A Comprehensive Review of Temporal Lobe Epilepsy

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1 Introduction

Epilepsy consists of more than 40 clinical syndromes affecting 50 million people worldwide. Approximately 30% of patients receiving medications have inadequate seizure control (Jacobs et al., 2001). The International League Against Epilepsy (ILAE) defines epilepsy as “a condition characterized by two or more recurrent epileptic seizures over a period longer than 24 hours, unprovoked by any immediate identified cause”. The term Temporal lobe epilepsy (TLE) was included in the classification of the ILAE in 1989 under the group of “localization-related symptomatic epilepsies characterized by seizures with specific modes of precipitation” (Commission on classification and terminology of the ILAE, 1989).

The temporal lobe is the most epileptogenic region of the human brain. Hippocampal sclerosis (HS) is the commonest cause of TLE. Therefore, mesial TLE (mTLE) is perhaps the best-characterized electro-clinical syndrome of all the epilepsies (Tatum, 2012). It is estimated that it represents about 40% of all epilepsies in adult people. It can be sporadic, commonly with a positive family history, or it can present with clear familial recurrence (Cendes, 2005). The common clinical pattern during the seizure episode includes staring and lack of responsiveness, frequently accompanied by mouth or hand automatisms. They represent approximately two thirds of the intractable seizure population requiring surgical management (Blair, 2012).

1.1 Epidemiology

There are few epidemiological studies in TLE. The majority of the studies have been generated in referral centers providing different estimates. Hauser and Kurland (Hauser & Kurland, 1975) provided the best available epidemiological data on TLE, the incidence rate was 10.4 per 100,000 and the prevalence was 1.7 per 1000 people. Few population-based studies have been published; in 1992 a study based on community physician’s records reported that the frequency of TLE is only 21% within the focal epilepsy cases (Manford et al., 1992). Other estimates regarding the prevalence of epilepsy have been obtained from tertiary referral centers; approximately 60-80% of patients with partial epilepsy have TLE (Oun et al., 2003). In epilepsy centers the TLE prevalence usually is 60-70% (Spencer & Spencer, 1985; Semah et al., 1998). The higher rates of TLE observed in epilepsy centers are probably related with its intractability. In general, patients with TLE have a better surgical outcome and a have a lower risk of neurological deficits related to excision of functional cortex compared to extratemporal lobe epilepsy (ETLE) cases. Because of this reason, neurologists and family practitioners more frequently refer patients with TLE for surgical assessment (Téllez-Zenteno & Hernandez-Ronquillo, 2012).

2 Etiology and Physiopathology

TLE could be sporadic or familial. TLE can be associated with a magnetic resonance imaging (MRI) lesion or be non-lesional (Téllez-Zenteno et al., 2010). The main causes of lesional TLE are HS, benign tumors, vascular malformations, cortical development malformations, and post-traumatic or post-infectious gliosis (Cendes, 2005). The most common low-grade tumors are gangliogliomas, low-grade gliomas, and dysembryoplastic neuroepithelial tumors (Woermann & Vollmar, 2009).
2.1 Neuropathology

HS is the most common cause of TLE, representing greater than 80% of cases (Tatum, 2012). It is a combination of atrophy and astrogliosis of the amygdala, hippocampus, uncus, parahippocampal gyrus, and the entorhinal cortex (Tatum, 2012). It implies selective neuronal loss that affects various sectors to a different degree. The most vulnerable to damage are the sector CA1 (Sommer’s sector) and CA3-CA4 (endfolium), whereas CA2 pyramidal and dentate gyrus granule cells are most seizure resistant (Cendes, 2005; Cendes, 2004). The majority of hippocampal specimens also reveal alterations within the dentate gyrus, i.e., granule cell dispersion. Granule cell dispersion may be associated with early seizure onset or status epilepticus at an initial stage of the disease (Blümcke, 2008). In addition, from neuroimaging and neuropathological studies it is well established that MTS can occur in combination with a second temporal lobe epileptogenic pathology such as cortical dyslamination (i.e., Focal Cortical Dysplasia type I), ectopic white matter neurons or low-grade glioneuronal tumors (Blümcke, 2008). The most common types of extra-hippocampal lesions found in dual pathology are developmental abnormalities, such as cortical dysgenesis, followed by gliotic lesions acquired in early childhood (Cendes et al., 1995). Additionally, anatomic data confirm the importance of the medial thalamus in mesial TLE. Volume loss is present in ipsilateral thalamus, caudate, and amygdala in mesial TLE, and thalamic cell loss is present in epilepsy patients. Furthermore, hippocampal cell density is significantly correlated with the amount of reduction in metabolism in bilateral thalamus and basal ganglia (Spencer, 2002b).

Relation between febrile seizures (FS) and mesial temporal sclerosis (MTS) remains controversial. One theory is that the early FS damages the hippocampus and is therefore a cause of HS; another possibility is that the child has a prolonged FS because the hippocampus was previously damaged as a result of prenatal or perinatal insult or by genetic predisposition (Cendes, 2004).

2.2 Single Focus Vs. Network Model

There are many questions about the etiology of TLE. Partial epileptic seizures were traditionally thought to originate in specific areas of the cortex known as seizure onset zones (SOZ), before spreading to other areas, known as epileptogenic zones (EZ). Surgical approaches to this condition include resection or disconnection of these areas, principally the SOZ (usually identified as the epileptic focus), from the rest of the brain. This ‘‘single focus’’ model has been challenged in favor of a “network model” in which the focus would be distributed along the limbic structures (Palmigiano et al., 2012).

A network is a set of cortical and subcortical brain structures and regions functionally and anatomically connected, in which activity in any one part affects activity in all the others. Therefore, vulnerability to seizure activity in any one part of the network is influenced by activity everywhere else in the network, and that the network as a whole is responsible for the clinical and electrographic phenomena associated with seizures (Spencer, 2002b). Interruption of the network, in a structural sense, or modification of network activity by electrical, biochemical or metabolic influences will modify the seizure expression. The most common human intractable epilepsy is TLE; this entity is the result of an abnormal circuitry in the medial temporal/limbic network. It is bilateral, cortical and subcortical, and includes the hippocampi, the amygdala, the entorhinal cortices, lateral temporal neocortices, and extratemporal components of the medial thalamus and the inferior frontal lobes (Spencer, 2002b). Surgery for TLE targets a wide area in which multiple rather than single structures are resected. It is difficult to determine whether the absence of postoperative seizures is a consequence of the resection of the focus or the destruction of the network topology (Palmigiano et al., 2012).
3 Semiology

Clinical semiology is the starting point to understand a seizure disorder and making the diagnosis of epilepsy. An accurate semiologic history is not only important in the diagnosis, but also relevant in localizing seizures particularly in patients with drug-resistant epilepsy (DRE) for potential surgical management (Jan & Girvin, 2008). Many times symptoms are not useful for localizing or lateralizing the seizure onset, but may give useful information about the activated network (Loddenkemper & Kotagal, 2005). Due to recall problems in many patients additional information has to be gathered from witnesses and family members. Sometimes requesting the interviewees to mimic the patient’s seizures provides the most important information leading to the diagnosis (Jan & Girvin, 2008).

The temporal lobe was divided by Wieser (Wieser, 1983) into five regions: temporobasal, temporopolar, neocortical, opercular and frontobasal cingular. Nowadays the ILAE (Commission on classification and terminology of the ILAE, 1989) recognizes two syndromes, mesial and lateral or neocortical temporal epilepsy (NTE). Mesial temporal epilepsy is the best known and the most frequent (Bercovici et al., 2012; Tatum, 2012).

3.1 Mesial Temporal Epilepsy

Mesial TLE is the most common form of partial epilepsy in adolescents and adults, and some studies have estimated that it represents about 40% of all epilepsies in this age range (Cendes, 2005). These patients usually have known risk factors such as perinatal injury, central nervous system (CNS) infection, FS, head trauma, and family history of epilepsy (Cendes, 2004). Up to 60% of patients with MTS may have a previous history of FS before developing seizures (French et al., 1993). Typically, by the end of the first or second decade, patients present with their first FS. It is usually a complex partial seizure, although it may be a simple partial or a generalized seizure. Afterwards, some patients remain seizure-free for variable periods that range from one to two decades, or even longer (honeymoon-period). Seizures restart as adults (Tatum, 2012).

More than 80% of patients report an aura (Acharya et al., 1998) with experiential and viscerosensory symptoms. Psychic phenomenon includes anxiety, déjà vu, jamais vu and fear. The typical aura is an indescribable rising epigastric sensation, often described as butterflies (Thompson et al., 2000), and followed by staring, behavioral arrest and orofacial or hand automatisms, accompanied by autonomic phenomena as pupillary dilatation, hyperventilation, piloerection, and tachycardia. Contralateral dystonic posturing with ipsilateral automatisms during the seizure are reliable lateralizing signs (Tatum, 2012). Prolonged seizures, secondary generalization and status epilepticus are relatively infrequent (French et al., 1993).

3.2 Neocortical Temporal Epilepsy

NTE has a different clinical profile than mesial epilepsy. A history of FS, CNS infection, perinatal complications or head injury is less common than in patients with MTS (Gil-Nagel & Risinger, 1997). Seizures in patients with NTE appear five or ten years later than in MTS (Bercovici et al., 2012). Around 60% of seizures are preceded by an aura, such as auditory phenomena, psychic experiences or déjà vu and jamais vu, visual distortions, and vertiginous symptoms (Maillard et al., 2004; Kennedy & Schuele, 2012). Motionless staring and unresponsiveness are the first objective clinical signs, often followed by early contralateral clonic movements and secondary generalization (O’Brien et al., 1996) (see Table 1).
## Mesial and Neocortical Temporal Epilepsy Clinical Features

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Mesial</th>
<th>Neocortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Risk factors</td>
<td>FS, CNS infections, head trauma, perinatal injuries (common)</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Adolescence or young adults</td>
<td>Five to ten years later than MTS</td>
</tr>
<tr>
<td>Type of aura</td>
<td>Abdominal, olfactory, gustatory, “dreamy state” and fear feelings</td>
<td>Psychic, auditory hallucination, vertigo, visual symptoms, cephalic sensation, nonspecific auras</td>
</tr>
<tr>
<td>Staring and unresponsiveness</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Ambiguous onset/offset</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Early, in the first 20 seconds, oral and manual automatism, frequent searching</td>
<td>Late or absent. Searching less frequent</td>
</tr>
<tr>
<td>Motor</td>
<td>Ipsilateral automatisms followed by contralateral dystonic posturing. Leg movements and body shifting more likely</td>
<td>Early contralateral dystonic posturing. Clonic movements more likely, leg movements less likely</td>
</tr>
<tr>
<td>Secondary generalization</td>
<td>Rare</td>
<td>More common</td>
</tr>
<tr>
<td>Postictal cough/sigh</td>
<td>More likely</td>
<td>Less likely</td>
</tr>
<tr>
<td>Seizure duration</td>
<td>&gt; 1 minute</td>
<td>&lt; 1 minute</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>A lateralized ictal change of rhythmic 5-10 Hz sharp activity, maximally at F7/F8 or sphenoidal electrode</td>
<td>A lateralized ictal change of irregular polymorphic 2-5 Hz temporal rhythm</td>
</tr>
<tr>
<td>MRI</td>
<td>Mostly lesional epilepsy. Hippocampal sclerosis.</td>
<td>Mostly non-lesional epilepsy*. Tumor, AVM or CDM</td>
</tr>
</tbody>
</table>

**Table 1:** Abbreviations. FS: febrile seizures, CNS: Central Nervous System, EEG: electroencephalogram, Hz: Hertz, MRI: Magnetic resonance imaging, AVM: Arterio-venous malformation, CDM: Cortical development malformation. *Lesional neocortical temporal cases are often not reported in the literature as compared to the nonlesional cases because they may be less likely to be admitted to an epilepsy-monitoring unit (EMU) for video-electroencephalography (EEG) telemetry unless the lesion is closely associated with eloquent cortex (Bercovici *et al.*, 2012).

### 3.3 Auras

Auras are usually subjective symptoms without objective signs that can be documented by an observer. These usually occur at the beginning of a seizure (“warning symptoms”) for seconds up to minutes, although they can be seen in isolation as well (Noachtar & Peters, 2009). Some authors have reported that auras have a good localizing value, similar to the electroencephalogram (EEG) and imaging (Palmini & Gloor, 1992). However, attempting to localize seizures based on their semiology is controversial. By definition, ictal discharges are generated in the epileptogenic zone. Theoretically, this can be any cortical region, but seizures often originate in so-called silent areas of the cortex and only become clinically manifest when they spread into areas that are able to produce symptoms (Rona, 2008). Another potential source of inaccuracy is the patient. Since auras are subjective by definition, the localizing value of the
reported symptoms critically relies on the ability of the patient to describe them, which depends on the age, intellectual level and mental state of the patient (Rona, 2008). Additionally, false localization should be suspected if the onset of clinical seizures occurs earlier than the onset of ictal EEG discharge (So, 2006; Jan & Girvin, 2008). With due consideration of the above-mentioned limitations, aura semiology can still be considered to provide essential clues for the localization, lateralization and prediction of surgical success (Palmini & Gloor, 1992).

Olfactory auras classically described, as “uncinate fits” are typically unpleasant smells, often associated with gustatory phenomena (Jan & Girvin, 2008). The brain areas associated with this type of auras include the amygdala, olfactory bulb, insular cortex, and orbitofrontal cortex (Noachtar & Peters, 2009; Foldvary-Schaefer & Unnwongse, 2011). Although historically these are typical auras, they are rare phenomena occurring in only 5% of TLE patients (Chen et al., 2003). Gustatory auras are hard to differentiate from olfactory sensations. Gustatory auras are even less common than olfactory auras, and are highly suggestive of a temporal onset (Noachtar & Peters, 2009; Foldvary-Schaefer & Unnwongse, 2011).

Psychic auras consist of a “strange feeling” that arises when the internal or external world is perceived in a distorted manner. These include emotional symptoms (fear, anxiety), distortions of familiarity (déjà vu, jamais vu) (Ebner, 1994) and multisensory hallucinations including revocation of complex memories. Patients consistently sense that the feelings are unreal and strange (Noachtar & Peters, 2009). Fear is a limbic aura, considered to be amygdaloid in origin. For this localization it must be “primary fear”, and not simply the often-secondary fear that is experienced by the epileptic patient in response to the realization that “another” seizure is about to occur (Jan & Girvin, 2008).

In epileptology, a clear separation of hallucinatory, illusional, and delusional phenomena is not easily achieved. Psychiatric symptoms mimicking seizure semiology are a great diagnostic challenge. If hallucinations are a manifestation of seizures, they should occur because of activation of a localized group of neurons, which can be investigated by cerebral recording and cerebral stimulation. The ‘Gold Standard’ investigation in such cases has been intracranial stereoelectroencephalography (SEEG) (Elliott et al., 2009a). It has also been shown that some complex psychotic states can occur because of continuous epileptic discharges. The best evidence for this can be found also in SEEG recordings showing episodes of complex partial status epilepticus with complex psychotic spells or with certain cases of apparent ‘postictal’ and possibly ‘interictal’ psychosis (Elliott et al., 2009b).

Autonomic auras include cardiorespiratory (palpitations, shortness of breath), gastrointestinal, and genitourinary symptoms (urinary urgency, genital sensations) (Loddenkemper & Kotagal, 2005). The symptomatogenic zone for these symptoms is the insular cortex, anterior cingulum, supplementary motor area (SMA), amygdala and hypothalamus (Foldvary-Schaefer & Unnwongse, 2011). Abdominal aura constitutes the most common type of autonomic aura. This consists of an indescribable unpleasant feeling in the peri-umbilical area that can be static, or ascend to the chest and throat, and can also descend into the lower abdominal region (Thompson et al., 2000; Foldvary-Schaefer & Unnwongse, 2011). They are often accompanied by autonomic symptoms such as nausea. The symptomatogenic zone for abdominal auras is the anterior insular cortex, frontal operculum, mesial temporal structures, and SMA (Noachtar & Peters, 2009).

Auditory auras usually manifest as auditory hallucination such as sounds, which are generated by activation of the Heschl’s gyrus. Complex auditory hallucinations, such as hearing voices or tunes, can also occur. They are attributed to activation of the temporal association cortex (Loddenkemper & Kotagal, 2005). Vertiginous aura consists of sensation of rotation or movement in all planes that are usually
associated with visual or auditory symptoms. These come from temporo-parietal junction (Foldvary-Schaefer & Unnwongse, 2011). The lateralizing value of these auras is poor (Jan & Girvin, 2008). Auras of right temporal origin are more commonly remembered than those from the left (Janszky et al., 2004).

3.4 Automatisms

Automatisms are repetitive, involuntary, purposeless movements that are usually inappropriate, but occasionally may simulate relatively normal events. Oro-alimentary automatisms, consisting of lip smacking, sucking, swallowing or chewing movements, along with gestural automatisms such as picking or fumbling movements are suggestive of TLE (Jan & Girvin, 2008).

Automatisms occur in 70% of patients with limbic seizures compared to 10% of patients with extra-limbic seizures (Manford et al., 1996). If the patient has preserved consciousness during automatisms, a non-dominant temporal focus is more likely (Ebner et al., 1995). When seizure spreads to the frontal lobes, they may produce proximal automatisms such as bicycling or thrashing.

A contralateral dystonic posturing of an arm is characterized by forced unnatural limb posturing, both in flexion or extension, proximal or distal, and with a rotatory component (Foldvary-Schaefer & Unnwongse, 2011). It can follow the ipsilateral automatism (Loddenkemper & Kotagal, 2005). It is more common in TLE than in ETLE. The unilateral dystonic posturing has been attributed to spread to the ipsilateral basal ganglia (Kotagal, 1991). Unilateral automatisms without contralateral dystonia have a lower lateralizing value (Dupont et al., 1999). The isolated dystonic posturing helps lateralize; however, it has no clear localizing value because it can originate from either temporal or frontal lobe (Jan & Girvin, 2008).

3.5 Motor Manifestations

In many patients, temporal seizures present only with staring, behavioral arrest, oro-alimentary and bimanual automatisms, the motor signs when present are usually related with spreading to the frontal lobe. Therefore, it is important to compare the motor and other features of seizures originating in frontal lobe versus temporal lobe (see table 2).

To be clinically significant a seizure-induced head version has to be forced, prolonged, assuming an unnatural position with the chin elevated and with the head hyperextended (Wyllie et al., 1986). The head movement may be tonic or clonic, and it is associated with ipsilateral conjugate gaze deviation. The direction of head version is contralateral to the epileptogenic zone in more than 90% of cases (Foldvary-Schaefer & Unnwongse, 2011). If this occurs at the onset of a seizure in the presence of normal consciousness, is a strong indication of a contralateral frontal dorsolateral cortical onset (So, 2006). In seizures of temporal lobe origin, patients can have an initial brief ipsilateral (non-versive) head turning associated with ipsilateral automatisms (Jan & Girvin, 2008). The contralateral version occurs immediately before the secondary generalization (Foldvary-Schaefer & Unnwongse, 2011). Brodmann area six leads to contralateral version prior to secondary generalization (Loddenkemper & Kotagal, 2005).

Eye movements are another important feature of partial seizures. Seizure-related eye version is forced, sustained, and the conjugate eye deviation typically accompanies the head version. Eye version that occurs before secondary generalization usually originates from the contralateral hemisphere (Wyllie et al., 1986; Foldvary-Schaefer & Unnwongse, 2011). Prominent contralateral head and eye deviation can occur with occipital seizures, which may even be accompanied by contralateral turning of the body (Jan & Girvin, 2008).
### Frontal and Temporal Lobe Epilepsy Features

<table>
<thead>
<tr>
<th>Type of epilepsy</th>
<th>Frontal lobe</th>
<th>Temporal lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures frequency</td>
<td>Frequent, often daily</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Sleep activation</td>
<td>Characteristic</td>
<td>Less common</td>
</tr>
<tr>
<td>Seizure onset</td>
<td>Abrupt, explosive</td>
<td>Less abrupt</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Less abrupt</td>
</tr>
<tr>
<td>Initial motionless staring</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Less common</td>
<td>More common and longer</td>
</tr>
<tr>
<td>Bipedal automatism</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Complex postures</td>
<td>Early, frequent and prominent</td>
<td>Less frequent and prominent, occurring later as seizure starts to generalize</td>
</tr>
<tr>
<td>Hypermotor (Hyperkinetic)</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Somatosensory symptoms</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Speech</td>
<td>Loud vocalization (grunting, screaming, moaning)</td>
<td>Verbalization speech in non-dominant seizures</td>
</tr>
<tr>
<td>Seizure duration</td>
<td>Brief</td>
<td>Longer</td>
</tr>
<tr>
<td>Secondary generalization</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Postictal confusion</td>
<td>Absent or less prominent and shorter</td>
<td>More prominent and longer</td>
</tr>
<tr>
<td>Postictal dysphasia</td>
<td>Rare, unless it spreads to the dominant temporal lobe</td>
<td>Common in dominant temporal lobe seizures</td>
</tr>
</tbody>
</table>

**Table 2:** Frontal and Temporal Lobe Epilepsy Features

Focal clonic activity is one of the most reliable lateralizing signs during epileptic seizures (Jan & Girvin, 2008). It is a sign related with activation of the primary motor cortex (Loddenkemper & Kotagal, 2005). The hand and face are most frequently involved. Clonic seizures that originate in the frontal cortex are early and before loss of awareness (So, 2006). In temporal lobe seizures, clonic movements usually occur late in the seizure when the patient is unconsciousness, and due to seizure spreading to the dorsolateral motor cortex (Loddenkemper & Kotagal, 2005; So, 2006; Jan & Girvin, 2008).

Asymmetric tonic limb posturing is usually observed during the early tonic phase of partial seizures. Figure of four sign usually localizes to temporal lobe (So, 2006). One arm is extended at the elbow while the other is flexed at the elbow, giving the appearance of a figure of “4”. Both arms are slightly raised in front of the chest. The seizure onset is contralateral to the extended limb (So, 2006). Further lateralizing and localizing aspects of partial seizure semiology are summarized in a table (see table 3).

### 3.6 Language

Language is important in localizing and lateralizing seizures (Loddenkemper & Kotagal, 2005; Noachtar & Peters, 2009; Foldvary-Schaefer & Unnwongse, 2011). Speech disturbances during seizures include receptive, expressive, or global dysphasia (Jan & Girvin, 2008). Ictal verbalization, consisting of understandable names, verbal phrases or sentences, should be distinguished from guttural vocalization such as moaning, grunting, and screaming. Verbalizations are more common in non-dominant temporal lobe seizures (Gabr et al., 1989). However, vocalizations are more commonly seen in frontal lobe seizures with no clear lateralizing value (Janszky et al., 2000). Postictal dysphasia is a very useful lateralizing sign for the dominant hemisphere, but it may not be detected unless the epilepsy monitoring unit staffs routinely
<table>
<thead>
<tr>
<th>Semiologic features</th>
<th>Localization</th>
<th>Lateralization</th>
<th>Lateralizing value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auras</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>Anterior insula, frontal operculum, mesial temporal lobe, and SMA (limbic system)</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Psychic (déjà vu/jamais vu)</td>
<td>Temporal neocortex</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Olfactory</td>
<td>Orbitofrontal region, amygdala, and insula</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td><strong>Hemifield simple visual</strong></td>
<td>Occipital (Brodmann areas 17-19)</td>
<td>Contralateral</td>
<td>100</td>
</tr>
<tr>
<td><strong>Hemifield complex visual</strong></td>
<td>Occipito-temporal or temporal posteromesial</td>
<td>Contralateral</td>
<td></td>
</tr>
<tr>
<td><strong>Simple auditory</strong></td>
<td>Primary auditory cortex (areas 41)</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td><strong>Complex auditory</strong></td>
<td>Auditory association cortex (areas 42 and 22)</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td><strong>Unilateral somatosensory aura</strong></td>
<td>Parietal (Brodmann areas 1, 2, and 3)</td>
<td>Contralateral</td>
<td>89</td>
</tr>
<tr>
<td>Gustatory</td>
<td>Mesiobasal temporal cortex and parietal operculum</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Vertiginous</td>
<td>Temporo-occipital junction</td>
<td>Often non-dominant</td>
<td></td>
</tr>
<tr>
<td>Cephalic/whole body</td>
<td>Amygdala, entorhinal cortex and temporal neocortex</td>
<td>Often non-dominant</td>
<td></td>
</tr>
<tr>
<td>Orgasmic</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td></td>
</tr>
<tr>
<td><strong>Automatism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral automatism</strong></td>
<td>Temporal lobe, typically hippocampal</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td><strong>Unilateral limb automatism</strong></td>
<td>Temporal</td>
<td>Ipsilateral</td>
<td>90</td>
</tr>
<tr>
<td><strong>Automatisms with preserved responsiveness</strong></td>
<td>Temporal</td>
<td>Non-dominant</td>
<td>100</td>
</tr>
<tr>
<td>Bipedal automatisms</td>
<td>95% Frontal and 5% temporal</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td><strong>Automatism followed by clonic seizure</strong></td>
<td>Temporal Neocortical</td>
<td>Ipsilateral</td>
<td></td>
</tr>
<tr>
<td><strong>Automatism followed by dystonic hand posturing</strong></td>
<td>Temporal mesial</td>
<td>Ipsilateral</td>
<td></td>
</tr>
<tr>
<td><strong>Unilateral eye blinks</strong></td>
<td>Temporal</td>
<td>Ipsilateral</td>
<td>83</td>
</tr>
<tr>
<td>Whistling</td>
<td>Temporal</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td><strong>Language abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ictal panic attack</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td></td>
</tr>
<tr>
<td>Ictal speech arrest</td>
<td>Temporal</td>
<td>Dominant</td>
<td>PPV 67</td>
</tr>
<tr>
<td>Ictal speech preservation</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td>83</td>
</tr>
<tr>
<td>Postictal dysphasia and aphasia</td>
<td>Temporal</td>
<td>Dominant</td>
<td>100</td>
</tr>
<tr>
<td>Vocalization</td>
<td>Frontal</td>
<td>Dominant</td>
<td>82</td>
</tr>
<tr>
<td><strong>Motor abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early non-forced head turn</td>
<td>Frontal or temporal</td>
<td>Ipsilateral</td>
<td>30</td>
</tr>
<tr>
<td>Late contraversive forced head turn</td>
<td>Frontal (Brodmann 6 area) or temporal</td>
<td>Contralateral</td>
<td>PPV 94</td>
</tr>
<tr>
<td>Late ipsiversive forced head turn</td>
<td>Temporal</td>
<td>Ipsilateral</td>
<td></td>
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<tr>
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<tr>
<td>Late non-forced head turn</td>
<td>Frontal or temporal</td>
<td>Ipsilateral</td>
<td></td>
</tr>
<tr>
<td>Forced eye deviation</td>
<td>Frontal (Brodmann 8 area)</td>
<td>Contralateral</td>
<td></td>
</tr>
<tr>
<td>Solitary eye deviation</td>
<td>Occipital</td>
<td>Contralateral</td>
<td></td>
</tr>
<tr>
<td>Epileptic nystagmus</td>
<td>Occipital</td>
<td>Contralateral</td>
<td>100</td>
</tr>
<tr>
<td>Unilateral clonic jerking</td>
<td>Frontal (Brodmann 4 area) peri-rolandic</td>
<td>Contralateral</td>
<td>PPV 95</td>
</tr>
<tr>
<td>Asymmetric clonic ending</td>
<td>Frontal (Brodmann 4 area) peri-rolandic</td>
<td>Ipsilateral</td>
<td>83</td>
</tr>
<tr>
<td>Unilateral tonic seizure (isolated)</td>
<td>Frontal</td>
<td>Contralateral</td>
<td>89</td>
</tr>
<tr>
<td>Dystonic limb/hand posturing</td>
<td>Temporal or frontal</td>
<td>Contralateral</td>
<td>100</td>
</tr>
<tr>
<td>Fencing posture (M2E)</td>
<td>Frontal (SMA)</td>
<td>Contralateral</td>
<td>PPV 90</td>
</tr>
<tr>
<td>Figure of 4 sign</td>
<td>70% Temporal, 30% extratemporal</td>
<td>Contralateral to the extended limb</td>
<td>PPV 89</td>
</tr>
<tr>
<td>Unilateral ictal paresis or immobile limb</td>
<td>Frontal (FIG)</td>
<td>Contralateral</td>
<td>PPV 100</td>
</tr>
<tr>
<td><strong>Postictal</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Postictal Todd’s paresis</td>
<td>Frontal</td>
<td>Contralateral</td>
<td>PPV 100</td>
</tr>
<tr>
<td>Postictal nose wiping/rubbing</td>
<td>Temporal</td>
<td>Ipsilateral</td>
<td>97</td>
</tr>
<tr>
<td>Postictal coughing</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td></td>
</tr>
<tr>
<td>Postictal disorientation</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td>85</td>
</tr>
<tr>
<td>Postictal verbal memory dysfunction</td>
<td>Temporal</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>Postictal visual memory dysfunction</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td></td>
</tr>
<tr>
<td>Tongue biting (side)</td>
<td>--</td>
<td>Ipsilateral</td>
<td>71</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ictal spitting</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td>76</td>
</tr>
<tr>
<td>Ictal drinking</td>
<td>Temporal, hypothalamic</td>
<td>Non-dominant</td>
<td></td>
</tr>
<tr>
<td>Ictal laughter (gelastic)</td>
<td>Hypothalamic, mesial temporal or frontal cingulate</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Dacrystic seizures</td>
<td>Temporal, more hippocampal and hypothalamic</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Ictus vomiting</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td>81</td>
</tr>
<tr>
<td>Ictal urinary urge</td>
<td>Temporal</td>
<td>Non-dominant</td>
<td>100</td>
</tr>
<tr>
<td>Unilateral ear plugging</td>
<td>Temporal (STG)</td>
<td>Contralateral</td>
<td></td>
</tr>
<tr>
<td>Piloerection (goose bumps)</td>
<td>Temporal</td>
<td>Ipsilateral*</td>
<td>84</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Temporal</td>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Unilateral emotional facial alteration</td>
<td>Temporal mesial (amygdala), prefrontal bitofrontal region, hypothalamus, insula</td>
<td>Contralateral</td>
<td>PPV 86</td>
</tr>
</tbody>
</table>

**Table 3**: Abbreviations. SMA: supplementary motor area, FIG: frontal inferior gyrus, STG: superior temporal gyrus, PPV: positive predictive value. NL: no lateralization. References: (Loddenkemper & Kotagal, 2005; So, 2006; Jan & Girvin, 2008; Noachtar & Peters, 2009; Foldvary-Schaefer & Unmwongse, 2011). *Piloerection occurs mostly in left TLE (So, 2006).
checks the postictal speech function (Gabr et al., 1989). Speech arrest may occur at the onset of a seizure from the dominant temporal lobe, but can also occur from involvement of inferior Rolandic cortex and the SMA (So, 2006).

3.7 Postictal Signs

Postictal nose wiping and cough are due to increased parasympathetic activity resulting in increased nasal and pharyngeal secretions. These behaviors are believed to be reflexive in nature, occurring postictically as they are inhibited during the ictal period (Leutmezer et al., 1998). Postictal paresis or “Todd’s paralysis” is one of the oldest described lateralizing signs corresponding to contralateral motor cortex. Postictal hemianopia is seen in the contralateral occipital seizures (Loddenkemper & Kotagal, 2005). Suspected mechanisms include neuronal exhaustion of the primary motor areas due to increased lactic acid levels, and cerebrovascular dysfunction. Additionally, active inhibition by endogenous endorphins has been proposed (Loddenkemper & Kotagal, 2005).

3.8 Other Signs

Cardiac manifestations are the most well recognized autonomic manifestations of partial seizures (Foldvary-Schaefer & Unnwongse, 2011). Ictal tachycardia, defines as a heart rate more than 100 beats per minute, is reported in more than 50% of seizures. Early and significant tachycardia is more common in TLE than in ETLE (Weil et al., 2002) and is associated especially with right mesial TLE (Weil et al., 2005). Pure ictal tachycardia without any other clinical symptoms is highly correlated with temporal rather than extratemporal epileptogenic activity (Weil et al., 2002). Ictal bradycardia, which is one of the causes of SUDEP, is more common in TLE as opposed to ETLE (Tinuper et al., 2001; Britton et al., 2006; So & Sperling, 2007). The lateralizing value of ictal bradycardia is questionable. Although in some reports left temporal lobe is more commonly involved (Tinuper et al., 2001), others suggest bilateral involvement (Britton et al., 2006).

Seizure semiology has several potential limitations in localizing seizure onset. Although many semiotic features have high positive predictive values for localization, each feature has some potential to falsely localize seizure onset (So, 2006). Therefore, the investigators must exercise caution when using these findings during evaluation of an epileptic patient for epilepsy surgery. It is also important to keep in mind those extratemporal regions, such as orbitofrontal area, cingulum, insula, and temporo parieto occipital junction might demonstrate similar electro-clinical characteristics to those of the temporal lobe (Loddenkemper & Kotagal, 2005; Ryvlin & Kahane, 2005; So, 2006; Jan & Girvin, 2008; Noachtar & Peters, 2009; Foldvary-Schaefer & Unnwongse, 2011).

4 EEG and Video-EEG

EEG is the most useful diagnostic test for epilepsy (Noachtar & Rémi, 2009). Activation procedures such as hyperventilation, photic stimulation, and sleep deprivation enhance the diagnostic sensitivity of EEG and should be a routine practice (Foldvary et al., 2001). Although surface EEG recordings are less sensitive than invasive studies, they provide the best overview and, therefore, the most efficient way to define the approximate localization of the epileptogenic zone (Noachtar & Rémi, 2009). Video-EEG allows increasing the likelihood of detecting interictal epileptiform activity, as well as allowing visual analysis of
the seizures and simultaneous clinical and electrographic correlation helpful in presurgical evaluation (Binnie et al., 1981; Chen et al., 1995).

4.1 Interictal Findings

Surface interictal EEG changes occur more commonly in TLE than in other kind of seizure locations (Noachtar & Rémi, 2009). Lateralized arrhythmic (irregular) delta activity may be found in up to 66% of patients with TLE and is highly concordant with temporal spiking (Koutroumanidis et al., 2004). Temporal intermittent rhythmic delta activity (TIRDA) is a more specific and accurate interictal indicator of TLE (Geyer et al., 1999; Jan et al., 2010). TIRDA consists of trains of rhythmic delta activity lasting 4-20 seconds (Javidan, 2012). It is related with epilepsy in 80% of cases (Geyer et al., 1999).

The classic interictal EEG abnormality of mesial TLE is a spike or sharp wave, which usually are electronegative waves over the anterior temporal region (F7/F8) (Javidan, 2012). Mid temporal (T3/T4) and posterior temporal (T5/T6) spikes or sharp waves are more likely to originate from the temporal neocortex (Williamson et al., 1993; Jan et al., 2010). Interictal spikes predict the epileptogenic focus with a probability greater than 95% (Holmes et al., 1996). Patients with TLE frequently have interictal epileptiform discharges independently in both temporal lobes (Serles et al., 1998; Noachtar & Rémi, 2009). The TLE is commonly a bilateral disease even though a unilateral focus is likely to predominate in the great majority of cases. According to different studies (Blume et al., 1993; Williamson et al., 1993; Chee et al., 1993; Ergene et al., 2000) independent bitemporal spikes (IBS) are present in 13% to 73% of patients with TLE and the incidence is higher when longer recordings are obtained (Ergene et al., 2000). The incidence of IBSs has been reported in 13-17% of patients with TLE and routine EEGs of 30 to 40 min duration (Williamson et al., 1993; Chee et al., 1993). The incidence is higher (61%) using 24-hour continuous recordings (Ergene et al., 2000), and (73%) with four or more consecutive EEGs recorded (Blume et al., 2000). Furthermore, there is a correlation between a successful outcome after surgery for TLE and a high degree of lateralization of interictal epileptiform discharges (IEDs) before surgery. Epileptiform activity has often been considered “lateralized” in TLE by many investigators if more than 80-90% of the discharges originated from one temporal lobe (Ergene et al., 2000).

4.2 Ictal Findings

The ictal EEG recording is the main component of the presurgical evaluation (Engel, 1993). Ictal EEGs are more localizing in TLE versus ETLE (Foldvary et al., 2001). Different temporal lobe ictal patterns have been described through history. In 1978 Geiger et al (Geiger & Harner, 1978) pointed out that focal hypersynchrony on the scalp EEG was an accurate localizing indicator of cortical irritability. In 1996 Ebersole et al (Ebersole & Pacia, 1996) described three different ictal rhythms in TLE. The Type I is characterized by rhythmic 5-9 Hz theta activity that slowly evolves and remains localized to the temporal or sub-temporal regions. It is the most specific pattern for seizures originating from the hippocampal areas. The Ebersole type II is characterized by rhythmic slow activity (2-5 Hz) with widespread temporal distribution. It is frequently associated with neocortical seizures. The Ebersole type III is characterized by diffuse ictal EEG changes or attenuation without clear lateralization. This pattern can be seen in hippocampal and temporal neocortical seizures (Ebersole & Pacia, 1996). Other ictal rhythms include background attenuation and start-stop-start (SSS) phenomenon (Jan et al., 2010).
4.2.1 Start-Stop-Start Phenomenon

Defined as a pair of sequential ictal potentials separated by complete or almost complete cessation of seizure activity, the SSS phenomenon was initially identified in 1993 by Blume et al on subdural recordings in 23% patients (Blume & Kaibara, 1993). Three years later, Atalla et al described the same ictal pattern in 13% of patients with TLE using scalp-sphenoidal electrodes. The first "start" usually has a narrow field, typically in the sphenoidal electrodes. The mean duration of the "start" is eleven seconds and usually the clinical onset correlates with these changes. The stop last eight seconds and the restart often had a different morphology, frequency, and a wider field (Atalla et al., 1996). A simple hypothesis for the unknown physiological mechanism underlying the SSS phenomenon in the same region may be that seizure-terminating factors act ineffectively, producing only a pause – then resumption. Theories for restart at a distance include those of seizure propagation, and an alternative mechanism might be a long-loop reverberating circuit. The stop phase may simply represent unrecorded continuing distant seizure activity located away from electrode placements, or masked due to muscle and movement artifact (Blume & Kaibara, 1993). The SSS phenomenon is a clinical electroencephalographic pattern that should be considered and recognized at seizure onset in some patients. If this phenomenon is missed, the restart may be misinterpreted as the actual seizure onset, and some seizures may be considered non-localized (Atalla et al., 1996).

A lateralized ictal change characterized by irregular polymorphic theta and delta (2-5 Hz) is most often associated with TLE originating from the neocortex. A lateralized ictal change of rhythmic 5-10Hz sharp activities, maximally at F7/F8 or sphenoidal electrode is most commonly seen in hippocampal onset (Jan et al., 2010). The ictal EEG manifestation of limbic seizures also could have a nonspecific beginning of low-voltage fast (electro-decrement) activity, with focal or regional background attenuation (Javidan, 2012). Some postictal patterns are described in TLE including polymorphic delta activity and regional attenuation of focal spikes (Jan et al., 2010). Postictal lateralized slowing is present in 67% of TLE patient (Williamson et al., 1993).

Another abnormality of possible significance is the potential bradycardia or tachycardia before the onset of ictal EEG discharges. This phenomenon is associated with EEG pattern of TLE originating from the mesial structures, suggesting activation of the neuronal circuits involved in sympathetic regulation (Jan et al., 2010).

Several “non-standard” electrodes can be used to further evaluate the EEG abnormalities including sphenoidal, nasopharyngeal, anterior temporal (T1/T2), foramen oval (FO) electrodes, and surface electrodes applied over the mandibular notch (MN) or zygoma (Jan et al., 2010). Sphenoidal electrodes especially have been suggested to be helpful in identifying the irritative and seizure onset zones in patients with TLE (Hamaneh et al., 2011). These electrodes are inserted bilaterally through the skin below the zygomatic arch, two to three centimeters anterior to the tragus and directed postero-superiorly towards foramen ovale. A qualified physician should perform this procedure with local anesthesia (Jan et al., 2010). T1, T2, and MN electrodes are able to record all the sphenoidal detected spikes, are not invasive, more comfortable, and easy to adjust (Sadler & Goodwin, 1989; Krauss et al., 1992; Blume, 2003). Although sphenoidal electrodes detect spikes from seizures rising from the mesial temporal region, they could also be present with seizures originating in the neocortical temporal or orbitofrontal area. Therefore, although sensitive, sphenoidal spikes are not very specific (Wilkus et al., 1991).
4.3 Foramen Oval Electrodes

In thirty percent of mesial TLE patients, scalp-sphenoidal EEG recordings fail to demonstrate a unilateral ictal onset; also showing contralateral, bitemporal independent, and non-lateralized ictal onsets. In addition, the surface EEG recordings may not be interpretable because of movement artifacts. Foramen ovale (FO) evaluation provides accurate neurophysiologic data about lateralization of seizures that were not clearly lateralized by surface EEGs (Velasco et al., 2006). FO electrodes are used to record from mesial temporal structures without requiring penetration of the skull; a multi-contact flexible electrode is placed in the ambient cistern with the aid of a needle inserted through the foramen ovale (Jan et al., 2010). This procedure is safe and can be an alternative to invasive implantation of depth electrodes in mesial TLE patients who are candidates for temporal lobectomy (Velasco et al., 2006). These electrodes are not as close to hippocampal structures as intracerebral electrodes and do not allow as large a recording field as grids and strips. However, they detect mesial temporal EEG discharges as well as sphenoidal electrodes (Jan et al., 2010); and the signal-to-noise ratio of FO is better than that in the scalp-sphenoidal electrode recordings (Velasco et al., 2006).

Alarcón et al., have used FO electrodes successfully in presurgical evaluation of TLE patients. As the FO is a natural hole, the implantation of FO electrodes does not involve disruption of the cranium (Alarcón et al., 2012). They introduce six electrodes through the FO, with the deepest contacts recording from mesial temporal structures. Such deep contacts usually show interictal and ictal patterns, which are not seen on the scalp and are considered as semi-invasive electrodes that provide significantly more information than scalp recordings (Kissani et al., 2001).

Figure 1 demonstrates a 36 years old right-handed male with an unremarkable past medical history, which began having daily complex partial seizures three years ago. The patient experienced an aura described as “feeling anxious, uneasy, and dreadful”, followed by loss of awareness lasting 60 seconds. He had mild postictal confusion and rare secondary generalization. Seizure control could not be achieved with a combination of levetiracetam, Lamotrigine and Clobazam. Brain MRI revealed atrophy of the left hippocampus, with an increased T2 (weighted) signal.

Figure 1: On the left: A coronal T2-weighted 3T MRI section shows reduced hippocampal volume and increased signal, consistent with left mesial temporal sclerosis. On the right: scalp EEG recording shows interictal epileptiform activity on the left anterior temporal region (maximum at F7 electrode).
Scalp video-EEG monitoring revealed abundant spikes over the left temporal region, maximum at F7-T3 with spread to T5 electrode. See figure 1. Three seizures were recorded during video-EEG monitoring; all of them had a clear left temporal onset (maximum at F7 electrode). See figure 2. His neuropsychological evaluation reported low average vocabulary skills, phonemic fluency, and verbal memory consistent with left temporal functional impairment. He underwent left temporal lobectomy. Histopathology revealed severe neuronal loss and gliosis involving predominantly hippocampal sector CA1 and the dentate gyrus, consistent with MTS. After resection his seizures resolved with no memory complaints. After 5-6 months of postoperative follow up he remains seizure free.

![Figure 2: Scalp EEG recording showing lateralized ictal rhythmic 7 Hz activity, maximally at F7 with involvement of the ipsilateral scalp sphenoidal electrode.](image)

### 5 Intracranial Recording

Non-invasive methods are sufficient to evaluate 60 to 85% of patients before surgical resection (Engel, 1993; Holmes et al., 1996). The main purpose of intracranial recording is to delineate the area of onset and early propagation of a seizure. It is therefore important to cover the suspected zone by placing electrodes in strategic areas. The idea is to confirm that seizures all arise in one area and not in another (Dubeau & McLachlan, 2000; Pondal-Sordo et al., 2007). Ultimately, the localization is achieved by combining the data from invasive monitoring with a detailed analysis of the clinical semiology, and the information obtained from the video-EEG monitoring and other tests such as MRI, SPECT or PET.

There are six main reasons for invasive recordings: 1) seizures lateralized, but not localized; 2) seizures localized, but not lateralized; 3) seizures neither localized, nor lateralized; 4) discrepancy between electrographic seizure location and the rest of the data (e.g. location of lesion on imaging); 5) seizures localized in eloquent cortical areas; and 6) relation of seizure localization to lesion (Dubeau & McLachlan, 2000).

Scalp electrodes detect activity generated from a large cortical surface (6 cm²) give reference, whereas subdural or depth electrodes will detect changes over only a few millimeters of cortex. Therefore, some interictal spikes that are not otherwise visible on scalp EEG can be easily identified with invasive electrodes. While invasive electrodes are more sensitive in detecting spikes and seizures from a lo-
calized area, they may miss epileptiform activity in other regions due to covering a limited surface (Jan et al., 2010).

Intracranial recordings have several advantages compared to surface EEG. These advantages include better spatial resolution and increased sensitivity, no attenuation from scalp and skull, reduced ictal electromyographic artifacts, and providing the option of cortical stimulation (Dubeau & McLachlan, 2000; Javidan, 2012). The disadvantages of invasive monitoring include: limited cortical sampling or risk for sampling error (tunnel vision), and risk of significant complications such as hemorrhage and infection (2-3%).

Subdural electrodes are inserted surgically to record over the cerebral cortex. Electrode grids are square or rectangular in shape with small platinum or stainless steel disks embedded into a soft silastic sheet with several contact points. Electrode strips, which come in various sizes, consist of a row of contacts and are usually inserted through a burr hole (Dubeau & McLachlan, 2000; Gonzalez-Martinez et al., 2012). Currently, subdural electrodes are the most common invasive method used in the United States. Despite the high spatial resolution provided by the subdural methodology, relatively deep epileptogenic foci cannot be sampled (Gonzalez-Martinez et al., 2012).

Depth electrodes or stereo-electroencephalography is a safe and accurate procedure for invasive assessment of the epileptogenic zone. Traditional Talairach’s methodology, implemented by multimodal planning and robot assisted surgery, allows direct electrical recording from superficial and deep-seated brain structures, providing essential information in the most complex cases of DRE (Cardinale et al., 2012). The main advantage from depth electrodes over subdural electrodes is that the former allow sampling from deep zones such as, amygdala, hippocampus, entorhinal cortex, and insular cortex (Dubeau & McLachlan, 2000).

Selection between subdural electrodes and depth electrodes depends on the experience of each epilepsy center. Several studies (Eisenschenk et al., 2001; Gonzalez-Martinez et al., 2012; Wellmer et al., 2012) comparing the two techniques have shown no superiority of one over the other.

Hader (Hader et al., 2013) published a systematic review about complications of invasive EEG monitoring. They described minor complications as those that resolved completely within three months. Major neurological complications persisted beyond that time frame. According to these definitions, minor neurological complications occurred in 10.9% of patients, whereas major complications were identified in 4.7% of patients. The overall frequency of minor complications associated with invasive monitoring was higher in the pediatric population than in adults (11.2% vs. 5.5%), possibly because in the pediatric population subdural grid implantation via craniotomy was more commonly utilized in the investigations. Major neurological complications were more common after extratemporal resections than temporal resections (6.5% vs. 4.1% respectively) (Hader et al., 2013).

Arya (Arya et al., 2013) published a systematic review about adverse effects of subdural electrodes. The most common adverse effects found were as follows: neurological infections (2.3%), superficial infections (3%), intracranial hemorrhage (4%), and elevated intracranial pressure (2.4%). The mean number of electrodes per patient varied from 52 to 95 and the mean number of electrodes placement duration varied from five to 17 days. Increased number of electrodes (>67) was found to be associated with increased incidence of adverse effects.

Figure 3 shows a case of a 49-years-old right-handed male with eight years of epilepsy history. His only epilepsy risk factor was head trauma at the age of 25 years. He suffered a closed brain injury secondary to a grenade explosion. His seizures were charactereized by staring followed by oroalimentary and bimanual automatisms and mild postictal confusion. Secondary generalization was rare. Complex
partial seizures occurred daily, and at times in clusters. Patient had failed treatment with Phenytoin, Carbamazepine, Levetiracetam, Clobazam; and he was taking Lamotrigine with no improvement. MRI was normal. Video-EEG showed equal number of electrographic seizures from each temporal lobe as well as independent bitemporal inter-ictal epileptiform discharges. An interictal PET showed right temporal hypometabolism. The intracranial recording with depth electrodes confirmed an equal independent bitemporal onset for seizures (see figure 3). Based on the PET findings a right temporal lobectomy was done. Twelve months after surgery, the patient had only had three complex partial seizures, always related with stressful situations or lack of compliance. In this case the intracranial recording did not help to lateralize the seizure onset and the PET scan was the key test for making the decision to offer a right temporal lobectomy.

Figure 4 demonstrates the case of a 33-year-old right-handed male with a long history of seizures. He had a head concussion at the age of 17 months secondary to falling out of his stroller. Seizures started after this event with two types of spells. The most common were complex partial seizures characterized by the lack of aura, staring, bimanual and oral automatisms and postictal confusion. The patient had ictal speech in many of the seizures. These events occurred daily for the last two years. The patient also had complex partial seizures with secondary generalization (one per month). He received treatment...
with Lamotrigine and Levetiracetam. He had failed in the past to Phenytoin, Carbamazepine, Clobazam. Several interictal EEGs showed right temporal spikes, and brain MRI showed right MTS.

Video-EEG telemetry was performed, showing independent bitemporal spikes. Ten seizures were recorded with a potential bitemporal onset, but no clear ictal activity in the right temporal region. Neuropsychological test reported a lower average cognitive function, with bilateral impairment on tasks of visual and verbal memory. The intracranial investigation showed frequent independent bitemporal spikes (see Figure 4). Five seizures were recorded with depth electrodes, all of them with clear onset over the head of right hippocampus (mesial electrodes), the left side was silent at the onset of the seizures (see Figure 5). In this case the depth electrodes helped to corroborate that the seizures were coming from the same side as the structural lesion.

6 MRI

After a careful evaluation of the clinical semiology and EEG findings, the next step in presurgical evaluation of epilepsy is the detection of structural abnormalities. MRI is the most sensitive and useful examination for identifying structural abnormalities in patients with partial epilepsy. Most partial epilepsies arise from the temporal lobe and HS is the most common underlying pathological substrate (Wehner & Lüders, 2008). MRI has been the single most important test to document and diagnose HS, as it is a non-invasive test with a high yield in localizing the abnormalities in patients with TLE (Spencer, 1994).

Although patients with normal MRIs have a less possibility to render seizure free after epilepsy surgery than patients with an obvious MRI lesion, the use of invasive monitoring can improve the outcomes and still a large percentage of patients with epilepsy (50 to 70%) can render seizure free after surgery (Téllez-Zenteno et al., 2005).
In patients with TLE, the mesial temporal structures should be carefully evaluated, (hippocampus, parahippocampal gyrus and amygdala) (Wehner & Lüders, 2008). The suggested sequences are FLAIR, T2-weighted and T1-weighted, with coronal sections perpendicular to the long axis of the hippocampus. Contrast medium is not necessary if there is no suspicion of a tumor (Woermann & Vollmar, 2009). Classic findings of HS are atrophy of the hippocampus (95%) with increased signal intensity on T2-weighted (85%) or FLAIR sequences; these changes are better appreciated when both sides are compared in the same subject. In addition, minor findings may be seen in TLE such as loss of hippocampal surface and internal structure (60-95%), enlargement of the cerebrospinal fluid (CSF) space in the temporal horn of the lateral ventricle, atrophy of ipsilateral temporal structures (temporal lobe, fornix, mammillary body, white matter of the parahippocampal gyrus), and decreased signal intensity on T1-weighted (10-95%). The minor findings are less consistent and their diagnostic value is limited (Woermann & Vollmar, 2009).

Cavernous angiomas are the most frequent forms of vascular malformation related with seizures. They are benign vascular lesions with thin-walled endothelium lined spaces that contain blood products in different stages of evolution. On MRI, they have a characteristic “popcorn” appearance with a core of mixed signal intensities, reflecting various stages of blood degradation, and a hypointense rim, reflecting hemosiderin deposition (see Figure 6). Gradient echo sequences increases the sensitivity of MRI by demonstrating punctuate micro hemorrhages (Wehner & Lüders, 2008).

Figure 5: Intracranial EEG recording with depth electrodes showed a clear onset over the mesial electrodes in the right temporal region (RHH1-2 (Right hippocampus head) and RHB1-2 (right hippocampus body).
The hemorrhages associated with cavernous angiomas are considered a major factor in their epileptogenicity. In the setting of a single cavernous angioma and consistent electro-clinical seizures, further testing is not required; even pure lesionectomy achieves seizure freedom in two-thirds of patients (Ferroli et al., 2006).

It is important to bear in mind the possibility of dual pathology that occurs in up to 15% of adult cases and 67% of pediatric cases (Alvarez-Linera Prado, 2007). Dual pathology refers to patients who have two (or more) distinct lesions on MRI, classically the combination of HS with another epileptogenic lesion. The most frequent clinical scenario is the coexistence of HS with a malformation of cortical development, most commonly focal cortical dysplasia, particularly type I (Bautista et al., 2003).

Figure 7 shows the case of a 29-year-old right-handed female. She began having complex partial seizures six years ago, and after one year they became intractable. Video-EEG showed three seizures, all with a clear onset over the right mesial temporal region. MRI shows dual pathology, HS and a focal region of heterotopic grey matter.

## 7 Functional Imaging

Functional imaging detects changes in cerebral metabolism or cerebral perfusion in the interictal or ictal state. It is important to obtain a strong correlation between clinical findings, EEG and the different imaging techniques. Ictal perfusion single photon emission computed tomography (SPECT) and interictal fluorodeoxyglucose (FDG) positron emission tomography (PET) are important imaging tools in the presurgical evaluation of patients with partial DRE. In SPECT scan, the largest and most intense ictal hyperperfusion cluster is assumed to represent the ictal onset zone; however, in PET scan, the region of predominant hypometabolism contains the epileptogenic zone (Van Paesschen et al., 2007).
Figure 7: Coronal T2-weighted 3T MRI (on the left), and coronal FLAIR (on the right) showing heterotopic grey matter nodules in the right temporal region, and atrophy of the ipsilateral hippocampus with loss of surface and internal structure, and enlargement of the CSF space in the respective temporal horn.

7.1 SPECT

Its application is based on the assumption that the increased ictal neuronal activity during epileptic seizures is associated with increased metabolism and regional cerebral blood flow (rCBF) (La fougeré et al., 2009). Ictal SPECT has a high sensitivity to localize the epileptic focus (Lee et al., 2011). Ictal SPECT is performed by injecting radiotracer intravenously during seizures. It utilizes 99m Tc-hexamethylpropyleneamine oxime (99m Tc-HMPAO) or 99m Tc-ethylcysteinate dimer (99m Tc-ECD) to study cerebral perfusion in the ictal state. Both of these tracers have a rapid first pass uptake and a relatively long half-life (Van Paesschen et al., 2007). This allows storing them at the bedside for ictal injection as well as a generous time window of up to six hours post-injection to acquire the images (Wehner & Lüders, 2008).

Cortical and subcortical rCBF changes during seizures may begin with hyperperfusion in the epileptic zone followed by rapid extension to other regions due to seizure spread and generalization. Thus, a SPECT hyperperfusion pattern often contains both the ictal onset zone and the propagation pathways (La fougeré et al., 2009). This phenomenon is followed by postictal hypoperfusion within one to two minutes in TLE (Richardson, 2010). It has been estimated that the seizure should last at least ten seconds after the injection in order to obtain localizing information (Wehner & Lüders, 2008). Ictal SPECT may result in a false localization or lateralization because of a delay between seizure onset and tracer injection, which is called “posictal switch” phenomenon (Newton et al., 1992).

7.2 SISCOM (Substraction Ictal SPECT Coregistered to MRI)

This multimodality imaging, combines the structural and functional imaging information, improves the
ability to detect and define the extent of epileptogenic lesions and to regionalize potentially epileptogenic foci in patients who have normal MRI scans (La fougère et al., 2009). The protocol was introduce by O’Brien and colleagues at Mayo Clinic.

SISCOM technique compares an ictal SPECT image with the same patient’s interictal SPECT image, and produces a difference image between the two SPECTs. Theoretically SISCOM is expected to reveal cerebral perfusion changes during seizure more accurately than the visual inspection of ictal SPECT. SISCOM significantly increased the sensitivity of ictal SPECT and provides a more accurate anatomic localization of seizures by also using MRI (Lee et al., 2011).

7.3 PET

The glucose analog FDG is the tracer most widely used. It is an indirect marker of neuronal activity. The epileptogenic focus in the interictal phase usually appears as a hypometabolic area on FDG-PET (La fougère et al., 2009). Although the underlying neurobiology of hypometabolism is not well understood, it has been ascribed to factors such as neuronal loss, diaschisis, inhibitory processes and reduction in synaptic density (Van Paesschen et al., 2007).

The area of decreased glucose utilization in TLE is typically more extensive than the epileptogenic zone and may extend into the adjacent inferior frontal or parietal lobe cortex, as well as the ipsilateral thalamus. The extent of cortical glucose metabolism on PET scan represents a dynamic process related to the frequency of seizures. Most patients with persistent or increased seizure frequency show enlargement in the area of hypometabolism on the second PET scan. In patients with improved seizure control, a decrease in the size of the hypometabolic cortex is observed (Van Paesschen et al., 2007). Additionally there is a direct relationship between severity of FDG-PET hypometabolism and interictal regional delta slowing in TLE, suggesting related underlying pathophysiological mechanisms for metabolic and electrical dysfunction in TLE (Van Paesschen et al., 2007; Richardson, 2010).

Thus FDG-PET has lateralizing value rather than localizing significance in TLE, mainly by confirming hypometabolism in the area considered for surgical resection (Wehner & Lüders, 2008). FDG-PET may offer localizing value in patients with TLE who do not have a structural abnormality on MRI, which led to coin the term “MRI-negative PET-positive TLE” (Carne et al., 2007). The patients with non-lesional epilepsy usually demonstrate more widespread PET abnormalities than those with HS.

As a rule, PET and SPECT scans must be used only as an adjunct test in surgical planning of patients with epilepsy.

8 Language and Memory Tests

8.1 Neuropsychological Evaluation

The assessment of the presurgical cognitive functioning can provide key information about seizure lateralization and localization and help to identify patients who are at risk of cognitive decline following surgical treatment (Sheth, 2002). Patients with TLE often show deficits of memory, particularly if the seizures are arising from the dominant temporal lobe. Patients with dominant TLE typically display deficits in verbal memory, whereas those with epilepsy arising from the non-dominant TLE show deficits in visuospatial memory (Giovagnoli & Avanzini, 1999). In addition to memory dysfunction, patient with mesial TLE in the dominant hemisphere often demonstrate confrontation-naming problems, marked by
8.2 The Wada Test

The intracarotid amobarbital procedure (IAP) was first reported by Wada in 1949 and was used for language lateralization. Since the early 60s the Wada test also has been used to predict postoperative amnesia, memory decline and language disability in the presurgical evaluation of TLE. This test uses the functional inactivation of a single hemisphere by injection of sodium amobarbital into the ipsilateral internal carotid artery. During this temporary deficit, the language and memory abilities of the active contralateral hemisphere can be assessed in isolation. Both hemispheres are tested consecutively with about 30 minutes between injections. There is a general consensus that over 90% of right-handed individuals show left hemispheric language dominance. Thus, language can often be reliably lateralized by the Wada test (Dinner & Loddenkemper, 2008).

Because of its invasiveness, IAP carries risks and therefore should be performed only in selected patients. The IAP is still valid in evaluating epilepsy surgery candidates with atypical or bilateral language representation and when functional MRI (fMRI) is inconclusive regarding language lateralization. When EEG or neuropsychological testing provides evidence of significant bitemporal dysfunction, the IAP can provide information regarding the risk for postoperative amnesia (Sharan et al., 2011).

8.3 fMRI

Changes in brain blood flow are accompanied by changes in blood oxygenation, which can be detected with fMRI through the so-called blood oxygenation-level-dependent (BOLD) response. If blood flow changes can be deliberately manipulated by controlling a subject’s activity, the brain regions responsible for that activity may be detected (Richardson, 2010). fMRI using BOLD techniques is increasingly used in patients with TLE, mainly in the presurgical evaluation, to determine the hemispheric dominance for language. Numerous studies have demonstrated a very good correlation between fMRI and the Wada test (Sabbah et al., 2003, Rabin et al., 2004). The fMRI has several advantages over Wada test, which include being a non-invasive risk-free technique, lower cost, repeatability, and generating continuous measure of language lateralization. The main limitations of the fMRI are the presence of artifacts mainly generated by movement and patients’ high cooperation demand in order to perform the tasks (Alvarez-Linera Prado, 2007).

Expressive language function is assessed with verbal fluency and verb generation tests, while receptive language function is tested with a reading comprehension task. The symmetry of activation can be calculated, allowing hemispheric language dominance to be estimated as a continuous variable. Considerable heterogeneity exists with regard to the degree of language reorganization in patients with epilepsy. This heterogeneity is related to the underlying pathology, and must be taken into account when planning surgical treatment adjacent to language areas (Duncan, 2010).

9 Treatment

9.1 Antiepileptic Drugs and Education

Antiepileptic drugs (AEDs) provide satisfactory control of seizures in most patients with epilepsy. About 60% of patients with TLE respond to AEDs, and 40% have DRE epilepsy (Kwan & Sander, 2004). If
two or three drug regimens have not brought seizure control, the diagnosis of TLE should be reevaluated, and if DRE epilepsy is confirmed, surgical or palliative options should be considered (Elger & Schmidt, 2008). To improve patient care and facilitate clinical research, the ILAE appointed a Task Force to formulate a consensus definition of DRE. This definition outlines DRE as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010).

The choice of the AED needs to be individualized taking into account the patient profile, tolerability, safety, ease of use, pharmacokinetics, including the current or likely future need for concomitant medication for comorbidity, and cost (Elger & Schmidt, 2008). The drug is started at the lowest effective dose. If seizures continue, the daily dose is increased by small increments to the average effective dose (Elger & Schmidt, 2008). When single-drug therapy is not able to control seizures, adding a second drug and substitution monotherapy are common options. When the initially prescribed AED fails to produce seizure freedom, transfer to monotherapy with an alternative agent (substitution) will lead to seizure control in as many as 15–30% of cases (Schmidt & Gram, 1995; Kwan & Brodie, 2001).

The new AEDs are generally similar in efficacy; none of the modern AEDs evaluated in the SANAD trials was more efficacious than carbamazepine or valproate in their respective comparison groups (Marson et al., 2007). Carbamazepine leads to complete seizure control in about 50% of patients; subsequent regimens with combination or substitution achieve control in up to 10-15% (Marson et al., 2007). In general, treatment with modern AEDs results in fewer adverse drug interactions and in fewer hypersensitivity reactions (Elger & Schmidt, 2008). Recently, Bolin & Forsgren evaluated the cost-effectiveness of newer AEDs as treatment for partial-onset seizures. Bolin concluded that some newer AEDs are cost effective and when used as adjunctive treatment they generate significant clinical effects (Bolin & Forsgren 2012). Although reviewed studies report the cost effectiveness of several new (second-generation) AEDs, the cost effectiveness for most drug-setting combinations is unknown.

Non-pharmacological measures play an important supporting role in treating patients with TLE. There is a broad and extensive literature documenting the psychiatric, behavioral, and psychosocial comorbidities of epilepsy. However, research evaluating formal psychosocial interventions to ameliorate these comorbidities is rare. Mittan described a tremendous lack of psychosocial support programs in epilepsy centers; low participation by patients was an unexpected barrier (Mittan, 2009). Undoubtedly, epilepsy targeted psychosocial treatments need to be integrated into the treatment flow of specialty clinics. Specific therapies such as cognitive behavioral therapy have demonstrated to be useful patients with epilepsy and comorbid depression and anxiety symptoms. A pilot study results demonstrated improvements in depression, anxiety, negative automatic thoughts, and cognitive therapy knowledge and skills (Macrodimitris et al., 2011b).

In general, patients with TLE need to know that continued treatment with AEDs is necessary. Family members must be taught a commonsense attitude toward the patient. Overprotection should be replaced with sympathetic support in order to reduce feelings of inferiority and self-consciousness and other emotional handicaps. Exercise is recommended; even such sports as swimming and horseback riding can be permitted when seizures are controlled. A normal life with social activities should be encouraged including challenges that healthy persons face. A seizure provoking life style should be avoided; in particular excessive alcohol intake and sleep deprivation. Cocaine and several other illicit drugs can trigger seizures (Elger & Schmidt, 2008). DRE is associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Early referral for epilepsy surgery is advisable in selected cases.
9.2 Surgical Treatment

Forty percent of patients with partial epilepsy will eventually become refractory to medical treatment and could be potential candidates for epilepsy surgery (Kwan & Sander, 2004). In this population successful surgery improves quality of life and reduces health care costs by minimizing hospitalization and use of AEDs (Unnwongse et al., 2010). Predictors of DRE are high frequency of seizures, presence of a structural lesion, neurological abnormalities, duration of epilepsy, early onset, previous history if FS, previous occurrence of status epilepticus and multifocal EEG findings (Spencer, 2002a). Mesial TLE is one of the most intractable partial epilepsies achieving seizure control with medical therapy in only 25-40% of patients (Spencer, 2002a).

The safety and efficacy of surgery for TLE was well established in a randomized clinical trial by Wiebe (Wiebe et al., 2001). In this study, patients with TLE were randomized to receive medical treatment versus surgical treatment. At the end of the first year of follow-up 58% of patients in the surgical group were seizure-free compared with only 8% of those receiving medical treatment (P < 0.0001). Recently Engel (Engel et al., 2012) conducted a multicenter randomized controlled trial in patients with mesial TLE, comparing a group of patients who underwent early surgery for epilepsy with another group who only used AEDs, with a minimum follow-up of two years. Seizure freedom was established as the primary outcome. Quality of life, cognitive function and social adaptability were the secondary outcomes. The calculated sample was 200 patients, but only 38 were included. The authors conclude that surgical intervention group has more probability of being seizure free at two years follow-up compared with the control group (Engel et al., 2012). The recruitment failure was due to patients with TLE not accepting to be operated in the early stages. This finding indicates that patients require a certain number of years with intractable epilepsy and a significant impairment in their quality of life to feel the need to be operated.

The most common epilepsy surgery procedure is temporal lobe resection. Hader (Hader et al., 2013) published a systematic review about epilepsy surgery complications. They found that the majority of postsurgical complications are trivial or temporary, and tend to resolve completely. Minor medical complications are reported in 5.1% of patients, whereas major medical complications occur in 1.5% of cases. The most common minor medical complication is CSF leak noted in 8.5% of patients followed by aseptic meningitis 3.6%, bacterial infection 3.0%, and intracranial hematomas 2.5%. Minor neurologic complications occur in 10.9% of patients, whereas major complications are identified in 4.7% of patients. Minor neurologic complications are twice as frequent in children. Major neurologic complications are also more common in children and they are usually seen after extratemporal resections. The most common neurologic complication after resective epilepsy surgery is a minor visual field deficit (one quadrant or less) seen in 12.9% of patients, and the majority of cases are asymptomatic (Hader et al., 2013).

Other studies have shown that despite effectiveness and safety of TLE surgery, it carries risks to memory and naming functions. The evidence shows that after left temporal lobectomy, 44% of patients exhibit verbal memory decline, and 34% show naming difficulties (Sherman et al., 2011). Underlying mood and psychiatric disorders may also worsen in up to 18% of patients (Macrodimitris et al., 2011a).

The procedures more frequently practiced are standard anterior temporal resection and amygdalo-hippocampectomy. Several studies report similar success rate with both techniques achieving seizure freedom between 60 and 70% (Lutz et al., 2004). It is believed that memory is better preserved in patients who undergo amygdalohippocampectomy compared with patients who receive anterior temporal resection (Wieser & Hane, 2003; Wieser et al., 2003; Lutz et al., 2004), however no randomized study exists to corroborate the information.
Téllez-Zenteno et al performed a systematic review evaluating long-term outcomes in epilepsy surgery. On average, 14% of the patients with temporal lobe surgery achieved long-term AED discontituion, 50% achieved monotherapy, and 33% remained on polytherapy. Long-term seizure freedom was consistently lower after extratemporal surgery and palliative procedures. Children achieved better AED outcomes than adults. Seizure freedom after surgery was associated with lower mortality. Intelligence was unchanged by surgery. Additionally, successful epilepsy surgery can halt or improve the cognitive decline seen in chronic epilepsy, and that left temporal resections have a higher risk of additional postoperative verbal memory impairment (Téllez-Zenteno et al., 2007).

9.3 Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) is a procedure that has been used in recent years (Cramer et al., 2001). The device produces intermittent electrical current to the cervical vagus nerve; it desynchronizes the cerebral cortical activity, thereby attenuating seizure frequency (Connor et al., 2012). When patients feel an aura, they can activate the stimulator and likely stop the seizure by swiping a magnet over the device (Cramer et al., 2001). VNS has been shown to reduce the frequency and intensity of seizures, but it has failed to produce any visible electroencephalographic changes (Hammond et al., 1992).

The stimulator is implanted around the left vagus nerve. The left side is chosen, as the stimulation of the right vagus nerve is more likely to cause bradycardia (Bingmann, 2008). Sometimes Left VNS implantation can be hindered because of the presence of acute side effects associated with its placement (wound infection, left vocal cord palsy, lower facial palsy, bradycardia or asystole), or intraoperative complications (severe bleeding during cervicotomy). Right side VNS placement may be considered in these cases. Navas et al described two patients with intractable epilepsy who underwent a Right VNS procedure due to complicated or failed previous Left VNS. In both patients, Right VNS therapy successfully reduced seizure activity without causing cardiac side effects. It seems that Right VNS placement is an optional therapy for children and adults with refractory epilepsy who are not candidates for Left VNS implantation. However, close follow-up and frequent electrocardiographic monitoring is required to detect the presence of cardiac side effects (Navas et al., 2010).

In 1997, The US Food and Drug Administration approved VNS as an adjunctive therapy in the reduction of seizures in adults and in adolescents older than 12 years with partial onset seizures, who are refractory to antiepileptic medications, and are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies (Fisher & Handforth, 1999). Since 1997, VNS has been an alternative treatment for intractable epilepsy worldwide (Burakgazi et al., 2011). Recently, a controlled clinical trial has reported a 50% seizure control rate in about 30% of patients (The Vagus Nerve Stimulation Study Group, 1995). However, VNS efficacy seems to vary among teams and the type of patients. For example, according to Burakgazi (Burakgazi et al., 2011) VNS is more effective in treatment of partial seizures originating from frontal lobe with 65% satisfactory response rather than in temporal lobe seizure with 15% satisfactory response.

Common adverse effects include coughing, hoarseness of voice, dyspnea, and headache. These effects are seen during stimulation and tend to habituate with time. Serious adverse effects have been reported and include vocal cord paralysis, infection, Horner’s syndrome, lower facial muscles paresis, and cardiac arrest (Bingmann, 2008).

García-Navarrete et al. performed a prospective study to assess the long-term outcome of VNS treatment in adults with DRE (García-Navarrete et al., 2013). They published 18-months follow-up data from a sample of patients treated with VNS and stable AEDs, they found that 62.8% of their series of
43 medication-resistant epileptic patients experienced a significant (similar or greater than 50% reduction in their seizure frequency) long-term seizure reduction after VNS, even in a situation of an unchanged medical therapy, concluding that VNS is an effective therapy in the long-term control of medication-resistant seizures (García-Navarrete et al., 2012). This finding is completely in line with the great number of reports on VNS from the last 15 years. Hoppe (Hoppe, 2013) commented in an editorial that the recommendation of VNS in patients with DRE is currently not supported by appropriate evidence, inquiring that the studies on therapeutic superiority are still missing and the clinical effectiveness of add-on VNS over best drug therapy has not been shown so far (Hoppe, 2013).

9.4 Electrical Brain Stimulation

Virtually all open-label electrical stimulation studies in epilepsy report beneficial effects, regardless of the stimulation target (thalamus, subthalamus, neocortex, hippocampus and cerebellum). These procedures hold the promise of an intervention that is nonresective, minimally invasive, dose adjustable, largely reversible, and presumably safe (Téllez-Zenteno & Wiebe, 2011).

The anterior thalamus is known to play a role in seizure propagation. Thalamic deep brain stimulation is a novel treatment for patients with generalized seizures, who are not typically candidates for resective surgery. Recently, a multicenter randomized blinded study explored the effect of electrical brain stimulation of the anterior nuclei of the thalamus for localization-related epilepsy. Half of 110 patients were randomized to receive stimulation and the other half received no stimulation during a three month blinded phase, followed by unblinded stimulation for all patients in the study. The mean seizure frequency decreased by 14.5% in the control group as opposed to 40% in the stimulation group during the first three months (blinded phase) of the study. By two years, 54% of patients had a seizure reduction of at least 50%, and 14 patients were seizure free for at least six months (Fisher et al., 2010).

The available evidence for Hippocampal stimulation (HS) is weak. The limited evidence suggests that the effects of HS appear to be cumulative and accrue with time, and the procedure seems to be safe. Neither the optimum target (amygdala, hippocampus, pes hippocampus, parahippocampal gyrus) nor the optimum stimulation parameters are known. However the reversibility of HS, supported partly by histopathological integrity of the stimulated tissue and lack of overt clinical or EEG changes on short-term studies, is also alluring. However, almost nothing is known about the late or long-lasting effects of electrical stimulation on synaptic physiology, connectivity, function, and epileptogenicity. Therefore, the HS may be considered for patients with contraindications for a resective procedure due to risks to memory and naming functions or because of bitemporal epilepsy. In addition, it could be an option for patients with a strong preference for a nonresective, minimally invasive procedure (Téllez-Zenteno & Wiebe, 2011).

9.4.1 Trigeminal Nerve Stimulation

Trigeminal nerve stimulation (TNS) is an emerging neuromodulation therapy with unique advantages: it can be delivered externally or subcutaneously, bilaterally, and at low cost. Initial experiments showed that TNS was effective at reducing pentylenetetrazole-induced seizures in awake-animals. Additionally, these studies showed that bilateral trigeminal stimulation was more effective than unilateral stimulation, and that TNS was effective when delivered in a closed-loop, seizure-triggered paradigm (DeGiorgio et al., 2011). The safety and preliminary efficacy of TNS for epilepsy was evaluated in a pilot feasibility study of transcutaneous stimulation of the infraorbital and supraorbital branches of the trigeminal
nerve. Four (57%) of seven subjects who completed three months or more experienced a more than 50% reduction in seizure frequency (DeGiorgio et al., 2006). On the other hand, external TNS of the supraorbital or infraorbital nerve is safe and well tolerated. No adverse hemodynamic effects have been observed (Pop et al., 2011). Results from early studies provide important data on effectiveness and safety. Future studies will be required to demonstrate the real efficacy of this therapy.

9.5 Radiosurgical Treatment

Radiosurgery is the precise application of focused radiation to a targeted volume area within the brain identified on MRI. Radiosurgery allows the neurosurgeon to deliver precise and accurate radiation to a smaller volume without effecting large portions of normal parenchyma allowing for a powerful radiobiologic effect on the chosen targeted volume (Nguyen & Spencer, 2003).

TLE is particularly amenable to radiosurgery because 80–90% of these cases show changes on MRI (Dillon & Barbaro, 1999). A prospective multicenter European study evaluating Gamma Knife(R) surgery for MTS showed comparable efficacy rates (65%) for seizure reduction by conventional surgery or radiosurgery, after two years of follow up (Régis et al., 2004). Although radiosurgery has proven effective and safe in ameliorating MTS associated seizures, the beneficial effects of radiosurgery are not displayed immediately. Most patients achieve seizure reduction at 9–12 months and complete cessation of seizures between 18–24 months after radiosurgical treatment (Yang & Barbaro, 2008). This procedure is an attractive option for TLE treatment because of its low morbidity and mortality, however prospective trials with larger numbers of patients will be required to establish radiosurgery as a standard therapy for mesial TLE.

9.6 Future Directions in the Management of TLE

Epilepsy is a disorder characterized by a diffuse brain dysfunction, not just a disorder that produces seizures. After some years of investigation finally we understand that there is a strong relationship between TLE and other comorbidities such as cognitive, behavioral, and psychiatric disorders (Linehan et al., 2011). This complex scenery will determine future directions in the management of patients. In the last years, there have had technological outbreaks in electrophysiological techniques, neuroimaging, and genetic testing. Integrated approaches, such as imaging and electrophysiology will be central to progress in predicting epileptogenic zone in people with epilepsy (Jacobs et al., 2001). At the same time, the range of available pharmacological and non-pharmacological treatments, including use of surgery, has greatly expanded.

Research directions for the future include determination of mechanisms of epilepsy development, identification of genes for common epilepsy syndromes through linkage analysis and gene chip technology, and validation of new models of epilepsy and epileptogenesis. Directions for therapeutics include identification of new molecular targets, focal methods of drug delivery tied to EEG activity, gene and cell therapy, and surgical and non-ablative therapies (Jacobs et al., 2001). The evaluation of patients with refractory epilepsy should use studies that better characterize the epilepsy network (specifically PET, functional MRI) in addition to studies that are aimed to localize the “seizure onset” like EEG (Spencer, 2002b).
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