Seizure Disorders in Children

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Seizure

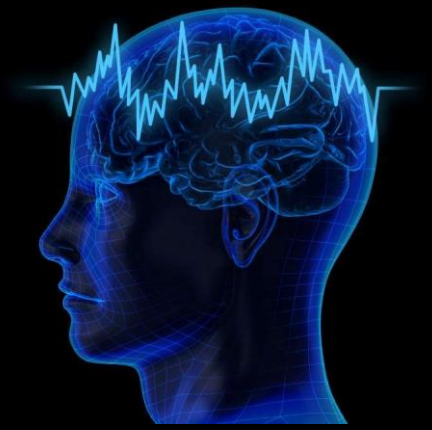
A transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain.

Epilepsy

Epilepsy is a disorder characterized by two or more unprovoked seizures occurring more than 24 hours apart beyond neonatal period.

Seizure *vs* Epilepsy

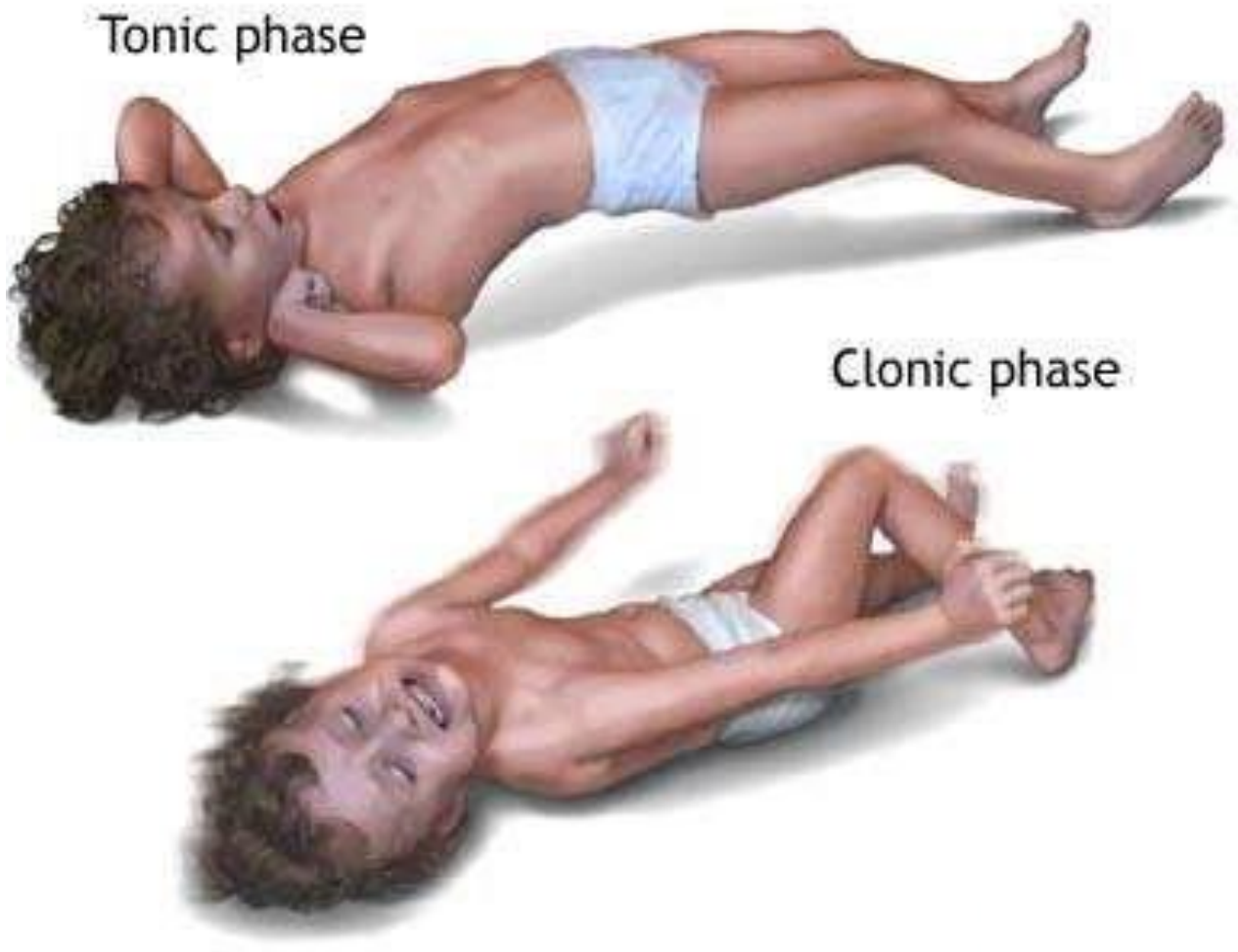
- A seizure is the event



- Epilepsy is the disease associated with spontaneously recurring seizures

Convulsion

A convulsion is any seizure (not necessarily epileptic) characterized by excessive, abnormal muscle contractions, which are usually bilateral.

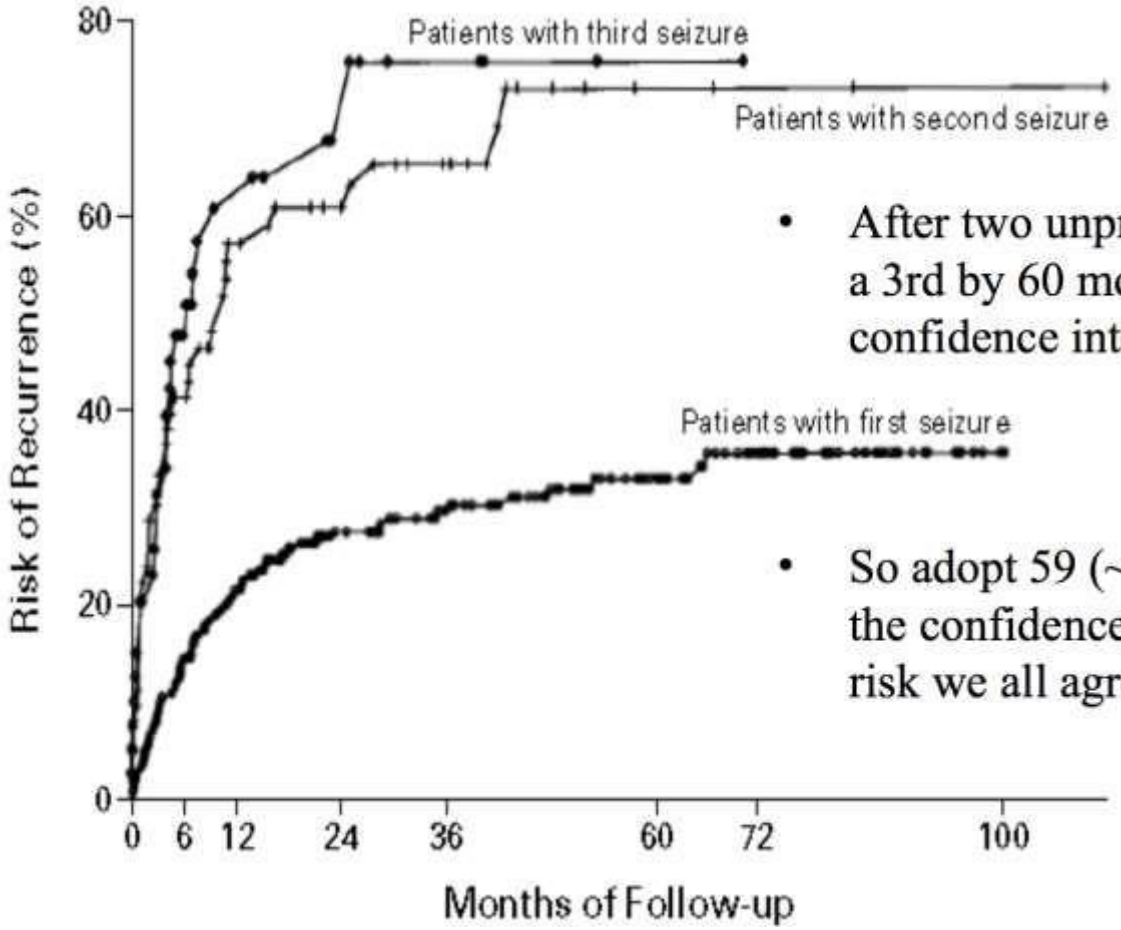


Epilepsy – new definition

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

1. A 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

Risk of epilepsy after 2 seizures



- After two unprovoked seizures, the risk of a 3rd by 60 months is 73% (59-87%, 95% confidence intervals.
- So adopt 59 (~ 60%) as the lower end of the confidence interval for the recurrence risk we all agree is epilepsy.

- Hauser et al. Risk of recurrent seizures after two unprovoked seizures. *NEJM* 1998;338:429.

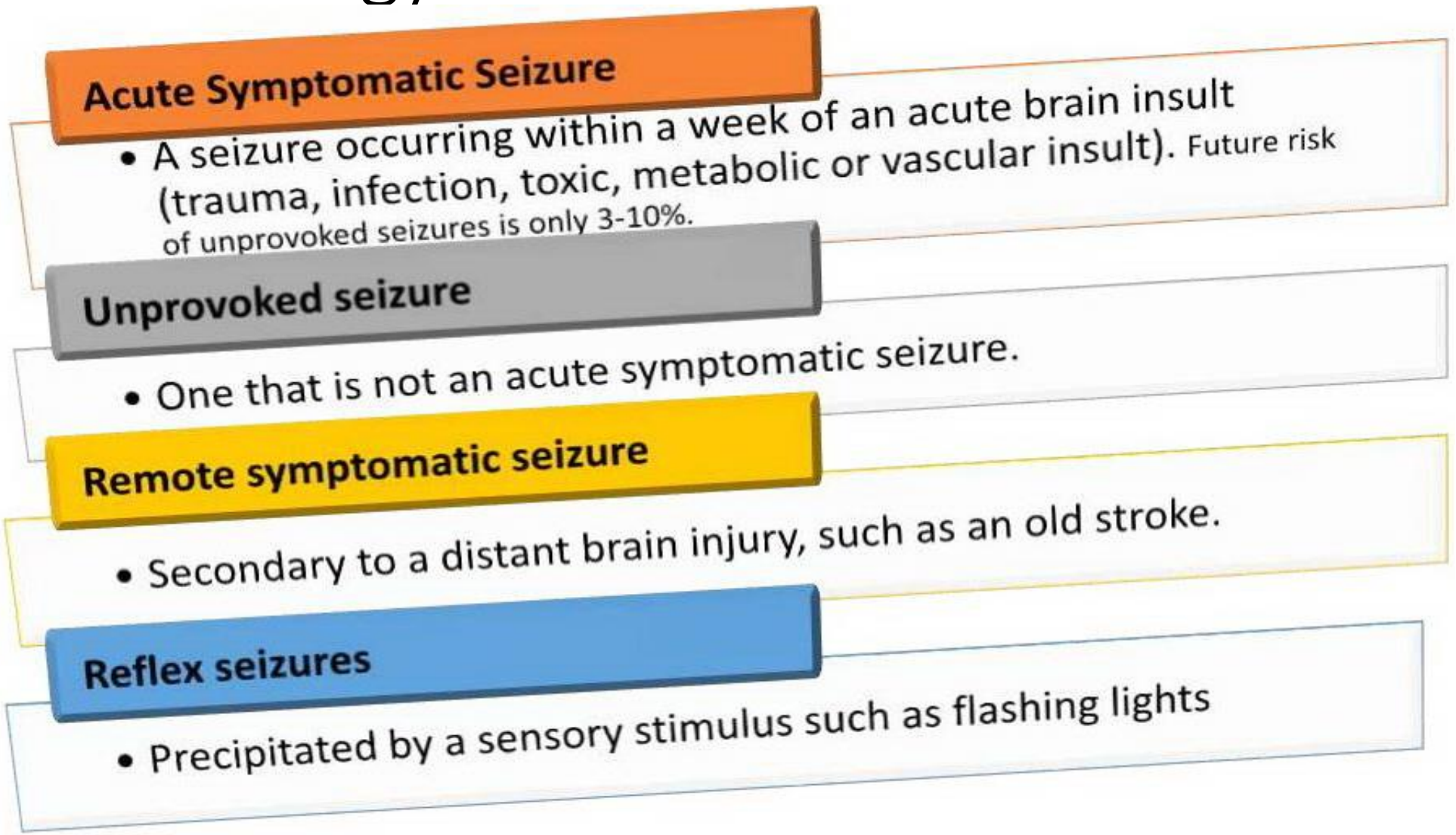
Focal

The first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of one cerebral hemisphere

Generalized

The first clinical and EEG changes indicate synchronous involvement of all of both hemispheres

Some terminology



- Dr Neeta Naik, ; Guidelines for Diagnosis and Management of Childhood Epilepsy; Expert Committee On Pediatric Epilepsy, IAP*; Ind Ped*, Vol 46___Aug 17, 2009: 681-698

Secondarily generalized seizures

- partial-onset seizures that spread and generalize.

Secondary generalized epilepsy

- a constellation of any number of generalized-onset seizure types.

Some terminology

Epilepsy 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.

Epileptic syndrome

- A disorder that manifests one or more specific seizure types and has a specific age of onset and a specific prognosis

Epilepsia Partialis Continua

Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed epilepsia partialis continua.

Can be caused by tumor, vascular etiologies, mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), and Rasmussen encephalitis.

Status Epilepsy (>100 / 100000 population)

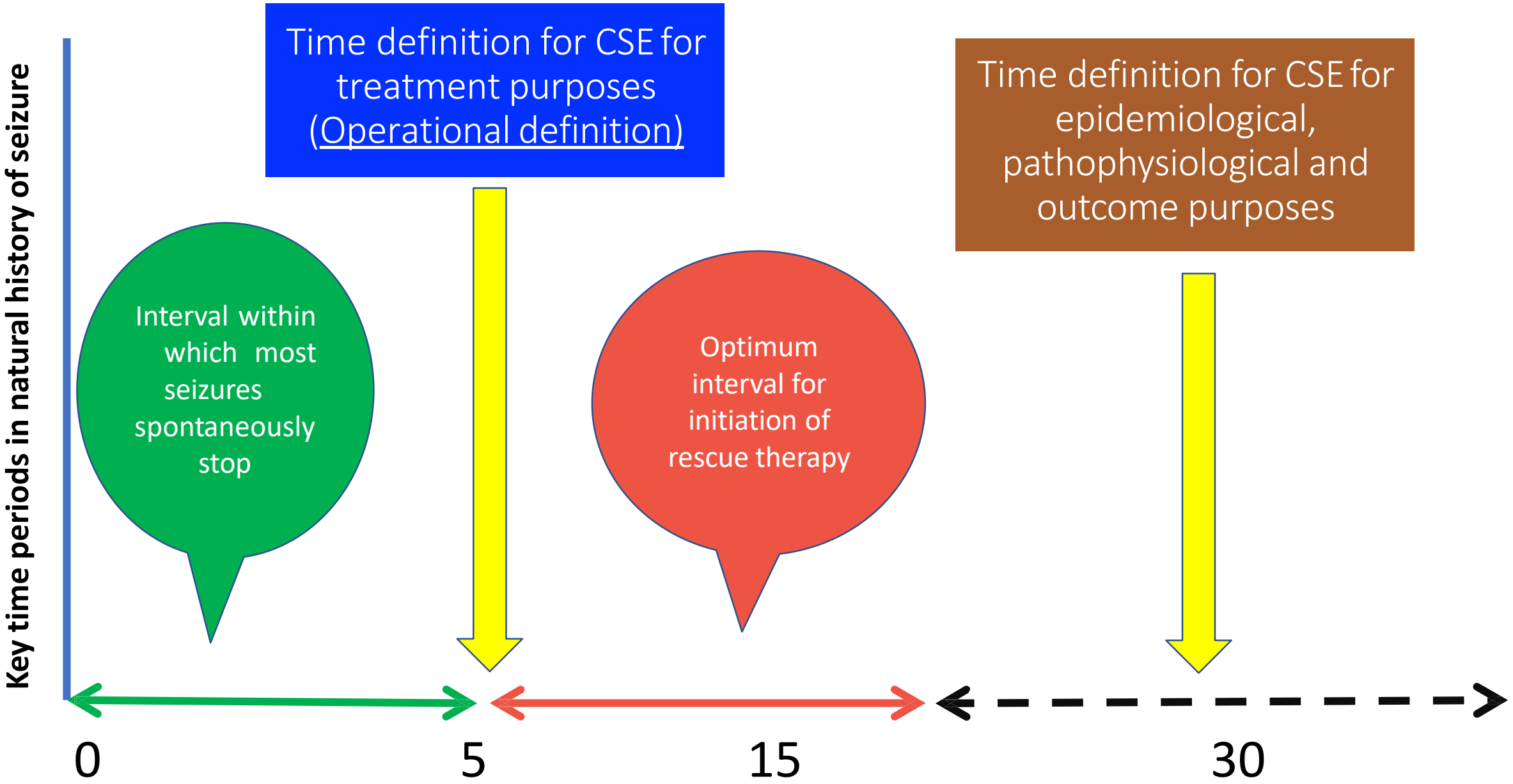
Clinical Definition

- Recurrent epileptic seizures continuing for more than 30 minutes without full recovery of consciousness before the next seizure begins, or continuous clinical and/or electrical seizure activity lasting for more than 30 minutes whether or not consciousness is impaired'

New Operational Definition (children > 5 yrs)

- "Greater than or equal to 5 minutes of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness."

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Eugen Trinka, et al; *Epilepsia*, 56(10):1515–1523, 2015 doi: 10.1111/epi.13121


Time definition for CSE for treatment purposes (Operational definition)
Time definition for CSE for epidemiological, pathophysiological and outcome purposes
Key time periods in natural history of seizure
Interval within which most seizures spontaneously stop
Optimum interval for initiation of rescue therapy
0
5
15
30

Status Epilepsy - ILAE

	Tonic-Clonic	Focal with impaired consciousness	Absences
Point 1 (t1) the earliest time when treatment should be started.	5 min	10-15 min	15 min
Point 2 (t2) when long-term consequences, such as neuronal injury, neuronal death	30 min	> 60 min	Unknown

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Eugen Trinka, et al; *Epilepsia*, 56(10):1515–1523, 2015 doi: 10.1111/epi.13121

Status Epilepticus

Convulsive Status epilepticus

- generalized tonic, clonic, or tonic–clonic

Non-convulsive Status epilepticus

- complex partial, absence, myoclonic status, epilepsia partialis continua, and neonatal status epilepticus, confusional state, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness catatonia, and or psychotic symptoms.

- *Nelson*

Mechanisms which Underlie Seizure Generation

- Abnormalities at the cell membrane level (ion channels and receptors) and in neuronal circuits
- Three main classes of voltage gated ion channels have been described: Na+, Ca^{2+} and K^{+}.
- Sodium currents are involved in the generation of action potentials.
- Potassium currents cause hyperpolarization and hence stabilize the neuronal membrane.
- Both calcium and sodium currents are involved in the generation of burst discharges, generated by certain classes of neurones when excited.
- Gamma amino butyric acid (GABA) and glycine are inhibitory neurotransmitters while glutamate and aspartate are excitatory neurotransmitters.
- A useful, though simplistic model of epilepsy is that it involves an imbalance of excitatory and inhibitory neurotransmitter systems within the CNS.

The 2017 ILAE Classification of Seizures

Robert S. Fisher, MD, PhD
Maslah Saul MD Professor of Neurology Director, Stanford Epilepsy Center

In 2017, the ILAE released a new classification of seizure types, largely based upon the existing classification formulated in 1981.

ILAE 2017 Classification of Seizure Types Basic Version [1]

Focal Onset

Generalized Onset

1 Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

2 Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset

Aware | Impaired Awareness

Motor Onset
- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

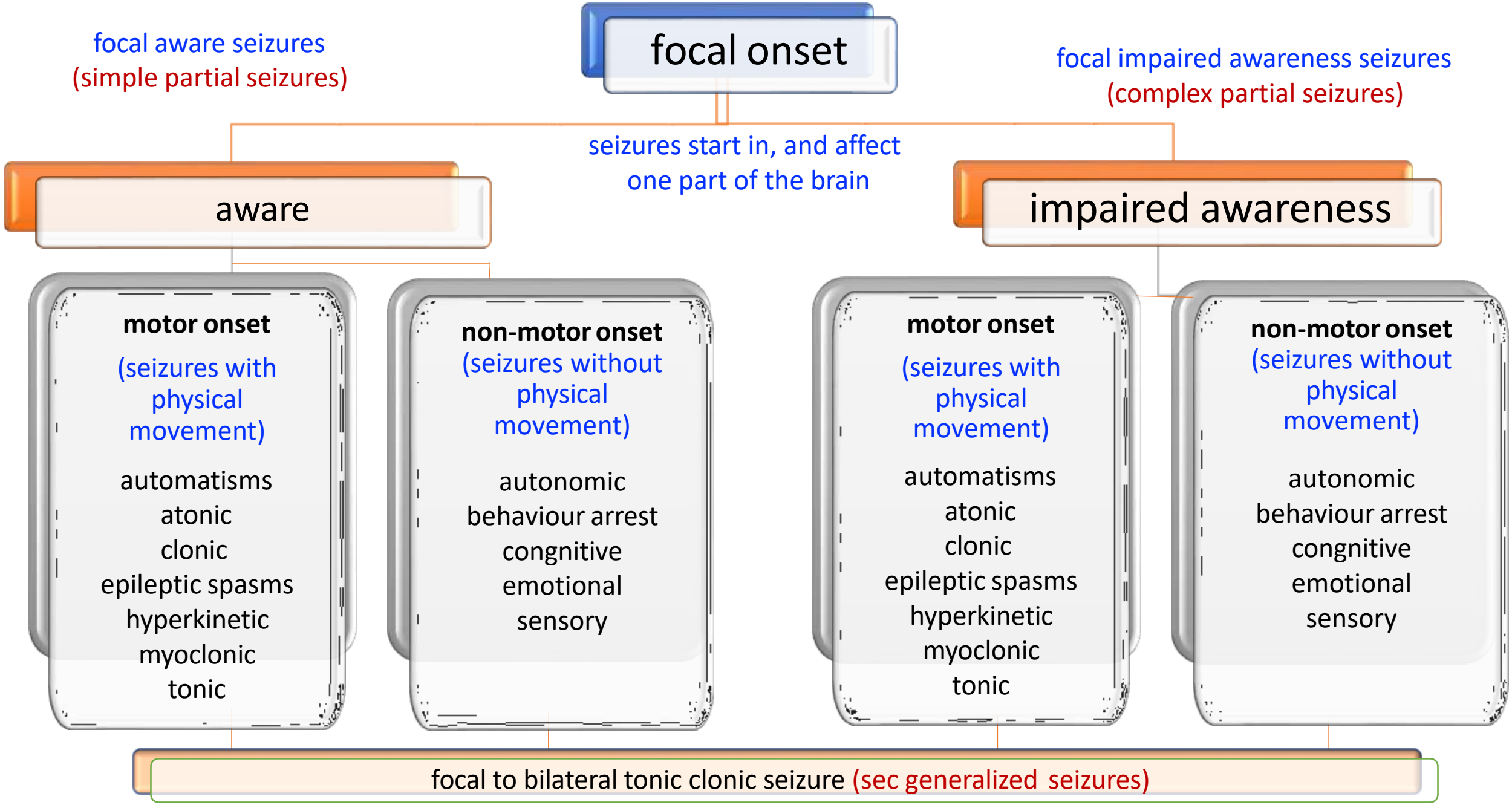
Non-Motor
- behavior arrest

Unclassified[3]

2 These could be focal or generalized, with or without alteration of awareness

3 Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*


focal aware seizures
(simple partial seizures)
focal onset
focal impaired awareness seizures
(complex partial seizures)
seizures start in, and affect
one part of the brain
aware
impaired awareness
motor onset
(seizures with physical movement)
automatisms
atonic
clonic
epileptic spasms
hyperkinetic
myoclonic
tonic
non-motor onset
(seizures without physical movement)
autonomic
behaviour arrest
congnitive
emotional
sensory
motor onset
(seizures with physical movement)
automatisms
atonic
clonic
epileptic spasms
hyperkinetic
myoclonic
tonic
non-motor onset
(seizures without physical movement)
autonomic
behaviour arrest
congnitive
emotional
sensory
focal to bilateral tonic clonic seizure (sec generalized seizures)

generalized onset

seizures start in, and affect both sides of the brain at once and happen without warning

motor (with physical movement)

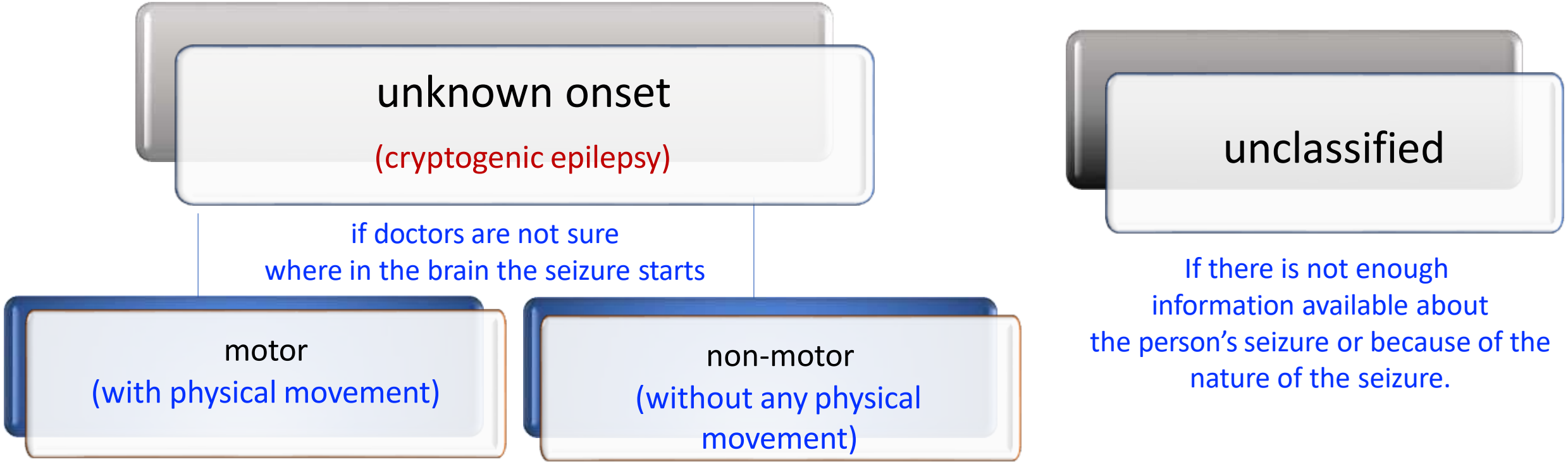
non-motor (absence) (without any physical movement)

Motor

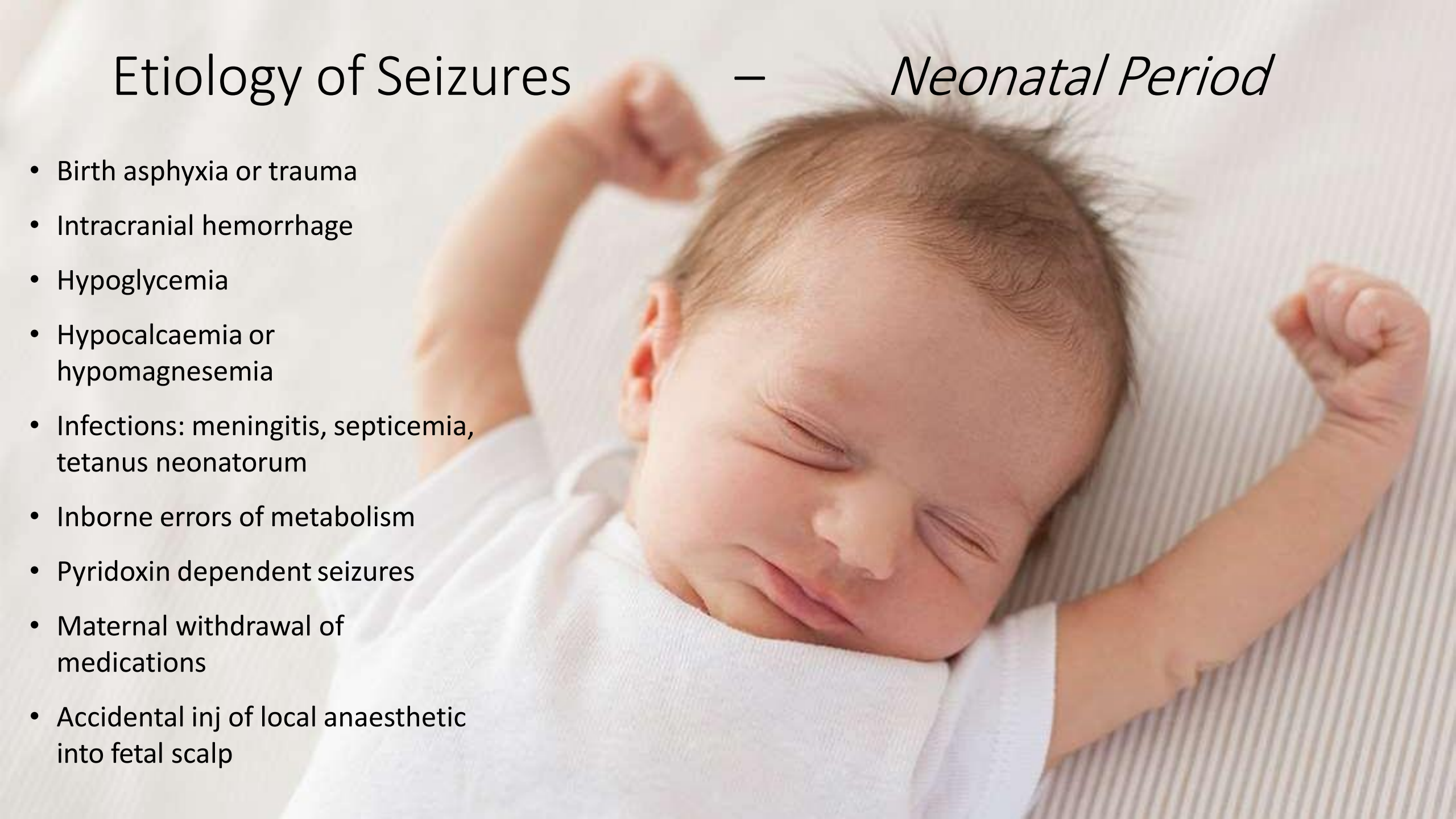
- **tonic-clonic**
- **clonic**
- **tonic**
- **myoclonic**
- **myoclonic-tonic-clonic**
- **myoclonic-atonic**
- **atonic**
- **epileptic spasms**[2]

Non-Motor (absence)

- **typical** (3 Hz spike & slow wave)
- **atypical** (1-2 Hz spike & slow wave with head atonia and myoclonus)
- **myoclonic**
- **eyelid myoclonia**


unknown onset
(cryptogenic epilepsy)
if doctors are not sure
where in the brain the seizure starts
motor
(with physical movement)
non-motor
(without any physical
movement)
unclassified
If there is not enough
information available about
the person's seizure or because of the
nature of the seizure.

Etiology of Seizures – *Neonatal Period*



- Birth asphyxia or trauma
- Intracranial hemorrhage
- Hypoglycemia
- Hypocalcaemia or hypomagnesemia
- Infections: meningitis, septicemia, tetanus neonatorum
- Inborne errors of metabolism
- Pyridoxin dependent seizures
- Maternal withdrawal of medications
- Accidental inj of local anaesthetic into fetal scalp

Etiology of Seizures – Beyond Neonatal Period

- Simple **febrile convulsions**
- **Epilepsy syndromes**
- **Infections**: meningitis, encephalitis, Reye syndrome, cerebral malaria
- **Metabolic causes**: Dyselectrolytemia, hypocalcemiam hypomagnesemia, IEM
- **Space occupying lesions:** Neoplasm, brain abscess, tuberculoma, cysticercosis
- **Trauma**:

- **Vascular**: hemorrhage , AV malformations, intracranial thrombosis
- **Cerebral malformation:** neurocutaneous syndromes, neuronal migration disorders
- **Drugs/Poisons**: Phenothiazines, lead salicylates, phenytoin, CO, strychnine
- **Miscellaneous:** Hypertensive encephalopathy, gray matter degeneration, storage disorders

Febrile Seizures

Nelson Text Book Definition:

Febrile seizures are seizures that occur between the ages of 6 and 60 mo (peak 12-18 mo) with a temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures

ILAE Definition:

FS is a seizure occurring in childhood after one month of age, associated with a febrile illness that is not caused by an infection of the central nervous system

Febrile Seizures – Types

Simple

- Primary generalized,
- usually tonic–clonic,
- attack associated with fever
- Lasting for a maximum of 15 min
- Not recurrent within a 24-hr period

Complex

- Focal
- Prolonged (>15 min)
- Reoccurs within 24 hours

Febrile status epilepticus

… is defined as one lasting over 30 minutes.

Febrile seizure plus

When the febrile seizures continue after age 5 or other types of seizure develop. FS+ usually end in early adolescence. …

- **Febrile infection–related epilepsy (FIRES):** In children >5 yr) usually male children and associated with an encephalitis-like illness but without an identifiable infectious agent. Children with FIRES were previously normal but subsequently develop difficult-to-treat epilepsy.

- **Generalised epilepsy with febrile seizures plus (GEFS+):** Children may go on to have febrile seizures well beyond 6 yrs age, even into adult life. They may also develop other seizure types not associated with a high temperature. An epileptic syndrome.

Febrile Seizures – Risk Factors

MAJOR

- Age < 1 yr
- Duration of fever < 24 hr
- Fever > 38-39^{0}C (100.4 – 102.2^{0}F)

MINOR

- Family history of febrile seizure
- Family history of epilepsy
- Complex febrile seizure
- Daycare
- Male gender
- Lower serum sodium at time of presentation

Risk factors for Recurrence	
No risk factors	12%
1 risk factor	25-50%
2 risk factors	50-59%
3 or more risk factors	73-100%

- *Nelson Textbook of Pediatrics, 21E*

Epilepsy Syndromes

- **Benign Rolandic Epilepsy**
  - Male
  - 2-13 yrs
  - Mostly nocturnal
  - Motor & somatosensory – older children
  - Hemiclonic / GTCS – younger children
  - Most AEDs effective
  - Recovery before 15-16 yrs
- **Juvenile Myoclonic Epilepsy**
  - Most common generalized epilepsy in in 5-16 yrs olds
  - GTCSs
  - 3-6 Hz generalized polyspikes and waves in EEG
  - Improve after 4th decade
- **West Syndrome** (Infantile Spasms)
  - 3-10 %
  - Genetic predisposistion
  - Male preponderance
  - Onset 1-8 yrs
  - Poor prognosis
  - Hypsarrhythmia
- **Lenox Gestaut Syndrome**
  - Typically in 3-5 yrs age group
  - Severe, Complex epilepsy
  - Multiple concurrent seizure types
  - Cognitive dysfunction

Seizure Evaluation on First Visit

1. Seizure / seizure mimic ?
2. Is it unprovoked / provoked seizure?
3. Generalized / focal seizure?
4. Etiology?
5. Any associated comorbidities?
6. Treatment received till now?

Role of Imaging

- MRI is the imaging modality of choice! But not urgent
  - Significant cognitive or motor impairment of unknown etiology
  - Unexplained abnormalities on neurologic examination
  - Focal seizure with or without secondary generalization
  - EEG that does not represent a benign partial epilepsy or primary generalized epilepsy
  - Seizure in children under 1 year of age
- Rarely CT is indicated

SWI (Susceptibility-Weighted Imaging)

- If MRI can not be done, better don't do imaging!! - *Epilepsia*, 50(9): 2147-2153, 2009

Role of EEG in Office practice

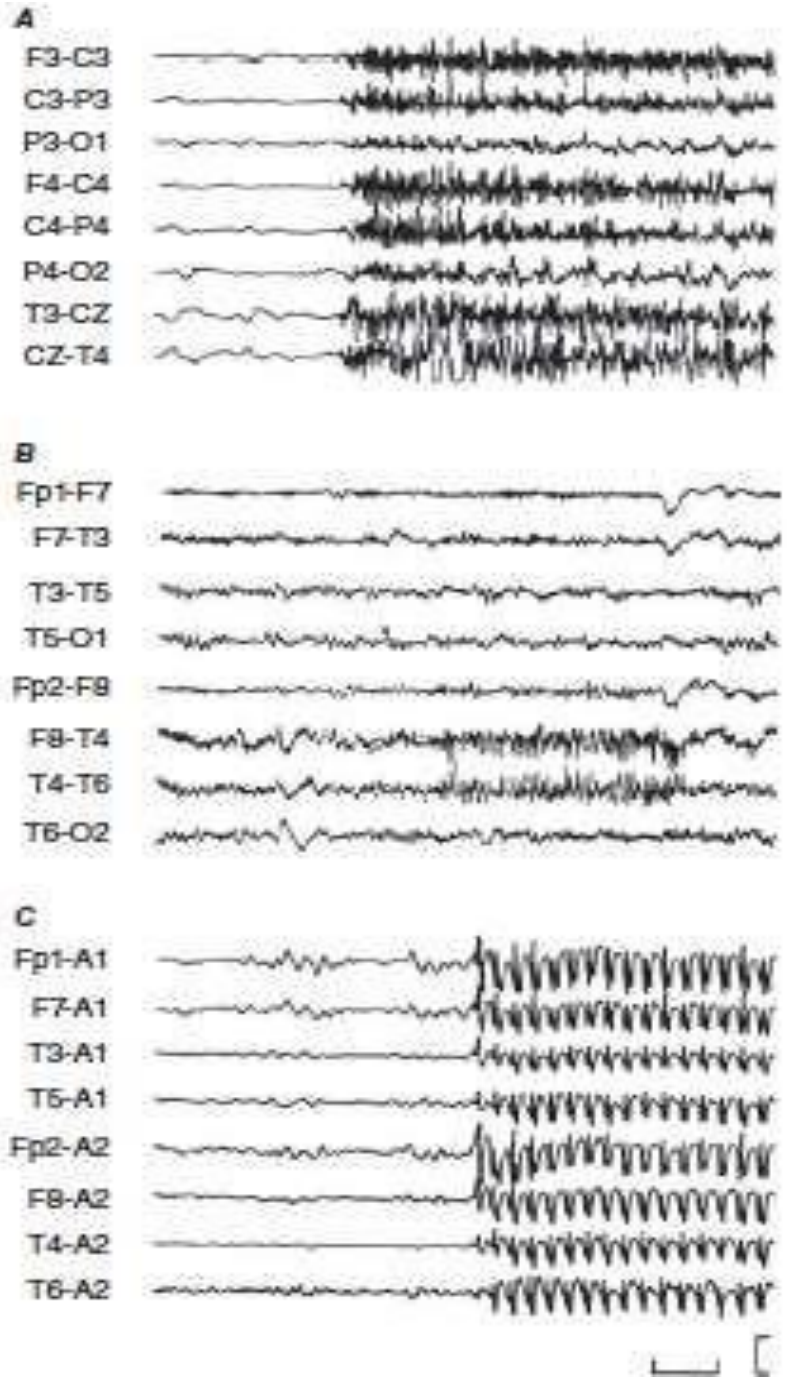
- Supports the clinical diagnosis of epilepsy
- To classify epilepsy : Focal vs Generalized epilepsy
- To identify epilepsy syndromes
- To predict recurrence risk and to prognosticate
- Unexplained GDD/worsening/autistic regression

- *K.M.Pearce, H.R. Cock, Seizure 2006*

A. Onset of a tonic seizure showing generalized repetitive sharp activity with synchronous onset over both hemispheres.

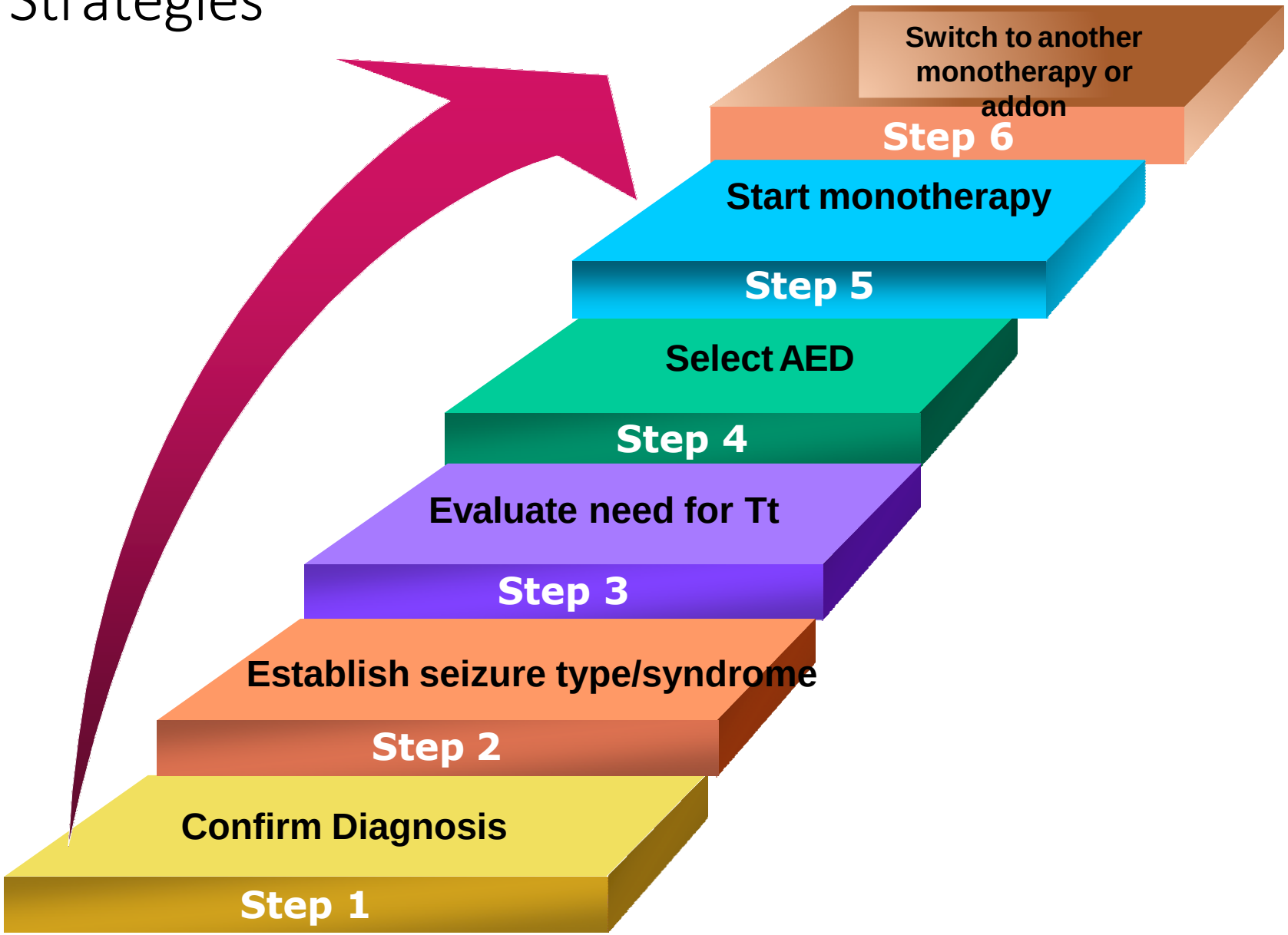
B. Burst of repetitive spikes occurring with sudden onset in the right temporal region during a clinical spell characterized by transient impairment of external awareness.

C. Generalized 3-Hz spike-wave activity occurring synchronously over both hemispheres during an absence (petit mal) attack. Horizontal calibration:

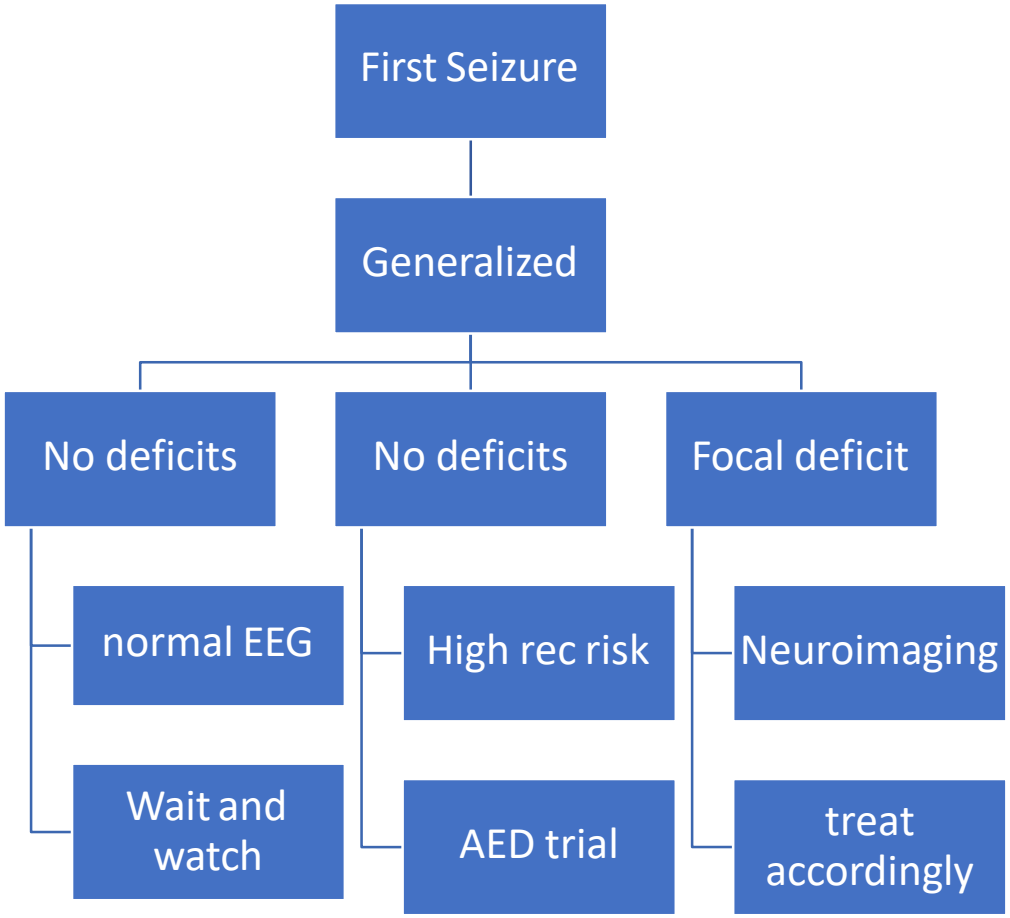


- *MJ Aminoff [ed]: Aminoff's Electrodiagnosis in Clinical Neurology, 6th ed. Oxford, Elsevier Saunders, 2012.)*

Management Strategies



Management Strategies



Principles of drug therapy in epilepsy

1. Start with a single AED
2. Start with low dose and increase gradually
3. Ensure compliance
4. Increase dose gradually to maximum tolerate
5. A seizure diary should be kept by the parents
6. AED is withdrawn after 2 year of seizure freedom.

"As much as needed BUT as little as possible"
Self evident but often forgotten

AED of Choice

Seizure	First Choice	Second Choice
Focal seizure	Oxcarbamazepine: Carbamazepine	Valproate, Phenytoin
Idiopathic Generalized Epilepsy	• BOYS: Valproate, Phenytoin • GIRLS: Levetiracetam, Lamotrigine	• Levetiracetam, Lamotrigine, Zonisamide • Valproate, Zonisamide
Absence	Valproate, Lamotrigine, Ethosuximide	Levetiracetam, Topiramate, Zonisamide
Epileptic spasms	ACTH, Steroids	Vigabatrine
Myoclonic	Valproate	Levetiracetam, Topiramate, Zonisamide
Tonic	Valproate, Lamotrigine	Levetiracetam, Topiramate, Zonisamide
Atonic	Valproate, Lamotrigine	Levetiracetam, Topiramate, Zonisamide
Neonatal seizures	Phenobarbitone, Phenytoin	Levetiracetam
Benign Rolandic Epilepsy	None	Valproate, Cobazam

Ketogenic Diet

- The ketogenic diet (KD) is a stringently controlled high fat and low protein/carbohydrate diet given with/without a restricted fluid intake to maintain ketosis on a long term basis.
- It has been shown that it is more efficacious than newer AEDs in controlling refractory seizures

Surgical Remedies

- Hemispheric epilepsies
- Developmental tumors, cortical dysplasias, AVMs
- Mesial temporal lobe epilepsy caused often by hippocampal sclerosis
- Drop attacks with injuries respond well to corpus callosotomy

Refractory Epilepsy

- Epilepsy which is uncontrolled despite adequate trials of three first line AEDs and when it disrupts developmental progress or normal childhood activity

Antiepileptic Drugs - Classification

- **Sodium channel blockers:**
  - **Fast Channel :** Carbamazepine, Oxcarbazepine, Phenytoin, Fosphenytoin, Lamotrigine, Zonisamide,
  - **Slow Channel :** Lacosamide, Eslicarbazepine
- **Calcium channel blockers:**
  - **Low Voltage :**Ethosuximide, Valpoate, Zonisamide
  - **High Voltage:**Ethosuximide, Valpoate, Zonisamide
- **GABA Modulators:**
  - **GABA Receptor Agonists:** Clobazam, Clonazepam, Midazolam, Phenobarbital, Primidone, Benzodiazepines, Phenobarbitone, Felbamate, Levetiracetam
  - **GABA Reuptake inhibitors:** Tiagabine
  - **GABA Transaminase Inhibitors :** Vigabatrin
  - **Potential GABA Mechanism of Action :** Gabapentin, Pregabalin, Valproate (enhance glutamic acid decarboxylase (GAD))
- **Glutamate blockers :** Felbamate (NMDA), Topiramate(AMPA/KA), Perampanel, Levetiracetam(AMPA), Valproate (NMDA)
- **Carbonic anhydrase inhibitors :** Topiramate and Zonisamide
- **SV2A-binding agents:** Levetiracetam, brivaracetam
- **Other Mechanism of Action:** Levetiracetam, Brivaracetam, Cannabidiol, Stiripentol
- **Neuronal Potassium Channel Openers :**Ezogabine, Retigabine

Summary of Role of AEDs

- Broad spectrum AEDs
  - CLB, LGT, TPM, ZNS – used in generalized and focal epilepsies
- CLOBAZAM: Most common and effective add-on AED in many situations
- LAMOTRIGENE:
  - Titrate slowly, otherwise bad skin rashes including SJ syndrome
  - Effective add-on for IGE, Absence and Focal epilepsy
- TOPIRAMATE:
  - Effective in focal epilepsy including in infants
  - Can be titrated quickly
  - Beware of speech, memory and cognitive side effects
- ZONISAMIDE: Effective in drop attacks, refractory spasms

Management of Status Epilepticus

Time / Phase	Treatment
0-5 min (Stabilization Phase)	Ensure adequate ventilation/O_2, vitals monitoring, IV line with NS, rapid assessment, blood draw
5 - 20 min (Initial Therapy Phase)	• Lorazepam 4 mg (0.1 mg/kg) or diazepam 10 mg (0.2 mg/kg) over 2 minutes via second IV line or • Rectal diazepam / Intranasal midazolam / buccal midazolam
20 - 40 min (Second Therapy Phase)	• IV - Fosphenytoin or Phenytoin (20 mg/kg) or Valproic acid (40 mg/kg) or Levetiracetam (60 mg/kg) single dose • IV phenobarbital (15 mg/kg) single dose
40 - 60 min (Third Therapy Phase)	• ?? Repeat of 2nd line therapy; Anaesthetic doses of Thiopental, midazolam, phenobarbital or propofol with continuous EEG monitoring

Take Home Message

- Approach a child with seizures systematically
- Seizures and epilepsy are clinical diagnoses
- Well reported good EEG supports the clinical diagnosis
- Use neuroimaging judiciously; avoid CT scans
- Treat the patient and NOT the EEG report
- Epilepsy treatment is tailor made

Role of EEG

- **EEG** when abnormal can suggest the nature of the seizure tendency as focal or generalized, but does not determine whether or not a spell was a seizure or whether or not to treat,.
- 50% of patients with partial seizures show focal spikes (or slowing), up to 75% after repeat studies or sleep deprivation.
- 90% of patients with generalized seizures show generalized spikes, more with sleep deprivation, hyperventilation, or photic stimulation.
- A normal EEG would favor partial onset seizures in a patient with epilepsy.
- 1-2% of nonepileptics have spikes on their EEGs.
- 20% of patients with spikes on the EEG do not have epilepsy.

Thank You