Temporal Lobe Epilepsy: From Electro-Clinical Semiology to Surgical Outcome*

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Summary

Temporal lobe epilepsy (TLE) is the most frequent localisation-related epileptic syndrome in adults and is frequently resistant to anti-epileptic drug treatment. Patients with pharmaco-resistant TLE should therefore be evaluated for the possibility of epilepsy surgery. We here review the electro-clinical semiology of TLE and the current state in presurgical diagnostic evaluation and surgical therapies. These advances will allow better post-operative seizure control while reducing the risks of deficits.

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Key words: Temporal lobe epilepsy, semiology, imaging, surgery

Epilepsie du lobe temporal: de la sémiologie électro-clinique aux traitments chirurgicaux

L'épilepsie du lobe temporal est le syndrome épileptique focal le plus fréquent chez l'adulte et est fréquemment résistante aux médicaments anti-épileptiques. Les patients avec épilepsie du lobe temporal pharmacorésistante devraient donc être évalués pour la possibilité d'une chirurgie de l'épilepsie. Cet article fait le point sur la sémiologie électro-clinique de l'épilepsie du lobe temporal et l'état actuel des avancées dans l'évaluation préchirurgicale et les thérapies chirurgicales. Ces avancées permettront un meilleur contrôle des crises et une réduction des risques de déficits post-opératoires.

Mots clés : Epilepsie du lobe temporal, sémiologie, imagerie, chirurgie

Temporallappenepilepsie: Von der elektro-klinischen Semiologie zur chirurgischen Therapie

Temporallappenepilepsie ist das häufigste epileptische Syndrom bei Erwachsenen und ist oft resistent auf Antiepileptika. Bei Patienten mit pharmako-resistenter Temporallappenepilepsie sollte eine Abklärung durchgeführt werden, um die Möglichkeit einer Epilepsiechirurgie zu evaluieren. Dieser Artikel beschreibt die elektro-klinische Semiologie der Temporallappenepilepsie und die heutigen Fortschritte in prächirurgischer Abklärung und chirurgischen Techniken. Diese Fortschritte werden eine bessere Kontrolle der post-chirurgischen Anfälle und eine Minderung des Defizitrisikos erlauben.

Schlüsselwörter: Temporallappenepilepsie, Semiologie, Bildgebung, Chirurgie

Introduction

The prevalence of epilepsy in the general population is around 5‰ [1]. In adults, Temporal Lobe Epilepsy (TLE) represents the most frequent form of localisation related epilepsy. The most common pathology associated with TLE is hippocampal sclerosis (HS) which is associated with febrile convulsions in early childhood, in particular when the febrile convulsions are complex or prolonged [2]. Other pathologies include low-grade tumours, cavernous angioma, malformation of cortical development or gliosis following infection or trauma with a proportion of cases labelled as cryptogenic when no visible lesion can be seen on Magnetic Resonance Imaging (MRI).

TLE is frequently pharmaco-resistant which means that seizures continue to occur despite a well conducted medical treatment with at least 2 antiepileptic drugs during at least 2 years [3].

Besides disabling epileptic seizures, TLE is associated with important cognitive (memory decline), psychiatric (anxiety, depression, psychosis) and socio-professional

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comorbidities, notwithstanding the potential side effect of anti-epileptic drug treatment, ranging from mild sedation and weight gain to rare fatal allergic or toxic reactions. Therefore, epilepsy surgery must be considered in suitable candidates. This article focuses on the electro-clinical semiology of TLE and the current state and advances in presurgical diagnostic evaluation and surgical therapies to enhance seizure control while reducing the risks of deficits.

Clinical semiology

Anatomically and functionally, the temporal lobe can be divided into its mesial limbic and its neocortical basal and lateral structures. The mesial (aggregation of "medial" and "basal") structures comprise the amygdala, hippocampus and parahippocampal gyrus.

The ictal manifestations in TLE can be very variable in presentation and evolution in relation to the seizure onset zone (where the seizure starts) and the symptomatogenic zone (the cortical regions whose involvement produces the ictal symptoms and signs). Seizures are typically complex partial with secondary generalisation being more frequent with neocortical TLE but simple partial seizures can also occur. Temporal lobe seizures have more gradual onset than can develop over more than a minute and have typically longer duration of the seizure itself and the post-ictal period compared to extra-temporal lobe seizures (particularly of frontal onset). The seizures often start with an aura that can have visceral, cephalic, gustatory, olfactory, auditory components.

Seizures originating in the mesial temporal lobe characteristically start with a "limbic" aura comprising a epigastric discomfort that can be associated with autonomic features (skin colour, pulse rate, blood pressure, papillary diameter, piloerection or sudation) or perceptual manifestations such as anxiety (amygdalar involvement) and "déjà-vu", "jamais vu". "Déjà vu" refers to an impression of familiarity associated with the present context; "jamais vu" is a rarer symptom and consists in a false feeling of unfamiliarity. Olfactory or gustatory hallucinations, usually unpleasant, are uncommon and related to involvement of the entorhinal cortex or the insula respectively. Following the aura, the seizure can progress to the complex partial seizure proper with typical clouding of awareness and blank spell (motor arrest, "dialeptic seizure"). Some verbal and motor responsiveness (in the form of repetitive production) can be preserved and be wrongly interpreted as preserved awareness. Ictal speech with identifiable words suggests an involvement of the hemisphere non dominant for language. Automatic verbal and motor behaviour is common with typical oro-alimentary automatisms (lip smacking, chewing, swallowing) and more or less purposeless repetitive manual activity (unbuttoning, rubbing, etc). These automatisms are less violent than those that are sometimes encountered in frontal lobe seizures. Unilateral dystonic posturing can occur, reflecting an involvement of the basal ganglia and can help lateralising the seizure focus to the contralateral hemisphere. A typical association of ipsilateral manual automatisms and contralateral dystonic posturing is frequently encountered in temporal lobe seizures.

Conversely, seizures of lateral onset can be characterized by simple auditory hallucinations (buzzing, humming) pointing to the superior temporal gyrus or by more complex illusory symptoms suggesting the involvement of temporo-parietal association areas.

Many of the non-motor ictal clinical signs can also have lateralising value. As a general rule, neurovegetative manifestations of temporal lobe seizures such as ictal vomiting, spitting, urinary urge, tend to lateralise to the hemisphere not dominant for language (the reader is refered to the review of Loddenkemper on lateralising ictal signs for more details [4].

Temporal lobe seizures typically show a rather long post-ictal period with confusion and persistence of semi-purposeful action (deambulating, repetitive motor actions). Post-ictal dysphasia lateralizes the focus to the language dominant hemisphere and the classical post-ictal nose-wiping sign is ipsilateral to the focus in 90% of cases when present [4].

Electroencephalographic (EEG) features

Interictal EEG

The interictal EEG in TLE patients can show ipsilateral slowing, ipsilateral epileptiform discharges (spikes, spike-waves) or can be normal. The abnormalities are enhanced during sleep. To complement the usual standard EEG recording, the use of anterior temporal electrodes (T1, T2) or invasive sphenoidal electrodes can increase the sensitivity for the detection of mesial temporal epileptiform discharges [5]. Up to two thirds of standard recordings show no epileptiform activity (only focal slowing or no abnormalities). When present, the epileptiform discharges can be unilateral or bilateral [6].

Ictal EEG

Studies have attempted to identify ictal EEG patterns that could help distinguish between mesial and lateral temporal seizure onset. The typical EEG ictal onset are a 5-9 Hz rhythmic activity at the temporal electrodes or a focal suppression of background activity associated with low-voltage fast rhythms followed by a 5-9 Hz activity. Alternatively, more or less rhythmic sharp waves can be seen at ictal onset [7]. Another study suggested that a regular recruiting 5-9 Hz persisting

for longer than 5 s over the temporal electrodes was associated with mesial temporal seizure onset. On the other hand, lateral neocortical onset was characterized either by 2-5 Hz rhythms of lesser stability, possibly evolving towards 5-9 Hz activity or by absent/diffuse modifications of the EEG background [8].

As for all localisation-related epileptic seizures, the localisation of a lesion does not necessarily coincide with the seizure onset zone. In patients with HS, intracranial EEG has helped to identify subtypes of temporal lobe epilepsy with varying localisation and extent of the zone of seizure onset and propagation. These subtypes (mesial, temporo-polar, mesiolateral, lateral and temporal "plus") are associated with different clinical presentation in terms of initial symptoms, evolution and the frequency of secondary generalisation (more often in lateral subtype) [9]. The duration of the epilepsy is correlated with the extent of the epileptic network and the number of structures involved, suggesting a dynamic epileptogenic process. Moreover, in patients with TLE and HS who are candidates for epilepsy surgery, the precise understanding of the epileptic networks may help decide whether intracranial EEG is necessary, determine the best surgical strategy (selective resection vs anterior temporal lobectomy) and predict the post-operative outcome.

High frequency oscillations (HFO) recorded by intracranial EEG have also recently emerged as marker of epileptogenicity. These rhythms are separated into ripples (80-250 Hz) and fast ripples (250-500 Hz). Recent studies have shown that the latter are a robust marker of focal epileptogenicity although their detection is currently still very time-consuming [10]. Their localisation is better correlated with epileptogenic lesions than classical interictal spikes and associated with segmental hippocampal atrophy [11]. The post-operative seizure control is improved if the structures generating HFO are removed [12].

Surgical treatment of temporal lobe epilepsy

The medical treatment of temporal lobe epilepsy with anti-epileptic drugs is similar to other localisation-related epilepsies. Patient with pharmaco-resistance, frequent in this condition, should be addressed to a tertiary centre for a comprehensive diagnostic evaluation in order to decide whether they could benefit from epilepsy surgery. The only randomized control study about epilepsy surgery involved patients with unilateral pharmaco-resistant TLE (with and without HS) and showed a clearly significant benefit of surgical treatment compared to the continuation of medical treatment in terms of seizure freedom [13].

Presurgical diagnostic work-up

The presurgical evaluation should confirm unilateral seizures and absence of bilateral hippocampal dysfunction to allow for an optimal outcome regarding seizure control and cognition. The work-up includes long-term video-EEG with seizure recording, brain MRI, and neuropsychological assessment. MRI with a modern epilepsy-specific protocol to detect signs of hippocampal sclerosis or other focal lesions is highly recommended [14] since focal imaging abnormalities can be missed in up to 50% of cases by suboptimal image acquisition or non-expert neuroradiologists [15]. It is notably very important to look for the presence of dual pathology (e.g. HS and lateral temporal cortical dysplasia). The neuropsychological assessment will particularly focus on verbal and non-verbal memory function to lateralize the epileptic focus and assess the risk of post-operative memory decline.

Isotopic imaging (Positron Emission Tomography with FluoroDeoxy-Glucose or Single Photon Emission Computed Tomography) can be useful to confirm a unilateral focus, especially in non-lesional cases (**Figure 1**) [16]. EEG source imaging (ESI) and Magnetic source imaging can estimate the intracerebral activity of epileptic sources from the electrical and magnetic potentials recorded on the scalp and its temporal resolution in the range of milliseconds can distinguish between the site of onset vs propagation of the epileptic discharge (**Figure 1**) [17]. It has now been shown that ESI can reliably estimate sources in the mesial temporal lobe [18] and can robustly localise the sources in TLE with no lesion on MRI ("cryptogenic" epilepsy) [19].

New structural and functional MRI (fMRI) developments are increasingly applied to the presurgical work-up of pharmacoresistant epilepsy. Voxel-based volumetric analysis [20, 21] or diffusion MRI [22] can detect subtle lesions and simultaneous EEG-fMRI can localise the epileptic focus by mapping hemodynamic changes (fMRI) correlated to epileptic discharges on the EEG [23].

Invasive procedures that are sometimes necessary include the intra-carotid amobarbital test (Wada test) to lateralise the language-dominant hemisphere [24]. The assessement of memory function is less robust and specific injection in the anterior choroidal artery is sometime used [25].

Invasive EEG recording can be done with foramen ovale electrodes to lateralise the mesial temporal lobe responsible for seizure onset. In other situations, subdural or intracerebral depth electrodes are necessary to precisely localise the epileptogenic cortext to be removed and to map the functional cortex (language, motor, sensory, etc) to be spared.

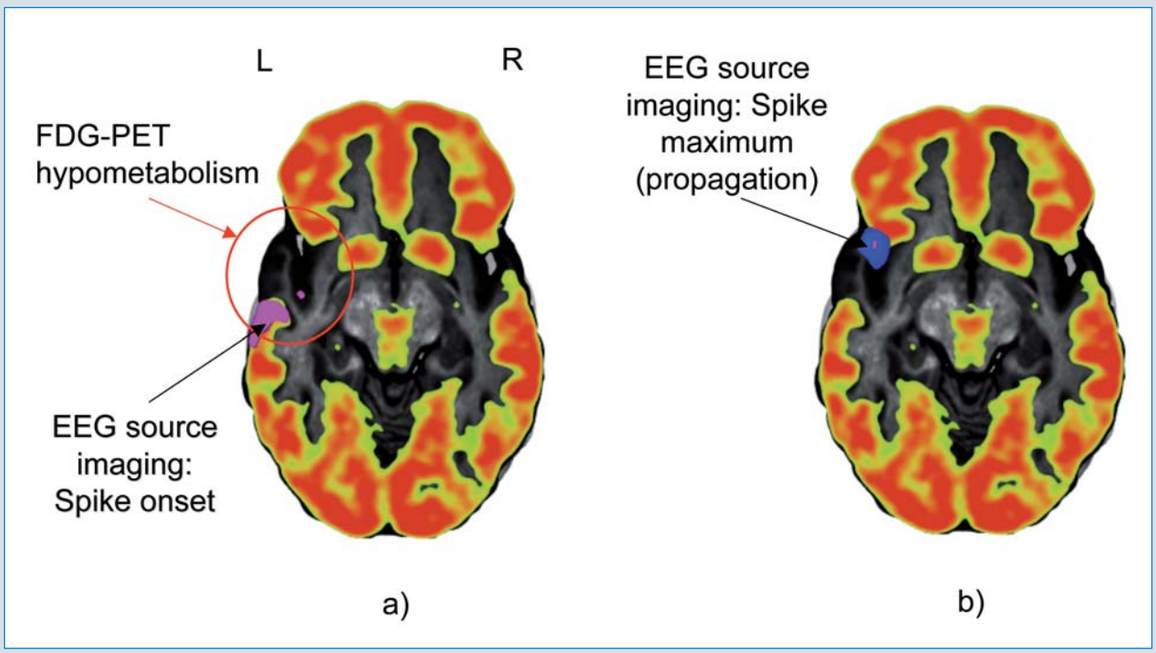

Figure 1*:
Simultaneous interictal Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) and EEG source imaging coregistered to anatomical MRI in non-lesional epilepsy.
a) FDG-PET shows anterior temporal hypometabolism (red circle) and EEG source imaging shows spike onset in the lateral temporal lobe (pink).
b) EEG source imaging showing propagation to the temporal pole and insula (blue). Same FDG-PET as in (a).
*** Courtesy of Dr. Laurent Spinelli, HUG.**

Resective surgery and outcome

The most common surgical procedure in TLE is anterior temporal lobectomy with removal of the temporal pole, the hippocampus, amygdala and parahyppocampal gyrus. More selective resection can target only the mesial temporal structures by a trans-temporal or infratemporal approach [26]. These more selective techniques seem to have a similar outcome in terms of seizure controls and potentially less risk of cognitive deficits provided of course that the temporal pole is not an important part of the epileptic network as mentionned above. In case of focal lesions, a lesionectomy can be performed or a corticectomy, the latter usually directed by intracranial EEG monitoring.

Surgical series of TLE report rates of seizure freedom between 60 and 90% [27]. Younger age at surgery (< 30 years) and shorter disease duration (< 20 years) are associated with a better seizure control [28]. Long-term studies show that seizure can recur in the long term even after a long seizure free interval. Anti-epileptic drug treatment is usually continued without modification after surgery for at least one year after which carefully monitored slow withdrawal can be proposed.

The general risk (haemorrhage, infection) of TLE surgery is around 2% and is similar to any significant neurosurgical intervention. The one-off risk of the intervention should always be compared to the cumulative increased mortality in epileptic patients, especially with poorly controlled seizures. In particular, SUDEP (Sudden Unexpected Death in Epileptic Patients) is usually associated with peri-ictal neuro-vegetative dysfunction and is estimated around 1%/year [29].

Specific risks related to TLE surgery include principally memory decline and visual field defect. Memory decline tends to be modality specific (verbal or non-verbal) depending on the hemispheric specialization [30]. The non-verbal memory decline after surgery on the hemisphere non-dominant for language is usually less marked than the verbal memory decline after surgery on the dominant hemisphere and less noticed by the patients. Post-operative global amnesia is extremely rare and all reported cases retrospectively had signs of bilateral hippocampal lesion or dysfunction [31]. Risks factors for post-operative verbal memory decline have been identified in group studies and include older age at surgery, resection in the dominant hemisphere, preserved pre-operative memory, absence of HS on MRI and absence of contralateral hippocampal reserve during the Wada test [30]. Volumetric studies can have a prognostic value [32] and recent studies suggest that fMRI with memory tasks might be a powerful predictor of post-operative memory [33].

Visual deficits after TLE affect the contralateral he-

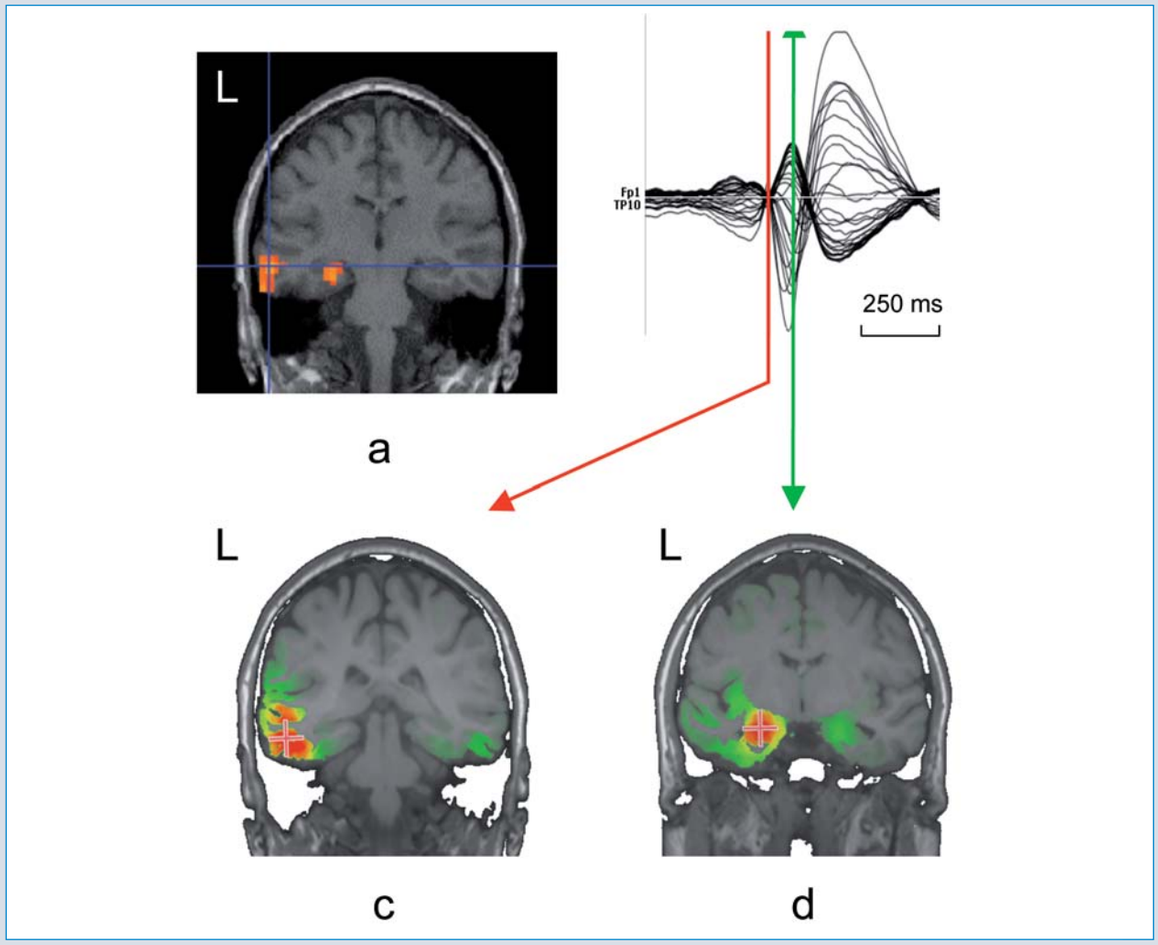

Figure 2:
Simultaneous EEG-fMRI and EEG source imaging coregistered to anatomical MRI. Non-lesional left temporal lobe epilepsy.
a) Simultaneous EEG-fMRI of interictal epileptic spikes shows spike-correlated haemodynamic changes localised in the lateral and medial left temporal lobe.
b) Average of the left temporal spikes recorded inside the MRI scanner (after correction for scanner induced artefacts)
c) EEG source imaging at spike onset shows source in the left lateral temporal lobe
d) EEG source imaging at a later time frame shows propagation of source activity to the mesial temporal lobe.

mifield or the contralateral superior quadrant (homonymous superior quadrantanopia). The former is associated with rare surgical lesions of the perforant arteries feeding the thalamus or the optic tract. The latter is more common and occurs when the anterior loop (Meyer's loop) of the optic radiatio situated in the temporal pole is included in the resection zone. The anterior extent of Meyer's loop is very variable between individual and can be individually mapped by tractography based on diffusion tensor MRI. A recent retrospective study showed that tractography could predict the presence and extent of visual deficit and appears as a useful tool to tailor surgery and estimate the risk of visual deficit [34]. This technique still requires a long postprocessing but could eventually be integrated into per-operatory neuro-navigation devices.

The development of brain imaging and electrophysiological monitoring techniques currently allow the surgeon to perform imaging-guided (neuro-navigation) and electrophysiology-guided (electrocorticography, somato-sensory and motor evoked potentials) during the procedure, improving the selectivity of surgery and minimizing the risks of post-operative deficits.

Functional surgical strategies

Some patients with pharmaco-resistant TLE are not suitable candidates for resective surgery. This is principally the case when seizures arise from both temporal lobes (which usually require confirmation with invasive EEG as unilateral seizures can propagate very fast and

be inacurately lateralised with scalp electrodes) or when surgery is estimated to produce inacceptable risks of cognitive deficits (memory resp. language for mesial resp. lateral temporal resection). Unilateral resection in the context of bilateral epileptic activity or hippocampal dysfunction carries the promise of poor seizure control and memory decline. In addition, the famous case of the patient H.M. who presented severe global amnesia after undergoing resection of bilateral mesial temporal structures in the late 50' reminds us of the unfeasability of bilateral surgical intervention in TLE [35].

For patients who cannot have surgery, deep brain stimulation is emerging as a promising therapeutical alternative. A chronically implanted electrode delivers electrical stimulation in the epileptic focus (usually the hippocampus) [36] or in other nodes of the epileptic network (e.g. the anterior nucleus of the thalamus) [37]. An increasing body of studies suggests a reduction of seizure frequency without cognitive impairment but only few cases with complete seizure freedom, while technical studies will help understand the exact underlying mechanisms and determine the optimal stimulation parameters [38].

Conclusion

TLE remains a difficult to treat form of epilepsy associated with important comorbidities. This form of localisation-related epilepsy is frequently amenable to epilepsy surgery with very good outcome and patients with pharmaco-resistant epilepsy should therefore be addressed for presurgical evaluation without delay. Recent improvement in diagnostic procedures and surgical techniques are now increasingly applied in the clinical management to improve post-operative seizure control and minimize the risk of deficit.

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