Review of Epilepsy - Etiology, Diagnostic Evaluation and Treatment

Hae Won Shin*, Valerie Jewells, Eldad Hadar, Tiffany Fisher and Albert Hinn

Director of Epilepsy Monitoring Unit and Epilepsy Fellowship Program, Department of Neurology, University of North Carolina, USA

Abstract

Epilepsy is the fourth most common neurological disorder in the US, affecting nearly 2.5 million Americans. The economic impact of epilepsy represents estimated direct and indirect costs of 12.5 billion dollars per year. Patients with this disorder experience increased morbidity and mortality with long term fatality rates of 24%. Multiple diagnostic tools are used to identify and classify the seizure type/syndrome, etiology and localization of seizures, including electroencephalogram (EEG), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT), magneto encephalogram (MEG), and neuropsychiatric testing. Despite 29 different antiepileptic medications that are available in the US, one third of patients remain refractory to pharmacological treatment. In these intractable epilepsy patients, non-pharmacological treatments can be considered. Commonly used non-pharmacological treatment options for epilepsy include epilepsy surgery, neurostimulation therapy, and diet therapy.

Keywords: Epilepsy; Seizure

Introduction

A seizure is a clinical manifestation, resulting from a brief episode of abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a brain disorder characterized by a chronic predisposition to generate epileptic seizures with secondary neurobiologic, cognitive, psychological, and social consequences. By definition, epilepsy requires typically two unprovoked seizures, separated by greater than 24 hours [1]. Epilepsy and seizures affect nearly 2.5 million Americans of all ages. Overall, epilepsy affects 1-3% of the US population. The incidence rate is U-shaped: the highest incidence rates are noted in young patients in neonatal and as well as in elderly patients over 75 years old [2,3]. Estimated direct and indirect costs from epilepsy and seizures are 12.5 billion dollars/year in the US, and there are approximately 200,000 new cases of epilepsy diagnosed every year [4,5]. This paper aims to introduce the current knowledge and understanding of epilepsy in various aspects of epidemiology, etiology, diagnostic work up and treatment options to rehabilitation specialists without neurology background.

Patients with epilepsy are at an increased risk of premature death with a mortality risk of 1.2-9.3 of all causes of death and a 24% long term fatality rate [6,7]. Sudden unexpected death in epilepsy (SUDEP) is well-known condition of sudden unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence for a seizure and excluding convulsive status epilepticus in which post-mortem examination does not reveal a toxicological or anatomical cause for death. The risk of SUDEP ranges from 1 to 9 per10000 epilepsy patients per year. The 40 year cumulative risk increases up to 7% for all epilepsy patients and 12% in poorly controlled epilepsy [6,7].

There are various treatment options for epilepsy, with antiepileptic medications being the first line treatment. Despite 29 different antiepileptic medications being available in the US (Table 1), one third of patients still experience intractable seizures [8]. Medically intractable or refractory epilepsy is defined as the failure of adequate trials of two tolerated and appropriately chosen antiepileptic medication schedules with adequate doses [9]. Patients with intractable epilepsy experience a significantly increased risk of injuries and premature death, as well as negative consequences upon their quality of life, cognition, and mood [4,5,10-19]. Patients with epilepsy suffer from lower socioeconomic status and lower quality of life compared to other general population in validated quality of life in epilepsy questionnaire (QOLIE). Fewer epilepsy patients married or had children, higher education or achievement in later life than the general population [4,5,10,14,15]. Also, patients with poorly controlled epilepsy experience decline in memory and cognition [10,12,14,15,17]. Co-morbid mood disorders such as depression and anxiety are common and more prevalent in patients with epilepsy compared to the general population [15,19]. In these uncontrolled patients, other treatment options are available and dependent upon the seizure type, localization of seizure onset, age, and co-morbid conditions. These treatment options include epilepsy surgery, neurostimulation therapy, and diet therapy.

Result and Discussion

Seizure type and classification

In 1981, the International League against Epilepsy (ILAE) recommended an updated and consistent classification of seizures. In 2010, the ILAE-revised the terminology and concepts for organization of seizures and epilepsy were introduced, and included many epilepsy syndromes and pathophysiologic etiologies. The classifications are shown in Figure 4 [20].

Seizures can be provoked by a variety of influences including severe metabolic disturbance, head trauma, alcohol intake and withdrawal, fever, illness and some medications. Causes of epilepsy are also broad, and include traumatic brain injury, stroke, tumor, central nervous system (CNS) infection such as viral and bacterial meningocerebralitis, inflammation or autoimmune diseases, genetic causes such as SCN1A mutation in Dravet syndrome, and structural brain abnormalities including hippocampal sclerosis, cortical dysplasia and vascular malformation.

*Corresponding author: Hae Won Shin, Assistant Professor, Director of Epilepsy Monitoring Unit and Epilepsy Fellowship Program, Department of Neurology, University of North Carolina, USA, Tel: 919-966-8175; Fax: 919-966-2922; E-mail: shinhw@neurology.unc.edu

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The sensitivity of EEG for epilepsy is 50% and specificity is 98-99%, while can be made only when a seizure is captured during an EEG. The with epilepsy, but are not pathognomic. EEG confirmation of seizures brain activity. Epileptiform discharges in EEG are highly correlated testing. EEG plays a critical diagnostic role via sampling of electrical (SPECT), magneto encephalogram (MEG), and neuropsychiatric tomography (PET), single photon emission computed tomography (SPECT), magneto encephalogram (MEG), and neuropsychiatric testing. EEG plays a critical diagnostic role via sampling of electrical brain activity. Epileptiform discharges in EEG are highly correlated with epilepsy, but are not pathologic. EEG confirmation of seizures can be made only when a seizure is captured during an EEG. The sensitivity of EEG for epilepsy is 50% and specificity is 98-99%, while serial EEGs can increase the sensitivity up to 80-90%. In addition, various activation procedures such as hyperventilation, photic stimulation and sleep deprivation can increase the sensitivity of the test [21].

Diagnostic Work-Ups for Seizure and Epilepsy

It is important to find possible causes of seizures so that proper treatment can be administered. When a patient presents to a neurologist for seizures or epilepsy, adetailed history and neurological examination are undertaken to determine the seizure etiology, type and localization of epilepsy foci to provide prognostic information. Routine laboratory tests in patients with new onset seizures include CBC, electrolytes, hepatic enzyme panel and toxicology screens to assess for potentially reversible causes [21]. Additionally, if bacterial, fungal, or viral infection other inflammatory brain disorders suspected, a lumbar puncture is performed for cerebral spinal fluid (CSF) analysis. In selected cases, further laboratory evaluation with genetic, autoimmune and paraneoplastic panels, may provide additional information about the cause of seizures and epilepsy. Genetic and autoimmune epilepsy are relatively new diagnoses and have provided additional information about the etiology of epilepsy and epileptogenesis [22-28]. Figure 4 summarizes common genetic and autoimmune epilepsies.

Various diagnostic tools are utilized to identify and classify the seizure type/syndrome and etiology, including electroencephalogram (EEG), magnetic resonance imaging (MRI), and positron emission tomography (PET), single photon emission computed tomography (SPECT), magneto encephalogram (MEG), and neuropsychiatric testing. EEG plays a critical diagnostic role via sampling of electrical brain activity. Epileptiform discharges in EEG are highly correlated with epilepsy, but are not pathologic. EEG confirmation of seizures can be made only when a seizure is captured during an EEG. The sensitivity of EEG for epilepsy is 50% and specificity is 98-99%, while serial EEGs can increase the sensitivity up to 80-90%. In addition, various activation procedures such as hyperventilation, photic stimulation and sleep deprivation can increase the sensitivity of the test [21]. Long term video-EEG monitoring has further provided improved diagnostic yield in seizures and epilepsy, and has been commonly used for seizure/spell characterization, rapid antiepileptic medication adjustment, and epilepsy surgery evaluation. The international 10-20 system is a standardized and widely used method to place scalp electrodes. Normal awake EEG is shown in Figure 1. A right temporal lobe seizure is shown in Figure 2.

Neuroimaging studies play an integral part of seizure and epilepsy evaluation for the determination of the structural and functional etiology of seizures. Current standard neuro-radiological imaging includes 3T brain MRI with coronal or oblique-coronal images using T1-weighted and T2-weighted sequences as well as fluid-attenuated inversion-recovery (FLAIR). Although 1.5T brain MRI can also localize seizure foci, it is less sensitive than higher field 3T MRI [29]. The sensitivity of MRI for intractable epilepsy is in general 82-86% [30,31]. Since many different lesions may cause seizures, MRI is often a starting point for differentiation. These lesions include mesial temporal sclerosis (MTS), congenital brain abnormalities both migrational and syndromic like Sturge Weber, tumors, infections and vascular malformations such as cavernous malformations and arteriovenous malformations. A classic case of MTS will exhibit hippocampal atrophy with abnormal T2 and FLAIR signal in the hippocampus (Figures 3a and 3b), as well as decreased FDG uptake in PET scan (Figure 3c).

In selected patients other imaging techniques are used including functional neuro-imaging. PET (Figure 3c) is used to demonstrate regional differences in metabolic activity, SPECT is used to analyze

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Table 1: Common Genetic and Autoimmune Epilepsies [19-25]

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes and loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Seizures</td>
<td>8q13-q21 (FEB1), 19p (FEB2), 2q23-q24 (FEB3), 5q15-q15 (FEB4), 6q22-24 (FEB5), 18q11 (FEB6)</td>
</tr>
<tr>
<td>Genetic epilepsy with febrile seizures plus</td>
<td>SCN1A, SCN2A, SCN1B, GABRD, GABRG2, PCDH19, ARX, CDK15, STXBP1</td>
</tr>
<tr>
<td>Severe myoclonic epilepsy of infancy and related syndromes</td>
<td>SCN1A, SCN2A, GABRG2</td>
</tr>
<tr>
<td>West syndrome and early infantile epileptic encephalopathy with suppression-burst</td>
<td>ARX, CDK15, STXBP1</td>
</tr>
<tr>
<td>Malignant migrating partial seizures of infancy</td>
<td>KCNT1</td>
</tr>
<tr>
<td>Other early onset epilepsies</td>
<td>PLCB1, PCDH19, KCTD7, BCKDK, SYN1, GRIN2B, GRIN2A, TNK2, KCNQ2</td>
</tr>
<tr>
<td>Benign familial neonatal convulsions</td>
<td>KCNQ2, KCNQ3</td>
</tr>
<tr>
<td>Benign familial neonatal-infantile seizures</td>
<td>SCN2A</td>
</tr>
<tr>
<td>Benign familial infantile seizures</td>
<td>PRRT2, ATP1A2, TBC1D24, EFHC1, GABRA1</td>
</tr>
<tr>
<td>Familial infantile myoclonic epilepsy</td>
<td>GABRG2, GABRA1, SLC2A1</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>SLC2A1</td>
</tr>
<tr>
<td>Childhood absence epilepsy</td>
<td>CHRNA4, CHRNA2, CHRNB2, KCNT1</td>
</tr>
<tr>
<td>Epilepsy + paroxysmal exercise-induced dyskinesia</td>
<td>LGI1</td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>DEPDC5</td>
</tr>
<tr>
<td>Familial lateral temporal lobe epilepsy</td>
<td></td>
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<tr>
<td>Familial focal epilepsy with variable foci</td>
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</tbody>
</table>

Common Genetic Autoimmune Epilepsies: Anti-NMDA antibody, Anti-GABAB antibody, Anti-AMPA antibody, Anti-LGI1 antibody, Anti-CASPR2 antibody, Anti-contactin-2 antibody, Anti-GAD antibody, Anti-VGKC antibody.
Figure 1: Electroencephalogram (EEG) of normal awake state. EEG setting: Bipolar montage, 15 sec/page, LFF 1Hz, HFF 70 Hz

Figure 2: Electroencephalogram (EEG) of a right temporal lobe seizure. The arrow indicates the seizure onset with rhythmic alpha activity. EEG setting: Bipolar montage, 22 sec/page, LFF 1Hz, HFF 70 Hz
regional differences in blood flow during a seizure (ictal SPECT) and between seizures (interictal SPECT) and MR Spectroscopy (MRS) is used to analyze the biochemical makeup of the imaged tissue [32-38]. MRS can be used to analyze a lesion to distinguish between tumor and gliosis. MEG and functional MRI have also been found to provide further information to localize a potential epileptogenic lesion and to identify the surrounding areas of eloquent cortex [39]. These studies are of particular assistance with cases in which focal seizures are suspected, but the brain MRI is negative.

**Treatment Options**

**Pharmacological treatment**

The primary treatment strategy for provoked seizures is the elimination of the underlying cause, such as correcting a metabolic disturbance, treating an underlying infection, etc [21]. Epilepsy is defined by two unprovoked seizures greater than 24 hours apart, and typically requires pharmacological treatment to prevent further seizures. Since the first anticonvulsant bromide was used in 1857, numerous antiepileptic medications have been developed and administered. Currently, there are 29 different antiepileptic medications available in the US (Table 2). Some of these medications including benzodiazepines, lamotrigine, levetiracetam, topiramate, valproic acid and zonisamide have broad spectrum coverage to treat both primary generalized and focal onset seizures, while others work better on focal onset seizures such as carbamazepine and oxcarbazepine. Only few medications have level A evidence in various types of epilepsy and epilepsy syndrome while most of medications have lower level evidence. The recent review of antiepileptic drug efficacy and effectiveness as initial monotherapy, conducted by international league against epilepsy showed level A evidence in levetiracetam, zonisamide, carbamazepine and phenytoin in adult patients with partial onset seizures while only oxcarbazepine is shown to have level A evidence in children with partial onset seizures. Valproic acid and ethosuximide have also level A efficacy and effectiveness in children with absence seizures. Other types of primary generalized epilepsy do not have clear level A evidence although there are multiple medications with level C and D evidence [40].

When neurologists choose medications to treat seizures, they consider the evidence of effectiveness/efficacy, seizure classification, potential side effects, comorbid conditions, age and gender in order to select an effective medication while minimizing side effects [21,40,41]. Vaproic acid has been shown to significantly increase the risk of major fetal malformation in women with childbearing age whereas lamotrigine and levetiracetam are found to be more safe choices. Chronic usage of antiepileptic medications can cause bone weakness. Certain hepatic enzyme inducing medications tend to have more drug-drug interactions and potentially become problematic in other co-morbid conditions, requiring anticoagulation, anti-tumoral or anti-HIV treatment. Some of antiepileptic drugs can affect the mood. Levetiracetam has higher risk of causing some irritability, depression and other mood disturbance whereas lamotrigine and valproic acid may have mood stabilizing effects. Certain medications such as topiramate and valproic acid are found to be useful to treat migraine headache [21,40,41].

Despite 29 different antiepileptic medications, one third of patients with epilepsy still suffer from medically refractory seizures [8]. Mohanraj and Brodie reviewed retrospective data of adolescent and adult patients’ responses to sequential antiepileptic medication treatment in Scotland. Overall response rates with the first, second and third treatment schedules were 50.4, 10.7 and 2.7%, respectively, with
Acetazolamide  |  Eslicarbazepine  |  Lacosamide  |  Phenobarbital  |  Tiagabine
Carbamazepine  |  Ethosuximide  |  Lamotrigine  |  Phenytoin  |  Topiramate
Clobazam  |  Ezogabine  |  Levetiracetam  |  Pregabalin  |  Valproic Acid
Clonazepam  |  Felbamate  |  Lorzepam  |  Primidone  |  Vigabatrin
Clorazepate  |  Fosphenytoin  |  Oxcarbazepine  |  Retigabine  |  Zonisamide
Diazepam  |  Gabapentin  |  Perampanel  |  Rufinamide

Table 2: Available Medications Used in the Treatment of Epilepsy in US

Figure 4: ILAE Classification of Seizures (A) and New Recommendation (B) [17]
only 0.8% patients responding optimally to further drug trials [8]. The response to the first medication is a strong predictor of future seizure control.

**Non-pharmacological treatment**

Medically intractable or refractory epilepsy is defined as a failure of adequate trials of two tolerated and appropriately chosen antiepileptic medication schedules with adequate doses [9]. In those patients with intractable epilepsy, other alternative non-pharmacological treatment can be considered including epilepsy surgery, neurostimulation therapy, and diet therapy such as the ketogenic diet. Epilepsy surgery may include focal resective surgery, multiple subpial transections, anterior corpus callosotomy, or hemispherectomy [21].

Neurostimulation therapies include the vagal nerve stimulation (VNS), responsive neurostimulator (RNS) and other investigational neurostimulation modalities [21,32].

Among medically intractable seizure patients, epilepsy surgery is most commonly considered if they have an identifiable seizure focus which is amenable to resection. Epilepsy surgery is an effective and safe alternative form of therapy for those patients with focal onset epilepsy [32,42-51]. Major complications from epilepsy surgery and subdural electrode evaluation have an incidence of less than 7% and long term permanent deficits have an incidence of less than 2% [32-38]. An epilepsy surgery evaluation typically starts with long term video-EEG monitoring to confirm the diagnosis and type of focal onset epilepsy, establish the seizure type and seizure onset zone and determine the disabling effects of ictal behavior [42,59]. In addition, various neuro-radiological imaging techniques are employed to further identify the structural or functional epileptogenic lesion(s). Multiple studies have shown that the prognosis of epilepsy surgery varies depending on the etiology and location of the epileptogenic zone [43-51,60-64]. Radiographically identifiable epileptogenic lesions provide information about the etiology and localization of epilepsy, and can provide prognostic information for focal respective epilepsy surgery. Identifying a structural lesion on MRI provides an excellent prognosis from epilepsy surgery, with 60-90% freedom from disabling seizures [43-51,60-64]. Temporal lobe epilepsy is the most common type of epilepsy, and mesial temporal sclerosis (MTS) is the most common temporal lobe epilepsy [65]. MTS, which can be readily identified on MRI with hippocampal atrophy and increased signal, is known to be medically refractory, but does respond well to anterior temporal lobectomy with better postoperative outcomes than other forms of temporal lobe epilepsy [10,43-48,50,61,63]. When MRI fails to detect a potentially epileptogenic lesion, the chances of an excellent surgical outcome are significantly lower, ranging from 20-65% [40-44]. This may reflect the difficulty in localizing and resecting the epileptogenic zone [60]. In order to improve the radiographic detection of epileptogenic lesions, more advanced imaging techniques have been used such as 7T MRI, volumetric analysis, Diffusion Tensor Imaging (DTI), arterial spin labeling and PET [38,66-74]. However, it is currently unknown if such techniques will improve outcomes.

Accurate localization of the seizure focus is a key component for successful surgical resection [32,42,58,64]. Despite extensive preoperative testing, placement of subdural grid electrodes (SDGE) and depth electrodes (DE) for invasive EEG monitoring is often needed when non-invasive studies have discordant data or fail to show possible seizure foci and areas of eloquent cortex [32,42,58]. SDGE and DE invasive EEG monitoring can help localize the focus of seizures to better delineate the area or areas that need to be resected (Table 3).

### Table 3: Summary of Non-pharmacological Epilepsy Treatment

<table>
<thead>
<tr>
<th>Epilepsy Surgery Techniques</th>
<th>Neurostimulation</th>
<th>Diet Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal Resection</td>
<td>Vagal Nerve Stimulation</td>
<td>Ketogenic Diet, Adkins Diet, Modified Adkins Diet, Others with low glycemic index</td>
</tr>
<tr>
<td>Multiple Subpial Transaction</td>
<td>Responsive Neurostimulation Investigational therapy</td>
<td></td>
</tr>
<tr>
<td>Corpus Callosotomy</td>
<td>Deep Brain Stimulation</td>
<td></td>
</tr>
<tr>
<td>Hemispherectomy</td>
<td>Transcranial Magnetic Stimulation</td>
<td></td>
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<tr>
<td>Electrocorticuive Therapy</td>
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</tbody>
</table>

### Conclusion

Although epilepsy only affects 1-3% of the US population, the economic burden and cumulative fatality are significant. Various diagnostic tools are used to find the etiology, type, and location of epileptic foci. It is important to have an accurate diagnosis and to start appropriate treatment. Despite 29 different antiepileptic medications available in the US, one third of patients remain refractory to pharmacologic treatment. In those patients, other treatments should be considered to improve the quality of life and decrease morbidity and mortality.

### References


