive functions.

A substantial subset of our patients (34/48, 71%) had unremarkable histological findings. The reported rate of negative or unspecific histological findings in surgical specimens of MRI-negative TLE patients is highly variable, ranging from 28 to 85% across series [11–15, 17, 55–58]. Discrepancies may be due to a number of factors, including methods used for specimen processing, criteria for definition of non-lesional MRI, evolution of MRI techniques allowing detection of subtle lesions with high-field magnets. Although our cohort was imaged by a 1.5-T magnet, the rate of histologically negative cases is in line with a case series of 3-T MRI-negative TLE [16], confirming the reliability of our neuroradiological selection. Moreover, in 11 (23%) of our patients, a type I FCD was found at histology. This type of cortical malformation, unlike HS that should be rarely missed, may be easily undetected at MRI [59, 60].

The question about the aetiology of TLE is particularly intriguing in patients presenting with negative MRI and unremarkable histology after surgery, especially in those who achieve seizure freedom after temporal lobectomy (55.9% in our cohort), in whom the etiological factor has been supposedly removed. Indeed, a 50% rate of postoperative seizure freedom in patients with no specific lesion at histology has been recently reported also in a large series of operated on patients [5]. Another study reported that 61.5% of patients operated on for MRI-negative TLE with unremarkable histology were seizure free [18]. Moreover, no difference in seizure outcome was recorded between cases with negative histology and those with a demonstrated pathological substrate (most of which with a diagnosis of FCD I), which one could ascribe to the small size of our sample. However, other studies have reported seizure freedom rates in histologically negative and, respectively, in FCD I cases operated on for TLE comparable to those reported in the present study [18, 61].

It is possible that the identification of etiological factors in histologically negative cases may be provided by processing surgical specimens not only with the aim to detect structural abnormalities using traditional histological procedures but also searching for molecular or genetic biomarkers. According to the heterogeneity of electro-clinical findings, pointing at mesial, neocortical or "temporal-plus" patterns, we may postulate that this undetected aetiology may underlie different types of epileptic networks within or close to the temporal lobe. The distinct nature of this non-lesional TLE is also suggested by the less favourable results obtained by surgery compared to lesional TLE. These features may legitimate the hypothesis of a genetic or metabolic aetiology, not exclusively localised in the temporal lobe and with a possible time-dependent evolution.

The retrospective, single-centre nature of the present study limits its general relevance. Another limitation of the study is represented by the small size of the selected cohort, probably for the current reluctance to refer for surgery MRI-negative TLE patients (5.5% of the total number of patients that underwent temporal lobe resections in our Institution). Also, an overestimation of MRI-negative cases may have occurred owing to the use of a 1.5-T magnet, which, especially in less recent years, could have missed some subtle structural abnormality. Furthermore, only few patients were imaged by ^{18}F-FDG PET, preventing a reliable assessment of the usefulness of this diagnostic tool in this clinical setting. On the other hand our study has considered a rather large constellation of factors, including anamnestic, clinical, EEG, neuropsychological, surgical, histological and outcome data of MRI-negative TLE.

The presented results may encourage further research, especially on MRI and histologically negative TLE. Improving the interpretation of ^{18}F-FDG PET findings to optimise surgical selection, establishing shared indications to invasive exams, investigating the possible aetiology of this specific disease are among the points which deserve attention.

Conclusions

The analysis of this cohort of operated on patients with MRI-negative TLE suggests that surgery can be an effective treatment option, provided that an accurate presurgical work-up is performed. A substantial subset of cases required a SEEG investigation for the identification of the EZ. Surgery should be considered with caution in patients with auditory aura and contralateral diffusion of the discharge, because they are more likely to experience an unfavourable outcome. Use of ^{18}F-FDG PET may contribute to a favourable seizure outcome. MRI-negative TLE is probably a distinct disorder, with often undefined aetiology deserving further investigation.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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

Informed consent All persons gave their informed consent prior to their inclusion in the study.

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