Seizure Disorders

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Seizure Definitions

- An **epileptic seizure** is a disorder of abnormal synchronous electrical brain activity.
- A **clinical seizure** is a epileptic seizure with symptoms.
- A **subclinical seizure** is a epileptic seizure without symptoms.
- A **non-epileptic seizure (pseudoseizure)** is a disorder with symptoms similar to a epileptic seizure. However, a non-epileptic seizure is not caused by abnormal synchronous electrical brain activity.
- A **cryptogenic seizure** is a seizure that occurs from an unknown cause. Older publications use idiopathic to describe a seizure of unknown etiology but the current ILAE guidelines discourage the use of idiopathic for describing a seizure of unknown etiology.
- A **symptomatic seizure** is a seizure that occurs from a known or suspected brain insult known to increase the risk of developing epilepsy.
    - An **acute symptomatic** seizure is a seizure that occurs following a recent brain insult
    - A r**emote symptomatic** seizure is a seizure that first occurs long after the brain insult occurred.
- A **provoked** seizure is an acute symptomatic seizure
- An **unprovoked** seizure is a remote symptomatic or cryptogenic seizure
- **Idiopathic epilepsy syndromes** are syndromes with specific age of seizures onset, clinical features, EEG features, prognosis and a presumed genetic mechanism.
- A person has **epilepsy** if they have a substantially increased risk for chronic recurrent unprovoked epileptic seizures unless treated by anticonvulsant medications or epilepsy surgery. Epilepsy is diagnosed when the person has a history of multiple unprovoked seizures.

- **Note:** There are two closely related but distinct terms. **Epileptic** means a seizure arising from abnormal synchronous electrical brain activity while **epilepsy** means recurrent unprovoked epileptic seizures.

Types of Seizures

- Simple Partial Seizures
  - Motor seizures
  - Somatosensory or special sensory seizures
  - Autonomic seizures
  - Psychic seizures
- Complex partial seizures
- Absence seizures
  - Typical absence seizures
  - Atypical absence seizures
- Myoclonic seizure
- Tonic seizures
- Clonic seizures
- Tonic-clonic seizures
- Atonic seizures

1 - Commission on classification and terminology of the international league against epilepsy, 1981

Partial Seizures

- A **partial (focal) seizure** is a seizure that involves a small region of the brain.
- A **simple partial seizure** occurs with intact awareness of self and surroundings.
- The **seizure aura** is the symptom produced by the simple partial seizure before the seizure changes to a complex partial or tonic-clonic seizure. The seizure aura precedes the loss of consciousness and is later recalled by the person.
- **Types of auras** include: fear, depersonalization, derealization, a rising epigastric sensation, visual phenomena, numbness, electrical feeling, paresthesias, olfactory sensation or an indescribable "funny" feeling.
- A **convulsive (motor) seizure** is a seizure with vigorous contraction of muscles.
- A **focal motor seizure** may occur with convulsive activity of the face, arm, trunk or leg. A simple partial seizure is usually confined to a single lobe of one cerebral hemisphere.
- The **seizure focus** is the cortical area where the seizure begins.
- A **complex partial seizure** is a partial seizure that occurs with impaired awareness of self and surroundings. The person may not communicate to others, follow commands, direct attention to others or retain memory of events during the

seizure. A complex partial seizure often involves bilateral limbic cerebral areas (Gloor, 1986).

- **Stereotyped posturing** consists of sustained postures that occur during a partial seizure
- **Versive** head or eye movements are movements of the head or eyes to one side during a partial seizure

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Generalized Seizures

- A **generalized seizure** involves large bilateral cortical areas.
- A **primary generalized seizure** involves both hemispheres of the brain at seizure onset
- A **secondary generalized seizure** involves both hemispheres of the brain following a partial seizure.
- **Rapid secondary generalization** occurs when a partial seizure rapidly spreads to both hemispheres. This secondary generalized seizure may be difficult to distinguish from a primary generalized seizure.
- A **absence seizure** is a generalized seizure distinguished by a **generalized spike and wave EEG pattern**. The absence seizure consists of a brief period (e.g. 10 seconds) of impaired responsiveness, stare, arrest of ongoing activity, a change in facial appearance and an immediate return to normal without a post-ictal state. The episodes may occur many times per day.
- A **typical absence seizure** is a absence seizure induced by hyperventilation;
- An **atypical absence seizure** is a absence seizure not induced by hyperventilation.
- A **myoclonic seizure** consists of brief body jerks. Limb movement or a startle will sometimes elicit these jerks. Unlike **clonic seizures**, the jerks of myoclonic seizures occur at irregular times.
- A **tonic seizure** occurs with the rapid onset of a rigid posture with head flexed forwards, elevation of both arms, and flexion of the trunk forwards at the thigh. If standing, the person often falls.
- A **tonic-clonic seizure** consist of a tonic and clonic phase. The tonic phase consists of a continuous rigid state. The clonic state consists of rhythmic lapses of this rigid state. Tonic-clonic seizures that occur with stereotyped asymmetric postures of the head, eyes or limbs indicate that the person has a focal cerebral seizure onset. Focal neurological findings after a tonic-clonic seizure suggest a focal cerebral seizure onset.
- An **atonic seizure** consists of a brief lapse of muscle tone. Atonic seizures are rare; epileptic drop attacks are usually due to myoclonic or tonic seizures (Egli et al., 1985). A lapse in muscle tone can occur during a atypical absence seizure.

Automatisms

- **Automatisms** are purposeless repetitive motor activities that often occur during a seizure. Automatisms may occur during complex partial or absence seizures.
- **Oral automatisms** include lip smacking and swallowing.
- **Gestural automatisms** include fumbling, picking and rubbing.
- **Complex motor automatisms** are more complex stereotyped series of motor actions usually involving the limbs bilaterally. Examples including swimming movements, kicking movements and bicycling movements.

Post-ictal state

- **Post-ictal state** is a period of somnolence and confusion that occurs after a complex partial or generalized convulsive seizure.
- **Post-ictal focal neurological abnormalities** are transient neurological abnormalities that occur after focal seizures and are related to the site of seizure onset. Examples include:
    - post-ictal hemiparesis (Todd's paralysis)
    - post-ictal aphasia
    - post-ictal unilateral extensor plantar reflex

Evolution of seizure type

- simple partial (aura) -> complex partial -> secondary generalized convulsive seizure
- complex partial -> secondary generalized convulsive seizure
- simple partial (aura) -> complex partial
- simple partial (aura) -> secondary generalized convulsive seizure
- myoclonic seizure -> primary generalized convulsive seizure
- absence -> primary generalized convulsive seizure

Provoked Seizures

- Seizure that is caused by a transient reversible disorder; when this disorder improves, the person is no longer at risk for seizures.
- A person with only provoked seizures does not have epilepsy.

Causes of provoked seizures

- Illicit Drugs
    - Cocaine
    - Phencyclidine

    - Amphetamines
- Drug Overdose
    - Isoniazid
    - Antidepressants
    - Theophylline
    - Cyclosporin A
    - Anticholinergics
    - Penicillin
    - Lidocaine
- Drug Withdrawal
    - Benzodiazepines
    - Alcohol
    - Barbiturates
- Toxins
    - Organophosphates
- Uremia
- Hyperthyroidism (very rare)
- Myxedema coma
- Hypoglycemia
- Non-ketotic Hyperglycemia
- Hyponatremia, water intoxication
- Hypocalcemia, hypoparathyroidism
- Hypomagnesemia
- Whipple's disease

Seizures induced by isoniazid respond to intravenous pyridoxine. Acute changes in electrolytes or osmolarity are more likely to cause a seizure. Acute liver failure might cause seizures because of hypoglycemia. Hypoparathyroidism might cause seizures because of hypocalcemia. Hypomagnesemia usually occurs with hypocalcemia; it is uncertain how much the hypomagnesemia contributes to seizures in this situation.

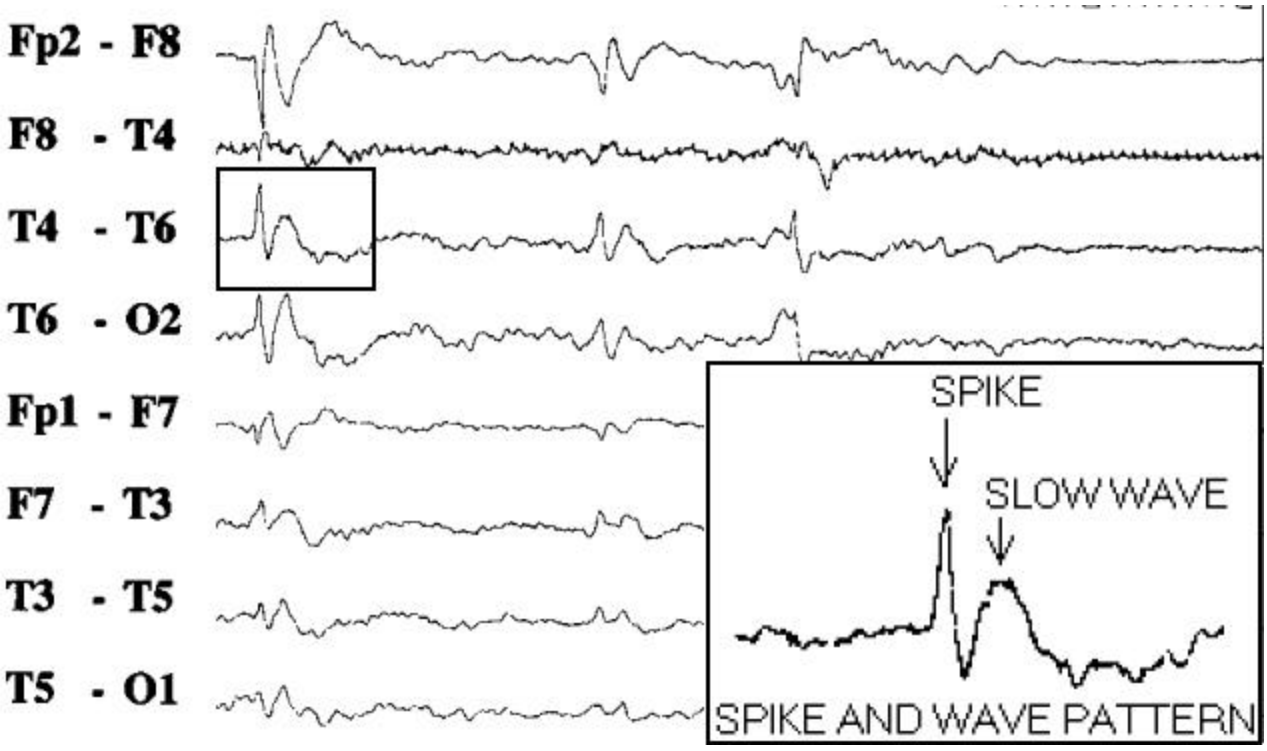
Causes of unprovoked seizures

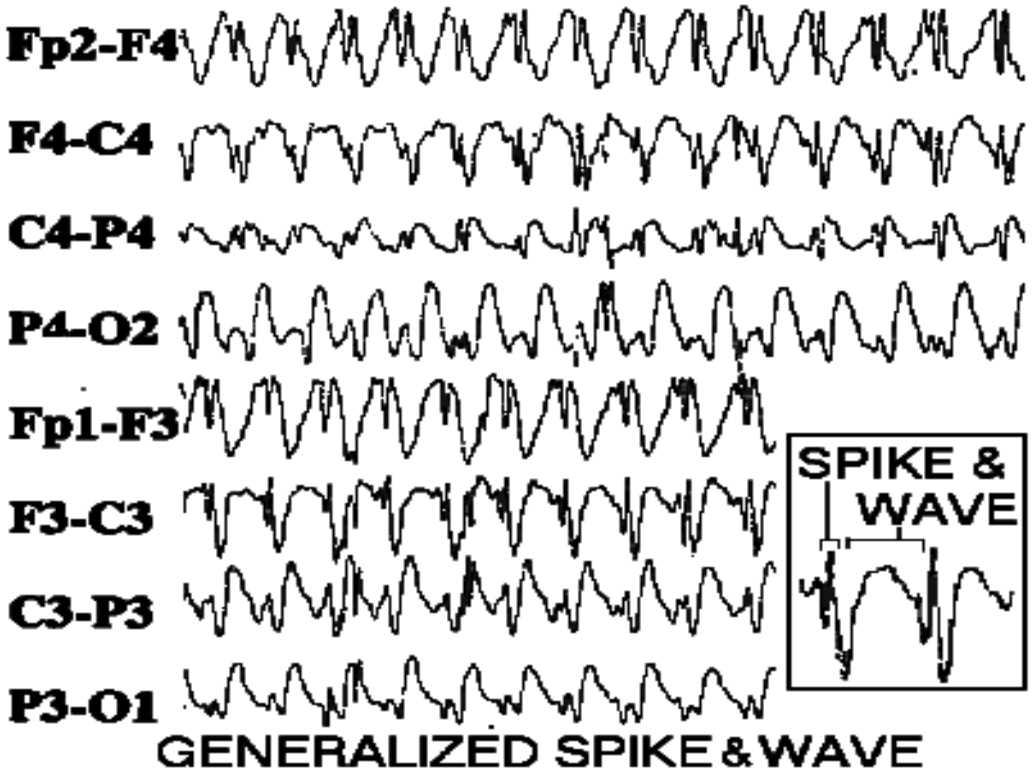
- Vascular: infarction, hematoma, hypoxic-ischemic injury, perinatal asphyxia, venous thrombosis, AVM.
- Infectious: viral encephalitis, post-meningitis, cysticercosis, toxoplasmosis, abscess, syphilis.
- Neoplasm: glioma, meningioma, metastatic tumor.
- Degenerative: Alzheimer's disease (10% risk), multiple sclerosis (5% risk).
- Immune mediated: SLE.
- Congenital malformations: heterotopia, schizencephaly, lissencephaly, macrogyria.
- Trauma: concussion, cerebral contusions, subdural hematoma

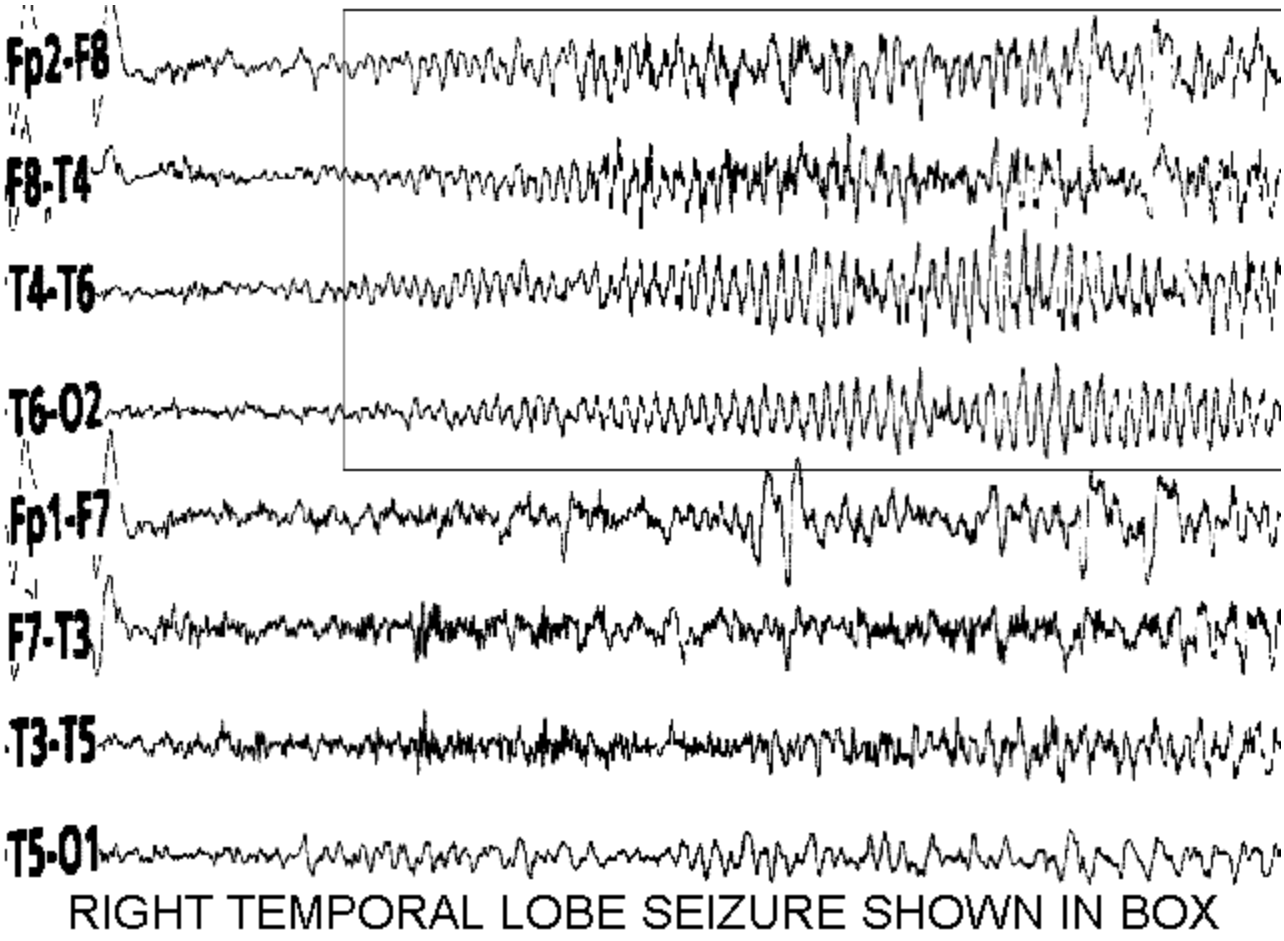
Mesial temporal sclerosis is the **most common** pathological finding in temporal lobe epilepsy. This lesion consists of neuronal loss in the hippocampus with relative sparing of granule cells and CA2 pyramidal cells. On MRI, this lesion appears as a shrunken atrophic hippocampus.

Electroencephalogram

- The **electroencephalogram (EEG)** records voltage differences between different scalp sites over time; these voltage differences are due to synaptic neural currents. The EEG appears as a series of tracings stacked one above the other; each tracing is the recording from a specific scalp location. A typical EEG recording lasts about 20 minutes.
- **Ictal EEG pattern** is the EEG recording during a seizure
- **Inter-ictal discharges or epileptiform discharges** are brief duration (< 1 second) abnormal EEG patterns that in epileptics between seizures.
- **Sharp waves, spikes, spike and wave and sharp and slow wave** are descriptive terms for different types of epileptiform discharges (inter-ictal discharges).
- Epileptiform discharges arise from the brain region causing epilepsy
- The **most common finding** used to diagnose epilepsy are epileptiform discharges; Only **rarely** are seizures recorded during a routine EEG study.
- A **single EEG** may be **normal** in a person with epilepsy
- **Sleep recording**, antecedent **sleep deprivation**, **multiple recordings** and **prolonged EEG recordings** increase EEG diagnostic sensitivity.
- The EEG should be done for **all patients** with suspected epilepsy. EEG is useful for:
    - Distinguishing epileptic seizures from non-epileptic disorders
    - Distinguishing idiopathic from symptomatic epilepsies.
    - Determining the location of the seizure focus


Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
SPIKE
SLOW WAVE
SPIKE AND WAVE PATTERN


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
SPIKE &
WAVE
GENERALIZED SPIKE & WAVE



Neuroimaging

- **MRI without gadolinium** is the best imaging test for epilepsy; CT with contrast is used when MRI is not available. MRI with gadolinium may be used in special cases such as when a brain tumor is suspected.
- A MRI abnormality occurs in **85%** of persons (Duncan, 1997).
- The most common abnormalities are **mesial temporal sclerosis** and **cortical dysplasia** (Duncan, 1997).
- MRI will detect lesions missed by CT scan such as **cavernous malformations, cortical dysplasia, mesial temporal sclerosis, hamartomas and some gliomas** (Chokroverty, 1996).

Epilepsy Syndromes

Temporal lobe epilepsy:

- Seizure auras of rising epigastric sensation, indescribable sensation, fear, unreality. The indescribable sensation is often described as a "funny feeling".
- Complex partial seizures begin with a motionless stare.
- Automatisms with lip smacking, picking and fumbling might then occur.

Frontal lobe epilepsy:

- Brief duration complex partial seizures with minimal confusion after the seizure.
- Motor behaviors such as automatisms, tonic, clonic or postural activity may occur at seizure onset.
- Rapid secondary generalized tonic-clonic seizures may occur.
- Complex motor automatisms such as kicking and bicycling are common.

Occipital lobe epilepsy:

- Simple partial seizure visual symptoms include: simple shapes, brightly colored or mobile images, blindness and geometrical patterns
- Complex partial and secondary tonic-clonic seizures may occur

Parietal lobe epilepsy:

- Simple partial seizure with tingling, burning, electrical sensation, and limb movement sensation.
- Complex partial and secondary tonic-clonic seizures may occur

West Syndrome

- **Triad**: consists of infantile spasms, hypsarrhythmia EEG pattern and developmental delay.
- **Onset** is between 3 - 12 months of age
- **Infantile Spasm** is the typical seizure and consists of bilateral rapid flexion or extension of head, trunk, and limbs lasting seconds. A period of reduced motor activity (akinesia) might follow the spasm.
- Spasms occur as **clusters** soon after awakening.
- **Developmental delay** is common.
- **Hypsarrhythmia EEG pattern** occurs between seizures (interictal EEG pattern).
- **Electrodecremental EEG pattern** is a flattening of the EEG that occurs during the infantile spasms (ictal EEG pattern).
- **Etiologies** - Aicardi's syndrome, strokes, tuberous sclerosis, hypoxia, cerebral hemorrhage, brain infections, brain malformations, inborn errors of metabolism
- The exact etiology may not be determined (cryptogenic epilepsy)
- **Poor prognosis** 67% of children develop severe impairment (Glaze et al., 1988).

Lennox Gastaut Syndrome

- **Onset** is between 1 - 10 years of age

- **Multiple seizure types** occur such as generalized tonic, atypical absences, myoclonic, generalized tonic-clonic seizures
- **Difficult to control** seizures despite multiple medications
- **Developmental delay** common
- EEG pattern may be 1 - 2.5 per second continuous spike and wave pattern (**slow spike and wave**) or epileptiform discharges from many different cerebral locations (**multifocal epileptiform discharges**)
- **Etiologies** - hypoxia, cerebral hemorrhage, brain infections, brain malformations, inborn errors of metabolism
- The exact etiology may not be determined (cryptogenic epilepsy)
- **Poor prognosis**

Benign partial epilepsy syndromes

- **Clinical types**
  - **Benign rolandic epilepsy** - Seizure originates from cerebral region representing the face. Seizure might begin as partial sensory or motor seizure of the face or as a generalized tonic-clonic seizure. Sensory symptoms of tingling or electrical feeling in mouth or gums. Speech arrest, salivation and facial convulsive activity. Seizures often occur out of sleep. Central or mid-temporal epileptiform discharges confirm the diagnosis.
  - **Benign occipital epilepsy**- Seizure originates from the occipital lobe.
- Genetic etiology
- Onset between 4 - 12 years
- Seizures end after age 16 years
- Children intellectually normal
- MRI normal
- Epileptiform discharges most often during sleep
- Benign rolandic epilepsy (BRE) is more common than benign occipital epilepsy (BOE)
- Most children will stop having seizures after reaching young adulthood

Childhood absence epilepsy

- Onset is age 4 - 8 years
- Presenting complaint - impaired school performance, inattention, day dreaming.
- Clinical Features - change in facial appearance, sudden cessation of motor activity, immediate return to normal, automatisms, impaired responsiveness, amnesia for event.
- Seizures are brief, e.g. 10 seconds, but occur many times per day.
- **Typical absence seizures** are absence seizures induced by slow deep breathing (hyperventilation). Typical absence seizures occur in childhood absence epilepsy.

- About 30 - 50% of persons with absence seizures also have generalized tonic-clonic seizures (Niedermeyer, 1990).
- Family history of absence seizures is often positive.
- Seizures often end by young adulthood.
- MRI is usually normal.
- Diagnosis is confirmed by a 2.5 - 4 per second continuous spike and wave EEG pattern from both cerebral hemispheres (generalized spike and wave pattern). This EEG seizure pattern is induced by hyperventilation.

Juvenile myoclonic epilepsy (JME)

- Onset is between 12 - 20 years of age
- Early morning tonic-clonic seizures and myoclonic jerks. Commonly occurs soon after awakening.
- Clinical Features - brief sudden early morning jerks (myoclonic jerks), or repeated jerks followed by a tonic-clonic seizure (clonic-tonic-clonic seizure).
- Seizures are induced by sleep deprivation, previous alcohol use the night before
- Family history might be positive for juvenile myoclonic epilepsy
- EEG shows a 3 - 6 per second bilateral irregular continuous spike and polyspike and wave discharges
- MRI normal.
- **Generalized tonic-clonic seizures on awakening** is a epilepsy syndrome similar to juvenile myoclonic epilepsy
- Seizures will almost always reoccur when medication is stopped.

Simple Febrile Seizure [1]

- **Onset** is between 3 months - 5 years of age
- **Common disorder**
- **Generalized tonic - clonic seizure** only
- **Duration** is brief (< 15 minutes).
- **Single seizure** occurs during the febrile episode
- **Febrile episode** with rising temperature at the time of the seizure
- **Typical causes of fever** are ear, respiratory, or GI infection or vaccination.
- **Family history** of febrile seizures is common; no family history of afebrile seizures.
- **Normal neurological exam**
- **Risk of a second febrile seizure** is 50% if child is less than 1 year of age and 33% if child is greater than 1 year of age (Rosman et al., 1993).
- **A second febrile seizure will occur** within 6 months in 50% of cases, 1 year in 75% of cases and within 2 years in 90% of cases (Rosman et al., 1993).
- **Rarely** more than 2 episodes of febrile convulsions will occur.
- **Lumbar puncture** should be strongly considered in children less than 1 year of age, considered in children less than 18 months of age and strongly considered in children who received prior antibiotic treatment. Lumbar puncture is recommended in all children with clinical signs of meningeal irritation or

intracranial infection (Provisional Committee on Quality Improvement; Subcommittee on Febrile Seizures, 1996).

- **Treatment:** Parents are given counseling on how to recognize early symptoms of infection, monitor temperature carefully and to reduce the persons body temperature with prompt administration of antipyretics and a sponge bath.
- **Oral diazepam** (0.33 mg/kg q 8 hrs.) given at the time of a fever will significantly reduce the risk of febrile seizures (Rosman et al., 1993).
- **Daily anticonvulsant therapy** has uncertain efficacy and is associated with poor compliance and medication side effects (Rosman et al., 1993).
- **Prognosis:** low risk (0.9%) of developing afebrile seizures if a simple febrile seizure occurs.

1 - Data from Duchowny, 1993

Complex Febrile Seizure [1]

- **Seizure duration** prolonged > 15 minutes.
- **Partial seizure** with or without secondary generalized tonic - clonic seizures.
- **Multiple seizures** occur within a single day.
- **Developmental or neurological abnormality**.
- **Afebrile seizures** in a family member.
- **Prognosis:** there is a increased risk of developing epilepsy when 2 or more of these risk factors are present.

1 - Data from Duchowny, 1993

Neonatal seizures

- **Types of Neonatal Seizures**
  - **Clonic** - arm, leg, or face clonic activity
  - **Tonic** - stiffening of trunk, limbs, or versive head/eye movement
  - **Myoclonic** - face, trunk, or limb jerk
  - **Subtle (Fragmentary)** - mouth movements, apnea, tremors, pedaling, eye movements, mouth movements, autonomic changes, complex limb movements
- **Generalized tonic-clonic seizures** do not usually occur in neonates.
- **Causes of Neonatal Seizures**
  - hypoxia-ischemia
  - hypoglycemia
  - intracranial hematoma
  - pyridoxine dependency
  - meningitis, encephalitis
  - inborn errors of metabolism
  - congenital malformations
  - metabolic - low sodium, high sodium, low calcium, low glucose

When to start and stop anticonvulsant therapy

- Anticonvulsant therapy is not required for seizures provoked by transient reversible medical disorders. These patients are treated by correcting the transient reversible medical disorder.
- A single unprovoked epileptic seizure usually does not require anticonvulsant therapy. The reason is that in most cases a second seizure will not occur (Hauser et al., 1990).
- Discontinuation of anticonvulsant therapy is appropriate when the risk of seizure recurrence is low. When the following favorable prognostic factors are present, the risk of a recurrent seizure off of medication is 31.6% (children) or 39.4% (adults) (Greenberg MK et al., 1996b).
    - Seizure free for a minimum of 2 years while taking anticonvulsants.
    - Single type of partial or generalized seizure.
    - Normal neurological exam.
    - Normal IQ.
    - EEG normal.
    - Not juvenile myoclonic epilepsy

Principles of anticonvulsant therapy

- Select the anticonvulsant that is most appropriate for the seizure type.
- Identify any special considerations that apply to a individual case that would make one anticonvulsant superior. Special considerations include anticonvulsant side effects, dosing schedule and availability of intravenous administration.
- Single drug therapy (**monotherapy**) is usually best; multiple anticonvulsant therapy (**polytherapy**) is more costly and more likely to cause medication side effects.
- Neurontin, lamictal, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide have minimal hepatic and protein binding interactions with other anticonvulsants. These drugs are good to use when polytherapy is required.
- Initial anticonvulsant therapy usually begins with the less expensive appropriate anticonvulsants. Phenytoin and carbamazepine are significantly less expensive than valproate, lamictal, gabapentin, topiramate, oxcarbazepine, zonisamide, tiagabine, levetiracetam and felbamate. Ethosuximide is less expensive than valproate.
- Phenobarbital is generally not used as a initial anticonvulsant because phenobarbital often causes intolerable sedative and cognitive side effects.
- Primidone is generally not useful. It has side effects similar to phenobarbital, is more expensive than phenobarbital and requires multiple daily doses.
- Benzodiazepines are generally not useful for chronic anticonvulsant management.

- Felbamate is used when other anticonvulsants fail because felbamate might cause aplastic anemia and hepatic failure. Periodic CBCs and transaminase levels are recommended by the FDA.

Epilepsy Therapy	
Epilepsy Syndrome	Medical Therapy
Partial seizures with or without secondary generalization	CBZ, PTN, VPA, GAB, LTG, TOP, LTA, ZON OCZ, TIA, PHB, PRI, FEL
Juvenile Myoclonic Epilepsy[2]	VPA, LTG, TOP, ZON, CLO
Absence Epilepsy	ETH, VPA, LTG
West Syndrome	VPA, ACTH, Corticosteroids, TOP, Nitrazepam VIG
Lennox-Gastaut Syndrome	VPA, LTG, TOP, ZON, CLO, PB, FEL, VIG, ketogenic diet

CBZ=carbamazepine, CLO=Clonazepam, ETH=ethosuximide, FEL=felbamate, GAB=gabapentin, LTA = levetiracetam, LTG=lamotrigine, OCZ = oxcarbazepine, PHB=phenobarbital, PRI=primidone, PTN=phenytoin, TIA=Tiagabine, TOP = Topiramate, VIG=vigabatrin, VPA=valproate, ZON = zonisamide

1 - Carbamazepine and rarely lamotrigine may worsen patients with Benign Rolandic Epilepsy (Genton, 2000; Catania et al., 1999)

2 - Carbamazepine and phenytoin may worsen patients with Juvenile Myoclonic Epilepsy (Genton, 2000). Progressive myoclonic epilepsy may worsen with lamotrigine.

3 - Carbamazepine, vigabatrin, tiagabine, gabapentin and phenytoin may worsen typical absence seizures (Genton, 2000)

4 - Vigabatrin's role in therapy may be revised because this drug may cause constriction of peripheral vision.

Anticonvulsant side effects

- There are general anticonvulsant side effects that occur with many different anticonvulsants; there are also specific anticonvulsant side effects that occur with one or a few anticonvulsants.
- In a prospective study by Heller et al. (1995), intolerable side effects resulting in anticonvulsant discontinuation occurred most frequently for phenobarbital (22%) and less frequently for the other anticonvulsants: phenytoin (3%), carbamazepine (11%), and sodium valproate (5%).

- Common dose related side effects
    - Fatigue
    - Dizziness
    - Ataxia
    - Nausea
    - Nystagmus
- Cognitive
    - Impaired concentration
    - Somnolence
    - Impaired memory
    - Psychomotor slowing
- Allergic reactions
    - Skin rash
    - Hypersensitivity syndrome - rash, fever, hepatitis, lymphadenopathy, eosinophilia, renal failure
    - Steven's Johnson syndrome/toxic epidermal necrolysis
    - At the time of the last revision of this document the author was not aware of severe allergic reactions reported with topiramate, gabapentin, levetiracetam, tiagabine or benzodiazepines
- Oral contraceptive failure with enzyme inducing anticonvulsants such as carbamazepine, phenytoin, phenobarbital, primidone, topiramate. In these cases, an alternative contraceptive method may be used or the the estrogen content of the oral contraceptive increased to compensate.
- Neonatal hemorrhage in children born to mothers who take anticonvulsants such as carbamazepine, phenytoin, phenobarbital, primidone
- Kidney stones with topiramate and zonisamide. Patients should drink lots of water with these medications and avoid carbonic anhydrase inhibitors.
- SLE like syndrome with phenytoin, carbamazepine, phenobarbital, ethosuximide, valproate
- The risk of congenital malformations is increased for children born to mothers who take anticonvulsants during pregnancy. Valproate is associated with a 1-2% risk of spina bifida; carbamazepine is associated with a 0.5-1% risk of spina bifida.
- Folate responsive anemia may occur for phenytoin, phenobarbital and primidone

Phenytoin

- Connective tissue - facial coarsening, gum hypertrophy, acne, hirsutism, lupus like syndrome
- Phenytoin is highly protein bound. If the person is hypoalbuminemic, a phenytoin level in the "therapeutic range" could cause drug toxicity.
- Pseudolymphoma and lymphoma are very rare side effects
- Decreased bone mineral mass, hypocalcemia, and increased alkaline phosphatase. Use of an anticonvulsants increases the risk for a foot fracture in elderly women and this risk is independent of the effects on bone mineral density (Seeley et al., 1996).

- There is a non-linear relationship between phenytoin dose and phenytoin serum concentration; a small dose increase can produce a large increase in serum concentration.
- Fosphenytoin is an intravenous medication that is converted to phenytoin rapidly after administration. Phenytoin should not be given intravenously because it causes phlebitis, tissue necrosis and is insoluble in many solutions.

Carbamazepine

- Hyponatremia - Carbamazepine causes a low serum sodium level that is usually asymptomatic. In these persons, repeat monitoring of serum sodium and a reduction of carbamazepine dose might be needed.
- Hematologic - Carbamazepine might cause a mild dose related leukopenia in 10 - 20% of cases (Holmes, 1995); The risk of aplastic anemia with carbamazepine is 1:200,000 and is no greater than most other anticonvulsants (Wyllie et al., 1991).
- Carbamazepine induces its own hepatic metabolism (autoinduction). The initial dose must be low and then increased slowly over several weeks.

Phenobarbital

- Impotence
- Depression
- Connective tissue - Dupuytren's contracture
- Osteomalacia, hypocalcemia, increased alkaline phosphatase.

Primidone

- Primidone is basically an **expensive form of phenobarbital**
- **Primidone** is a anticonvulsant that is transformed into two active metabolites **phenobarbital** and **phenylethylmalonamide.**
- The phenobarbital metabolite accounts for most all of the anticonvulsant benefit of primidone.
- Primidone has no significant advantages as compared to phenobarbital.

Valproate

- Appetite increase with weight gain
- Hair loss
- Hepatic failure - Valproate hepatotoxicity risk is 1:45,000 for single drug therapy in persons greater than 2 years old (Dreifuss, 1995). Monitoring is indicated for high risk cases: <2 yrs old, multiple medications, mental retardation, mental delay, congenital anomalies where the hepatotoxicity risk is increased to 1:500. AST> 3x normal upper limit might predict some cases of valproate hepatotoxicity (Wyllie et al., 1991).

Lamotrigine

- Severe drug rashes such as Stevens-Johnson syndrome or toxic epidermal necrolysis are rare in adults (0.3% risk) but are may be more common in children (1% risk). This risk is reduced by slowly increasing the dose over several weeks.

Felbamate

- Aplastic anemia - the risk of aplastic anemia is 1:3600-1:5000 (Pellock, 1996).
- Liver failure - the risk of fatal toxicity is 1:24000-1:34000 (Pellock, 1996).
- Monthly blood cell counts and AST, ALT liver function tests (Pellock, 1991, Pellock, 1996) are advised because of the risks of aplastic anemia and drug induced liver failure. This risk appears to occur during the first year of therapy.
- Felbamate inhibits the metabolism of other anticonvulsants and this may cause medication side effects from the other anticonvulsants

ACTH/Corticosteroid [1]

- Cushing's syndrome - protuberant abdomen, "moon face", supraclavicular fat and thin arms and legs.
- Irritability
- Hypertension
- Sepsis
- Glucose intolerance
- Electrolyte problems
- Congestive heart failure
- Cerebral ventriculomegaly with risk for subdural hematoma

1 - Data from Snead, 1995

Oxcarbazepine

- Hyponatremia (2.5%) usually asymptomatic.
- Most anticonvulsant effect is from the 10-monohydroxy active metabolite (MHD)

Zonisamide

- Patients who are allergic to sulfonamides may have an increased risk of allergic reactions to zonisamide

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Status Epilepticus

- **Status epilepticus** refers to seizures that persist for more than 30 minutes or occur repeatedly without a return to consciousness between seizures.
- This is an emergency condition and requires urgent treatment and complete control of seizures within 60 minutes.

- Mortality is 3 - 35% (Dodson et al., 1993)
- Failure to provide urgent treatment will result in brain damage or death.
- A convulsive seizure that is unusually prolonged for more than several minutes or a cluster of convulsive seizures over a short time interval indicate that the person is at risk for status epilepticus. In this case, the person should be treated immediately according to the status epilepticus protocol.
- Stabilize vital functions
- Respiration: intact airway, give oxygen as nasal cannula or mask, intubation and ventilation if needed, oximetry or blood gas as needed.
- Blood pressure: treat shock, monitor blood pressure, establish IV line, use central IV line if needed.
- Pulse: treat life threatening cardiac arrhythmia, monitor with ECG.
- Temperature: treat hyperthermia.
- Blood tests
- Blood tests: glucose, serum chemistries, hematology, toxicology, anticonvulsant levels.
- Administer thiamine 100 mg IV and then 50 ml of 50% glucose IV.

Drug Therapy

- **Lorazepam** 0.1 mg/kg IV at a rate of 2 mg/minute.
- **Fosphenytoin**: 18 mg/kg PE (phenytoin equivalents) intravenous loading dose; next day maintenance dose is 5 mg/kg-d.
- **Phenobarbital**: 18 mg/kg intravenous loading dose; next day maintenance dose is 1 - 5 mg/kg-d.
- **Midazolam**: 0.1 - 0.3 mg/kg bolus loading dose; maintenance dose 0.05 - 0.6 mg/kg-hr. (Fountain NB, Adams RE, 1999)
- **Midazolam** has less hypotensive side effects as compared to phenobarbital.
- **Excessive sedation** might occur after a prolonged midazolam infusion due to high lipid solubility and reduced clearance in elderly or severely ill persons. Dosage should be based on ideal body weight.
- **Propofol**: 1 mg/kg loading dose; maintenance dose of 3 - 6 mg/kg-hr
- **Pentobarbital**: 5 mg/kg bolus loading dose; maintenance dose 1 - 5 mg/kg-hr adjusted to the stop seizures or produce a **EEG burst suppression. pattern**. EEG monitoring useful to demonstrate cessation of seizure activity.
- **Hypotension** is a common problem with pentobarbital. Dopamine might be needed to support blood pressure.
- **Pentobarbital** produces a drug coma over several days and the pentobarbital is then gradually reduced after the person is on a adequate dose of anticonvulsants.
- **Rectal diazepam and buccal midazolam** have been used to treat acute exacerbation of seizures (Scott RC, Besag FM, Neville BG, 1999). Bucccal administration of other benzodiazepines such as lorazepam might be found to be effective in future studies.

Epilepsy Surgery

- The goal is to make patients with epilepsy seizure free
- Even one seizure every 6 months may prevent someone from operating a motor vehicle or prevent them from being employed
- Many patients who do not respond to medications will become seizure free with epilepsy surgery
- Epilepsy surgery should be considered when someone has not responded to several different anticonvulsants
- Other therapies include vagal nerve stimulator, electrical brain stimulation

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Counseling and patient education

- The person should be advised to not operate a motor vehicle, dangerous machinery or participate in activity where he would be at risk for injury to himself or others if he were to have a seizure. The minimum seizure free time interval for driving and the physician notification requirements vary from state to state. Cooking is best done using a microwave. Most non-contact sports can be done but supervision for some sports is desirable e.g. swimming.
- The person should know the dose, name and side effects of all his anticonvulsant medications.
- Women should be advised about the risk of oral contraceptive failure associated with some of the anticonvulsants.
- Women who take anticonvulsants and who are capable of becoming pregnant can be given folate 1 mg per day.
- During pregnancy, there is a risk of congenital malformations from anticonvulsants. The risk is minimized by taking the fewest anticonvulsants and using the lowest appropriate anticonvulsant dose.
- The anticonvulsant that is most effective for controlling seizures prior to pregnancy is usually the best anticonvulsant to take during pregnancy.
- Pregnant women may require a vitamin K shot before delivery.
- Breast feeding is not usually a problem.
- Women who can bear children will benefit best from counseling on these issues before they become pregnant.

Self Assessment Examination

Q1. A 55 year old man develops recurrent convulsions beginning 6 months after a traumatic brain injury. Does this person have epilepsy? Is anticonvulsant therapy required?

Q2. A 60 year old alcoholic man has seizures about 1 day after he stops drinking alcohol. Does this person have epilepsy? Is anticonvulsant therapy required?

Q3. A 22 year old woman develops a "funny" feeling followed by a blank stare, arrest of spontaneous motor behavior and then picking movements with her hands. After 1 minute, she turns her head to the right, stiffens and jerks. She is somnolent and weaker on the right side for about 1 hour after the seizure. What are the types of seizures? What is the significance of the transient right sided weakness after the seizure?

Q4. A 16 year old boy jerks both his arms and legs as if he was startled. This later occurs several times that morning. What is the seizure type? Is this a partial or generalized seizure?

Q5. Juvenile myoclonic epilepsy has a typical age of onset, typical behavioral features, typical EEG pattern and a genetic etiology. Is this a symptomatic, cryptogenic or idiopathic seizure disorder?

Q6. A 8 year old child develops infantile spasms. The MRI and all laboratory tests are normal. Is this a symptomatic, crytogenic or idiopathic seizure disorder?

Q7. A 40 year old woman develops recurrent seizures after a traumatic brain injury. Is this a symptomatic, crytogenic or idiopathic seizure disorder?

Q9. A 5 year old girl develops brief 10 second spells of a blank stare during hyperventilation. EEG shows 20 brief 10 second episodes of rhythmic repetitive 3 per second bilateral spike and wave discharges. What are these 20 brief episodes on the EEG? What type of epilepsy does this child have? What is the drug of choice?

Q10. A 18 year old man has episodes of a blank stare and unresponsiveness. The EEG is normal. Does this exclude the diagnosis of epilepsy? What additional diagnostic tests would confirm the diagnosis of epilepsy?

Q11. A patient with episodes of confusion, unresponsiveness and a blank stare. The EEG shows right temporal lobe epileptiform discharges. Did the EEG record a seizure? What is the diagnosis?

Q12. An 18 year old woman develops recurrent complex partial seizures. CT is normal. What should be done?

Q13. What are two common MRI finding in epilepsy patients?

Q14. A patient describes a deja vu aura. What is the epileptic syndrome?

Q15. A patient describes an aura of bright rotating multi-colored rotating circles. What is the seizure type?

Q16. A 6 month old develops episodes of brief rapid trunk flexion that occurs in clusters on awakening. What is the name for this type of seizure? What is the EEG finding between seizures? What is the EEG finding during the seizures? What is the prognosis? What is the epileptic syndrome? What is the common associated neurocutaneous syndrome?

Q17. A 2 year old child develops recurrent seizures with bilateral stiffening of both arms, trunk flexion and a fall to the ground. EEG shows slow 1-2 per second spike and wave discharges. What is the diagnosis? What is the prognosis?

Q18. A 6 year old cries out in the middle of the night. The parents find the child with convulsive left facial seizures. The older sibling had the same problem but now at age 17 years no longer has this problem. EEG shows a right central epileptiform discharge. What is the diagnosis? What is the prognosis?

Q19. A 16 year old develops early morning myoclonic jerks and later that morning, a generalized convulsion. What is the probable diagnosis? What is the prognosis? What is appropriate anticonvulsant therapy?

Q20. An 8 month old develops a high fever from a ear infection. The child has a single one minute generalized convulsion. What is the diagnosis? What is the prognosis? Should the child be treated with anticonvulsants?

Q21. An 8 month old develops a high fever from a respiratory infection. The child has 3 focal motor seizures over a 24 hour period. What is the diagnosis? What is the prognosis? Should the child be treated with anticonvulsants?

Q22. A 25 year old woman has juvenile myoclonic epilepsy. Her Ob-Gyn doctor changes her medication from valproate to carbamazepine. Her seizures worsen. How do you explain this?

Q23. What anticonvulsants are effective for absence epilepsy?

Q24. What anticonvulsants are effective for partial seizures?

Q25. What anticonvulsant will make you fat and bald?

Q26. What anticonvulsant will give you hirsutism, bad gums, coarse facial features and acne?

Q27. Which 2 anticonvulsants can be given intravenously to rapidly control seizures in a person with status epilepticus?

Q28. Which anticonvulsants may cause an increased risk of kidney stones?

Q29. Which anticonvulsant has the highest risk for causing aplastic anemia and hepatotoxicity? Are monitoring tests recommended

Q30. An epileptic woman who takes phenytoin becomes pregnant despite oral contraceptive use. How did this happen? What should be done in the future?

Q31. Which anticonvulsant commonly causes hyponatremia and reduced white blood cell count?

Q32. Which 2 anticonvulsants have been associated with spina bifida?

Q33. What is considered to be an acceptable seizure frequency?

Q34. What is appropriate management for a woman with epilepsy?

Q35. An epileptic patient with temporal lobe epilepsy has not responded to 4 different anticonvulsants. What should be done?

Answers

A1. This person has epilepsy because he has recurrent unprovoked seizures. This person will require chronic anticonvulsant therapy.

A2. This person has seizures but does not have epilepsy because the seizures are provoked by alcohol withdrawal. This person will not require chronic anticonvulsant therapy but will need to participate in an alcohol detoxification program.

A3. This seizure begins with a seizure aura of a "funny" feeling. The aura is a simple partial seizure. The seizure then evolves to a complex partial seizure with automatisms. After one minute, the seizure evolves to a secondary generalized tonic-clonic seizure with versive head turning to the right. The right sided weakness is a post-ictal symptom that suggests a left hemisphere seizure focus.

A5. These are myoclonic seizures which are a form of primary generalized seizures.

A5. This is an idiopathic seizure disorder.

A6. This is a cryptogenic seizure disorder.

A7. This is a symptomatic seizure disorder.

A9. The 20 episodes were absence seizures. This patient has childhood absence epilepsy. Drug of choice is ethosuximide.

A10. No the EEG may be normal in a person with epilepsy. Repeat EEG or prolonged EEG monitoring may confirm the diagnosis of epilepsy.

A11 The EEG did not record a seizure. The EEG recorded an interictal discharge. The EEG finding in combination with the clinical history indicates that this patient has right temporal lobe epilepsy.

A12. An MRI should be done. The MRI may identify a lesion that was missed by the CT scan. A focal brain lesion could be resected and lead to a cure of this person's epilepsy.

A13. Mesial temporal sclerosis and cortical dysplasia

A14. Temporal lobe epilepsy

A15. Occipital lobe epilepsy?

A16. Hypsarrythmia EEG pattern between seizures, electrodecremental EEG pattern during seizures, prognosis is poor, epileptic syndrome is West syndrome, neurocutaneous syndrome is tuberous sclerosis.

A17. Diagnosis is Lennox - Gastaut. Prognosis is poor, mental retardation is likely. Seizures likely to persist despite medications.

A18. Benign rolandic epilepsy. Excellent prognosis, after age 16 years, seizures are unlikely to occur.

A19. Most likely Juvenile Myoclonic epilepsy. Prognosis is good, anticonvulsant therapy will probably stop all future seizures but the patient will require therapy life long. Appropriate drug therapy would be valproate, topiramate or lamotrigine.

A20. Diagnosis is simple febrile seizure. Prognosis is good, it is likely that this will be the only seizure the child will ever have. The child does not have a significant increase in the risk for developing epilepsy and will not require anticonvulsant therapy.

A21. Diagnosis is complex febrile seizure. There is an increased risk for developing epilepsy later in life.

A22. Carbamazepine is appropriate for partial seizures with or without secondary generalization. Juvenile myoclonic epilepsy is a primary generalized epilepsy, carbamazepine is not effective and may actually worsen the seizure disorder.

A23. Ethosuximide, valproate, lamotrigine and topiramate

A24. Phenytoin, carbamazepine, phenobarbital, primidone, valproate, topiramate, lamotrigine, tiagabine, oxcarbazepine, zonisamide, felbamate

A25. Valproate

A26. Phenytoin

A27. Lorazepam and fosphenytoin

A28. Topiramate and zonisamide

A29. Felbamate. Monthly CBCs and transaminases are recommended. The risk is greatest in the first year.

A30. Some anticonvulsants increases the metabolism of estrogen and cause anticonvulsant failure. The options for the future are non-enzyme inducing anticonvulsants, an alternative contraceptive method or an oral contraceptive pill with more estrogen (50 mcg or greater).

A31. Carbamazepine

A32. Valproate 1-2% risk and carbamazepine 0.5-1% risk

A33. No seizures. Even one seizure every 6 months can prevent a person from operating a motor vehicle and working at many jobs.

A34. The woman should be advised on the need to take folate 1 mg per day with daily multivitamins, increased risk of congenital malformations associated with anticonvulsant therapy, and risk of oral contraceptive failure. The patient should receive the minimum dose and minimum number of anticonvulsants needed to control her seizure disorder. Oral vitamin K may be needed during the last month of pregnancy. Breast feeding is not a problem in most cases if she takes anticonvulsants.

A35. The patient should consider epilepsy surgery. The fifth anticonvulsant is not likely to control the seizures, epilepsy surgery may cure his epilepsy.

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