IS EPILEPSY THE DIAGNOSIS?

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Epileptic seizures are a common medical problem. Ten percent of the population will have one seizure and the cumulative lifetime incidence of epilepsy is 3 percent.[1] In the United States, approximately 2.5 million people have epilepsy and 65 million people worldwide have epilepsy. Epilepsy affects people of every background and age and is associated with impaired quality of life and an increased mortality rate of 2-3 times higher than the general population. In addition, epilepsy, as well as its treatment, can have serious consequences and over one half of all patients with epilepsy continue to experience at least occasional seizures despite treatment.[2]

Optimal diagnosis and classification of seizures can reduce the risk of morbidity and mortality and greatly improve the quality of life. Optimal diagnosis of epilepsy is one of the most frequent and greatest challenges facing neurologists. Seizures are one of the leading diagnoses treated by neurologists.[3] Epileptic seizures are challenging to diagnose and the stakes are high. An episode of transient neurologic change could be a seizure, but it is rare that the event is witnessed by the neurologist (unlike movement disorders for example) and other than a video-EEG showing a definite clinical-electrical event, there is no gold standard diagnostic test. Even our most frequently used diagnostic test of EEG, can result in misdiagnosis.[4] Failure to diagnose epilepsy can have significant consequences as seizures can be life threatening. Misdiagnosis of epilepsy can leave the underlying etiology untreated with potentially fatal consequences and result in a reduced quality of life from patient distress, unnecessary driving restrictions, employment difficulties and the unnecessary use of antiepileptic drugs (AEDs) with their inherent immediate and long term side effects.

There are several useful and evidence-based practice parameters from the American Academy of Neurology regarding the diagnosis of epilepsy: Evaluating an Apparent Unprovoked First Seizure in Adults[5], Management of a First Unprovoked Seizure in Adults[6], Reassessment: Neuroimaging in the Emergency Patient Presenting with Seizure[6], Use of Serum Prolactin in Diagnosing Epileptic Seizures[7]. Additionally, there are 3 Epilepsy Quality Measures approved January 2012 by the Centers for Medicare and Medicaid Services (CMS) that are in bold below. Eight measures were approved by the AAN workgroup in 2014[8].

2014 Epilepsy Update Quality Measurement Set
1A. Seizure frequency specified at each encounter (paired measure) (2009 measure revised) **1B. Seizure intervention specified at each encounter (paired measure) (2009 measure revised)**
2. Etiology, seizure type, and epilepsy syndrome specified at each encounter (2009 measure revised)
3. Querying and intervention for side effects of antiseizure therapy specified at each encounter (2009 measure revised)
4. Personalized epilepsy safety issue and education provided yearly (2009 measure revised)
5. Screening for psychiatric or behavioral health disorders specified at each encounter (new measure)
6. Counseling for women of childbearing potential with epilepsy yearly (2009 measure affirmed with updated specifications)
7. Referral of treatment-resistant epilepsy to comprehensive epilepsy center every 2 years (new measure)

Differential Diagnosis of Epilepsy

1. **"Was it (really) a seizure?"**

Patients may present for evaluation of "seizures" or have been diagnosed in the emergency room with a "seizure" and sometimes already are taking an AED. However, no matter how or when the diagnosis of seizure was made,

the first question should be “Was it a seizure?” A thorough and complete history from the patient and eye-witnesses is one of the strongest diagnostic tools (Level B evidence),[9] with the caveat that eye-witness reports can be misleading and/or inaccurate.[10,11] An excellent “Tips for Seizure Observation and Recording” is provided by the American Epilepsy Society. [12]

A seizure is defined as a temporary alteration in brain function due to abnormal excessive or synchronous neuronal activity. However, other causes of altered consciousness and/or bodily shaking are often misdiagnosed as a seizure. Additionally, there are unusual presentations of seizures that are not be initially considered as consistent with seizures[13]. The aphorism: “Not all seizures shake and not all shakes are seizures” is useful to keep in mind. Some of the most common mimickers of seizures in adults are psychogenic events and episodes of reduced cerebral perfusion [14](Tables 1 and 2). Specific questions are more sensitive in differentiating epilepsy from PNES and syncope[15].

Table 1 Clinical distinction of psychogenic nonepileptic seizures (PNES) from tonic-clonic epileptic seizures (ES)

Clinical Feature	PNES	ES
Trigger	Frequent	Rare
Onset	Often gradual	Usually sudden
Movements	May stop and stop, pelvic thrusting, back arching, erratic movements and absence of stereotypy	Usually synchronized and stereotyped
Eyes	Closed	Open
Lateral tongue bite	Rare	Common
Self-injury	Rare	Common
Incontinence	Rare	Common
Post-ictal confusion	Rare	Common
Duration	lengthy (hours)	1-2 minutes
Serum prolactin	usually normal	usually elevated

Syncope commonly results in myoclonic movements that can mimic seizures,[16] referred to as “syncopal convulsions.” Electroencephalograms done during even the most dramatic convulsive movements, do not show seizure activity and rather show slowing or minimal cerebral activity.

Table 2 Features that distinguish syncope versus seizure

Clinical Feature	Syncope	Seizure
Loss of consciousness	Typical	Common
Episode duration	Seconds	Minutes
Involuntary movements	Common	Typical
Triggers	Frequent	Rare
Preceding Symptoms	nausea, blurred vision, feeling hot, tinnitus, palpitations	sensory, motor, psychic auras
Post-Ictal	Amnesia for event, somnolence, headache	Amnesia for event plus confusion, somnolence, headache
EEG	Slow waves, flattening	Focal or generalized spike-wave

Nonepileptic disorders that can be mistaken for epileptic seizures in adults
Syncope (vasovagal/neurocardiogenic, decreased cardiac output, volume depletion, arrhythmia)
Migraine (classic, basilar, confusional, acephalgic)
Cerebrovascular (transient ischemic attack, amyloid angiopathy)
Sleep disorders (REM behavior disorder, narcolepsy, parasomnias)
Movement disorders (tics, nonepileptic myoclonus, tremor)
Transient global amnesia
Psychiatric (panic, dissociation, conversion, malingering)
Syncope (vasovagal/neurocardiogenic, decreased cardiac output, volume depletion, arrhythmia)
Migraine (classic, basilar, confusional, acephalgic)
Cerebrovascular (transient ischemic attack, amyloid angiopathy)

2. Was it a provoked seizure?

Seizures are commonly provoked rather than due to epilepsy. Although determination of a provoking factor may not change the initial work-up, it will significantly impact patient counseling and management. Medications are a common source of provoked seizures, either directly by lowering the seizure threshold or indirectly by leading to metabolic changes such as hyponatremia or hypoglycemia. Illicit drug use and alcohol can lead to provoked seizures as well (Table 4). More comprehensive lists of medications that can provoke seizures are easily available. [17]

Table 4: Some causes of provoked seizures	
Drugs	**Metabolic**
Penicillins	Hyponatremia
Cephalosporins	Hypoglycemia
Metronidazole	Hyperthyroidism
Isoniazid	Nonketotic hyperglycemia
Tramadol	Hypocalcemia
Bupropion	Hypomagnesemia
Phenothiazines	Renal failure
Stimulants (amphetamines, cocaine, ecstasy, PCP)	Porphyria
Withdrawal from CNS depressants (ETOH, baclofen, benzodiazepines, barbiturates, diphenhydramine)	

Acute neurologic injury can lead to provoked seizures, which may require short term treatment with an AED, but do not necessarily lead to epilepsy (e.g., acute head injury, acute stroke, encephalitis).

3. Does the patient have epilepsy?

Epilepsy is defined as the tendency to have recurrent unprovoked seizures. Historically, the operational definition had been having 2 or more unprovoked seizures, but the more recent definition by the International League Against Epilepsy (ILAE) in 2014 only requires 1 seizure and a risk of >60% of having another seizure.

The most recent definition of epilepsy is:

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Additionally, the definition includes that of when epilepsy is resolved: epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

This definition has utility in guiding management and addressing the risk of recurrent seizures after a single seizure, similar to how risk of stroke is managed in individuals with transient ischemic attacks or cerebrovascular disease.

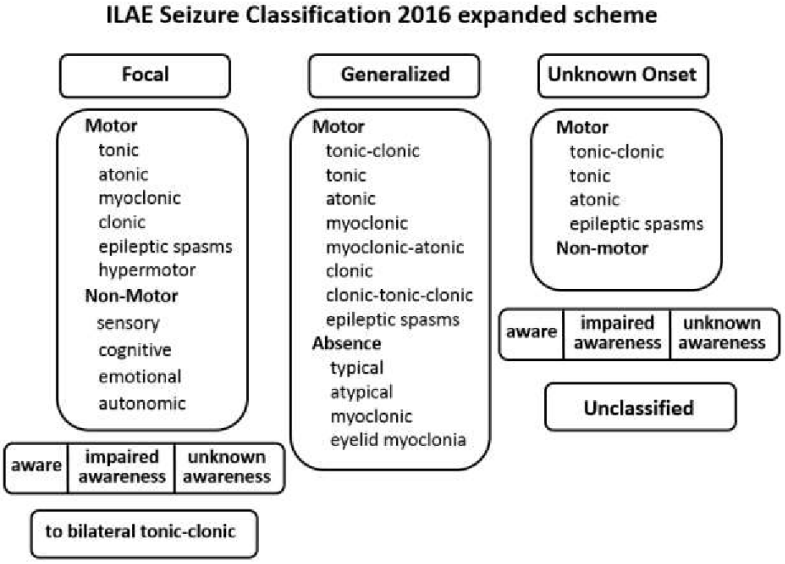
In addition, a detailed history after a recognized single seizure, can often lead to the diagnosis of epilepsy. A clearly recognized seizure after an aura that has occurred in the past in isolation, screening for myoclonic seizures or other events which in retrospect were seizures can lead to the diagnosis of epilepsy. An abnormal EEG, strong family history of epilepsy, or abnormal MRI may also increase the risk sufficiently after a single seizure to allow the diagnosis of epilepsy.

4. Classify epilepsy

The correct classification of epilepsy can be challenging but is critically important for the best care of the patient with epilepsy. Classification leads to determination of the appropriate track in diagnostic testing, treatment, prognosis and patient counseling. The treatment for different kinds of epilepsy varies and a treatment for one can be specifically contraindicated in another. The classification of epilepsy, like other diseases in neurology, is changing with the growing scientific knowledge, particularly in the field of genetics. The ILAE currently has an evolving classification schemes for epilepsy. The first classification system, developed in 1981,[17] divides seizures in to three types, with subtypes of each: partial (focal seizures involving only part of the brain), generalized (seizures involving both hemispheres in the brain), and unclassifiable. This system allowed for simple classification that helped determine diagnostic evaluation, the choice of medication, and prognosis. A supplement to this system of classification was developed in 1989- the ILAE Classification of Epilepsies and Epileptic Syndromes. [18] Epilepsies were divided into four groups: localization-related (involves one or more focal areas of the brain), generalized (involves both hemispheres of the brain at the same time), undetermined, and special syndromes. Within the localized and generalized groups, there are further subdivisions into idiopathic (no identifiable cause), symptomatic (identified or suspected cause), or cryptogenic (a suspected cause that cannot be definitively identified). In 2010, the ILAE proposed a new classification system with new, alternative concepts and terminology. [19] Originally a 5 axis description was proposed (Axis 1:ictal phenomenology, axis 2: seizure type, axis 3: syndrome-when known, axis 4: genetic defect or specific pathological substrate for symptomatic focal epilepsies, and axis 5: impairment classification). More recently, the changes were summarized in the table on the next page. [20]

The most recent classification system in part stresses the importance of seizure description. A glossary of terminology is easily available. [21]

The implications of the newest proposal include an increased flexibility and transparency. Important changes include: 1. “partial” becomes “focal”; 2. Seizures of unknown onset can still be classified; 3. Awareness is used as a classifier of focal seizures; 4. The terms dyscognitive, simple partial, complex partial, psychic, secondarily generalized are eliminated; 5. Focal tonic, clonic, atonic, myoclonic and epileptic spasms seizure types are recognized, along with bilateral versions of these seizure types. 6. Addition of new generalized seizure types: absence with eyelid myoclonia, myoclonic absence, myoclonic-atonic, clonic-tonic, clonic, epileptic spasms. Epileptic spasms can thus be focal, generalized or unknown. 7. Bilateral tonic-clonic seizure replaces secondarily generalized seizure[30].



http://www.ilae.org/Visitors/Centre/documents/ClassificationSeizureILAE-2016.pdf

5. Use appropriate diagnostic testing

The following tests are often used in patients who have had a possible seizure: laboratory testing, EEG, and neuroimaging. In general, studies have shown a low yield of laboratory diagnostic testing, unless otherwise suggested by history or examination. Leukocytosis and metabolic acidosis can be seen after a seizure, but tend to be quite transient. After a convulsion, a raised CPK to a level that requires intervention can be seen. The American College of Emergency Physicians recommends testing levels of sodium, glucose and pregnancy testing in women of childbearing age. [21] Calcium testing in patients with malignancy is also advised. Other laboratory tests are frequently performed as they can reveal information which helps with etiology and changes in management; these tests include: electrolytes, renal function, liver function, toxicology screening.

Prolactin testing done correctly can help distinguish PNES from ES, but is not reliable in distinguishing between ES and other causes of loss of consciousness such as syncope. The AAN Practice Parameter states: Elevated serum prolactin assay, when measured within 20 minutes after a suspected event, is a useful adjunct for the differentiation of GTC or CPS from PNES among adults and older children (Level B). [7] There is variation in the protocols used in the studies reviewed for this Practice Parameter, but a possible protocol within these guidelines is: 1) Measure prolactin level after possible CPS/GTC versus PNES event within 10-20 minutes; 2) Measure another level after the patient has been event free for at least 6 hours (baseline level); 3) Consider a positive elevation of prolactin if it is 2X baseline level. This degree of prolactin elevation has a positive predictive value for ES. There is a low sensitivity (47-58.2%) and high specificity (89.9-95.7%) for ES.

Lumbar puncture may be helpful in patients with immunosuppression or fever (Level U). [5] It can be considered in other instances, although it is generally not performed without suspicion of an acute neurologic process.

EEG should be performed in every patient with a suspected seizure or epilepsy. The AAN Practice Parameter is worded less strongly and states that after a first seizure an EEG should be considered as part of the routine neurodiagnostic evaluation (Level B). [5] Although only approximately 40% of patients with epilepsy will have an abnormal routine EEG ,[22] the implications are significant. An EEG may be diagnostic and lead to further information about the type of epilepsy and syndrome that lead to a change in management (focal vs. primary generalized, absence, JME) (Level C). [5] EEG can also assist in the diagnosis of the etiology of seizures or epilepsy syndrome (e.g., CJD, HSV, SSPE, BRE, Absence). The EEG results can also guide further testing and review of neuroimaging. EEG can occasionally capture the event and assist in the diagnosis of alternative etiologies. EEG is helpful in assessing the risk of seizure recurrence after a first unprovoked seizure (Level B) as the risk of a second seizure within 2 years is 55% in patients with an abnormal EEG versus 10% if the EEG was normal. A longer EEG recording in patients with epilepsy may increase the sensitivity to 90% [23] and an EEG done within 24 hours of the seizure also has a higher yield for epileptiform discharges (51% vs. 34%) King 98**. Sleep deprivation** can also increase the yield of obtaining epileptiform discharges.[24] **Ambulatory EEG monitoring**

has a modestly increased yield over routine EEG (34% versus 24%) and a greater likelihood of capturing an event (15%). [25] EEG sensitivity and specificity is related to the skills of the interpreter and striving towards specificity rather than sensitivity yields a more accurate prediction. [26] **Video-EEG monitoring** is indicated when diagnosis is unclear, the patient fails to respond to treatment, and when full characterization of seizures is required for other reasons.

Neuroimaging is indicated in all adults presenting with a seizure. AAN Practice Guidelines state that brain imaging using CT or MRI should be considered as part of the neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B). [5] MRI is the preferred neuroimaging modality and has a yield of approximately 10%. The type of MRI and review of the MRI results are best determined and performed by the patient's neurologist in consultation with a neuroradiologist. Neuroimaging can identify structural abnormalities that cause certain epilepsies and lead to a high risk of recurrence. It is not indicated routinely when a diagnosis of idiopathic generalized epilepsy has been made, [9] however should be considered when seizures continue despite appropriate AED therapy.

Concluding Remarks

The correct diagnosis of seizure and type of epilepsy is the foundation for excellent neurologic care in this patient population. Diagnosis is best accomplished by history including that of the event and predisposing conditions, examination, diagnostic testing including EEG and MRI. Even after a thoughtful and thorough diagnosis, reconsideration is indicated when the patient does not respond to initial management. Referral to an epilepsy center is indicated for all patients who do not have their seizures fully controlled without adverse side effects.

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