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Mesial Temporal Lobe Epilepsy: A Distinct Electroclinical Subtype of Temporal Lobe Epilepsy

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ABSTRACT. *Mesial temporal lobe epilepsy is a common subtype of temporal lobe epilepsy. Its most common cause is hippocampal sclerosis, which contributes to its distinct electroclinical phenotype that is seen commonly in the epilepsy monitoring unit setting. The common electrophysiological data show anterior temporal interictal sharp waves as well as rhythmic theta activity in the same localization. While the electrophysiological data can at times be misleading, its stereotyped and characteristic semiology can often allow for accurate diagnosis on its own. As patients with mesial temporal lobe epilepsy often fail medical therapy, surgical therapy can be considered. Early accurate diagnosis in these patients is essential for optimal care.*

KEY WORDS. Abdominal aura, automotor seizures, EEG, epilepsy, hippocampus, mesial temporal lobe, semiology.

INTRODUCTION

Epilepsy is a common neurological diagnosis, affecting 70 million people worldwide (Brodie et al. 2012). However, the diagnosis of epilepsy is a heterogeneous group consisting of multiple types of both generalized and focal epilepsy. It is vital to correctly classify the epilepsy diagnosis, as the etiology of the epilepsy diagnosis can impact prognosis (Wiebe and Jette 2012). By obtaining a precise history, most pertinently a detailed analysis of the seizure semiology, one can often correctly classify the type of epilepsy nearly 50% of the time. If the history remains unclear, video review of an ictal event in an epilepsy monitoring unit (EMU) can provide a
significant amount of information. If the diagnosis is still uncertain, electroencephalo­
graphy (EEG) can further increase the correct classification of diagnosis to nearly
80%.

Of all the focal epilepsies, temporal lobe epilepsy is the most common localization
(King et al. 1998). Temporal lobe epilepsy comprises a vast array of clinical
syndromes, but one specific type, mesial temporal lobe epilepsy (MTLE), remains
the single most common indication for epilepsy surgery (Berg 2008). The specific
electrophysiological, pathological, and clinical signatures of mesial temporal lobe
epilepsy will now be further reviewed.

NATURAL HISTORY

Mesial temporal lobe epilepsy has been linked to hippocampal dysfunction (Tatum
2012). Hippocampal sclerosis is a pathological finding of atrophy and gliosis of the
hippocampus and has been linked as both a cause of epilepsy as well as the result of
ongoing uncontrolled seizures (Theodore et al. 1999). There is evidence that febrile
status epilepticus causes acute hippocampal injury as demonstrated by magnetic
resonance imaging (Shinnar et al. 2012). Moreover, epidemiological data demon­
strate the risk of developing epilepsy in people with prior febrile seizures is 10 times
greater as compared to the general population (Neligan et al. 2012). MTLE has an
onset at three different ages: 5, 15, and 26, with subsequent studies indicating that
a later age of onset was found to be a good prognostic indicator for good seizure
outcome (Janszky et al. 2004, Aguglia et al. 2011). It generally takes around nine
years for a MTLE patient to become medically refractory (Berg 2008). Therefore,
early recognition of MTLE is important, as a randomized trial supports early surgical
intervention for those medically refractory patients (Engel et al. 2012).

NEUROANATOMY AND PERTINENT PATHOLOGY

The mesial temporal lobe (MTL) comprises the hippocampus, parahippocampus
(entorhinal and perihinal cortex), amygdala, and dentate gyrus (Wen et al. 1999). The
generic pathological cause of epilepsy in MTLE patients is mesial temporal sclero­
sis; a combination of gliosis and atrophy of all these structures. The most important
area within the MTL is the hippocampus. Therefore, hippocampal sclerosis, the glio­
sis and atrophy of the hippocampus, is the single most common pathology seen in
epilepsy surgery series with a distinct magnetic resonance imaging (MRI) signature,
although it can be normal appearing on MRI 30% to 40% of the time. The hippocam­
pus is divided into layers of the Cornu Ammonis (CA1 to CA4). These CA layers are
further surrounded by the dentate gyrus, which connects via the parahippocampus to
a mixture of temporal and extratemporal cortical association areas (Tatum 2012).
There are several important fascicles connecting the mesial temporal region to other brain areas. These include the connection between the two temporal lobes called the intertemporal portion of the anterior commissure, the connection between the two hippocampi called hippocampal commissure or fornix, the connection between the ipsilateral frontal and temporal lobes called the uncinate fascicle, and lastly diffuse associative fibers (Sindou and Guenot 2003). These connections are what allow seizures that begin in the mesial temporal lobe to spread throughout the brain during secondary generalization.

**CLINICAL FEATURES**

The average MTLE patient presents in the fourth decade of life and has likely failed numerous antiepileptic medications. A history of febrile seizures is common, occurring in about one-third of MTLE patients (Berg 2008). However, when discussing clinical features of MTLE, we are mainly discussing semiology. Semiology is a very important tool in the diagnosis of epilepsy. There are two dominant features of MTLE semiology: the abdominal aura and automotor seizures (Lüders 2008, Blair 2012, Tatum 2012). Some type of aura occurs in 96% of MTLE patients, with abdominal auras being the most frequent (French et al. 1993). Abdominal auras are characterized by a sense of nausea or discomfort in the abdominal area. Sometimes this sensation will rise up into the throat (Lüders 2008). The abdominal aura has excellent localizing value to the mesial temporal region, especially when followed by automotor seizures (Henkel et al. 2002). Other common types of aura include the sense of fear, abnormal olfactory hallucinations, or the feeling of déjà vu (French et al. 1993). Fear in particular is an excellent indicator of MTLE (Maillard et al. 2004). Often times the abdominal aura will lead to the automotor seizure. The semiology of an automotor seizure is defined by stereotyped motor movements such as chewing (as seen in oral automatisms) or repetitive, seemingly purposeful hand movements (such as pill rolling movements or manipulating buttons on a shirt). Consciousness is nearly always affected, although if affecting the non-dominant hemisphere, an unimpaired state of consciousness can be seen clinically (Lüders 2008).

Patients with untreated MTLE (electively done in an epilepsy monitoring unit setting when antiepileptic medications are withdrawn) will often have secondary generalization of the seizures. Careful analysis of the semiology during this phase of the seizure can yield additional localizing and lateralizing information. Dystonic posturing is sustained, forceful unnatural posturing of a limb that reliably lateralizes to the contralateral hemisphere (Bleasel et al. 1997). Similarly, a versive seizure is defined as sustained, unnatural turning of the head and body towards one side. This typically occurs just prior to secondary generalization in MTLE and reliably lateralizes to the contralateral side (Chee et al. 1993). The presence or absence of speech is
important. If speech occurs during the seizure, the seizure focus lateralizes to the nondominant hemisphere (most often the right hemisphere) (Yen et al. 1996). Conversely, postictal aphasia or dysphasia points to involvement of the dominant hemisphere (most often the left hemisphere) (Gabr et al. 1989). The last clonic movement, if unilateral, as well as a unilateral postictal nose wipe lateralizes to the hemisphere ipsilateral to the moving limb (Chee et al. 1993, Hirsch et al. 1998).

The actual tonic and clonic phases often do not add much to the localizing or lateralizing of the seizure focus. However, when the tonic phase occurs asymmetrically and the arms make a sign of 4, this is a localizing sign to the hemisphere contralateral to the extended arm. The “sign of 4” occurs when one arm extends and the other arm is flexed creating a 4 with the arms. In fact, this sign of 4 is often part of the typical motor sequence of a temporal lobe seizure. It begins with the above mentioned automatisms and then evolves into the versive seizure, subsequent asymmetric tonic posturing with sign of 4, followed by the onset of the clonic phase of seizure (Tufenkjian and Lüders 2012).

**ELECTROPHYSIOLOGY**

Mesial temporal lobe epilepsy has both a typical scalp and intracranial electrophysiological signature. To begin, it is important to remember what an epileptiform discharge represents from an electrophysiological perspective. A sharp wave or spike occurs when a large number of neurons’ postsynaptic potentials fire in a synchronous manner that disrupts normal brain activity (Tatum 2012).

**Scalp Interictal EEG**

Typical interictal findings are seen in 96% of patients (Williamson et al. 1993) and consist of spikes or sharp waves that localize to the anterior temporal region (F7/F8) in the International 10–20 System of electrode placement (Figure 1). The F7/F8 electrodes are more anterior than one might expect given the typical hippocampal etiology of MTLE. Therefore, these epileptiform waves most likely represent activation of the parahippocampal tissue (Lüders 2008). Along these lines, true hippocampal epileptiform activity is not seen on scalp EEG due to its small area of activation as intracranial EEG has indicated that approximately 10 cm of cortex is required to generate scalp interictal discharges (Tao et al. 2005).

Placement of basal temporal electrodes (i.e., sphenoidal or FT9/FT10 electrodes) can provide additional localizing information that is useful in both scalp EEG (Figure 2) as well as more advanced modalities such as electrical source imaging (ESI) (Cherian et al. 2012). This is especially true in MTLE with bitemporal epileptiform discharges. Bilateral scalp epileptiform discharges are not uncommon, being
noted in around 40% of the patients (Williamson et al. 1993). However, bitemporal intracranial EEG can often localize the seizure onset zone to just one temporal lobe, making resective therapy a viable therapeutic option (Henry et al. 1999). Sphenoidal electrodes can also increase the accuracy of electrical source imaging (Hamaneh et al. 2011). However, it is important to note that if ESI is to be done, analysis of individual spikes seems to be unreliable, but averaging eight or more spikes can produce more reliable results that localize to within 1 cm of the intracranial generator (Wennberg and Cheyne 2014).

**Scalp and Intracranial Ictal EEG**

There are three well described ictal patterns in MTLE. Ictal patterns are not typically seen at clinical onset due to the small area (the hippocampus) involved in the seizure onset zone of MTLE (Lüders 2008). The first and most typical scalp ictal pattern consists of a progressive build-up of sinusoidal theta/alpha activity in the temporal (F7/F8) or subtemporal (FT9/FT10) electrodes (Figure 3). When this rhythmic theta activity is evident within 30 seconds of clinical onset, the pattern was found
to be highly correlated with mesial temporal seizure onset, specifically the hippocampus (Risinger et al. 1989, Ebersole and Pacia 1996, Pacia and Ebersole 1997). Intracranial EEG (iEEG) shows a typical pattern of pre-ictal hippocampal spiking followed by an electrodecremental response before giving way to more sinusoidal 12 to 20 Hz rhythms (Pacia and Ebersole 1997) (Figure 4).

The second ictal pattern for MTLE is characterized by irregular 2 to 5 Hz activity that lateralizes well to the affected hemisphere, but is not typically localizing to a specific electrode (Figure 5). Sometimes this activity will eventually evolve into the more typical sinusoidal alpha/theta activity noted above. While occasionally associated with hippocampal onset on iEEG, this ictal pattern was more often noted with temporal neocortical onset (Ebersole and Pacia 1996, Pacia and Ebersole 1997). The third type of ictal onset is when there is no identifiable ictal activity. Rather, there is diffuse, irregular slowing (Figure 6). Again, this third type was occasionally associated with hippocampal onset on iEEG, but more often was seen in temporal neocortical onset (Ebersole and Pacia 1996, Pacia and Ebersole 1997).

In many cases, careful consideration of the above clinical and electrophysiological factors will remove the need for iEEG recording. However, if an incomplete answer
FIG. 3. Type 1 temporal lobe seizure pattern typically associated with mesial temporal lobe epilepsy (MTLE). Note the rhythmic theta maximal at FT9.

FIG. 4. Ictal pattern seen emanating from the left hippocampus on intracranial EEG (iEEG). LH – left hippocampal head; LB – left hippocampal body.
is found from this evaluation, iEEG is vital for determining the seizure onset zone, with the realization of the inherent sampling bias of iEEG. Therefore, one should expect to see iEEG onset before clinical onset if in the seizure onset zone. Indeed, when the iEEG onset precedes the clinical onset by >10 seconds, the probability of postsurgical seizure freedom is increased (Weinand et al. 2001). Both depth electrodes and grid/strip electrodes have been used to good effect in iEEG monitoring.
Intracranial Interictal EEG

Sharp waves or spikes are readily identifiable on iEEG and have similar morphological characteristics as seen on scalp EEG (Figure 7). It is important to remember that the number of epileptiform discharges may be significantly increased on iEEG. This is explained by the fact that in order to see activity on the scalp EEG, approximately 10 cm of synchronous neuronal activity is needed. While spikes and sharp waves are also readily identifiable on intracranial EEG, the ability to record faster frequencies than the 1 to 35 Hz seen with scalp EEG offers a unique opportunity for other interictal activity. This activity is termed high frequency oscillations (HFOs) (Jacobs et al. 2012) (Figure 8). There are two types of HFOs: ripples (80 to 200 Hz) and fast ripples (>250 Hz) (Engel et al. 2009). High frequency oscillations were actually first discovered in hippocampal cells as ripples. Ripples are a normal electrophysiological finding and are thought to represent the process of consolidating plasticity and episodic memory (Le Van Quyen et al. 2008). Conversely, fast ripples appear to be uniquely associated with the epileptogenic zone and correlate with hippocampal atrophy. They are thought to represent the synchrony of abnormally firing neurons (Engel et al. 2009, Bragin et al. 2010). HFOs have been shown to occur in the seizure onset zone and not within areas of seizure propagation and are thus thought to possibly be a biomarker of epileptogenicity (Jacobs et al. 2009, Salami et al. 2014). Perhaps more importantly, the resection of tissue containing HFOs has been correlated with better surgical outcomes (Jacobs et al. 2010).

FIG. 7. Intracranial (iEEG) interictal discharge. Note the accompanying Sp2 sharp wave with diffuse cerebral activation. The second discharge approximately one second later that is more focal in distribution does not have a scalp correlate.
(Fast Ripples visible in spike)

FIG. 8. High frequency oscillations (HFOs) as seen with different EEG parameters. Note the change in waveform morphology as slower frequencies are filtered out. Figure adapted from Jacobs et al. 2012 with permission from Elsevier.
**Pseudotemporal Patterns and Benign Variants**

The other difficulty seen in the electrographic diagnosis of MTLE is pseudotemporal ictal rhythms. These are EEG seizure patterns that have typical rhythmic theta in the temporal regions as in MTLE, but actually represent spread from a distant epileptogenic site that may not be well localized on EEG. One study reported that 11% of patients with an extratemporal MRI lesion had ictal temporal seizure patterns (Rémi et al. 2011). Pseudotemporal ictal patterns have been reported for nearly all anatomic localizations (i.e., orbitofrontal lobe, parietal lobe, occipital lobe, etc.). Additionally, many different developmental abnormalities including nodular heterotopias and hypothalamic hamartomas can cause ictal temporal seizure patterns. Unfortunately, there does not appear to be a morphological difference between true temporal ictal rhythms and pseudotemporal rhythms (Elwan et al. 2013). Therefore, it is imperative to always match a patient’s clinical semiology with the EEG pattern for the most accurate localization of the epileptogenic zone.

Benign variants can be confused for epileptiform discharges and lead to an inappropriate diagnosis of epilepsy. They occur in approximately 3.4% of individuals (Santoshkumar et al. 2009). These waveforms can either be isolated, as seen in benign sporadic sleep spikes or wicket spikes. They can also occur in prolonged runs, as seen in 14 and 6 Hz positive waves, rhythmic temporal theta of drowsiness, or subclinical rhythmic electrographic discharges (Klass and Westmoreland 1985, Santoshkumar et al. 2009) (Figure 9). Awareness of these different waveforms can minimize the possibility of an inappropriate diagnosis of epilepsy.

**TREATMENT AND OUTCOMES**

In general, around 68% of epilepsy patients will achieve seizure freedom with medical treatment alone (Brodie et al. 2012). However, patients with hippocampal sclerosis have a markedly lower rate of seizure freedom (11 to 42%) with medical treatment alone (Tatum 2012). A randomized controlled trial of early surgical therapy in patients with medically refractory MTLE showed a seizure freedom rate of around 60% (Engel et al. 2012). While surgery remains the cornerstone for treatment of medically refractory epilepsy, it is important to note that some seemingly medically refractory patients may in fact go into seizure remission following introduction of a new antiepileptic drug, all the more relevant as the number of seizure medications available to clinicians increase (Luciano and Shorvon 2007). However, this observation is intriguingly contested by recent studies demonstrating that remission in a medically refractory patient after change to a new antiepileptic drug may actually be the result of the spontaneous and/or periodic remissions seen in the natural course of epilepsy (Wiebe and Jette 2012, Wang et al. 2013).
FIG. 9. Examples of various benign variants: A) benign sporadic sleep spikes, B) left temporal wicket waves, C) 14 and 6 Hz positive spikes, D) six hertz spike-waves, E) rhythmic temporal theta burst of drowsiness, and F) subclinical rhythmic electrographic discharge of adults (SREDA). Reprinted with permission from Elsevier from Santoshukumar et al. 2009.
CONCLUSIONS

In conclusion, MTLE is a very specific subtype of temporal lobe epilepsy with distinct clinical and electrophysiological characteristics. Hippocampal sclerosis is the most common pathological cause of MTLE noted in surgical series and helps to explain the semiology seen. Characteristic semiological signs such as the abdominal aura or automotor seizures remain vital clues to a mesial temporal epileptogenic zone. When these signs are accompanied by the typical ictal 5 to 9 Hz rhythmic activity in the temporal leads, one can be fairly comfortable with the diagnosis of mesial temporal lobe epilepsy. In the end, while some MTLE patients will respond to medical therapy alone, surgical therapy does represent a viable treatment strategy for those patients who do not. The accurate diagnosis and localization of the MTLE epileptogenic zone is essential so that patients may be provided with optimal information when counseling them on their disease.

REFERENCES


