SEIZURES & EPILEPSY

Carter Wray, MD
Jason Coryell, MD
Pediatric Epilepsy

Objectives:
1. Know the definition of seizures, epilepsy and status epilepticus
2. Understand the general categories of seizure classification
3. Learn how to manage status epilepticus

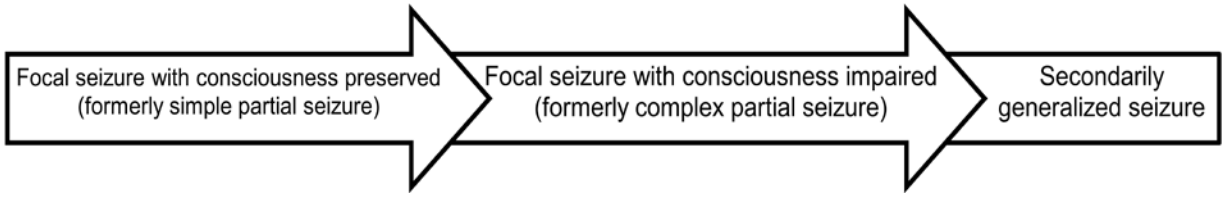
Seizure- A transient disturbance of cerebral function due to abnormal neuronal discharges

Epilepsy- A disorder characterized by recurrent unprovoked seizures

Seizures:

Seizures are stereotyped events due to synchronous electrochemical discharges of neurons. The incidence of new-onset seizures in the general population is 100 per 100,000 per year. They are most common in young children and adults over 65. They can be due to a recent provocation, in which case they are called acute symptomatic seizures. The most common causes of these are fever in toddlers, trauma, toxins, and infection. Others are due to injury in the more distant past, in which case they are called remote symptomatic seizures. These two types represent the majority of seizures in adults, while children are more likely to have seizures without a clear cause. Recurrence of remote symptomatic or seizures of unclear cause constitutes epilepsy.

Seizures are described based on their semiology, or how they appear. The most common seizures, especially in adults, are focal seizures, which have onset in one part of the brain. Clues to focality of onset include preservation of consciousness at onset, involvement of one side of the body before the other, deviation of eyes and sensory involvement. They are sometimes called *simple* when consciousness is preserved, and *complex* when consciousness is impaired. An aura is a simple partial seizure. Focal seizures can evolve and secondarily generalize, meaning they spread from site of origin to involve the whole brain as shown below.



Primary generalized seizures rapidly engage bilaterally distributed networks, and are most commonly of genetic origin. They more commonly have onset in childhood. The principal types of generalized seizures are absence, atypical absence, myoclonic, atonic, tonic, and tonic-clonic. While most seizures are called generalized tonic-clonic, or "GTC" by non-neurologists, true GTCs are actually only a small minority of seizures. Often secondarily generalized seizures are only caught at the end, and the focal onset is

missed. A generalized convulsion can be a final common pathway of many seizure types.

Distinction of seizure type is helpful for understanding what the cause of the seizure was. This will in turn affect work-up to evaluate for treatable causes of acute symptomatic seizures. Primarily generalized seizures also respond to a narrower set of antiepileptic medications than do focal seizures.

Etiologies of Seizures by age:

Neonates	Infants and children	Adolescents and Young adults	Older adults
- Prenatal Hypoxia and Ischemia -Intracranial Hemorrhage and Trauma -CNS infection -Metabolic disorders -Genetic disorders -Drug Withdrawals	-Fever -Genetic disorders -CNS infection -Trauma -Developmental disorders	-Trauma -Genetic Disorders -Infection -Brain tumor -Drug use	-Trauma, -Stroke -Brain tumor -Alcohol withdrawal -Metabolic disorders -Alzheimer's disease -Other neurodegener-ative disease

Epilepsy:

Epilepsy is a common chronic neurological disorder. Approximately 1/3 of patients with first time seizure will go on to have epilepsy. The diagnosis of a particular seizure type, and of a specific type of epilepsy (epilepsy syndrome), directs the diagnostic workup of these patients and their initial therapy.

Epilepsy classification in the past has been variable; based on etiology, semiology (outward manifestations of the seizure), location in brain where seizure originates, the underlying syndrome, or the events that trigger seizures (for instance with reflex epilepsies such as reading epilepsy.)

In 2009, the International League Against Epilepsy (ILEA) attempted to update the standardized classification. Epilepsies can be divided in many ways, including into those that are focal at onset, also called partial (or localization-related) versus those that are more broadly distributed at onset (generalized). They can also be grouped by cause with those having a known structural or metabolic etiology (formerly symptomatic), versus those with presumed genetic predisposition (formerly idiopathic), versus those where the cause is unknown, (formerly called cryptogenic).

Selected epilepsy syndromes are listed below by typical time of onset. Epilepsy syndromes do not necessarily have a known single gene cause, but are described by commonly shared features, such as age of onset, seizure types, EEG patterns, and response to treatments.

Infancy	Childhood	Adolescence	Adulthood
-West S. -Severe Myoclonic E. of Infancy (Dravet S.)	-Childhood absence E. -Lennox-Gastaut S. -Benign Rolandic or Centrotemporal E.	-Autosomal Dominant Nocturnal Frontal Lobe E. -Juvenile absence E. -Juvenile myoclonic E.	-Temporal lobe E. due to mesial temporal sclerosis

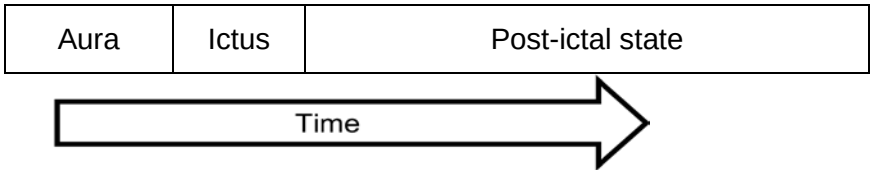
E. = Epilepsy, S. = Syndrome

Diagnosis:

Epilepsy is a clinical diagnosis. The clinical description of the events is the most important element in diagnosis, with an emphasis of the initial observed changes at seizure onset The seizures are typically stereotyped within one patient and usually resemble seizure types observed in other patients.

An MRI of the brain and electroencephalogram (EEG) are important ancillary tests that can augment the clinical impression. The EEG is an electrophysiologic test that records the electrical activity of the cerebral cortex through electrodes placed on the scalp, measuring the electrical potentials of cortical neuronal dendrites near the brain's surface. More information on EEGs is found in the “Clinical Neurophysiology” section.

Since most seizures are unobserved by physicians, the diagnosis is usually made retrospectively. The observers' descriptions of the ictus and the post-ictal state are crucial to a clinical diagnosis. There are three important elements in the description of seizures:



-Auras are often associated with seizures of focal onset and can involve focal sensation or more abstract ones, such as *déjà vu* (feeling that something novel has been experienced before) or *jamais vu* (feeling that something familiar has never been experienced before). They may provide a clue to the origin or type of seizure.
-The loss of consciousness during a generalized seizure is typically sudden and complete. In contrast, in syncope, the patient may remember dimming of vision and falling to the ground before loss of consciousness.
-Stereotyped occurrences during ictus such as automatisms (e.g. lip smacking, chewing, picking/fumbling), sensory disturbances, or repetitive twitching of a limb are important.
-Goal-directed behavior is almost never due to a seizure, however some partial complex seizures have bizarre features, particularly those with frontal lobe onset.
-The typical generalized tonic-clonic seizures last 1-3 minutes; if much longer, it may be either status epilepticus (then it is an emergency) or it may be non-epileptic. This rule of thumb doesn't apply to other seizure types.
-The post-ictal confusional state that follows a generalized seizure typically lasts more than 10-15 minutes. Headache, tiredness and confusion may also follow loss of consciousness of other causes (e.g. syncope), but they are usually briefer (5-10 minutes).

There are many other disorders that can cause changes in behavior and can be confused with epilepsy. In young children, breath holding spells and gastro-esophageal reflux are common seizure mimics. Below are things to consider in all age groups.

Differential Diagnosis:

	Seizure	Hypoglycemia	Syncope	TIA
Postural relationship	-	-	++	+/-
Aura	+/-	++	+/-	-
Duration	1-5 minutes	many minutes	30 sec	Min - hrs
Ass. Signs	flush, cyanosis	sweats, pallor	sweats, pallor	focal signs
Bodily injuries	+/-	-	+/-	-
Incontinence	+/-	-	+/-	-
Recovery	slow	rapid	rapid	slow

-Urinary incontinence and a few jerking movements of the limbs may be seen in syncope.

The diagnosis of non-epileptic spells of psychogenic origin (NES), sometimes called non-epileptic “seizures” (formerly pseudo-seizures) can be quite complicated. They are typically subconscious phenomena, falling in the psychiatric conversion disorder group, but can be intentional, and represent malingering, although that depends largely on the context. The table below is outlines some typical features of true epileptic seizures versus those of NES. Some patients unfortunately have both.

	Seizure	Non-Epileptic Spell
Onset	Abrupt	Usually gradual
Occurrence during sleep	Common	Uncommon, but possible
Aura	Special senses, epigastric, unilateral sensory or motor syptoms	Same, but also palpitation, malaise, choking, dizziness
Cry	Epileptic cry at onset, grunting during ictus	During ictus
Motor	Synchronous movements; rarely rigidity alone, often lateralized	Rigidity, flailing, pelvic thrusting, contralateral arm and leg
Injury	Post/lateral edge of tongue, bruises	Tip of tongue, bruises
Avoidance test	Respond only during post-ictal state	Respond to avoidance test
Duration	<5 minutes (rmost: 50-90 secs, mean ~70 sec)	Variable (range: 3 sec-30 minutes, ~50%>2 minutes)
Micturition	++	+
Defecation	+	-
EEG	Epileptiform activities during ictus	No epileptiform activities during ictus, posterior dominant rhythm on EEG maintained while “non-responsive”
Signs	Pupillary dilatation during ictus, post-ictal focal signs	Often fluctuating course

Long-term video-EEG monitoring, also known as video telemetry EEG is a diagnostic technique used in certain patients with epilepsy or events of undetermined etiology. The purposes of long-term video-EEG monitoring include:

1) Evaluating the underlying epilepsy syndrome.
2) Pre-surgical (assess candidacy for focal resection)
3) Distinguishing epileptic from non-epileptic events.

Treatment:

Recognizing the distinction between seizures and epilepsy is essential. Epilepsy may require chronic treatment (with antiepileptic medication and, in some cases, surgery) whereas therapy for an isolated seizure is directed toward the underlying cause.

Seizures associated with metabolic and systemic disorders usually respond poorly to anticonvulsant drugs, so treatment should focus on the underlying cause. Acute withdrawal from alcohol and other centrally acting medications such as benzodiazepines in general produce self-limited seizures that should be treated in the acute setting, but do not require long term treatment as a rule. Acute head trauma and other structural brain lesions that result in seizures must be rapidly diagnosed and treated, and the associated seizures controlled by anticonvulsant drug therapy. In general, generalized seizures of unknown etiology occurring for the first time in an individual are not treated with anticonvulsant therapy, though a thorough evaluation including EEG is warranted, and head imaging in adults.

In approximately 2/3 of patients with epilepsy, seizures can be controlled safely and effectively with medication alone. Surgical options for medically refractory patients include resection to remove the epileptogenic tissue causing seizures and vagal nerve stimulation (VNS). Many patients also respond to high fat diets such as the ketogenic or modified Atkins diets which shift the energy substrate for the brain from glucose to ketone bodies.

Anti-seizure Medication* Use:

1. Establish epilepsy diagnosis, then start prophylactic anti-seizure medication
2. Slowly increasing dosage while monitoring compliance, blood level, toxicity.
3. Balance efficacy & toxicity – If good control is achieved, continue same regimen. If not, first reassess diagnosis and classification of seizure. If diagnosis is correct, decide if dosage is adequate. In the adjustment of dosage, *don't rely solely on blood levels*. The decision on dosage should be based primarily on clinical assessments (i.e. side effects, seizure frequency, and compliance).
4. If there is occasional increase in seizure frequency, consider: compliance, intercurrent illness, alcoholism, stress, sleeplessness and drug interaction.

Anti-seizure drug (brand name)	Focal/partial seizures	generalized seizures
carbamazepine (Tegretol, Carbatrol)	x	
clobazam (Onfi)	x	x
clonazepam (Klonopin)	x	x
clorazapate (Tranxene)	x	x
ethosuxamide (Zarontin)		x
felbamate (Felbatol)	x	x
gabapentin (Neurontin)	x	

lacosamide (Vimpat)	x	
lamotrigine (Lamictal)	x	x
levetiracetam (Keppra)	x	x
methsuxamide (Celontin)		x
oxcarbazepine (Trileptal)	x	
phenobarbital	x	x
phenytoin (Dilantin)	x	
pregabalin (Lyrica)	x	
rufinamide (Banzel)	x	x
tiagabine (Gabatril)	x	
topiramate (Topamax)	x	x
valproic acid (Depakote)	x	x
vigabatrin (Sabril)	x	
zonisamide (Zonegran)	x	x

*****While the term anti-epileptic drug (AED) is commonly used, none of the medications has been demonstrated to prevent or reverse epileptogenesis. These medications are used for symptomatic management, and therefore, the more accurate description of these medications are as anti-seizure medications, or anti-convulsants.

Status Epilepticus:

Status Epilepticus is the seizure that keeps on seizing, and can present as a single continuous seizure or multiple discrete seizures without recovery of consciousness in between. Most self-limited seizures last less than 5 minutes, although permanent brain injury takes much longer to occur. This is a true emergency, since uncontrolled convulsions are complicated by hyperthermia, metabolic and respiratory acidosis, cardiovascular dysfunction, and occasional sudden death. Uncontrolled neuronal discharges during seizures can lead to irreversible brain cell injury or death. The outcome is largely determined by the underlying cause of the seizure, but the duration also impacts it. Seizures become more refractory to treatment with time, so as with strokes, time is brain. Prompt initiation of anti-seizure medications is necessary, and should be done concurrently with evaluation for underlying etiology, as described below.

Treatment algorithm for Status Epilepticus