Temporal lobe surgery in patients with normal MRI

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Purpose of review

The surgical approach to nonlesional temporal lobe epilepsy presents a significant challenge due to uncertainties regarding the extent of resection necessary to result in a seizure-free state. To outline an optimum surgical strategy, an understanding of the clinical and diagnostic presentation of mesial and lateral temporal epilepsy is required in order to properly characterize the location of the ictal onset zone. This review focuses on several methods used to identify this ictal onset zone, with emphasis on the impact each modality has on surgical outcome.

Recent findings

Factors predicting an excellent surgical outcome include the presence of a discrete zone of low voltage fast activity and prolonged propagation time on the electroencephalogram, and the absence of metabolic dysfunction in the contralateral temporal lobe. Identifying epileptogenic regions in the temporal lobe using magnetic source imaging is a recent technique that has also yielded promising surgical outcomes. Recent prospective studies have shown that a temporal neocortical resection is very effective in providing a seizure free outcome given strict localization of the ictal onset zone to the lateral temporal region, highlighting the need for accurate characterization of mesial versus lateral nonlesional epilepsy.

Summary

With accurate identification of the ictal onset zone with intracranial electroencephalography, a tailored temporal resection can yield excellent surgical results.

Keywords

intracranial EEG, nonlesional, surgical outcome, temporal lobe epilepsy

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Abbreviations

^{1}H-MRS	proton magnetic resonance spectroscopy
EEG	electroencephalogram
FDG-PET	fluorodeoxyglucose positron emission tomography
MEG	magnetoencephalography
MSI	magnetic source imaging
MTLE	mesial temporal lobe epilepsy
NTLE	neocortical temporal lobe epilepsy
TLE	temporal lobe epilepsy

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Introduction

The surgical approach to nonlesional temporal lobe epilepsy (TLE) presents a significant challenge due to the lack of a specific target for resection, the uncertainty in the involvement of mesial or lateral (neocortical) temporal lobe, or a combination of temporal structures in the generation of seizures. Even with the presence of a discernible lesion on MRI, neocortical temporal lobe epilepsy (NTLE) has yielded less favorable surgical outcomes than the historically better characterized mesial temporal lobe epilepsy (MTLE), which has consistently had high rates of seizure freedom (70–90%) following standard anterior temporal lobe resection [1]. This is likely due to the rapid and diffuse nature of ictal spread of seizures originating from the lateral temporal neocortex, the majority of which is spared with a standard temporal lobe resection. The presence of eloquent regions in the dominant temporal neocortex is also another factor in limiting the extent of resection in this patient population. Lastly, in the absence of a structural lesion, it is a difficult task to outline the contributions of mesial and lateral temporal sources to the initiation of the ictal discharge, creating a difficult task when attempting to isolate the optimum region for resection.

An effective surgical strategy to nonlesional TLE is dependent on an in-depth understanding of the semiologic, metabolic, and electrographic characteristics of TLE, with an emphasis on the differentiating characteristics of MTLE and NTLE. These factors can guide placement of intracranial electrodes in the absence of a lesion, with the goal of localizing the electrographic onset zone, which can provide a target for a more extensive and tailored lateral temporal resection. This approach has yielded good outcomes, with 60–70% of patients with NTLE undergoing tailored resections guided by intracranial electroencephalogram (EEG) experiencing seizure freedom, and over 90% achieving marked reductions in their seizure frequencies [1,2]. This review will outline the specific clinical features of MTLE and NTLE and their relationships to surgical outcome, with the objective of effectively characterizing TLE when there is not a lesion available to guide the surgical approach.

Clinical features

Due to the extensive interconnections between the lateral neocortex and the mesial structures of the temporal lobe, it is difficult to outline a consistent set of distinguishing factors between MTLE and NTLE. Pfander *et al.* [3] found a significantly increased presence of contralateral hand dystonia and abdominal auras in MTLE, as opposed to the presence of nonspecific sensory auras and early clonic activity following automatisms in NTLE. In the series by Pacia *et al.* [4], over 70% of patients with NTLE had auras, the majority of which were associated with mesial temporal and insular activation. Auditory and vertiginous auras, which are classically considered of lateral temporal origin, occurred rarely. These findings are consistent with other investigators [5], and likely indicate dual activation of neocortical and mesial structures, in which neocortical activation is necessary for the visceral sensations commonly localized to the mesial temporal region to be consciously experienced [6]. In the same series by Pacia, the majority of nonlesional NTLE patients also experienced a more frequent combination of contralateral or bilateral automatisms, which is in contrast with the ipsilateral automatisms seen with MTLE.

Patients with MTLE also appear to have a clear lateralizing neuropsychological profile. Burgerman *et al.* [1] reported that with the Intracarotid Amobarbital Test (Wada test), MTLE patients were significantly more likely to have a lateralized memory impairment on neuropsychological testing than those with NTLE. Pacia *et al.* [4] also found a trend towards better memory function in the hemisphere of seizure onset in NTLE. Half of the NTLE patients in the study suffered from a significant impairment of memory function on the Wada test, leading to the assumption that there was combined variable dysfunction of both lateral and mesial temporal structures.

Electrophysiology

The scalp EEG is surprisingly reliable for temporal lobe localization when compared to the other nonlesional extratemporal epilepsies [7]. Interictally, Ebersole and Wade [8] characterized two types of spikes originating from the temporal lobe: type 1 spikes, generated mainly by the basal and inferolateral temporal cortex, originated in the inferior temporal leads. Alternatively, type 2 spikes were thought to originate from the lateral temporal cortex and propogated in an anterior–posterior direction along the lateral convexity. Although this classification scheme has been demonstrated as overtly rigid, the presence of well localized unilateral temporal spikes in the anterior temporal region has been associated with improved surgical outcomes, with worse outcomes for extratemporal spread of spikes [9]. These well defined anterior tempo ral spikes were highly correlated with mesial temporal sclerosis [10]. The temporal lobe epilepsies present in a similar fashion on ictal scalp EEG, however, with rhythmic θ activity in the temporal derivations seen most frequently in both NTLE and MTLE [11,12]. Rhythmic θ discharges have also been seen in extratemporal seizures [13], thereby making a characterization of temporal epilepsy based on scalp EEG alone an extremely difficult task, particularly in the setting of a nonlesional MRI.

The intracranial EEG can be of particular aid in the absence of a defined MRI lesion. This is a clinically important tool, as this can guide the extent of the surgical resection. Pacia and Ebersole [14] described the ictal characteristics of MTLE, starting with periodic spiking activity in the hippocampus followed by paroxysmal high voltage ictal rhythm, which is correlated to neuronal loss in the CA1 hippocampal region [15]. This can last several seconds and up to a minute, followed by the development of a regular 5–9 Hz ictal rhythm, which can also be seen in the anterior temporal region on scalp EEG. Alternatively, Jung *et al.* [2] described NTLE ictal onsets, which display highly variable features, but most commonly present with a low voltage, high frequency discharge, often associated with a widespread electrodecremental response. Rhythmic lower frequency sharp waves (<5 Hz) were also shown to be highly specific for a neocortical origin. The association of MTLE with faster ictal frequencies was corroborated by Spencer *et al.* [16], who demonstrated that subdural and depth electrode ictal recordings in MTLE were significantly more likely to be higher frequency (>13 Hz) than NTLE recordings. In the same study, periodic spiking activity was also seen with MTLE seizure onset.

Jung *et al.* [2] confirmed prior studies [1,4] that indicated that patients with NTLE had the potential of having excellent surgical results [17], with a 66.7% seizure free rate and 96.7% Engel Class I or II outcomes, after intracranial EEG characterization of the ictal onset zone and a tailored temporal neocorticectomy in addition to a standard temporal lobe resection. Combined with the above characterization of NTLE versus MTLE, there are other features of the intracranial EEG that appear to correlate with surgical outcome. Faught *et al.* [18] demonstrated an association with improved surgical outcomes and the presence of low voltage fast ictal activity localized to one temporal gyrus on intracranial strip electrodes. In cases of MTLE, Spencer *et al.* [15] showed association of excellent outcome with low voltage fast activity in the entorhinal cortex or hippocampus. Kutsy *et al.* [19] showed the localization of the ictal discharge to the anterior temporal region was strongly suggestive of excellent outcome, and that rapid spread of the ictal discharge to the contralateral hemisphere predicted poorer surgical results. This was demonstrated earlier by Lieb *et al.* [20], who found that an interhemispheric propagation time of less than 5 s was associated with poor outcome, with excellent outcomes noted in patients with propagation times longer than 50 s. Other investigators have also characterized the phenomenon of longer interhemispheric propagation times being associated with improved seizure outcome [21].

Functional and metabolic imaging

In a prospective study of 33 patients with nonlesional epilepsy with scalp EEG evidence of temporal lobe onset, Lee *et al.* [13] examined fluorodeoxyglucose positron emission tomography (FDG-PET), and subtraction ictal single photon emission computed tomography (SPECT) studies on each patient and compared these results with intracranial EEG ictal onsets. Both modalities were found to have a 73% localizing accuracy, with far less success seen in localizing extratemporal ictal onset zones. The reliability of FDG-PET in revealing temporal lobe hypometabolism in nonlesional NTLE has been reported in the range of 60–70% in patients with refractory seizures and a normal MRI [22,23].

Proton magnetic resonance spectroscopy (^{1}H-MRS) has also been examined in nonlesional NTLE to define regions of metabolic dysfunction. Shih *et al.* [24] examined a series of 20 subjects with nonlesional NTLE by ^{1}H-MRS on source areas of interictal spiking as defined by magnetoencephalography (MEG). Fifteen out of the 20 subjects showed a significant decrease in the N-acetyl aspartate to choline containing compound ratio (NAA/Cho) in the MEG spike zone when compared to the contralateral homologous region, indicating metabolic dysfunction in discrete cortical areas of spiking. This result was corroborated by an earlier study by Connelly *et al.* [25]. All subjects with concordant MEG/^{1}H-MRS data who underwent resective surgery had excellent seizure outcomes (Engel I/II). In addition, one of two patients with discordant MEG/^{1}H-MRS data had a good seizure outcome. The association of poor surgical outcomes with ^{1}H-MRS metabolic dysfunction in the contralateral temporal lobe has been demonstrated in patients with MTLE [26], and could serve as an indicator of outcome in nonlesional NTLE as well.

Magnetic source imaging

Magnetic source imaging (MSI) using MEG is a modality that has been recently used for the electrographic characterization of different types of epilepsies. MSI has been particularly helpful in the case of nonlesional TLE, with the association of particular locations and orientations of dipoles with mesial or lateral localization on intracranial EEG [27–29]. Surgical outcomes have also been correlated with dipoles characterized by MSI. Assaf *et al.* [30] examined a series of 26 patients with TLE using MSI, and compared results to intracranial EEG and surgical outcome. Twenty-three patients in the study demonstrated an anterior temporal dipole (with variable orientations); five of these patients had a mesial ictal onset on invasive EEG. All 23 patients were seizure-free following a standard anterior temporal lobectomy. The three remaining patients had lateral temporal dipoles in a vertical orientation, with invasive EEG demonstrating a lateral temporal source. These three patients were rendered seizure-free following neocortical resections with sparing of the mesial structures. These findings were corroborated by Iwasaki *et al.* [31], with all patients demonstrating anterior temporal dipoles having seizure-free surgical outcomes following anterior temporal lobectomy, and patients having nonanterior temporal dipoles having either residual seizures or spike activity. Based on these findings, it was recommended that patients with a nonanterior temporal dipole have an extensive intracranial EEG evaluation prior to surgery, due to the likely localization of these dipoles to the lateral temporal or extratemporal neocortex.

Surgical approaches

Previous investigations have demonstrated poor surgical outcomes in nonlesional NTLE patients following standard anterior temporal lobectomy or selective amygdalohippocampectomy [32,33]. This is likely due to the lateral temporal origin of the ictal discharges, which can spread in a rapid fashion though the temporal neocortex, as well as the mesial temporal structures. This 'dual pathology' was described by Weiser *et al.* [34], who showed that the rapid electrographic spread of a neocortical ictal discharge can easily spread mesially, and vice versa. These neocortical regions are not resected with a standard temporal lobectomy, which usually involves resection of the amygdala, hippocampus, and parahippocampal gyrus, with a resection line extending from 3–3.5 cm from the superior to inferior temporal gyrus [35]. These resections are likely to spare a significant amount of the posterior and superior lateral temporal lobe, which may be involved in either initiation or propagation of the ictal discharge. An additional factor in limiting the extent of the resection is the likelihood of a large portion of the lateral temporal cortex being eloquent cortex, and that potential wide resections could damage memory, visuospatial or linguistic functions [36,37]. Therefore, the widely accepted surgical strategy in nonlesional NTLE has involved anterior temporal lobectomy with a tailored resection of the lateral temporal neocortex, and possible multiple subpial transections, with antecedent functional cortical mapping to elucidate eloquent cortex. As mentioned above, several centers have described excellent surgical outcomes with this approach, with Engel Class I outcomes ranging from 54 to 80% [1,2,38–40].

In cases without electrographic involvement of the mesial temporal structures, it is also possible to perform an exclusively lateral temporal resection. Schramm *et al.* [41] investigated a series of patients with exclusive NTLE without mesial involvement, the majority of which were lesional cases. Using intracranial depth and grid electrode data to ensure strict electrographic localization to the lateral temporal lobe, a combination of corticetomy/lesionectomy or lobectomy was performed. Resection margins of the lobectomy extended 4.5 to 5.5 cm from the superior to inferior temporal gyrus in the nondominant hemisphere, and 4.5 cm in the dominant hemisphere, with sparing of the mesial structures. Functional mapping was not used to guide resections in this series. Outcomes were excellent in this series, with 79% of patients achieving Engel class I outcomes at a mean follow-up time of 21.9 months, with 90% of patients experiencing significant improvement in seizure status. Although the majority of the cases in this series were lesional, it does indicate the potential for good surgical outcomes in NTLE without mesial involvement. Additionally, the sparing of mesial temporal structures has demonstrated less postoperative impairment of verbal and visual memory [42].

Conclusion

The clinical features of nonlesional TLE can be highly variable due to the dense connectivity of mesial and lateral temporal lobe structures, making anatomic localization based on clinical findings alone very difficult. Mesial TLE, however, appears to be more commonly associated with the 'classical' features of TLE, including visceral auras and contralateral upper extremity dystonias. In the setting of NTLE, presentations of auras, dystonia, and automatisms can be extremely diverse, but can mimic the clinical features of mesial TLE.

Although scalp EEG can often be unreliable in differentiating MTLE from NTLE, especially during ictal onset, the presence of well defined spikes originating from the anterior temporal derivations can point to a mesial temporal source. The increased sensitivity of the intracranial EEG is usually necessary to characterize the ictal onsets, especially in the absence of a lesion. Intracranial EEG features that are predictive of excellent seizure outcome included a discrete zone of low voltage fast activity (particularly in the anterior temporal region) and prolonged propagation time to the contralateral hemisphere.

The interictal and ictal scalp EEG data can be helpful for planning optimum placement of intracranial electrodes, and can be augmented by the utilization of FDG-PET and ictal SPECT studies, which can reliably highlight metabolic and perfusion abnormalities in the temporal lobes. ^{1}H-MRS can determine metabolic abnormalities in small regions of temporal neocortex, which can be utilized when planning placement of smaller intracranial grid electrodes or strip electrodes. ^{1}H-MRS can also point out metabolic abnormalities in the contralateral temporal lobe, which can provide valuable information about surgical outcome following temporal lobectomy, especially in nonlesional cases. MSI is a relatively recent technique that has been shown to be extremely reliable in the characterization of a mesial versus lateral temporal ictal source, and has been associated with reliable surgical outcome data.

An understanding of the clinical, electrophysiologic, and metabolic features of both MTLE and NTLE can provide clues for the best placement of intracranial electrodes for monitoring in nonlesional TLE. Following electrographic characterization of the ictal onset zone and functional cortical mapping, combinations of surgical strategies, including standard temporal lobectomy, lateral lobectomy, focal corticetomies, and mutiple subpial transections, have been shown to provide improved surgical outcomes with sparing of eloquent cortex.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 226).

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