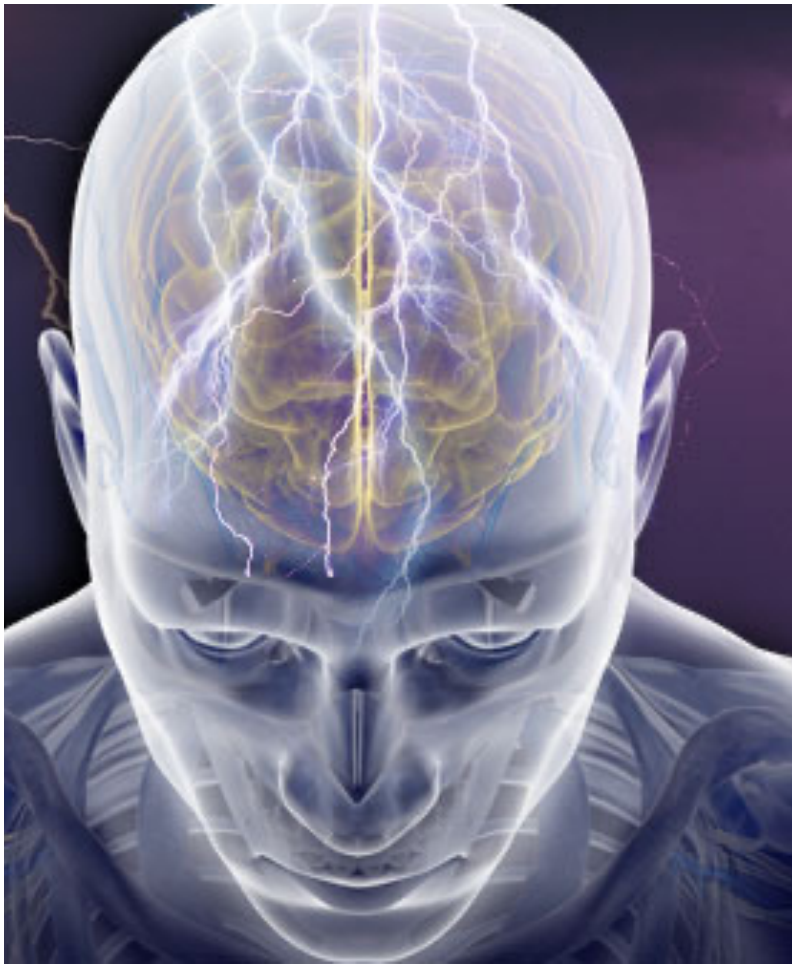
SEIZURES AND EPILEPSY

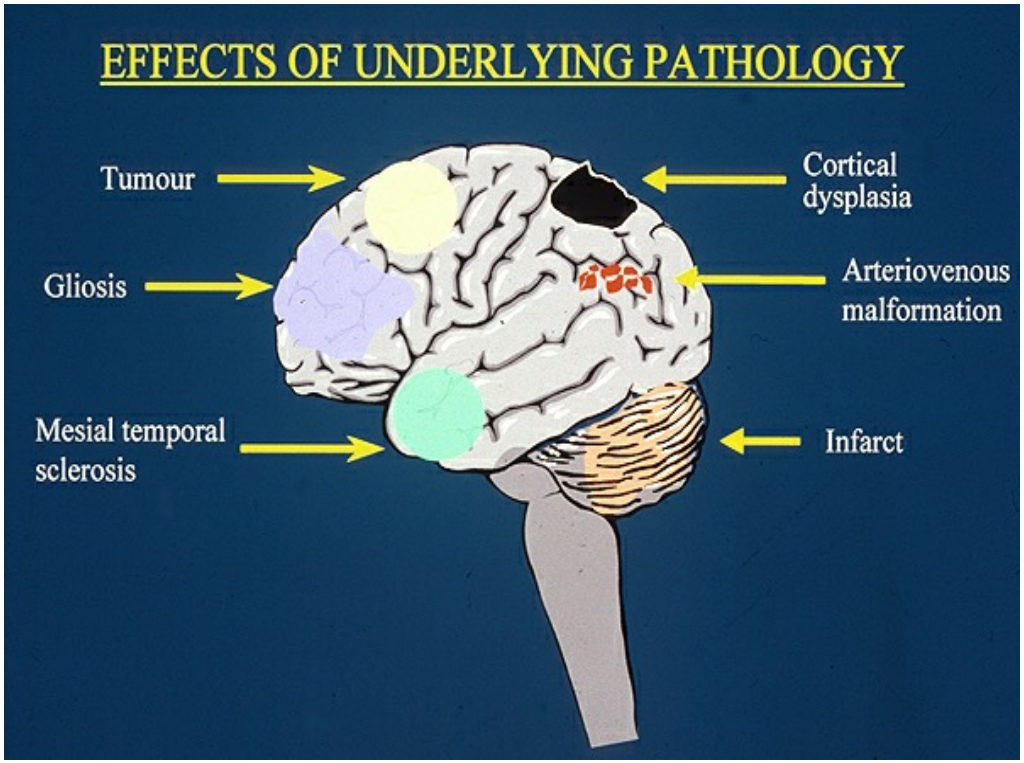
Mihail Iosif GAVRILIUC

What Is Epilepsy?



- Epilepsy is a disorder of the brain's electrical system. Abnormal electrical impulses cause brief changes in movement, behavior, sensation, or awareness. These interruptions, known as seizures, may last from a few seconds to a few minutes. People who have had two or more seizures are considered to have epilepsy.

Causes of Epilepsy



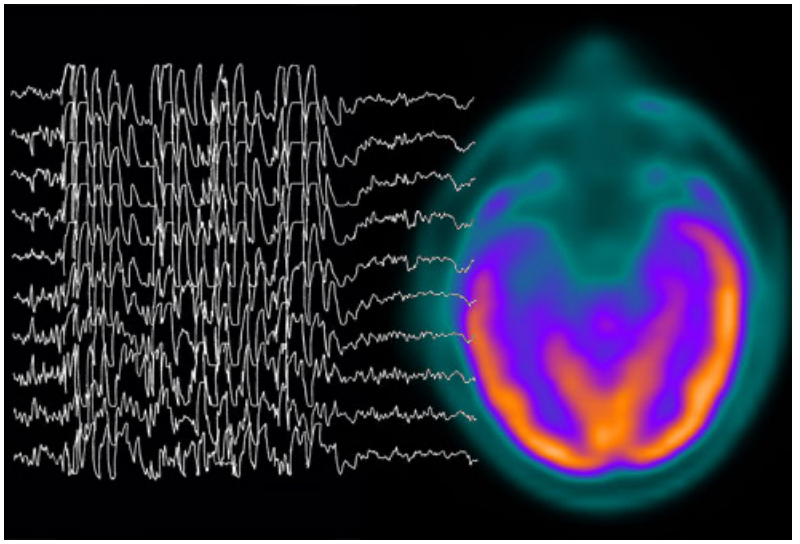
Epilepsy may result from anything that disrupts the brain's natural circuitry, such as:

- Severe head injury
- Brain infection or disease
- Stroke
- Oxygen deprivation

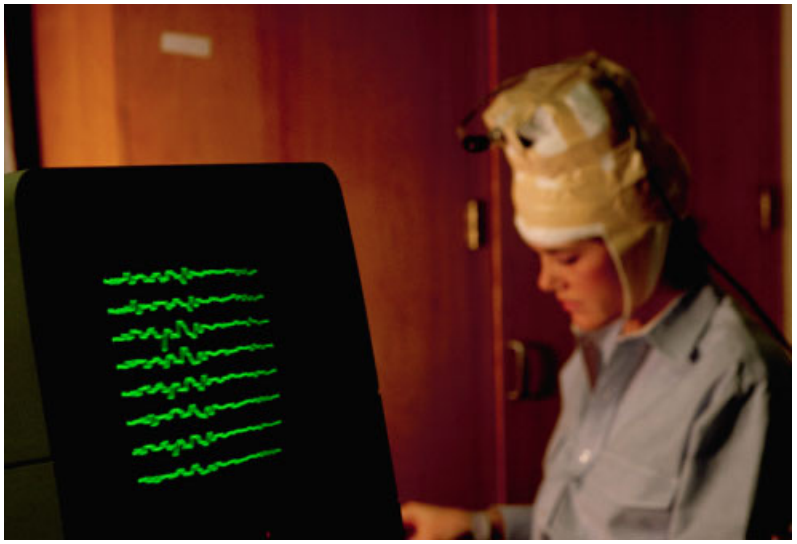
In nearly two-thirds of people with epilepsy, a specific cause is never found.

Epilepsy Symptoms

- Epilepsy is best known for causing convulsions. But seizures can trigger a wide range of symptoms, from staring to falling to fumbling with clothes. Seizures are divided into several types depending on how the brain is affected. Each type has a distinct set of symptoms.



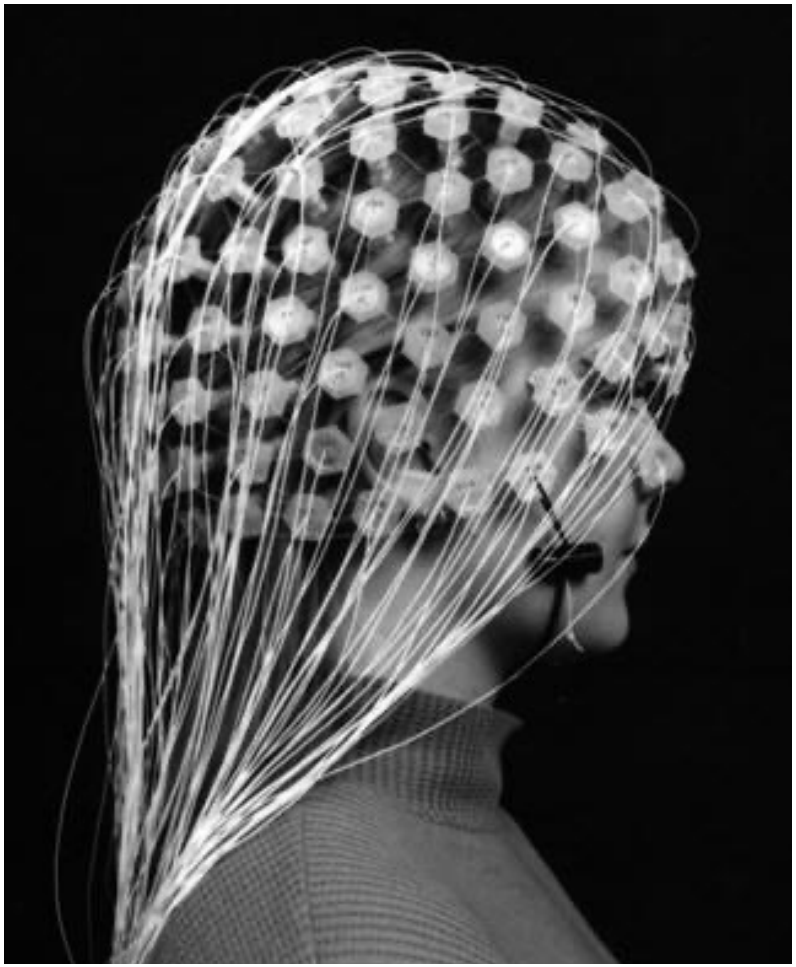
Diagnosis: EEG



- To diagnose epilepsy a doctor will review the description of an individual's seizures, along with a medical history and physical exam. An EEG (electroencephalogram) can confirm the diagnosis and offer more information about the seizures. This painless procedure records the brain's electrical activity as wavy lines. The pattern changes during a seizure and may reveal which part of the brain is prone to seizures. Results may help guide treatment.

Electroencephalogram

The electroencephalogram (EEG) is a record of the oscillations of brain electric potentials recorded from perhaps 20 to 256 electrodes attached to the human scalp.

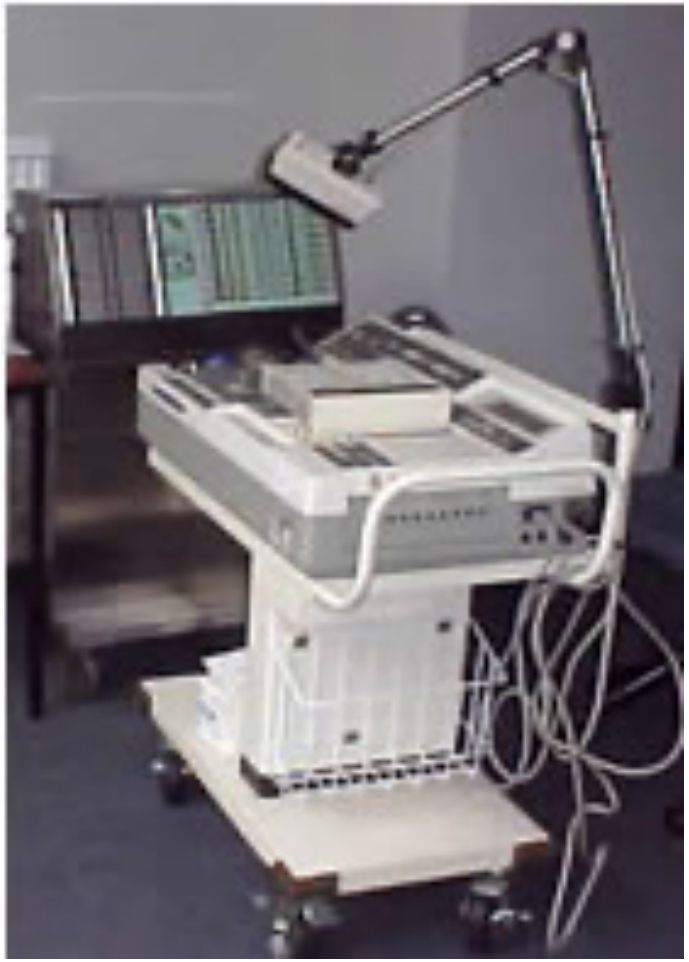


Electroencephalogram

- The recorded signals are transmitted to an EEG system composed of amplifiers, filters, and paper chart or computer monitor.

Electroencephalogram

- The recorded signals are transmitted to an EEG system composed of amplifiers, filters, and paper chart or computer monitor.

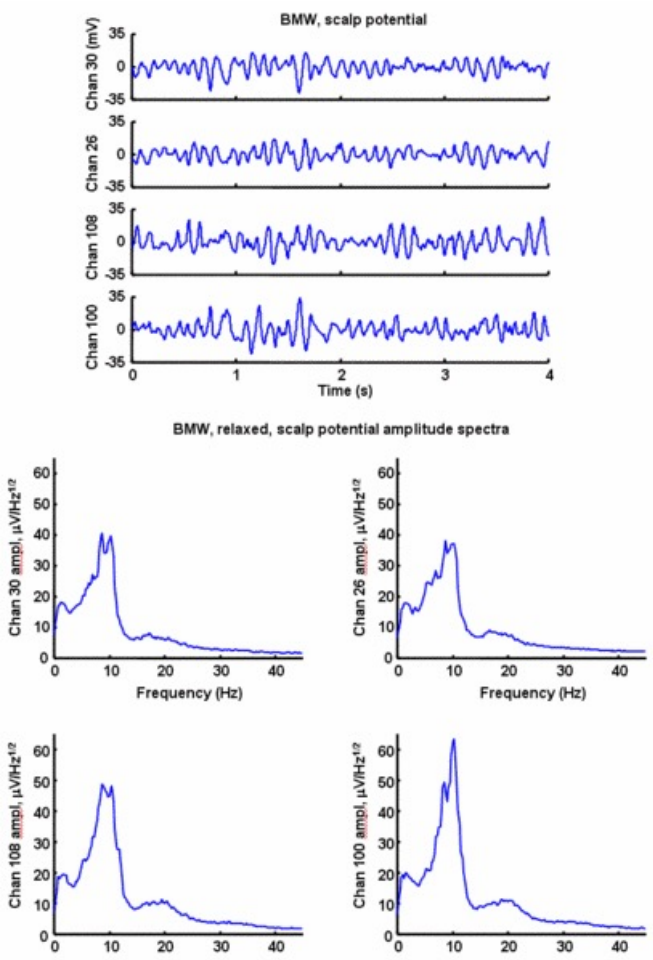


Electroencephalogram

- The first human EEG recordings were accomplished by the German psychiatrist Hans Berger in 1924 in Jena.
- The scientific community was at first quite skeptical that these scalp signals originated in brain tissue but by 1934 their brain origins had been established.

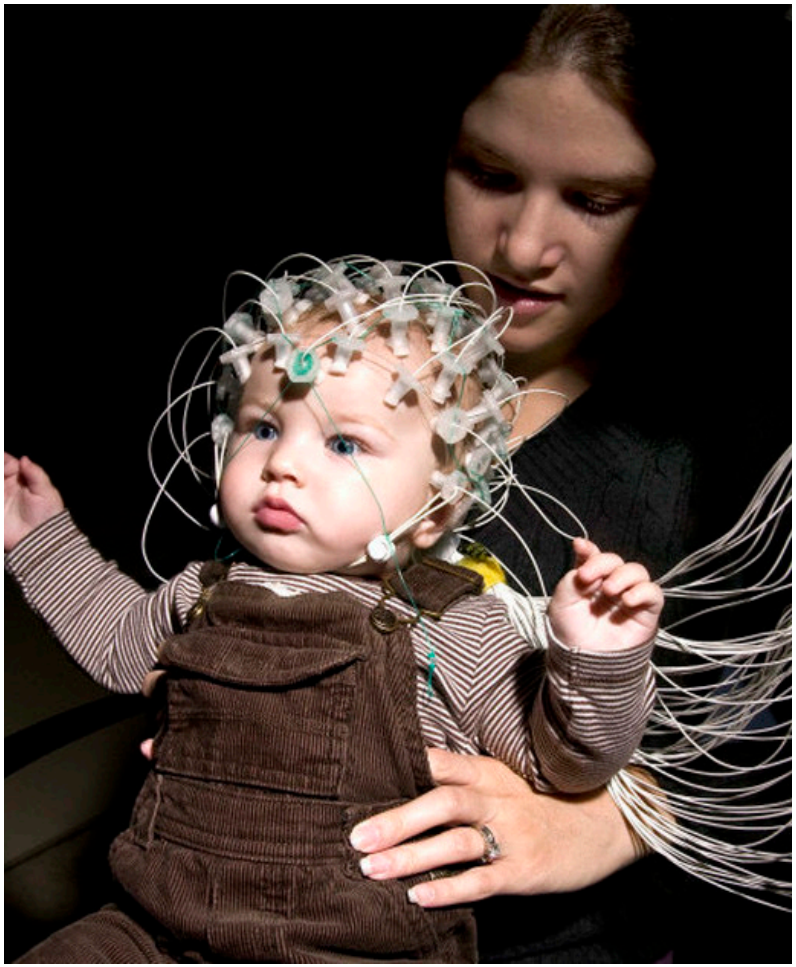
A Window on the Mind

- The EEG provides a convenient *window on the mind*, revealing the synaptic action that is moderately to strongly correlated with brain state.
- Most EEG signals originate in the cerebral cortex.



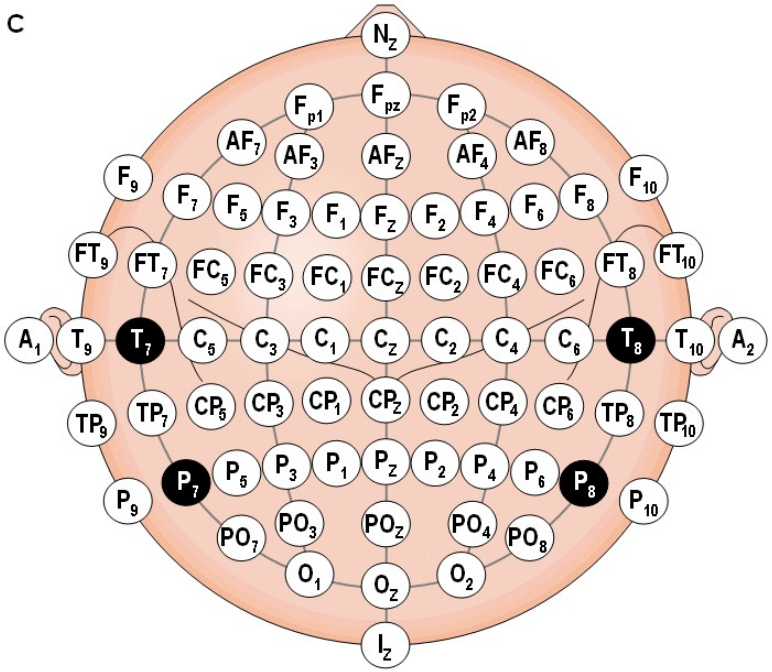
EEG Recording Methods

- Human EEG is recorded using electrodes with diameters typically in the 0.4 to 1.0 cm range, held in place on the scalp with special pastes, caps or nets.

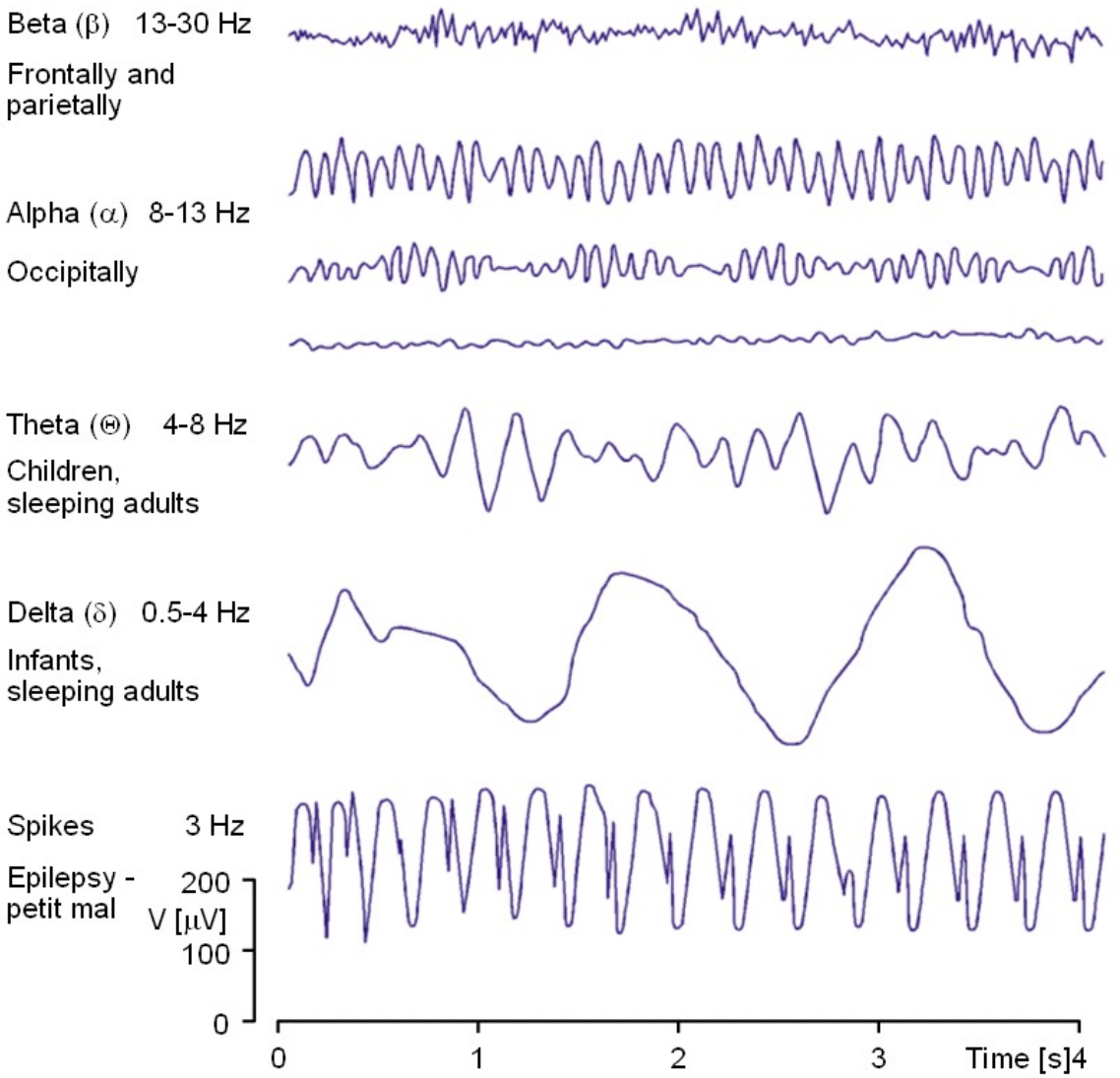


EEG Recording Methods

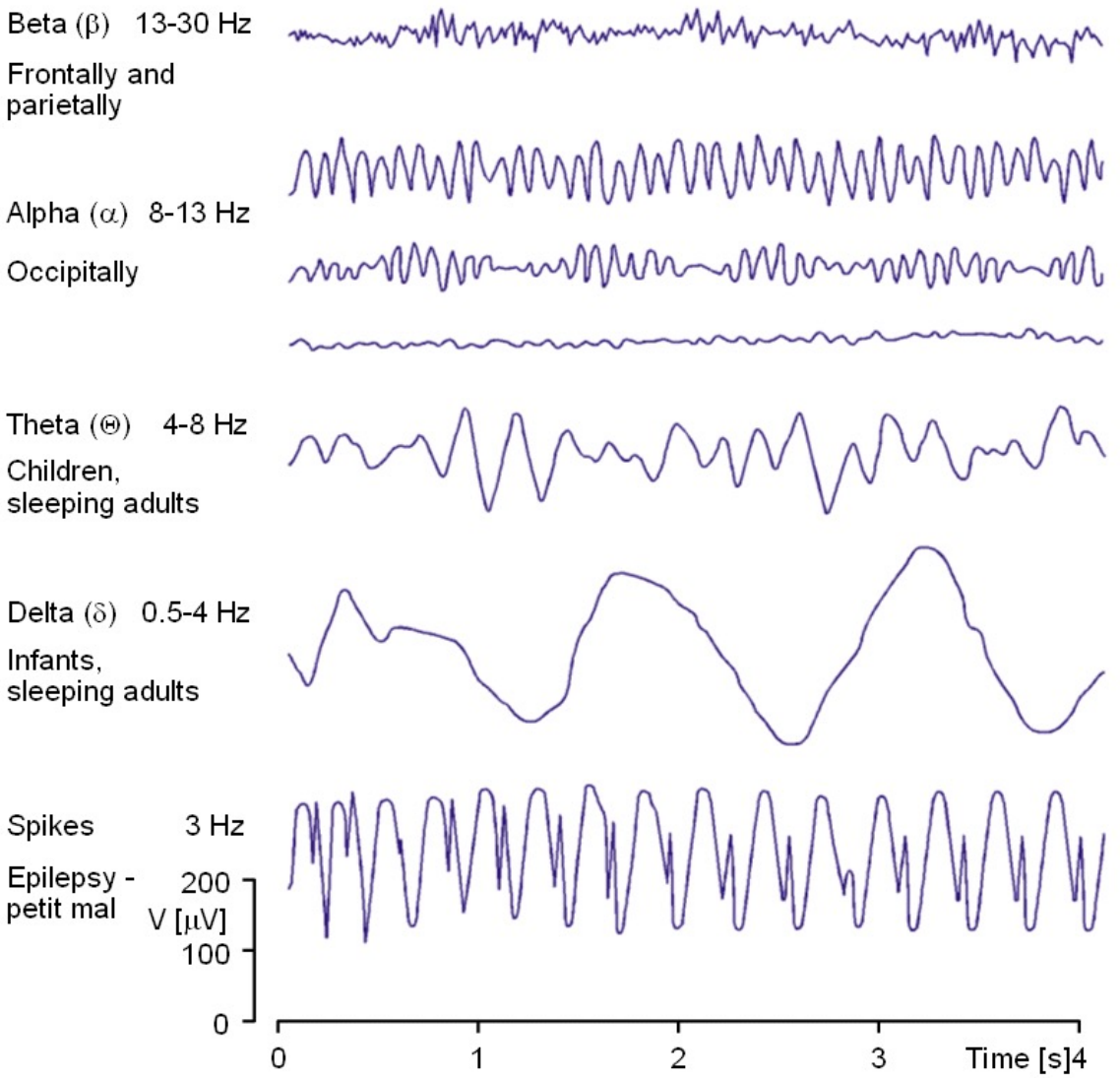
- In standard clinical practice, 19 recording electrodes are placed uniformly over the scalp (the **International 10-20 System**).
- In addition, one or two reference electrodes (often placed on ear lobes) and a ground electrode (often placed on the nose to provide amplifiers with reference voltages) are required.



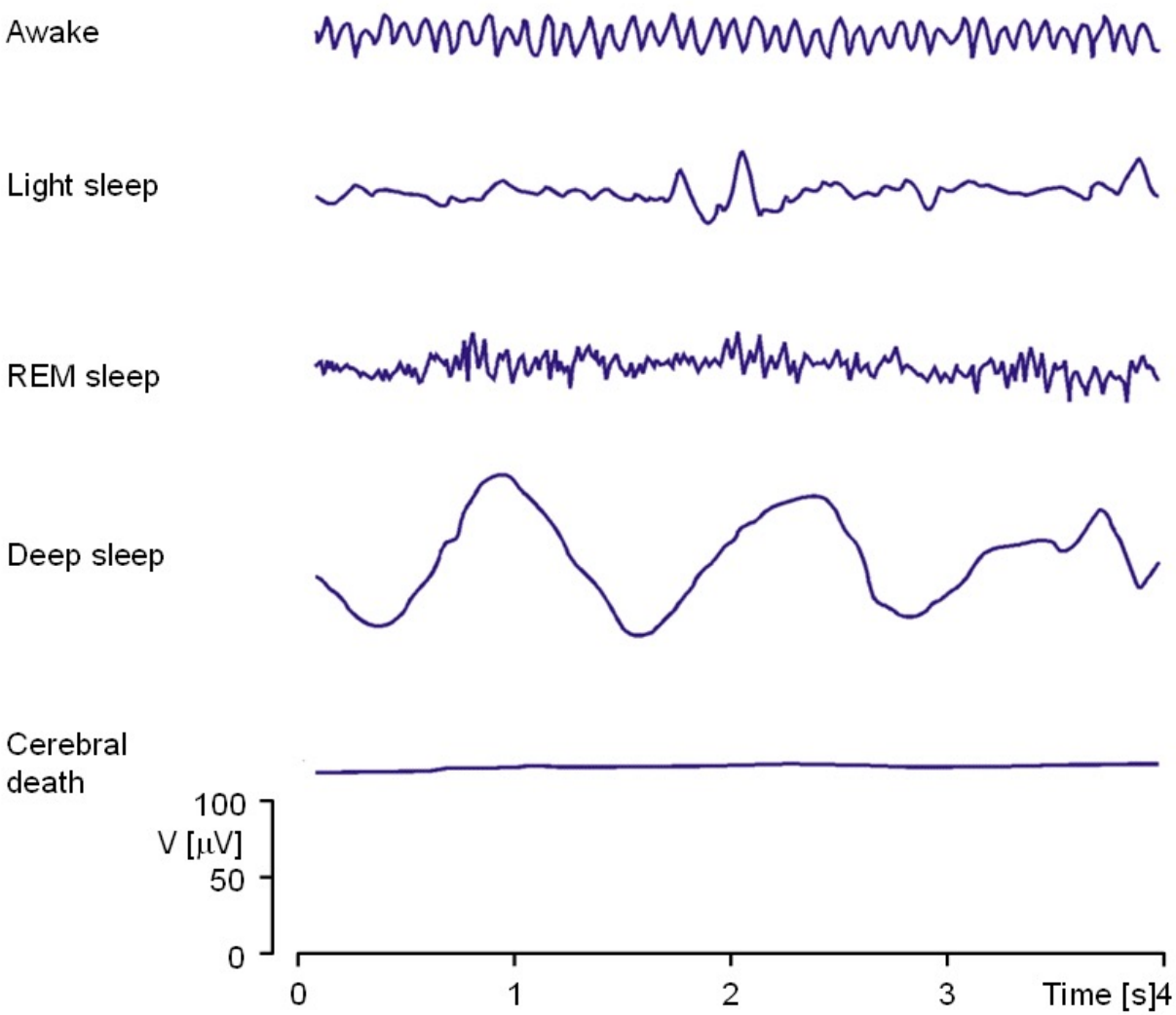
From the EEG signal it is possible to differentiate alpha (α), beta (β), delta (δ), and theta (Θ) waves as well as spikes associated with epilepsy.



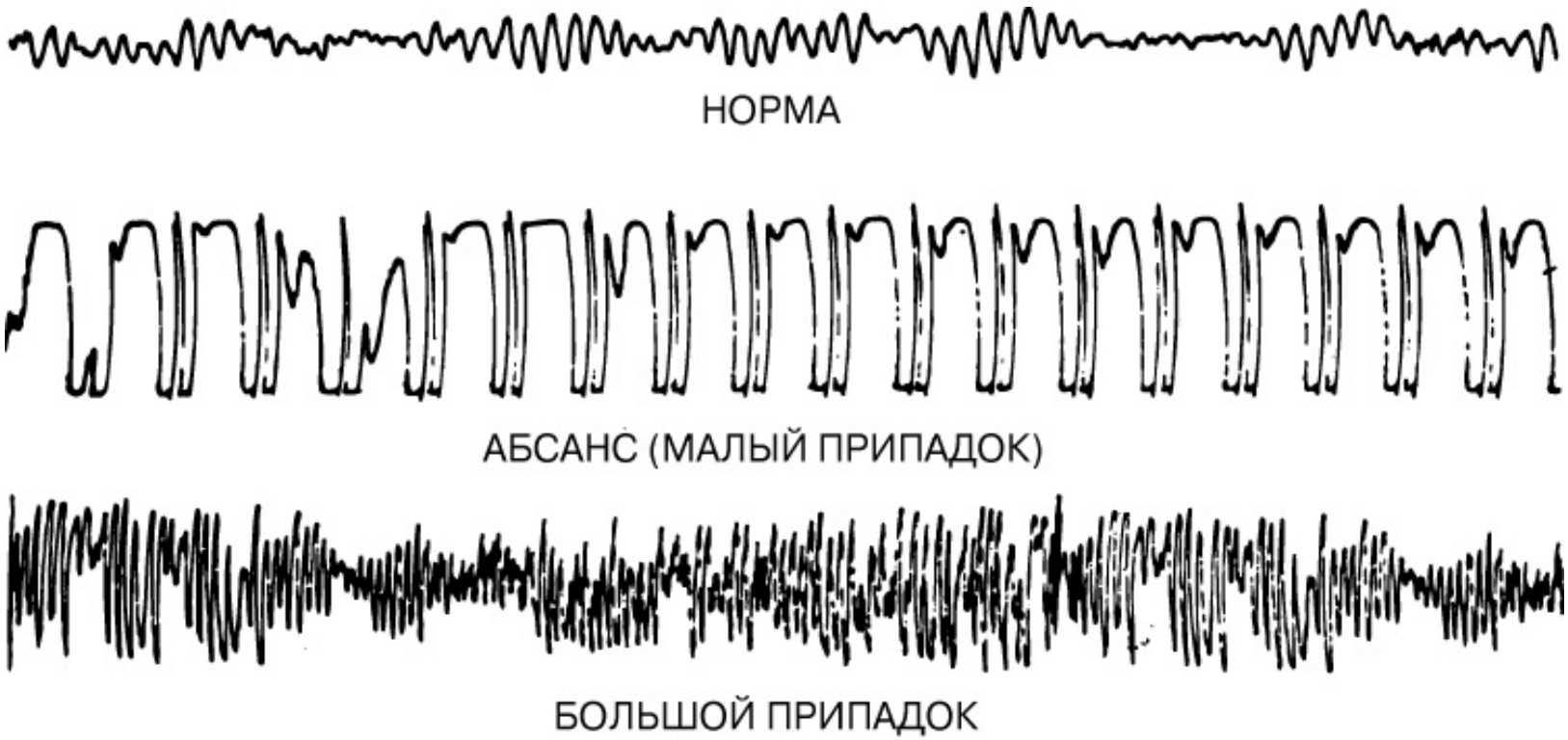
From the EEG signal it is possible to differentiate alpha (α), beta (β), delta (δ), and theta (Θ) waves as well as spikes associated with epilepsy.



The EEG signal is closely related to the level of consciousness of the person.

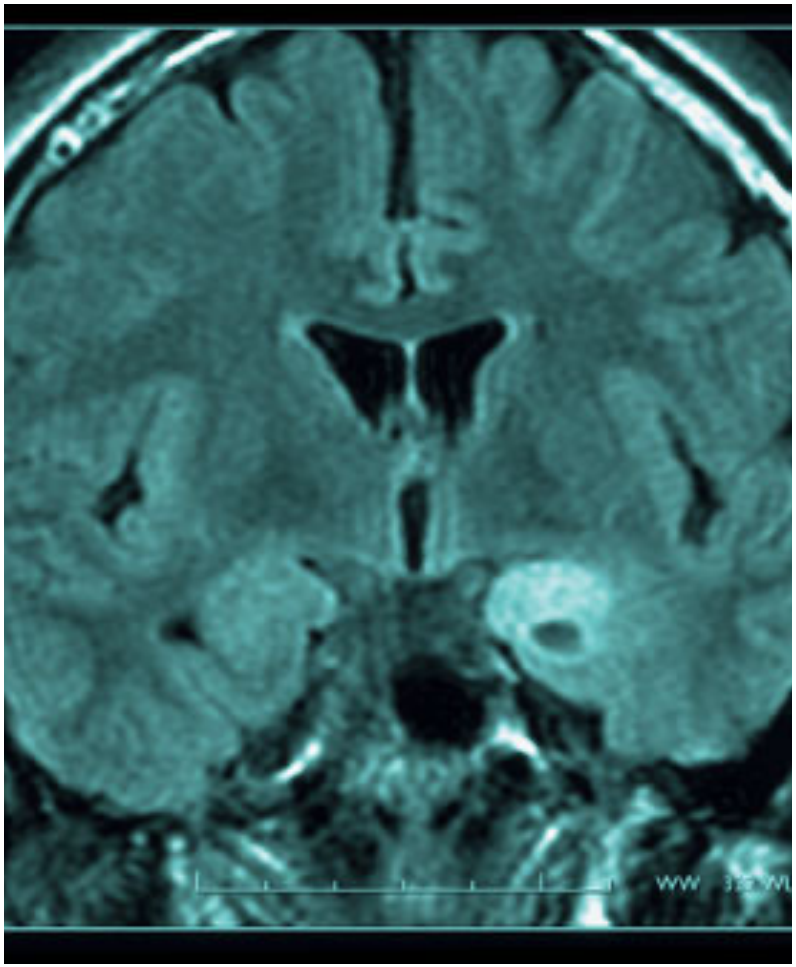


ELECTROENCEPHALOGRAM



Diagnosis: Brain Scan

- Detailed images of the brain from CT or MRI scans can help doctors rule out tumors or blood clots as a possible cause of seizures. This information is essential in planning surgery to treat epilepsy.

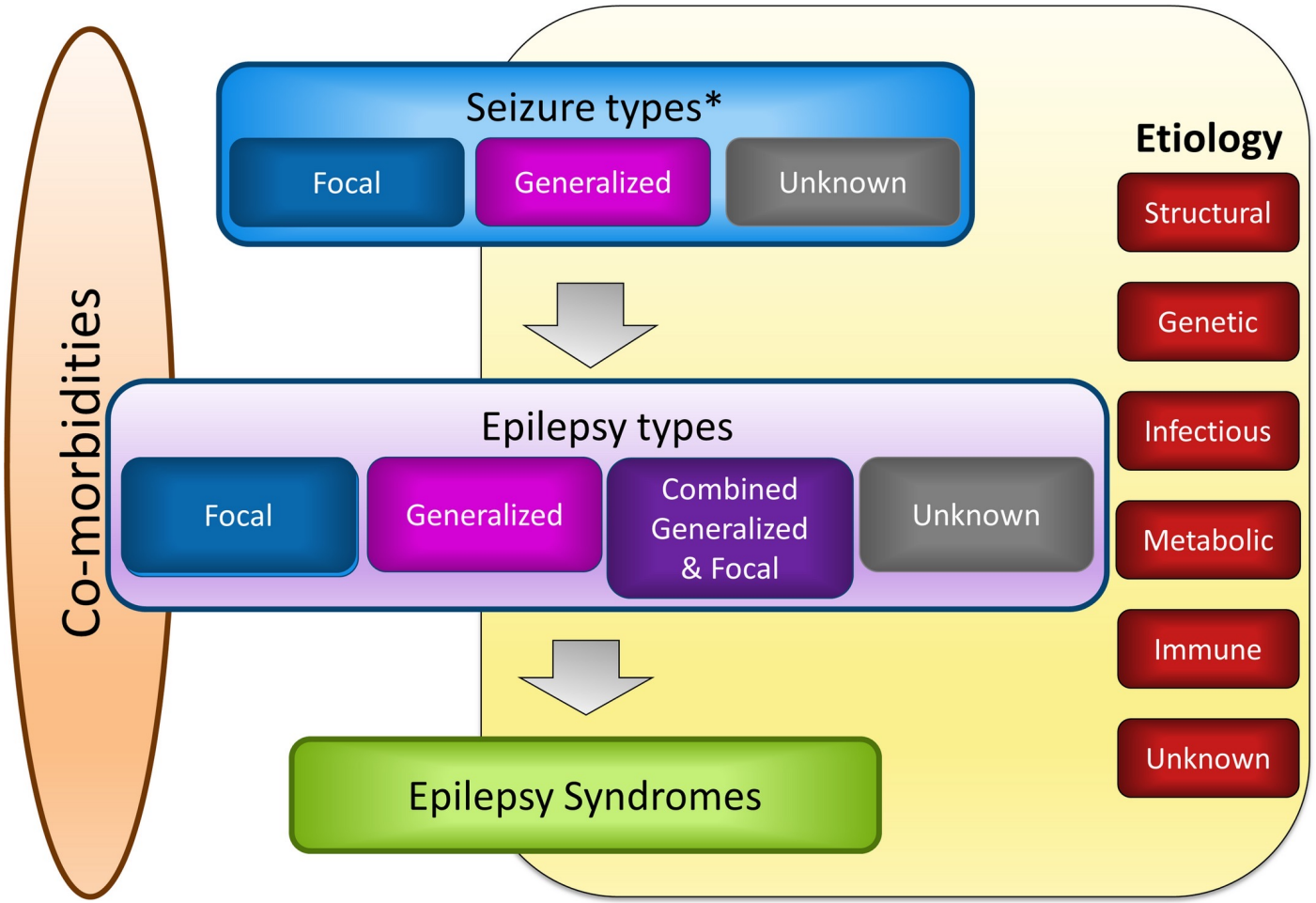


SEIZURE

SEIZURE

- A *seizure* (from the Latin *sacire,* "to take possession of" is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons.
- The meaning of the term seizure needs to be carefully distinguished from that of epilepsy.
- *EPILEPSY* describes a condition in which a person has *recurrent* seizures due to a chronic, underlying process. Epilepsy refers to a clinical phenomenon rather than a single disease entity, since there are many forms and causes of epilepsy. However, among the many causes of epilepsy there are various *epilepsy syndromes* in which the clinical and pathologic characteristics are distinctive and suggest a specific underlying etiology.

International League Against Epilepsy 2017 classification of eplipesies

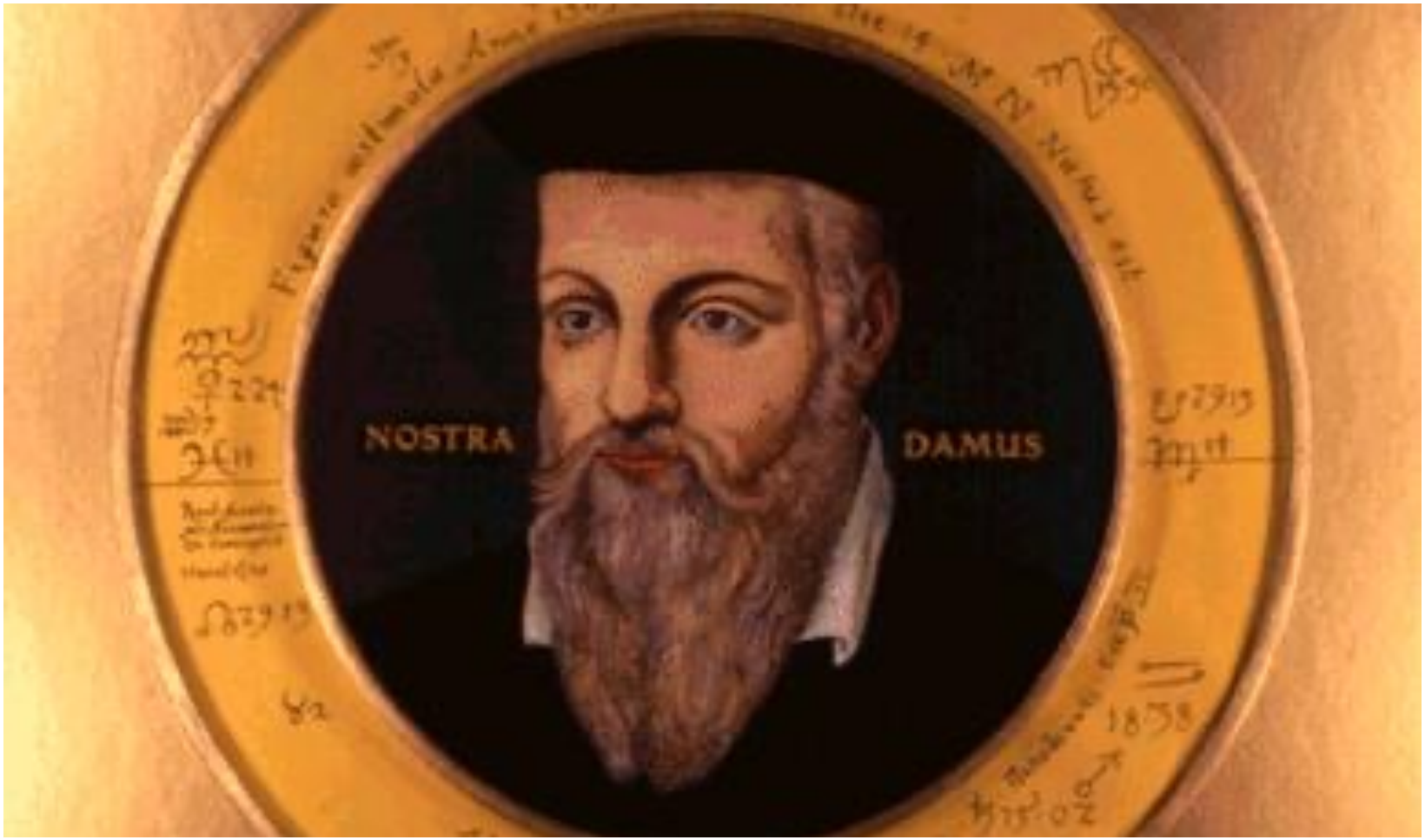


MILESTONES IN THE HISTORY OF EPILEPSY

- In ancient times, epileptic attacks were thought to be the result of invasion and possession of the body by super- natural forces, usually malign or evil influences, requiring exorcism, incantations or other religious or social approaches.

The oldest account of epilepsy: Tablet 25 or 26 in a Babylonian text on medicine (Sakikku) which was written over 3000 years ago, i.e. before 1000 BC.

Michel de Nostredame



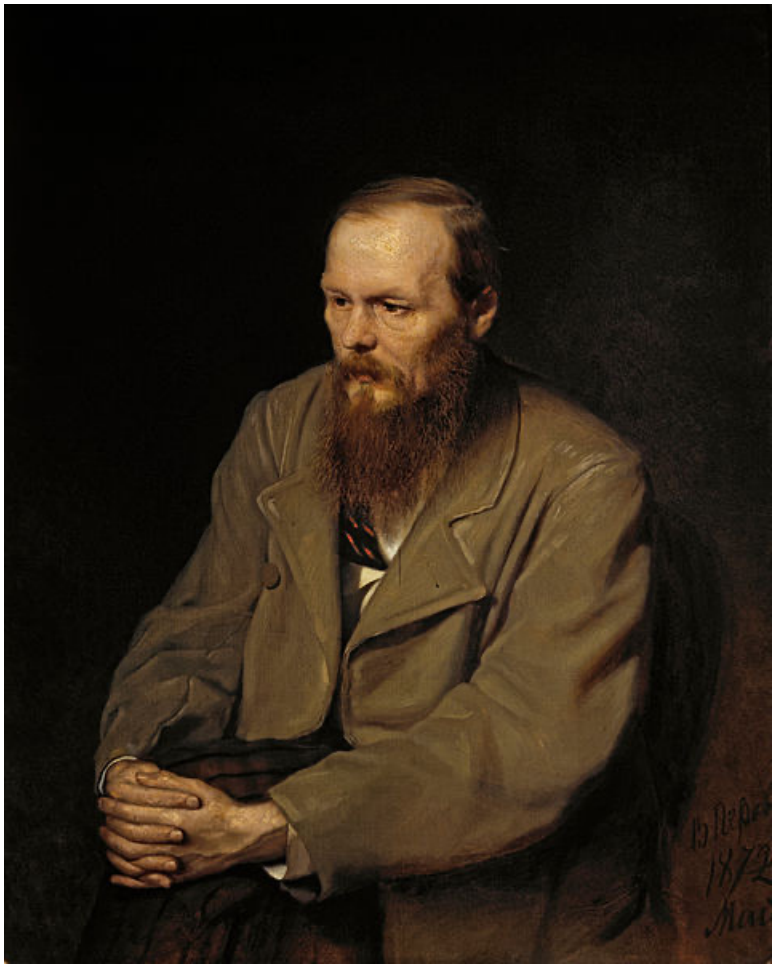
The Emperor Napoleon

Charles XII, King of Sweden (reign 1697 -1718)

Gaius Julius Caesar

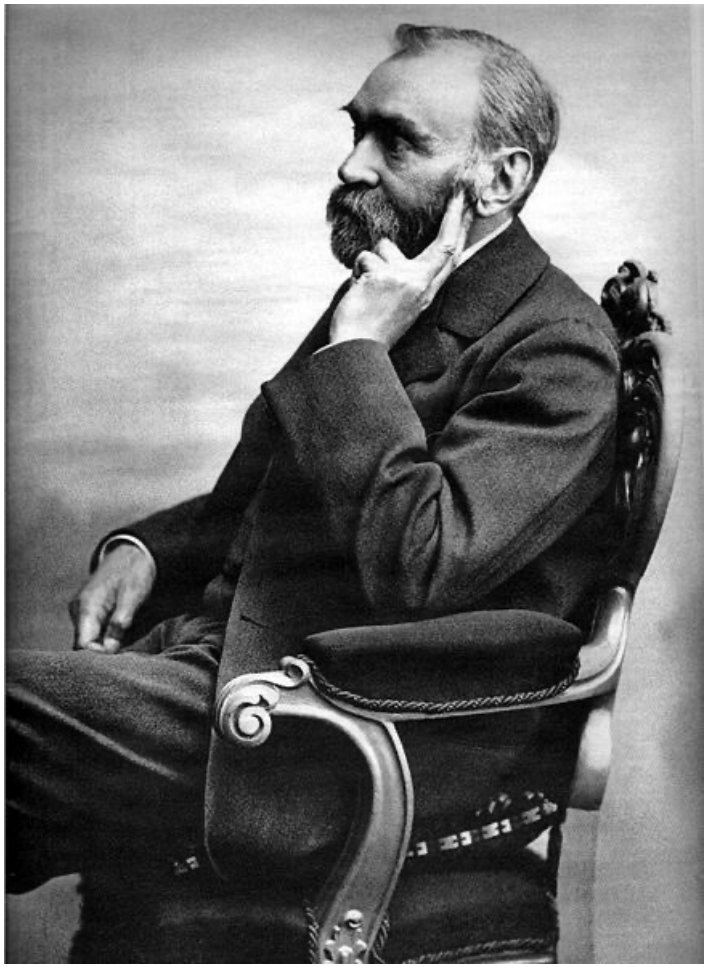
Dictator of the Roman Republic (reign 49 BC – 44 BC)

Fyodor Mikhaylovich Dostoyevsky (1821 – 1881)

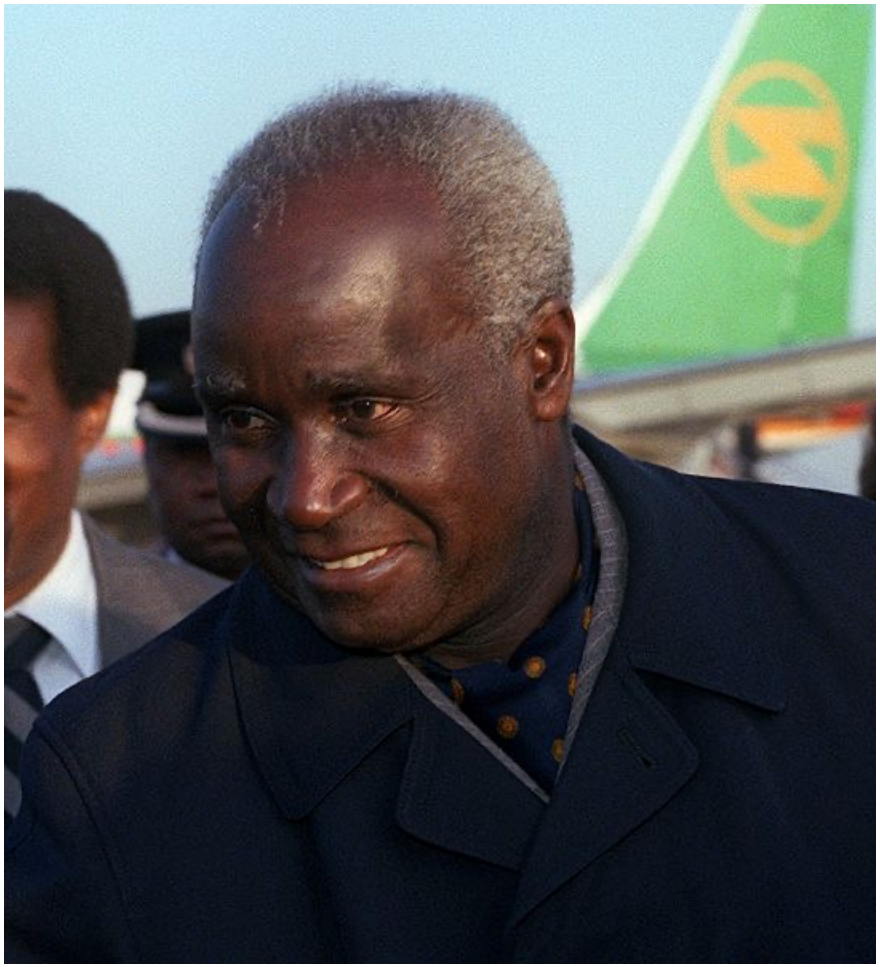


Georg Friedrich Händel
(1685 – 1759)

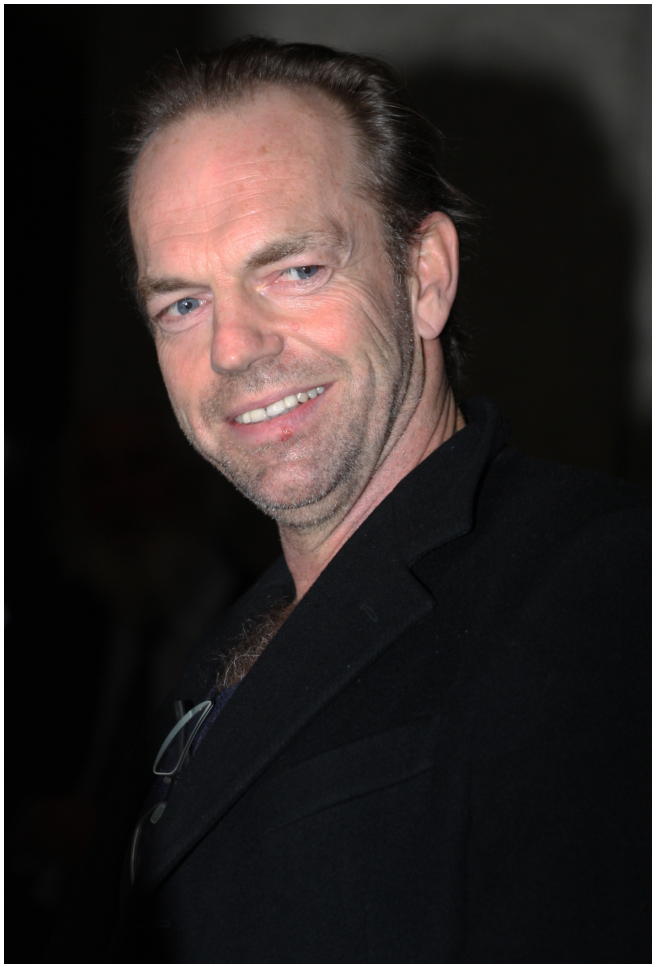
Alfred Nobel
(1833 – 1896)



Kenneth Kaunda, first President of Zambia (1964 – 1991)

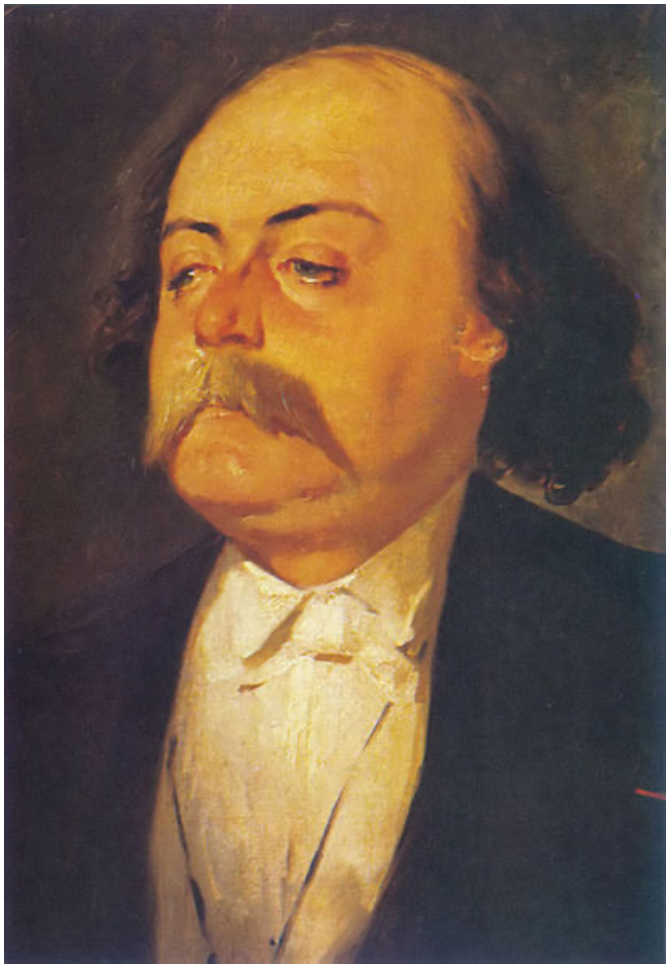


Hugo Weaving, actor (The Matrix trilogy)



Amadeus IX, Duke of Savoy (1432 – 1472)

Gustave Flaubert, a French writer (*Madame Bovary*) *(1821-1880)*



Charles V, Holy Roman Emperor (1519 – 1556)

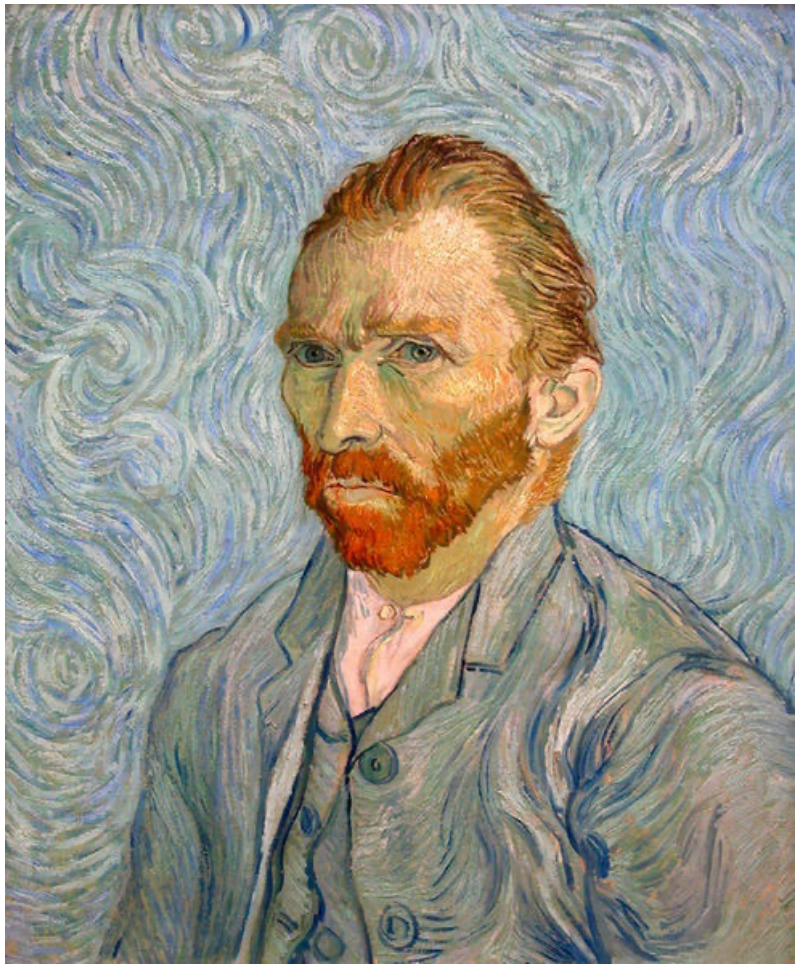
Stendhal
(1783 – 1842)

Alexander III of Macedon (336 BC – 323 BC)

Иван IV Васильевич Грозный

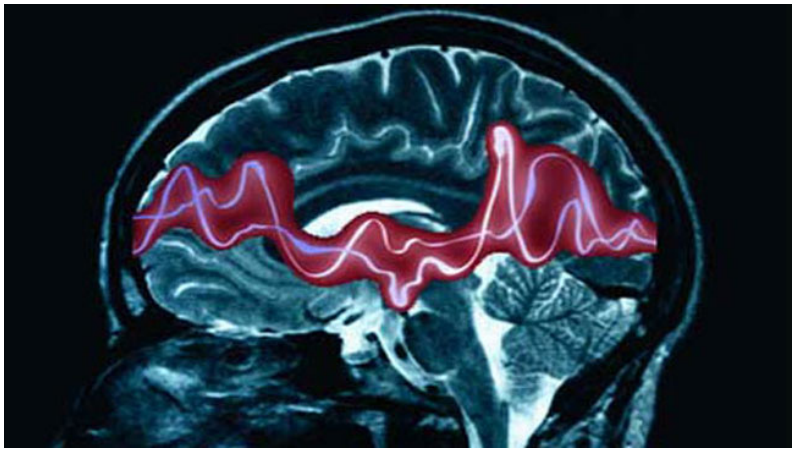
(1547 – 1584)

Vincent van Gogh
(1853 – 1890)



MILESTONES IN THE HISTORY OF EPILEPSY

- Today, seizures are viewed as electromagnetic discharges in the brain in predisposed individuals, attributable in part to putative genetic factors, underlying neurological disorders, and largely unknown neurochemical mechanisms.

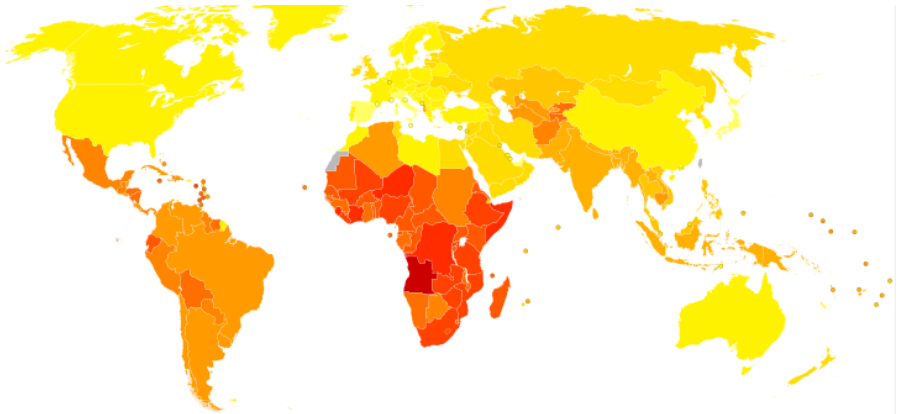


SEIZURES AND EPILEPSY

- Although a variety of factors influence the incidence and prevalence of seizures, ~5 to 10% of population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.

SEIZURES AND EPILEPSY

- A total of about **43 704 000** people with epilepsy are reported from 108 countries covering 85.4% of the world population.

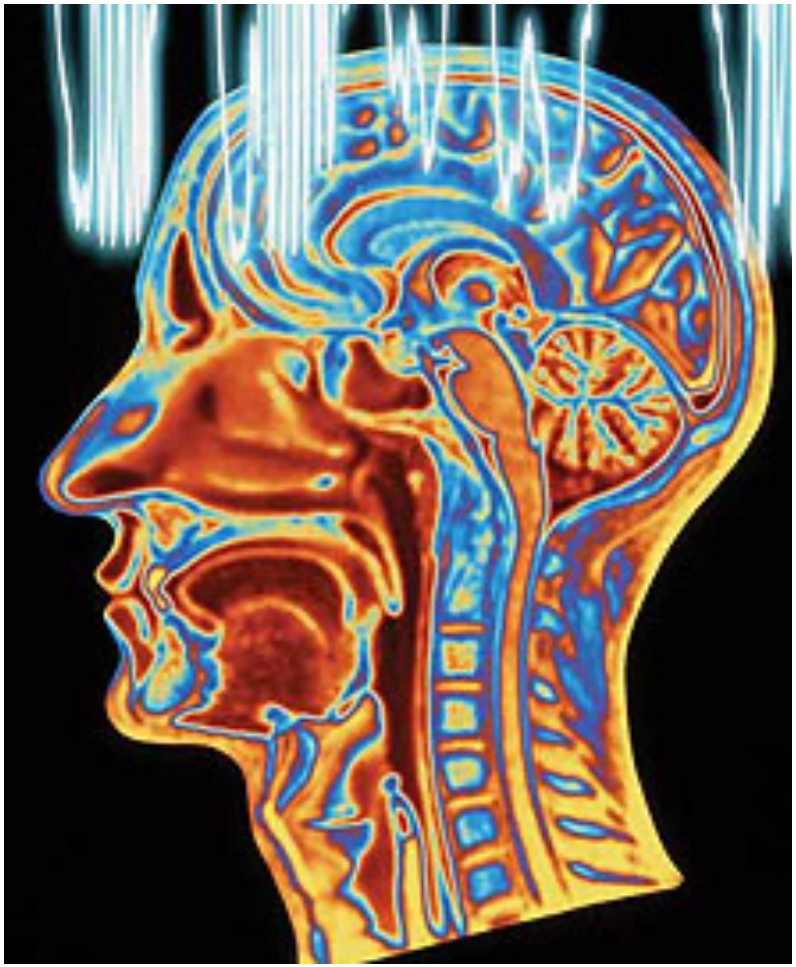


SEIZURES AND EPILEPSY

- Using the definition of epilepsy as two or more unprovoked seizures, the incidence of epilepsy is ~0.3 to 0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5 to 10 persons per 1000.

CLASSIFICATION OF SEIZURES

- Determining the type of seizure that has occurred is essential for focusing the diagnostic approach on particular etiologies, selecting the appropriate therapy, and providing potentially vital information regarding prognosis. In 2017, the International League Against Epilepsy (ILAE) published a modified version of the International Classification of Epileptic Seizures.

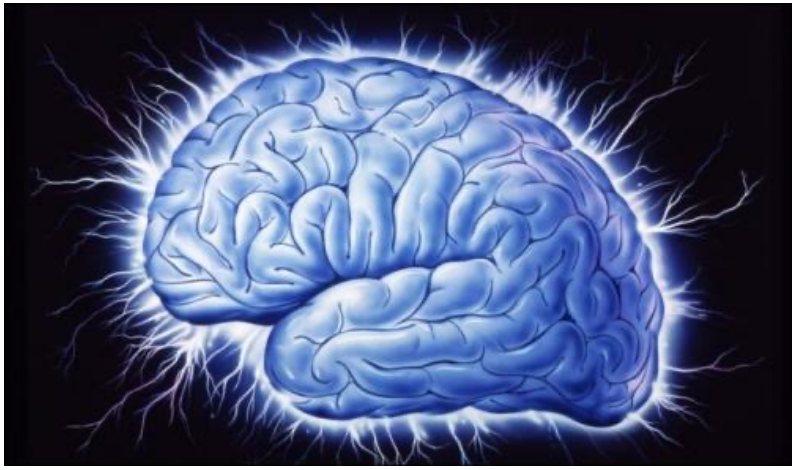


CLASSIFICATION OF SEIZURES

- This system is based on the clinical features of seizures and associated electroencephalographic findings.

MECHANISMS OF SEIZURE INITIATION AND PROPAGATION

- *Seizure initiation* phase is characterized by two concurrent events in an aggregate of neurons: (1) high-frequency bursts of action potentials and (2) hypersynchronization.



MECHANISMS OF SEIZURE INITIATION AND PROPAGATION

Normally, the spread of bursting activity is prevented by intact hyperpolarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there is a recruitment of surrounded neurons via a number of mechanisms. Repetitive discharges lead to the following: (1) an increase in extracellular K^+, which blunts hyperpolarization and depolarizes neighboring neurons; (2) accumulation of Ca^{2+} in presynaptic terminals, leading to enhanced neurotransmitter release; and (3) depolarization-induced activation of the *N*-methyl-D-aspartate (NMDA) subtype of the excitatory amino acid receptor, which causes Ca^{2+} influx and neuronal activation.

MECHANISMS OF EPILEPTOGENESIS

- *Epileptogenesis* refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable.

There is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure.

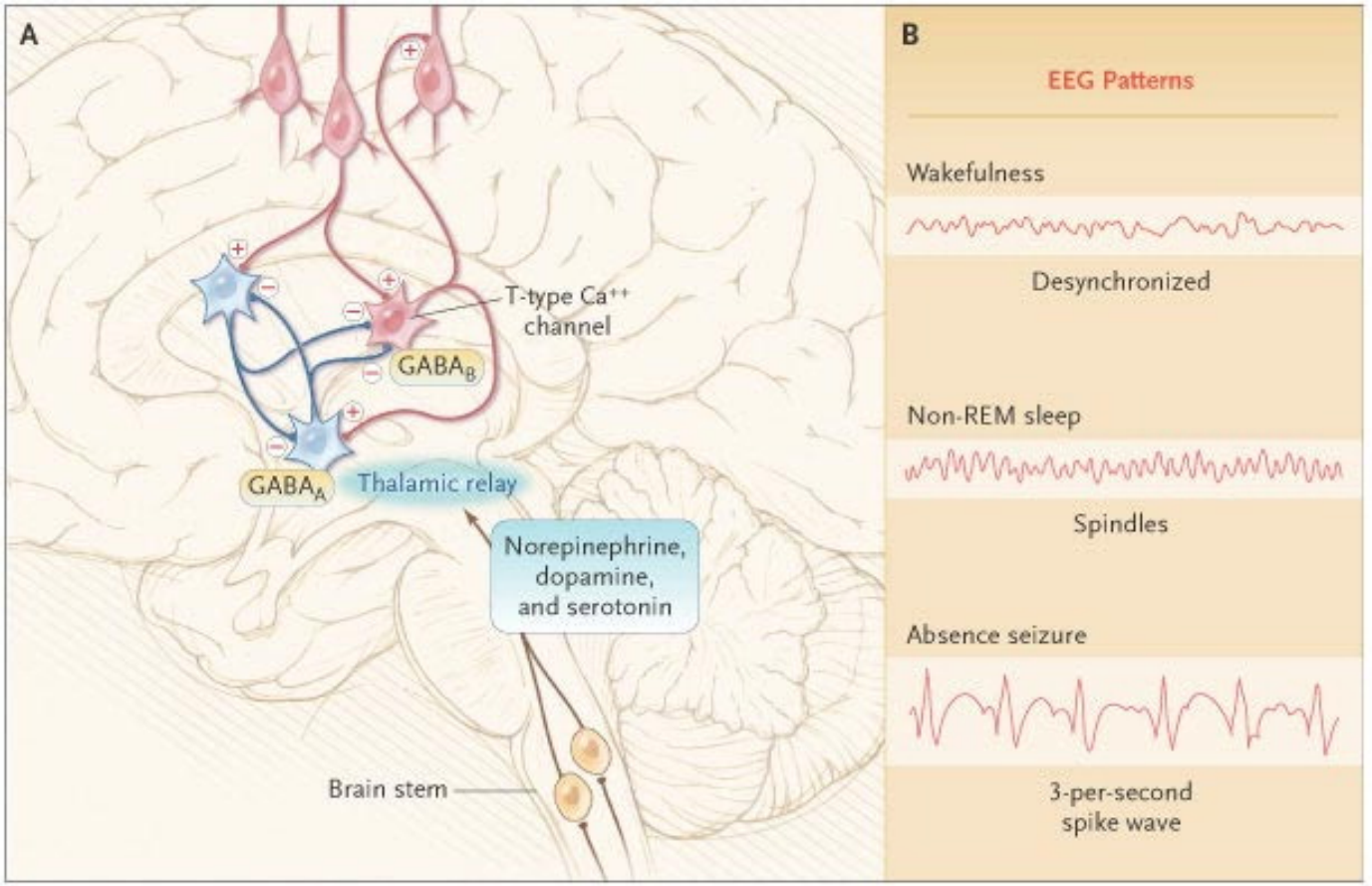
The injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs.

In many genetic and idiopathic form of epilepsy, epileptogenesis is presumably determined by developmentally regulated events.

MECHANISMS OF EPILEPTOGENESIS

- Pathologic studies of the hippocampus from patients with temporal lobe epilepsy have led to the suggestion that some forms of *epileptogenesis are related to structural changes in neuronal networks.*

For example, many patients with MTLE have a highly selective loss of neurons that may contribute to inhibition of the main excitatory neurons within the dentate gyrus. There is also evidence that, in response to the loss of neurons, there is the reorganization or "sprouting" of surviving neurons in a way that affects the excitability of the network. Local hiperexcitability leads to further structural changes and long-term alterations in *intrinsic, biochemical properties of cells* within the network, such as chronic changes in glutamate receptor function.



The Normal Thalamocortical Circuit and EEG Patterns during Wakefulness, Non–Rapid-Eye-Movement (Non-REM) Sleep, and Absence Seizures

MECHANISMS OF SEIZURE INITIATION AND PROPAGATION

- *Seizure initiation* phase is characterized by two concurrent events in an aggregate of neurons: (1)
  high-frequency bursts of action potentials and (2)
  hypersynchronization.

The bursting activity is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the opening of voltage-dependent sodium (Na^{+}) channels, influx of Na^{+}, and generation of repetitive action potentials. This is followed by a hyperpolarizing afterpotential mediated by γ-aminobutyric acid (GABA) receptors or potassium (K^{+}) channels, depending on the cell type. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG.

Classification of Seizures

1. Focal (partial) seizures
   a. Simple partial seizures (with motor, sensory, autonomic, or psychic signs)
   b. Complex partial seizures
   c. Partial seizures with secondary generalization
2. Primarily generalized seizures
   a. Absence (*petit mal*)
   b. Tonic-clonic (*grand mal*)
   c. Tonic
   d. Atonic
   e. Myoclonic
3. Unclassified seizures
   a. Neonatal seizures
   b. Infantile spasms

FUNDAMENTAL: *focal* or *generalized* seizures

- *Partial* (synonymous with *focal*) *seizures* are those in which the seizure activity is restricted to discrete areas of the cerebral cortex. Partial seizures are usually associated with structural abnormalities of the brain.
- *Generalized seizures* involve diffuse regions of the brain simultaneously and may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution.

PARTIAL SEIZURES

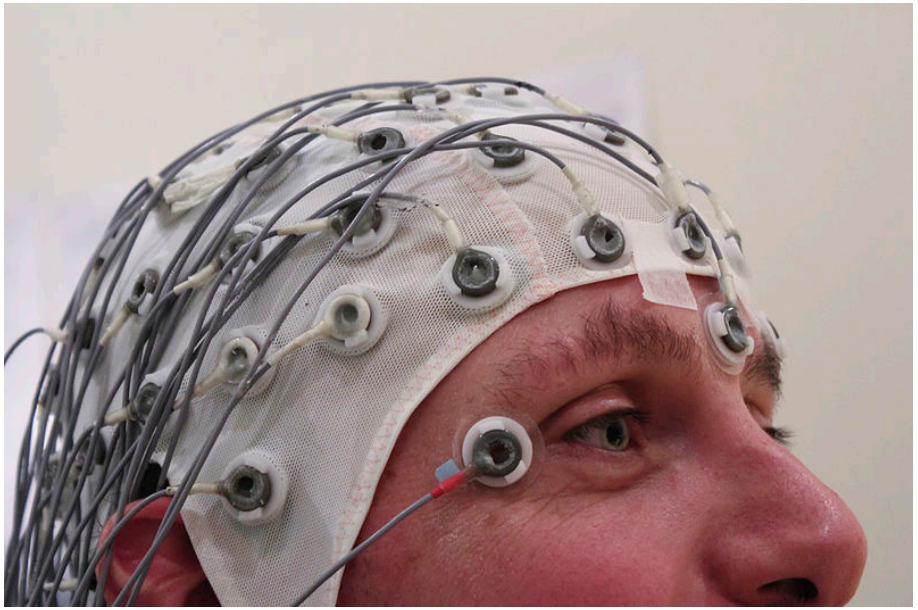
- Partial seizures occur within discrete regions of the brain. If consciousness is fully preserved during the seizure, the clinical manifestations are considered relatively simple and the seizure is termed a *simple partial seizure*.
- If consciousness is impaired, the symptomatology is more complex and the seizure is termed a *complex partial seizure*.
- An important additional subgroup comprises those seizures that begin as partial seizures and then spread diffusely throughout the cortex, i.e., *partial seizures with secondary generalization*.

Partial Seizures

- In partial seizures, just one side of the brain is affected. Simple partial seizures may cause jerking motions or hallucinations, but the person often remains aware of what is happening. During complex partial seizures, people may wander, mumble, smack their lips, or fumble with their clothes. They appear to be conscious to observers, but are actually unaware of what they are doing.

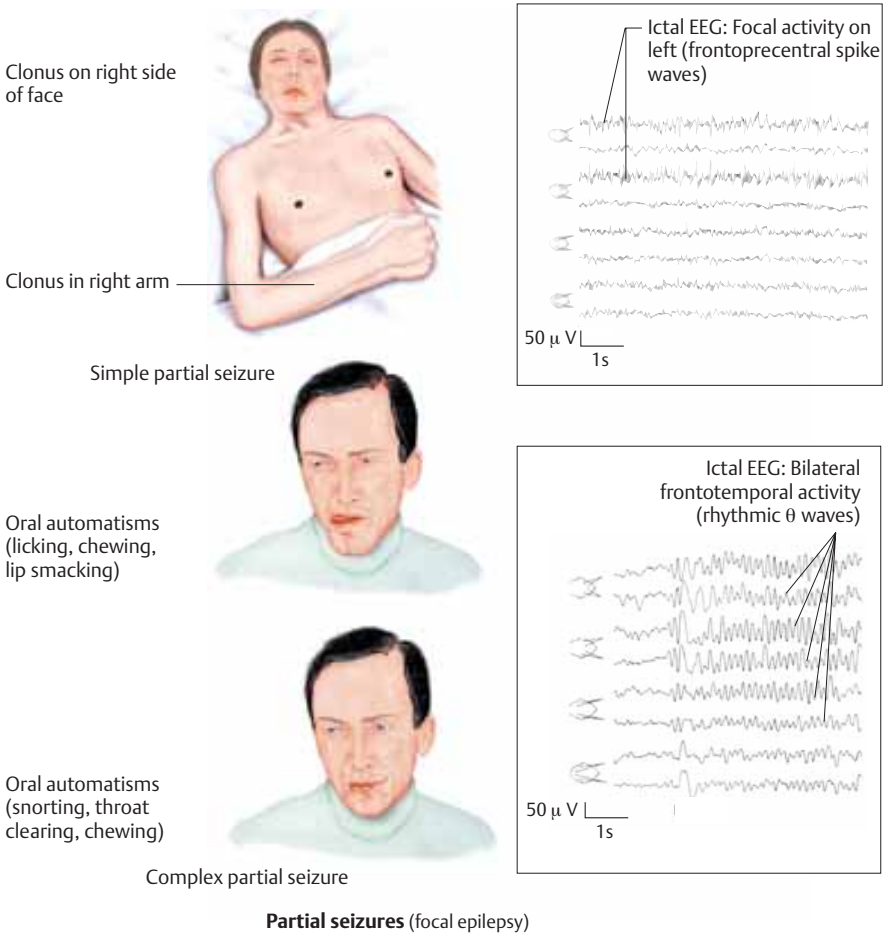
Simple Partial Seizures

- Simple partial seizures cause motor, sensory, autonomic, or psychic symptoms without an obvious alteration in consciousness.
- The electroencephalogram (EEG) recorded with scalp electrodes during the seizure (i.e., an ictal EEG) may show abnormal discharges in a very limited region over the appropriate area of cerebral cortex if the seizure focus involves the cerebral convexity. Seizure activity occurring within deeper brain structures is often not recorded by the standard EEG.



Simple Partial Seizures

- Motor - typically clonic (i.e., repetitive, flexion/extension movements) at a frequency ~2-3 Hz. Three additional:
  1) "Jacksonian march";
  2) Todd's paralysis;
  3) *Epilepsia partialis continua*.
- Changes in somatic sensation (e.g., paresthesias), vision (flashing lights or formed hallucinations), equilibrum (sensation of falling or vertigo), or autonomic function (flushing, sweating, piloerection).



Partial seizures (focal epilepsy)

Simple Partial Seizures

- Simple partial seizures arising from the temporal or frontal cortex may also cause alterations in hearing, olfaction, or higher cortical function (psychic symptoms). This includes the sensation of unusual, intense odors (e.g., burning rubber or kerosene) or sounds (crude or highly complex sounds), or an epigastric sensation that rises from the stomach or chest to the head. Some patients describe odd, internal feelings such as fear, a sense of impending change, detachment, depersonalization, *déjà vu,* or illusions that objects are growing smaller (*micropsia*) or larger (*macropsia*). When such symptoms precede a complex partial or secondarily generalized seizure, these simple partial seizures serve as a warning, or *aura.*

Complex Partial Seizures

- Complex partial seizures are characterized by focal seizure activity accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase. The seizures frequently begin with an aura (i.e., a simple partial seizure) that is stereotypic for the patient. The start of the ictal phase is often a sudden behavioral arrest or motionless stare, which marks the onset of the period of amnesia. The behavioral arrest is usually accompanied by *automatisms*, which are involuntary, automatic behaviors that have a wide range of manifestations.

Complex Partial Seizures

- Automatisms may consist of very basic behaviors such as chewing, lip smacking, swallowing, or "picking" movements of the hands, or more elaborate behaviors such as display of emotion or running. The patient is typically confused following the seizure, and the transition to full recovery of consciousness may range from seconds up to an hour. Examination immediately following the seizure may show an anterograde amnesia or, in cases involving the dominant hemisphere, a postictal aphasia.

Complex Partial Seizures

- The routine interictal (i.e., between seizures) EEG in patients with complex partial seizures is often normal or may show brief discharges termed *epileptiform spikes*, or *sharp waves*. Since complex partial seizures can arise from the medial temporal lobe or inferior frontal lobe, i.e., regions distant from the scalp, the EEG recorded during the seizure may be nonlocalizing. However, the seizure focus is often detected using sphenoidal or surgically placed intracranial electrodes.

Partial Seizures with Secondary Generalization

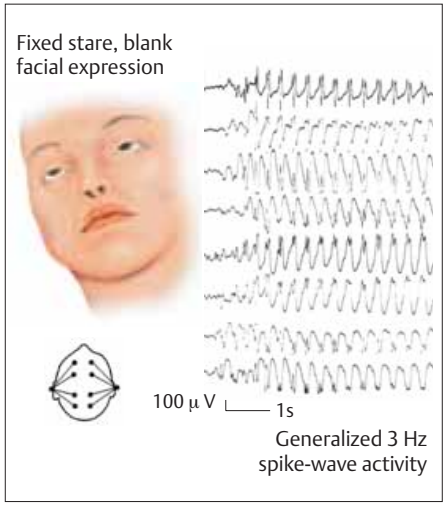
- Partial seizures can spread to involve both cerebral hemispheres and produce a generalized seizure, usually of the tonic-clonic variety. Secondary generalization is observed frequently following simple partial seizures occurring elsewhere in the brain. Often the focal onset is not clinically evident and may be established only through careful EEG analysis. Nonetheless, distinguishing between these two entities is extremely important, as there may be substantial differences in the evaluation and treatment of partial versus generalized seizure disorders.

GENERALIZED SEIZURES

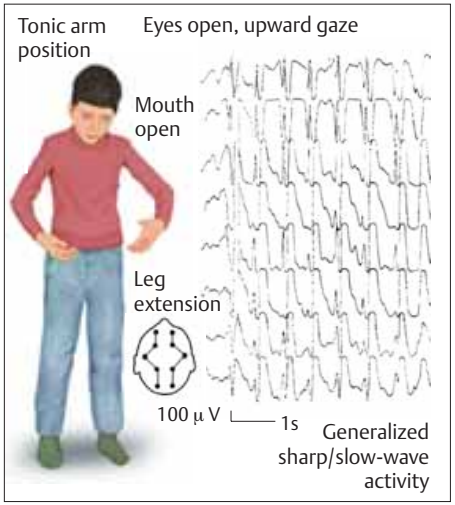
- Generalized seizures arise from both cerebral hemispheres simultaneously.
- It is impossible to exclude entirely the existence of a focal region of abnormal activity that initiates the seizure prior to rapid secondary generalization.
- For this reason, generalized seizures may be practically defined as bilateral clinical and electrographic events without any detectable focal onset.
- Fortunately, several types of generalized seizures have distinctive features that facilitate clinical diagnosis.

GENERALIZED SEIZURES
Absence Seizures (*Petit Mal*)

- Absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control.
- The seizure typically lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion.
- Although the brief loss of consciousness may be clinically inapparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands.



Absence



Tonic seizure
(in myoclonic/astatic epilepsy)

Absence Seizures

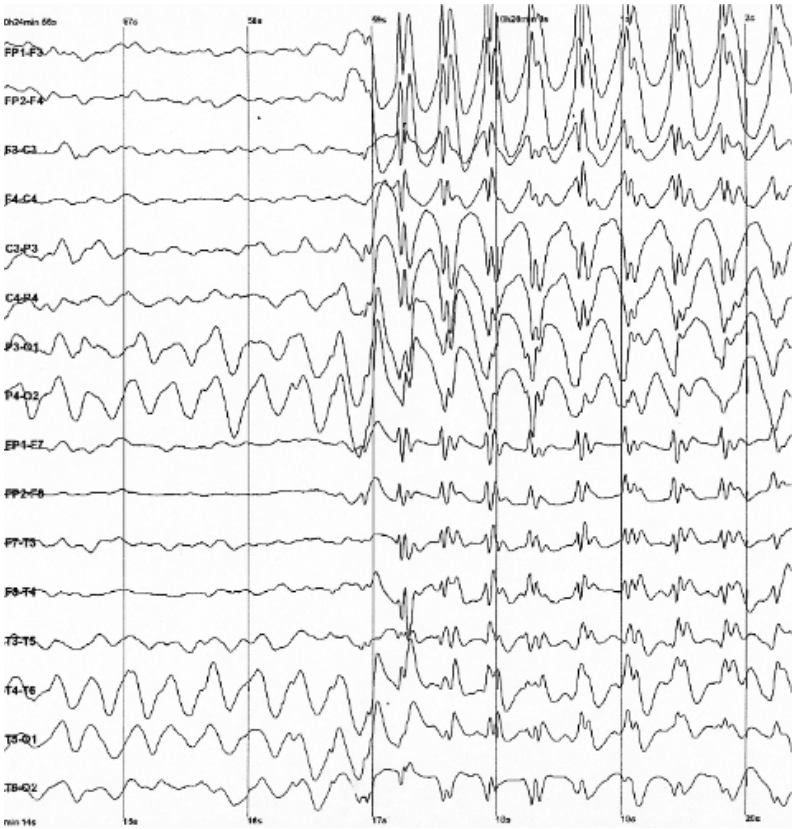
- Absence seizures are often described as staring spells. The person stops what he or she is doing and stares vacantly for a few seconds, then continues as if nothing happened. This type of seizure is more common in children and usually starts between the ages of 4 and 12. Some children experience up to 100 absence seizures in a day.

GENERALIZED SEIZURES
Absence Seizures (*Petit Mal*)

- Absence seizures usually begin in childhood (ages 4 to 8) or early adolescence and are the main seizure type in 15 to 20% of children with epilepsy.
- The seizures can occur hundreds of times per day, but the child may be unaware of or unable to convey their existence.
- The patient may be constantly piecing together experiences that have been interrupted by the seizures.
- Since the clinical signs of the seizures are subtle, especially to new patients, it is not surprising that the first clue to absence epilepsy is often unexplained "daydreaming" and a decline in school performance recognized by a teacher.

GENERALIZED SEIZURES
Absence Seizures (*Petit Mal*)

- The electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3-Hz spike-and-wave discharge that begins and ends suddenly, superimposed on a normal EEG background.

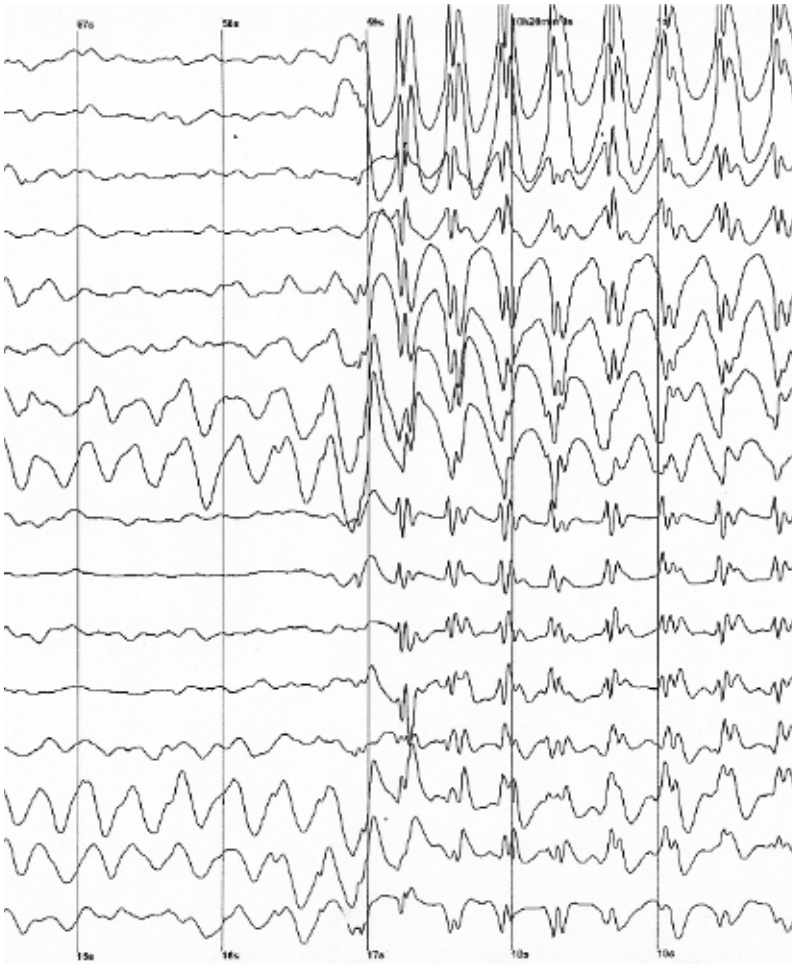


GENERALIZED SEIZURES
Absence Seizures (*Petit Mal*)

- Periods of spike-and-wave discharges lasting more than a few seconds usually correlate with clinical signs, but the EEG often shows many more brief bursts of abnormal cortical activity than were suspected clinically.

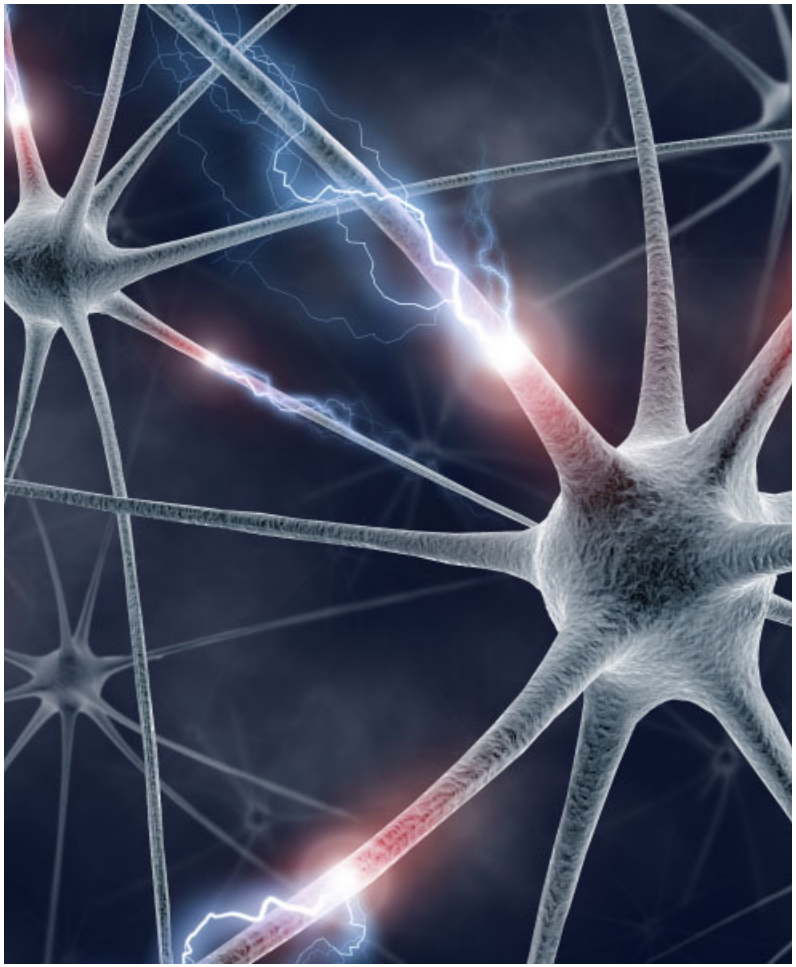
GENERALIZED SEIZURES
Absence Seizures (*Petit Mal*)

- Hyperventilation tends to provoke these electrographic discharges and even the seizures themselves and is routinely used when recording the EEG.



GENERALIZED SEIZURES
Absence Seizures (*Petit Mal*)

- Typical absence seizures are often associated with generalized, tonic-clonic seizures, but patients usually have no other neurologic problems and respond well to treatment with specific anticonvulsants.
- Although estimates vary, ~60 to 70% of such patients will have a spontaneous remission during adolescence.



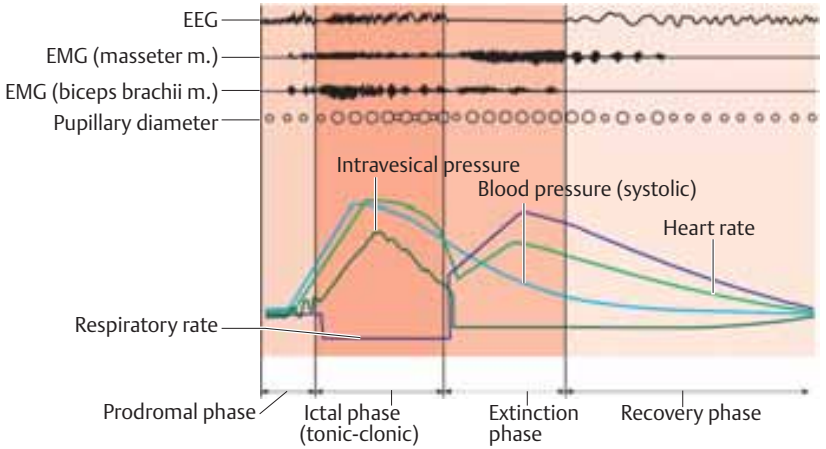
GENERALIZED SEIZURES
Atypical Absence Seizures

- Atypical absence seizures have features that deviate both clinically and electrophysiologically from typical absence seizures.
- For example, the lapse of consciousness is usually of longer duration and less abrupt in onset and cessation, and the seizure is accompanied by more obvious motor signs that may include focal or lateralizing features.
- The EEG shows a generalized, slow spike-and-wave pattern with a frequency of ≤2.5/s, as well as other abnormal activity.
- Are usually associated with diffuse or multifocal structural abnormalities of the brain and therefore may accompany other signs of neurologic dysfunction such as mental retardation.
- Are less responsive to anticonvulsants compared to typical absence seizure.

GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

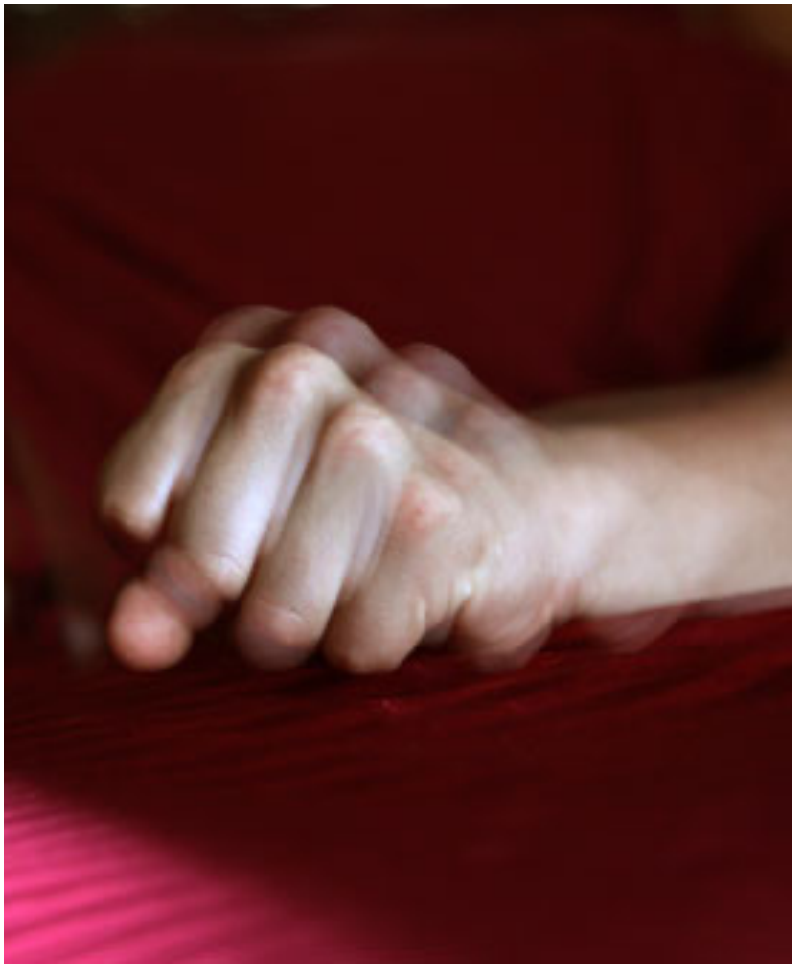
- Are the main seizure seizure type in ~10% of all persons with epilepsy.
- Are the most common seizure type resulting from metabolic derangements and are therefore frequently encountered in many different clinical settings.
- Usually begins abruptly without warning, although some patients describe vague premonitory symptoms in the hours leading up to the seizure.
- This prodrome is distinct from the stereotypic auras associated with focal seizures that secondarily generalize.

Generalized tonic-clonic seizure
(Grand mal, tonic phase; transition to clonic phase with forceful, rhythmic convulsions)



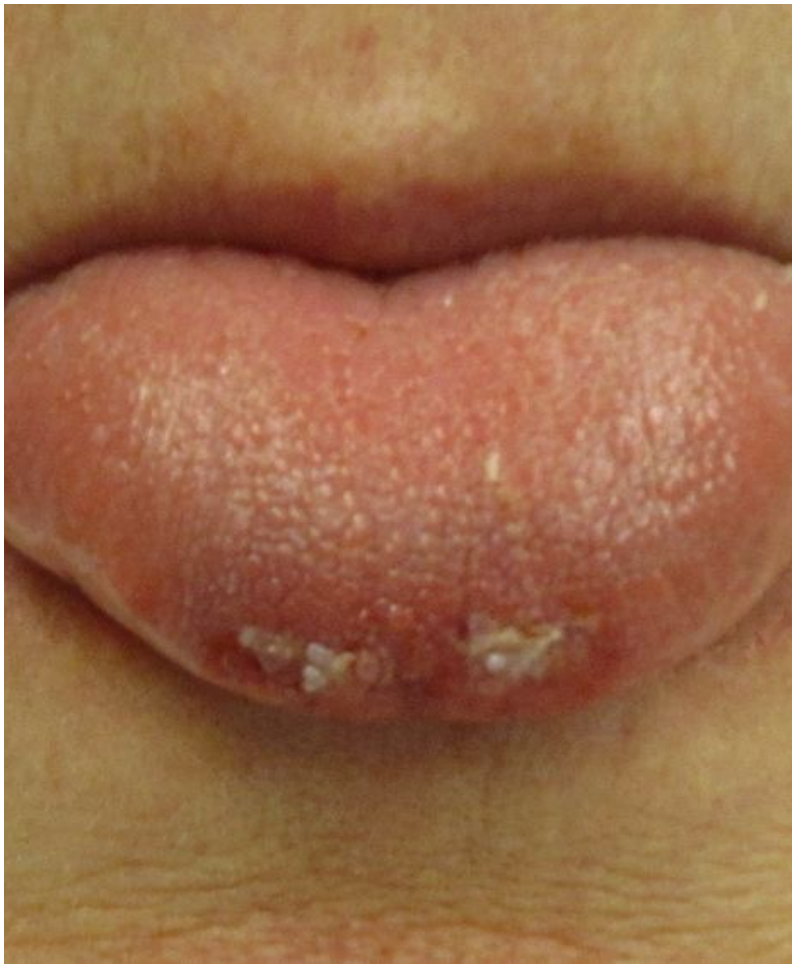
GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

- The initial phase of the seizure is usually tonic contraction of muscles throughout the body, accounting for a number of the classic features of the event.
- Tonic contraction of the muscles of expiration and the larynx at the onset will produce a loud moan or "ictal cry".
- Respirations are impaired, secretions pool in the oropharynx, and cyanosis develops.



GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

- Contraction of the jaw muscles may cause biting of the tongue.



GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

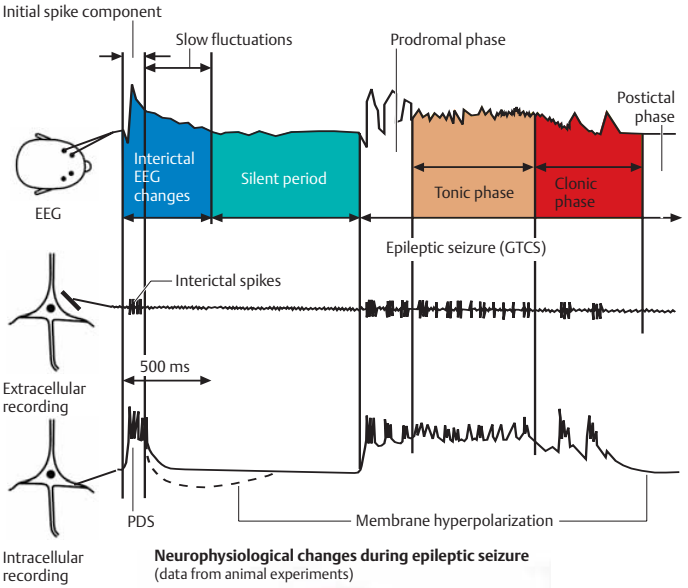
- A marked enhancement of sympathetic tone leads to increases in heart rate, blood pressure, and pupillary size.
- After 10-20 s, the tonic phase of the seizure typically evolves into the clonic phase, produced by the superimposition of periods of muscle relaxation on the tonic muscle contraction.
- The periods of relaxation progressively increase until the end of the ictal phase, which usually lasts no more than 1 min.
- The postictal phase is characterized by unresponsiveness, muscular flaccidity, and excessive salivation that can cause stridorous breathing and partial airway obstruction.
- Bladder or bowel incontinence may occur at this point.

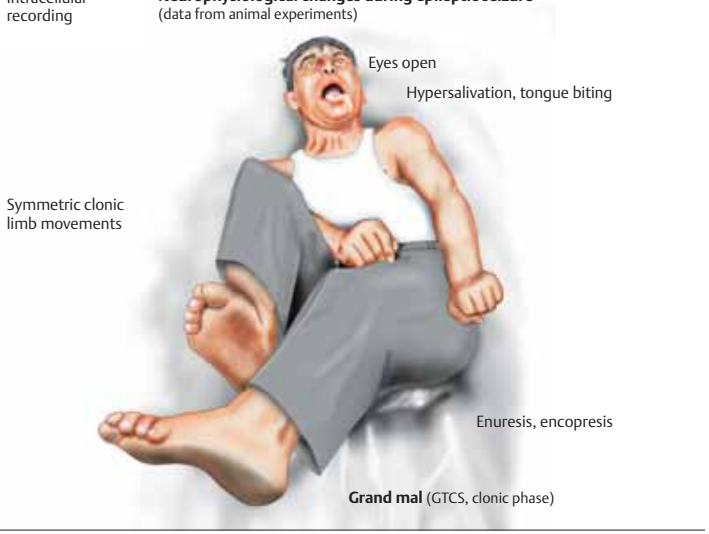
GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

- Patients gradually regain consciousness over minutes to hours, and during this transition there is typically a period of postictal confusion.
- Patients subsequently complain of headache, fatigue, and muscle ache that can last for many hours.
- The duration of impaired consciousness in the postictal phase can be extremely long, i.e., many hours, in patients with prolonged seizures or underlying CNS diseases such as alcoholic cerebral atrophy.

GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

- The EEG during the tonic phase of the seizure shows a progressive increase in generalized low-voltage fast activity, followed by generalized high-amplitude, polyspike discharges.
- In the clonic phase, the high-amplitude activity is typically interrupted by slow waves to create a spike-and-wave pattern.
- The postictal EEG shows diffuse slowing that gradually recovers as the patient awakens.





GENERALIZED SEIZURES
Tonic-Clonic Seizures (*Grand Mal*)

- There are many variants of the generalized tonic-clonic seizure, including pure tonic and pure clonic seizure.
- Brief tonic seizures lasting only a few seconds are especially noteworthy since they are associated with specific epileptic syndromes having mixed seizures phenotypes, such as the Lennox-Gastaut syndrome.

GENERALIZED SEIZURES
Atonic Seizures

- Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1-2 s.
- Consciousness is briefly impaired, but there is usually no postictal confusion.
- A very brief seizure may cause only a quick head drop or nodding movement, while a longer seizure will cause the patient to collapse. This can be extremely dangerous, since there is a substantial risk of direct head injury with the fall.
- The EEG shows brief, generalized spike-and-wave discharges followed immediately by diffuse slow waves that correlate with the loss of muscle tone.
- Similar to pure tonic seizures, atonic seizures are usually seen in association with known epileptic syndromes.

GENERALIZED SEIZURES
Myoclonic Seizures

- Myoclonus is a sudden and brief muscle contraction that may involve one part of the body or the entire body.
- A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep.
- Pathologic myoclonus is most commonly seen in association with metabolic disorders, degenerative CNS diseases, or anoxic brain injury.
- Although the distinction from other forms of myoclonus is imprecise, myoclonic seizures are considered to be true epileptic events since they are caused by cortical (versus subcortical or spinal) dysfunction.

GENERALIZED SEIZURES
Myoclonic Seizures

- The EEG may show bilaterally synchronous spike-and-wave discharges synchronized with the myoclonus, although these can be obscured by movement artifact.
- Myoclonic seizures usually coexist with other forms of generalized seizure disorders but are predominant feature of juvenile myoclonic epilepsy.

UNCLASSIFIED SEIZURES

- Not all seizure types can be classified as partial or generalized.
- This appears to be especially true of seizures that occur in neonates and infants.
- The distinctive phenotypes of seizures at these early ages likely result, in part, from differences in neuronal function and connectivity in the immature versus mature CNS

EPILEPSY SYNDROMES

- Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence (e.g., through clinical, EEG, radiologic or genetic observations) to suggest a common underlying mechanism.
- Three important epilepsy syndromes are:
  1) JUVENILE MYOCLONIC EPILEPSY;
  2) LENNOX-GASTAUT SYNDROME and
  3) MESIAL TEMPORAL LOBE EPILEPSY SYNDROME.

Examples of genes associated with epilepsy syndromes[a]

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
CHRNA4 (20q13.2)	Nicotinic acetylcholine receptor subunit; mutations cause alterations in Ca^{2+} flux through the receptor; this may reduce amount of GABA release in presinaptic terminals	Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE); childhood onset; brief, nighttime seizures with prominent motor movements; often misdiagnosed as primary sleep disorder	Rare; first identified in a large Australian family; other families found to have mutations in CHRNA2 or CHRNB2, and some families appear to have mutations at other loci

[a]The first four syndromes listed in the table (ADNFLE, BFNFC, GEFS+, and ADPEAF) are examples of idiopathic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.

Examples of genes associated with epilepsy syndromes[a]

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
KCNQ2 (20q13.3)	Voltage-gated potassium channel subunits; mutation in pore regions may cause a 20-40% reduction of potassium currents, which will lead to impaired repolarization	Benign familial neonatal convulsions (BFNC); autosomal dominant inheritance; onset in 1st week of life in infants who are otherwise normal; remission usually within weeks to months; long-term epilepsy in 10-15%	Rare; other families found to have mutations in KCNQ3; sequence and functional homology to KCNQ1, mutations of which cause long QT syndrome and a cardiac-auditory syndrome

[a]The first four syndromes listed in the table (ADNFLE, BFNFC, GEFS+, and ADPEAF) are examples of idiopathic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.

Examples of genes associated with epilepsy syndromes

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
SCN1B (19q12.1)	β- subunit of a voltage-gated sodium channel; mutation disrupts disulfide bridge that is crucial for structure of extracellular domain; mutated β-subunit leads to slower sodium channel inactivation	Generalized epilepsy with febrile seizures plus (GEFS+); autosomal dominant inheritance; presents with febrile seizures at median 1 year, which may persist >6 years, then variable seizure types not associated with fever	Incidence uncertain; GEFS+ identified in other families with mutations in other sodium channel subunits (SCN1A and SCN2A) and $GABA_A$ receptor subunit (GABRG2 and GABRA1; significant phenotypic heterogeneity within same family, including members with febrile seizures only

Examples of genes associated with epilepsy syndromes

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
LGI1 (10q24)	Leucine-rich glioma-inactivated 1 gene; previous evidence for role in glial tumor progression; protein homology suggests a possible role in nervous system development	Autosomal dominant partial epilepsy with auditory features (ADPEAF); a form of idiopathic lateral temporal lobe epilepsy with auditory symptoms or aphasia as a major simple partial seizure manifestation; age of onset usually between 10 and 25 years	Mutations found in approximately 50% of families containing two or more subjects with idiopathic localization-related epilepsy with ictal auditory symptoms, suggesting that at least one other gene may underlie this syndrome. LGI1 is the only gene identified so far in temporal lobe epilepsy

Examples of genes associated with epilepsy syndromes

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
CSTB (21q22.3)	Cystatin B, a noncaspase cysteine protease inhibitor; normal protein may block neuronal apoptosis by inhibiting caspases directly or indirectly (via cathepsins), or controlling proteolysis	Progressive myoclonus epilepsy (PME) (Unverricht-Lundborg disease); autosomal recessive inheritance; age of onset between 6-15 years, myoclonic seizures, ataxia, and progressive cognitive decline; brain shows neuronal degeneration	Overall rare, but relatively common in Finland and Western Mediterranean (>1 in 20,000); precise role of cystatin B in human disease unknown, although mice with null mutations of cystatin B have similar syndrome

Examples of genes associated with epilepsy syndromes

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
EPM2A (6q24)	Laforin, a protein tyrosine phosphatase (PTP); may influence glycogen metabolism, which is known to be regulated by phosphatases	Progressive myoclonus epilepsy (Lafora's disease); autosomal recessive inheritance; onset age 6-19 years, death within 10 years; brain degeneration associated with polyglucosan intracellular inclusion bodies in numerous organs	Most common PME in Southern Europe, Middle East, Northern Africa, and Indian subcontinent; genetic heterogeneity; unknown whether seizure phenotype due to degeneration or direct effects of abnormal laforin expression

Examples of genes associated with epilepsy syndromes[a]

Gene (Locus)	Function of Gene	Clinical Syndrome	Comments
Doublecortin (Xq21-24)	Doublecortin, expressed primarily in frontal lobes; function unknown; potentially an intracellular signaling molecule	Classic lissencephaly associated with severe mental retardation and seizures in males; subcortical band heterotopia with more subtle findings in females (presumably due to random X-inactivation); X-linked dominant	Relatively rare but of uncertain incidence, recent increased ascertainment due to improved imaging techniques; relationship between migration defect and seizure phenotype unknown

[a]The first four syndromes listed in the table (ADNFLE, BFNFC, GEFS+, and ADPEAF) are examples of idiopathic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.

EPILEPSY SYNDROMES
JUVENILE MYOCLONIC EPILEPSY

- Is a generalized seizure disorder of unknown cause that appears in early adolescence and is usually characterized by bilateral myoclonic jerks that may be single or repetitive.
- Are most frequent in the morning after awakening and can be provoked by sleep deprivation.
- Consciousness is preserved unless the myoclonus is especially severe.
- Many patients also experience generalized tonic-clonic seizures, and up to one-third have absence seizures.

EPILEPSY SYNDROMES
JUVENILE MYOCLONIC EPILEPSY

- The condition is otherwise benign, and although complete remission is uncommon, the seizures respond well to appropriate anticonvulsant medication.
- There is often a family history of epilepsy, and genetic linkage suggest a polygenic cause.

EPILEPSY SYNDROMES
LENNOX-GASTAUT SYNDROME

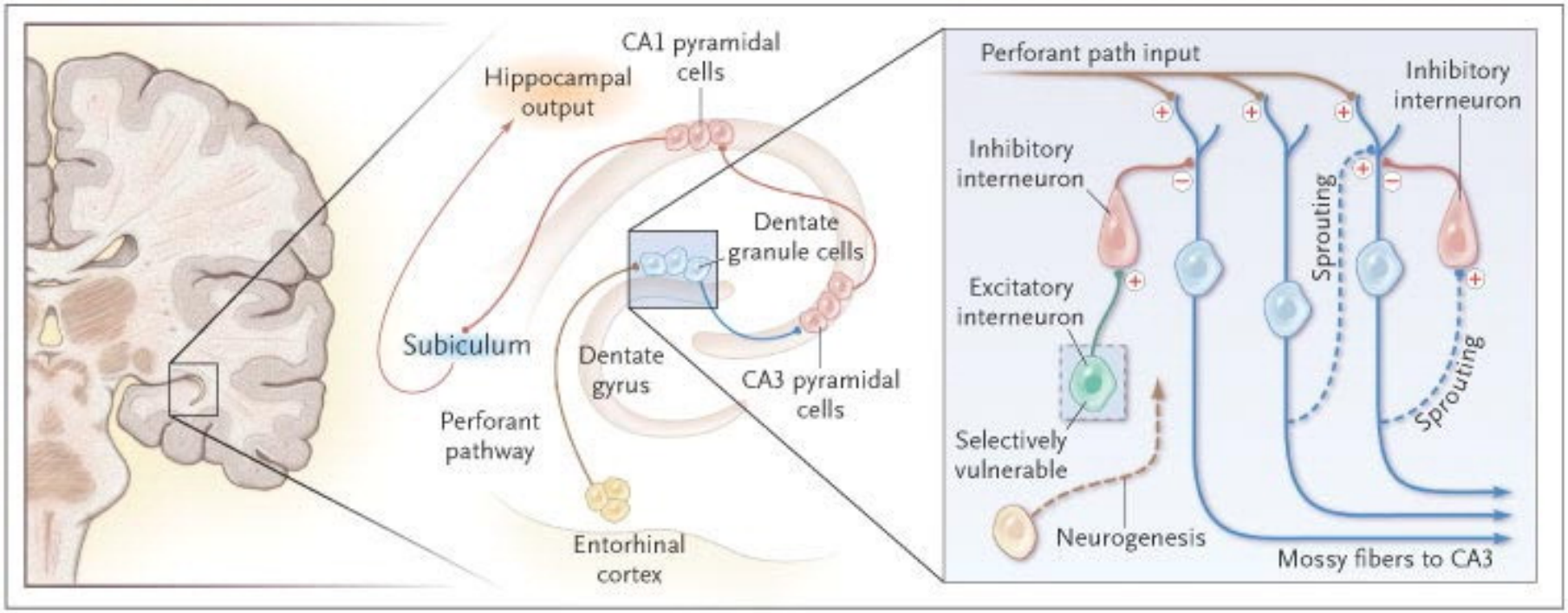
- Occurs in children and is defined by the following triad:
  (1) multiple seizure types (usually including generalized tonic-clonic, atonic, and atypical absence seizures);
  (2) an EEG showing slow (<3 Hz) spike-and-wave discharges and a variety of other abnormalities; and
  (3) impaired cognitive function in most but not all cases.
- Lennox-Gastaut syndrome is associated with CNS disease or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions.

EPILEPSY SYNDROMES
LENNOX-GASTAUT SYNDROME

- The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neural injury.
- Unfortunately, many patients have a poor prognosis due to the underlying CNS disease and the physical and psychosocial consequences of severe, poorly controlled epilepsy.

EPILEPSY SYNDROMES
MESIAL LOBE EPILEPSY SYNDROME

- Is the most common syndrome associated with complex partial seizures and is an example of a symptomatic, partial epilepsy with distinctive clinical, EEG and pathologic features.
- High-resolution MRI can detect the characteristic hippocampal sclerosis that appears to be essential in the pathophysiology of MTLE for many patients.
- Recognition of this syndrome is especially important because it tends to be refractory to treatment with anticonvulsants but responds extremely well to surgical intervention.



Hippocampal sclerosis is the most common identified pathological feature in cases of mesial temporal-lobe epilepsy.

characteristics of the mesial temporal lobe epilepsy syndrome

History **History of febrile seizures** **Family history of epilepsy** **Early onset**	**Rare secondarily generalized seizures** **Seizures may remit and reappear** **Seizures often intractable**
Clinical observations Aura common Behavioral arrest/stare Complex automatisms Unilateral posturing	Postictal disorientation, memory loss, dysphasia (with focus in dominant hemisphere)
Laboratory studies Unilateral or bilateral anterior temporal spikes on EEG Hypometabolism on interictal PET Hypoperfusion on interictal SPECT Material-specific memory deficits on intracranial amobarbital (Wada) test	
MRI findings Small hippocampus with increased signal on T2-weighted sequences Small temporal lobe Enlarged temporal horn	
Pathologic findings Highly selective loss of specific cell populations within hippocampus in most cases	

THE CAUSES OF SEIZURES AND EPILEPSY

- Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. Three clinical observations emphasize how a variety of factors determine seizures:

1. *The normal brain is capable of having a seizure under the appropriate circumstances, and there are differences between individuals in the susceptibility or threshold for seizures.*

2. *There are a variety of conditions that have an extremely high likelihood of resulting in a chronic seizure disorder.*

3. *Seizures are episodic.*

causes of seizures according to age

Neonates (<1 month)	**Perinatal hypoxia and ischemia** **Intracranial hemorrhage and trauma** **Acute CNS infection** **Metabolic disturbances** (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) **Drug withdrawal** **Developmental disorders** **Genetic disorders**
Infants and children (>1 month and <12 years)	**Febrile seizures** **Genetic disorders** (metabolic, degenerative, primary epilepsy syndrome) **CNS infection** **Developmental disorders** **Trauma** **Idiopathic**
Adolescents (12-18 years)	**Trauma** **Genetic disorders** **Infection** **Brain tumor** **Illicit drug use** **Idiopathic**

causes of seizures according to age

Young adults (18-35 years)	**Trauma** **Alcohol withdrawal** **Illicit drug use** **Brain tumor** **Idiopathic**
Older adults (>35 years)	**Cerebrovascular disease** **Brain tumor** **Alcohol withdrawal** **Metabolic disorders** (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia) **Alzheimer's disease and other degenerative CNS diseases** **Idiopathic**

Cerebrovascular disease may account for ~50% of new cases of epilepsy in patients older than 65.

drugs and other substances that can cause seizures

Alkylating agents (e.g., busulfan, chlorambucil)
Antimalarials (chloroquine, mefloquine)
Antimicrobials/antivirals
β- lactam and related compounds
Quinolones
Acyclovir
Izoniazid
Ganciclovir
Anesthetics and analgesics
Meperidine
Tramadol
Local anesthetics
Dietary supplements
Ephedra (ma huang)
Gingko
Immunomodulatory drugs
Cyclosporine
OKT3 (monoclonal antibodies to T cells)
Tacrolimus
Interrferons

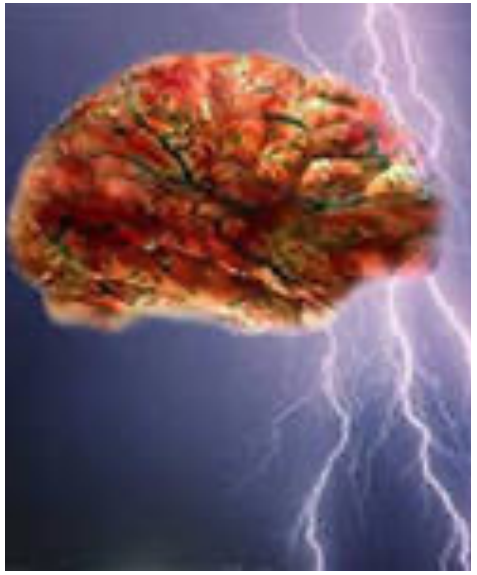
Psychotropcis
Antidepressants
Antipsychotics
Lithium
Radiographic contrast agents
Theophyline
Sedative-hypnotic drug withdrawal
Alcohol
Barbiturates (short-acting)
Benzodiazepines (short-acting)
Drugs of abuse
Amphetamine
Cocaine
Phencyclidine
Methylphenidate
Flumazenil

GENETIC CAUSES OF EPILEPSY

- The most important recent progress in epilepsy research has been the identification of genetic mutations associated with a variety of epilepsy syndromes.
- It appears that many of the inherited, idiopathic epilepsies (i.e., the relatively "pure" forms of epilepsy in which seizures are the phenotypic abnormality and brain structure and function are otherwise normal) are due to mutations affecting ion channel function.
- These syndromes are therefore part of the larger group of channelopathies causing paroxysmal disorders such as cardiac arrhythmias, episodic ataxia, periodic weakness, and familial hemiplegic migraine.

GENETIC CAUSES OF EPILEPSY

- Gene mutations observed in symptomatic epilepsies (i.e., disorders in which other neurologic abnormalities, such as cognitive impairment, coexist with seizures) are



First Aid for Seizures

If you see someone having a seizure, take the following steps:

- Time the seizure with your watch.
- Clear the area of anything hard or sharp.
- Loosen anything at the neck that may impair breathing.
- Turn the person onto his or her side.
- Put something soft beneath the head.
- Do not place anything inside the mouth.

- Call 911 if a seizure lasts more than 5 minutes, recurs, or the person is pregnant, injured, or diabetic.

Treatment: SEIZURES AND EPILEPSY

THERAPY for a patient with a seizure disorder is almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with antiepileptic medications or surgery, and addressing a variety of psychological and social issues.

Treatment: Medication

- Anti-seizure drugs are the most common treatment for epilepsy. If medication is not successful at first, doctor may adjust the dosage or switch to a different drug. About two-thirds of people with epilepsy become seizure-free by taking their medication regularly.

Treatment: SEIZURES AND EPILEPSY

Treatment plans must be individualized, given the many different types and causes of seizures as well as the differences in efficacy and toxicity of antiepileptic medication for each patient.

SELECTION OF ANTIEPILEPTIC DRUGS

PRIMARY GENERALIZED TONIC-CLONIC	PARTIAL[a]	ABSENCE	ATYPICAL ABSENCE, MYOCLONIC, ATONIC
First-Line			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Lamotrigine Oxcarbazepine Valproic acid	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternatives			
Zonisamide[b] Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Levetiracetam[b] Topiramate Tiagabine[b] Zonisamide[b] Gabapentin[b] Phenobarbital Primidone Felbamate	Lamotrigine Clonazepam	Clonazepam Felbamate

[a]Includes simple partial, complex partial, and secondarily generalized seizures.
[b]As adjunctive therapy.

Treatment: Ketogenic Diet

- When followed carefully, a ketogenic diet can eliminate or nearly eliminate seizures in a third of children with epilepsy who try it. The diet is very high in fat and low in carbs, a combination that makes the body burn fat instead of sugar. This creates changes in the brain that reduce or eliminate seizures. It's a very strict diet that is created by a dietitian and monitored by a medical team. It may be recommended when medications fail or cause unacceptable side effects.

Epilepsy in Children

- Children who are diagnosed with epilepsy may outgrow the condition in a few years. In the meantime, many kids are able to prevent seizures by taking regular medication. If drugs fail to keep seizures under control, other precautions may be needed. A well-informed school staff can help a child with epilepsy safely participate in most activities.

Treatment for Status Seizures

- Prolonged or recurring seizures may be a condition called status epilepticus. This can have serious complications and requires emergency treatment. To bring the seizures to an end quickly, hospitals typically administer a sequence of drugs by IV and supplemental oxygen.

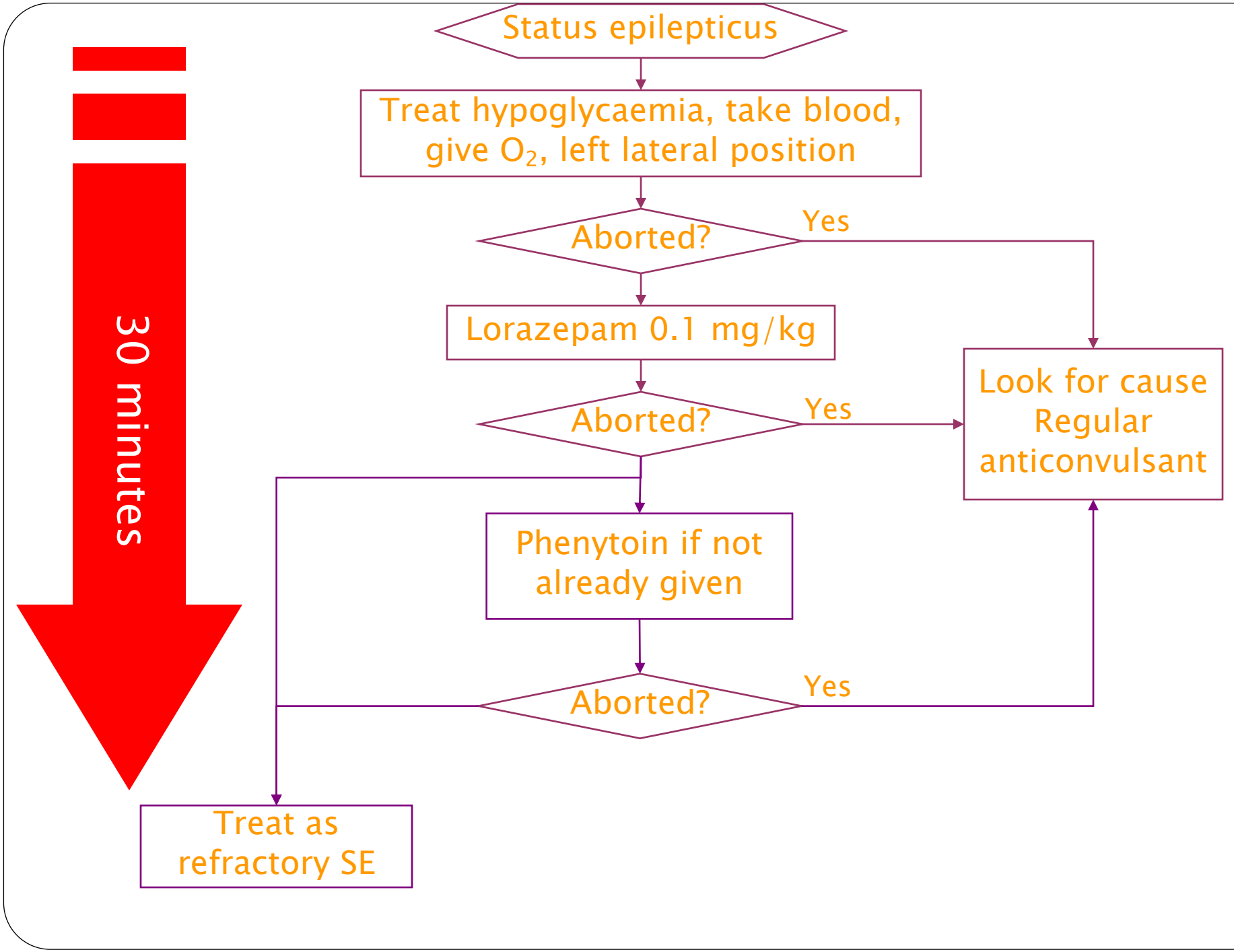
STATUS EPILEPTICUS

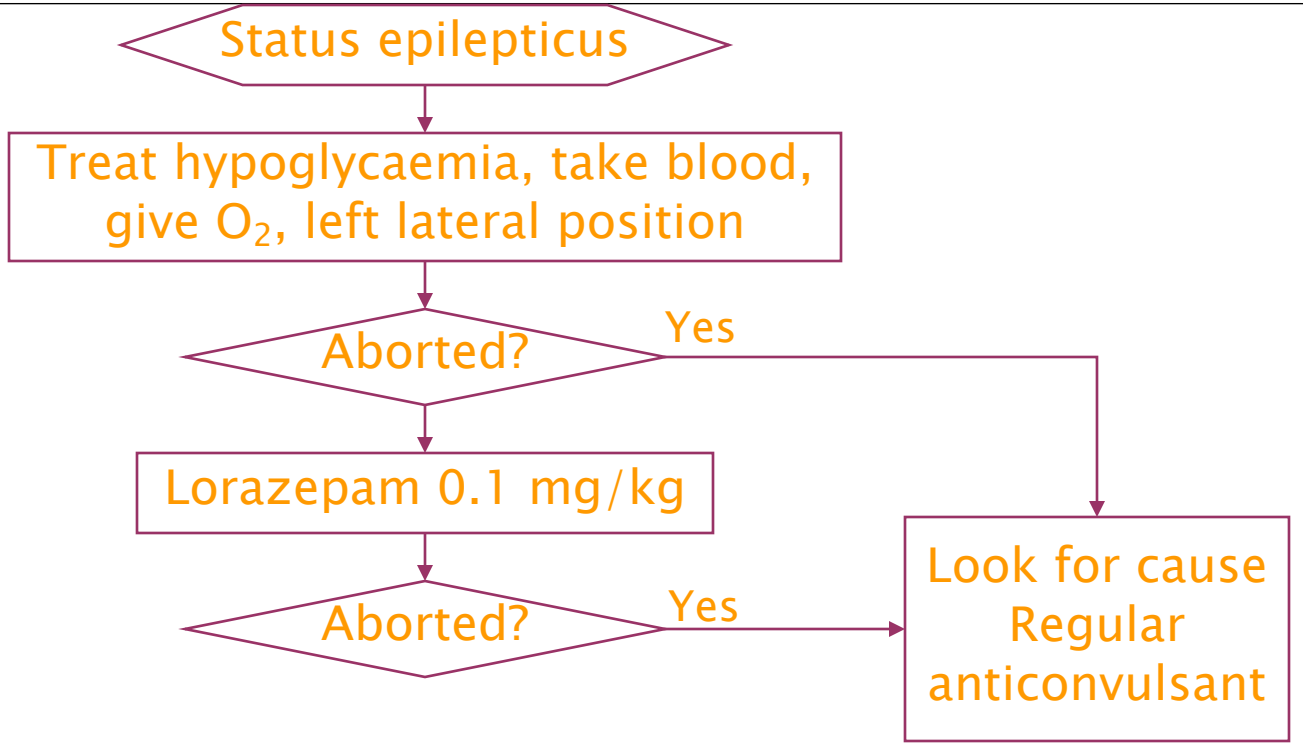
Status epilepticus refers to continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. Status epilepticus has numerous subtypes, including generalized convulsive status epilepticus (GCSE) (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements), and non- convulsive status epilepticus (e.g., persistent absence seizures or partial seizures, confusion or partially impaired consciousness, and minimal motor abnormalities).

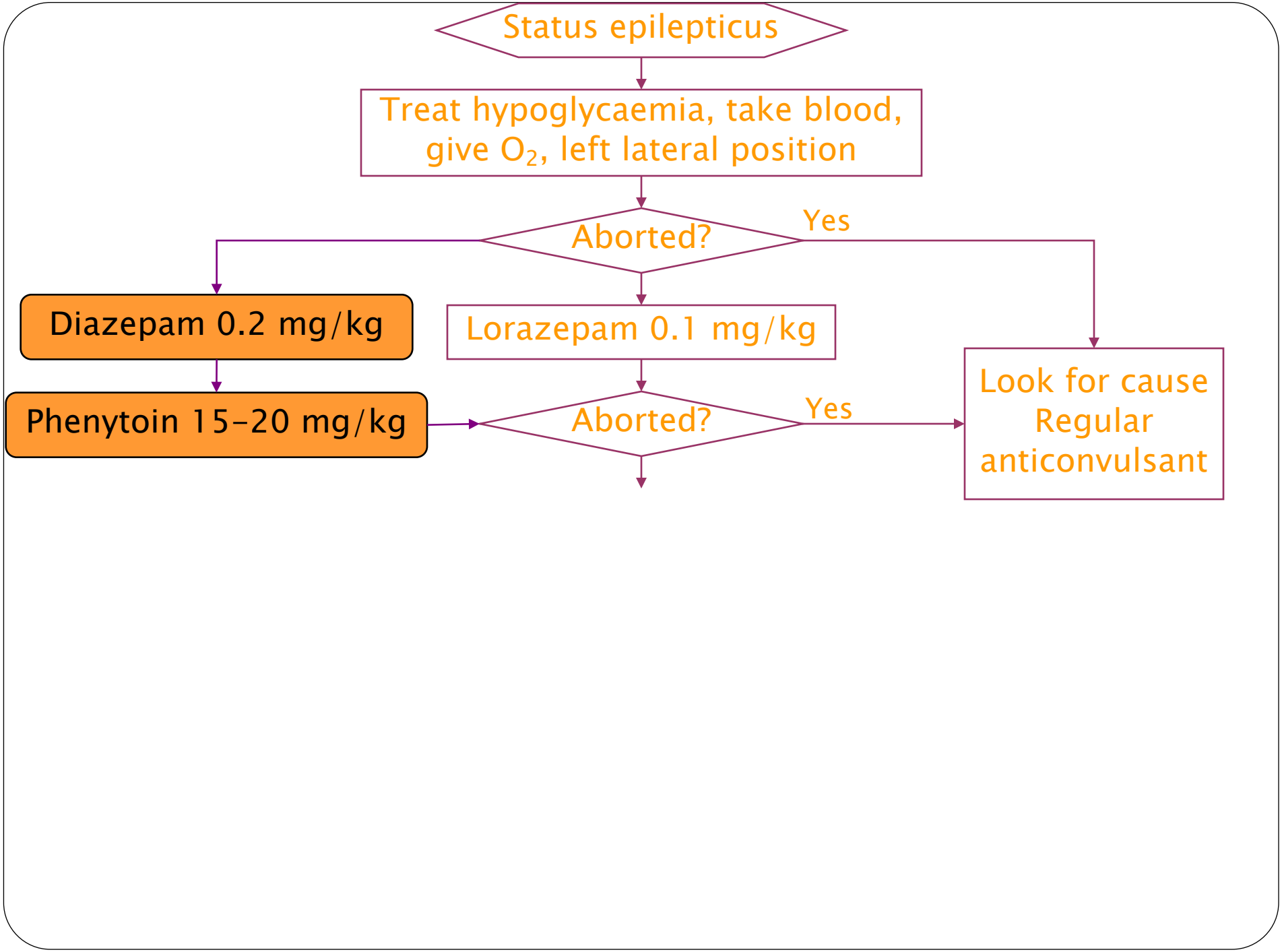
STATUS EPILEPTICUS

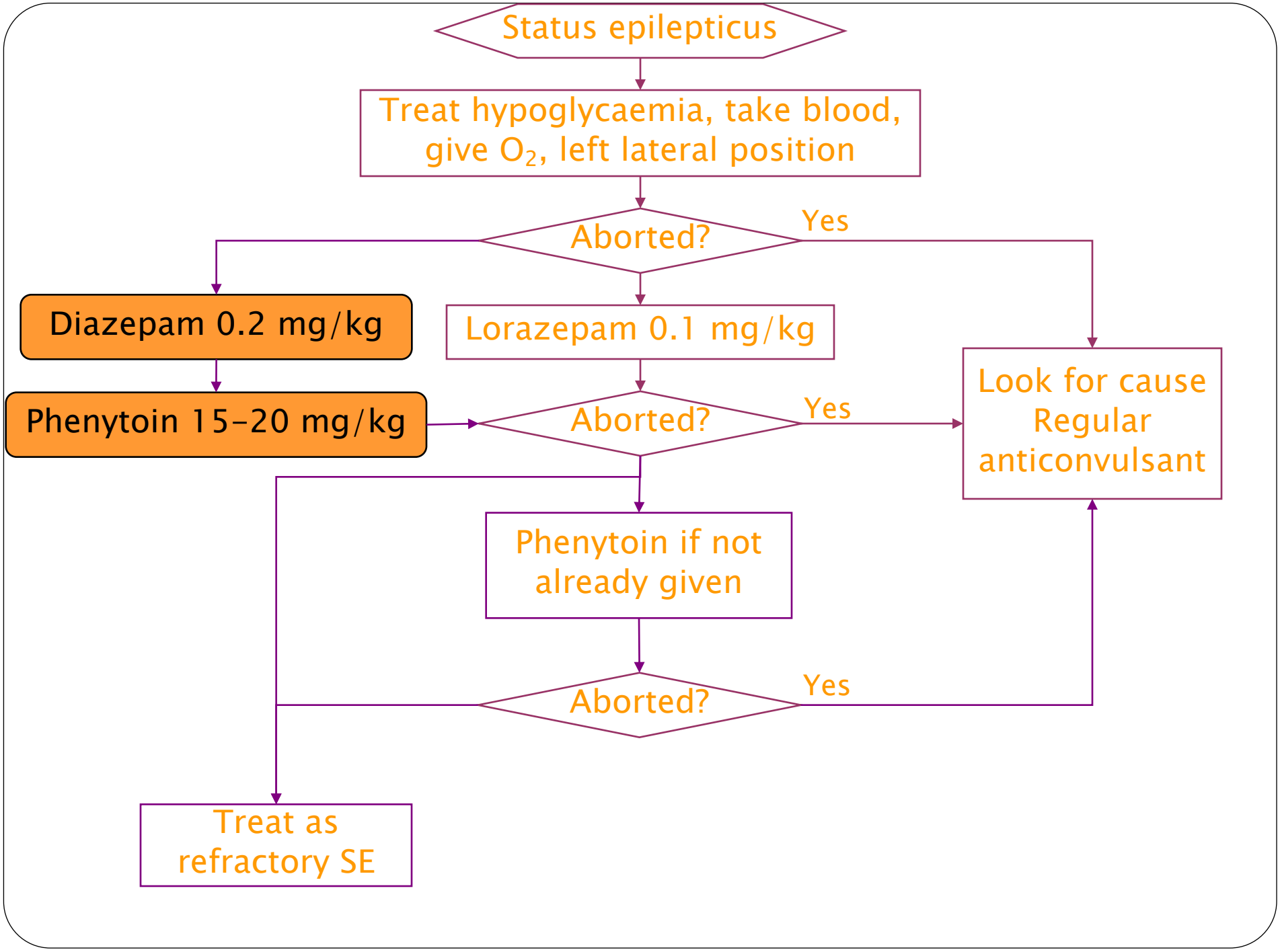
- *GCSE is an emergency and must be treated immediately,* since cardiorespiratory dysfunction, hyperthermia, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury. Furthermore, CNS injury can occur even when the patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures. The most common causes of GCSE are anticonvulsant withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infection, CNS tumors, refractory epilepsy, and head trauma.

Status epilepticus


Status epilepticus
Treat hypoglycaemia, take blood, give O_2, left lateral position
Aborted?
Yes
Lorazepam 0.1 mg/kg
Aborted?
Yes
Look for cause Regular anticonvulsant
Phenytoin if not already given
Aborted?
Yes
Treat as refractory SE
30 minutes

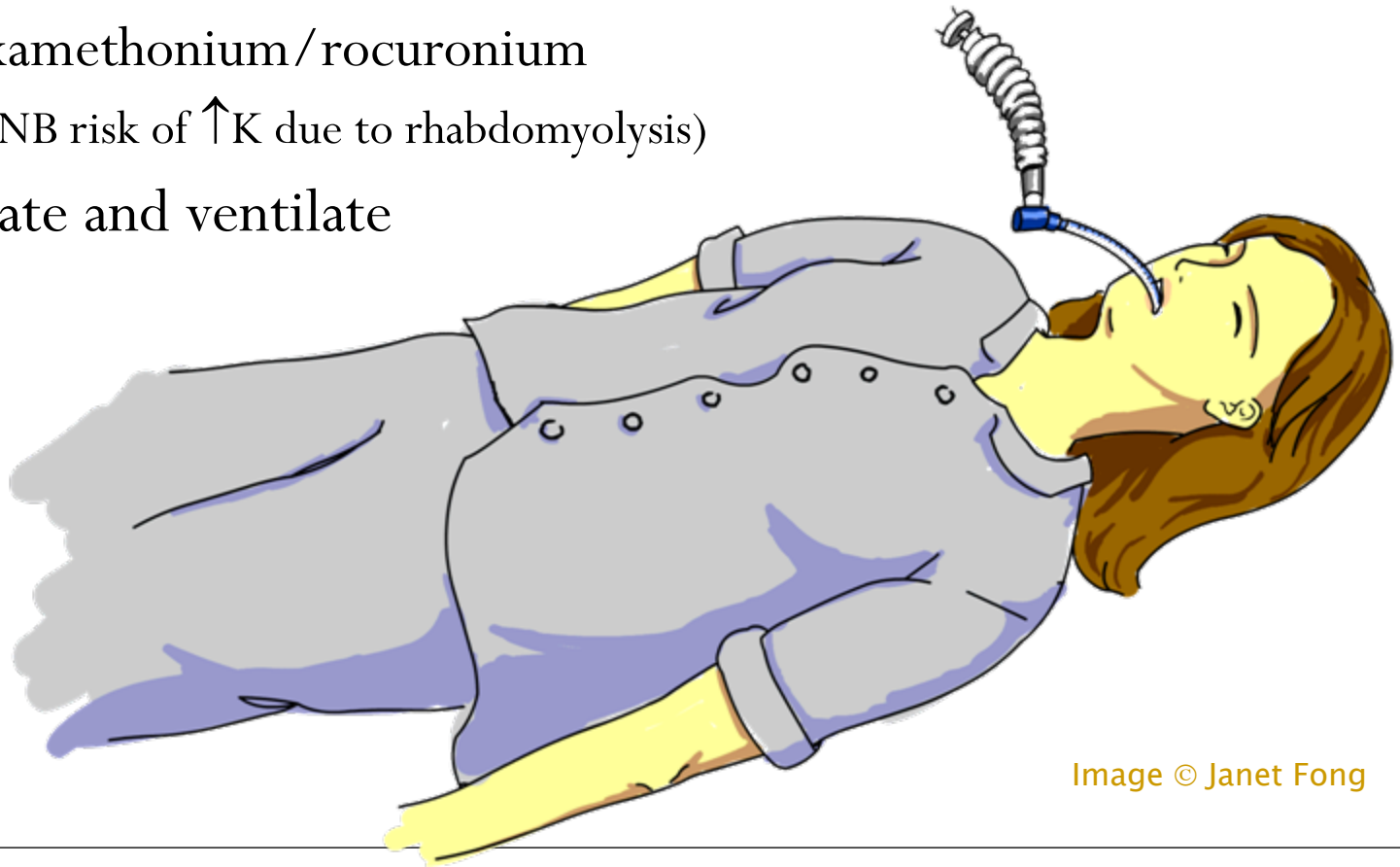

Status epilepticus
Treat hypoglycaemia, take blood, give O_2, left lateral position
Aborted?
Yes
Lorazepam 0.1 mg/kg
Aborted?
Yes
Look for cause
Regular anticonvulsant


Status epilepticus
Treat hypoglycaemia, take blood, give O_2, left lateral position
Aborted?
Yes
Diazepam 0.2 mg/kg
Lorazepam 0.1 mg/kg
Look for cause
Regular anticonvulsant
Phenytoin 15–20 mg/kg
Aborted?
Yes


Status epilepticus
Treat hypoglycaemia, take blood, give O_2, left lateral position
Aborted?
Yes
Diazepam 0.2 mg/kg
Lorazepam 0.1 mg/kg
Look for cause Regular anticonvulsant
Phenytoin 15-20 mg/kg
Aborted?
Yes
Phenytoin if not already given
Aborted?
Yes
Treat as refractory SE

Refractory status epilepticus

- Rapid sequence induction
  - Thiopentone/propofol
  - Suxamethonium/rocuronium
    - (NB risk of ↑K due to rhabdomyolysis)
- Intubate and ventilate



Refractory SE

- Treatment options
  - Midazolam
  - Propofol
  - Thiopentone
- Target
  - Abolition of clinical and electrical seizure activity

Midazolam

- Dose
  - 0.2 mg/kg loading
  - 0.1-0.2 mg/kg/h
- Tachyphylaxis
  - Requires significant dose increase after 24-48 h to maintain seizure control

Propofol

- Dose
  - Loading dose 3-5 mg/kg
  - Infusion 30-100 µg/kg/min
- Propofol infusion syndrome
  - Severe metabolic acidosis
  - Rhabdomyolysis
  - Cardiovascular collapse

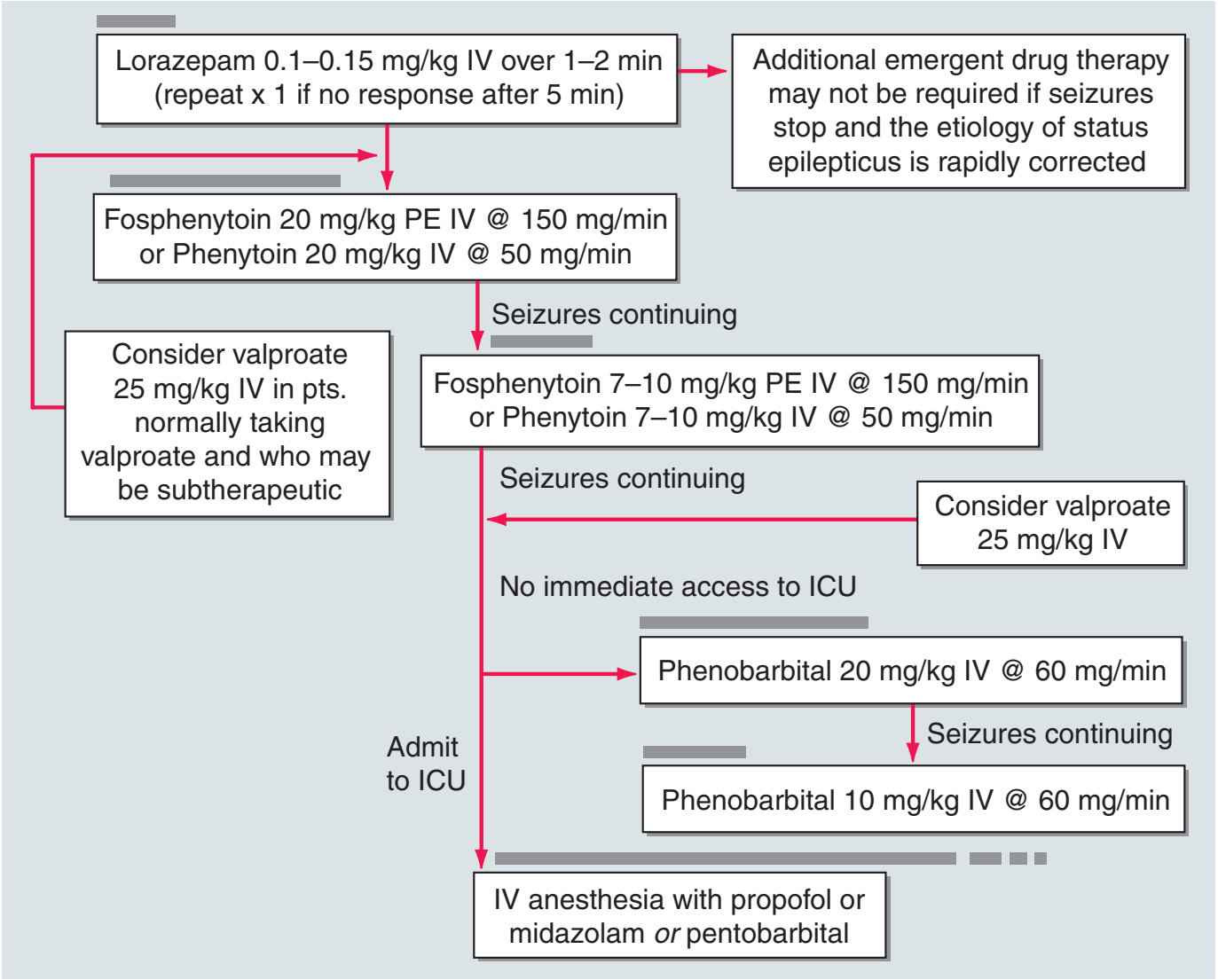
Key points

- Head injury
  - Resuscitate first
  - Maintain CPP >60 mmHg
  - Reduce ICP with evacuation of SOL, drainage of CSF, mannitol and ventilation to $PaCO_2$ 4-4.5kPa
  - Sedate, nurse head up, prevent fits & fever, prevent hyperglycaemia

Key points

- Status epilepticus
  - True emergency
  - Treat hypoglycaemia
  - Lorazepam 0.1 mg/kg
  - Sedate, intubate and ventilate
  - Thiopentone/propofol/midazolam infusion

Pharmacologic treatment of generalized tonic-clonic status epilepticus in adults. The horizontal bars indicate the approximate



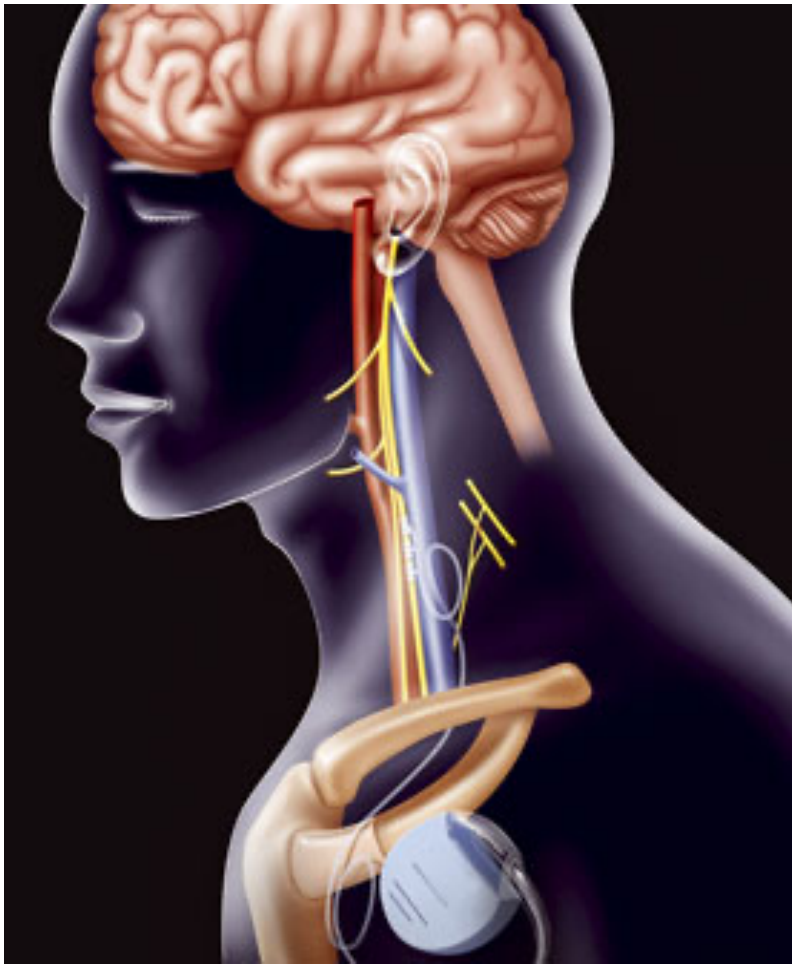
Epilepsy and Pregnancy

- In most cases, it is safe for women with epilepsy to become pregnant and start a family. More than 90% of babies born to women with epilepsy are healthy. It may be necessary to adjust anti-seizure medication. Some drugs appear to be less risky during pregnancy than others.

Seizure Dogs

- Some dogs appear to sense a person's seizure before it begins, providing an early warning system. But more research is needed before seizure alert dogs are widely used. In the meantime, many dogs can be trained to behave a certain way during a seizure. For example, the dog can lie next to the person to help prevent injury. In the case of a child, a dog may be trained to alert the parents during a seizure.

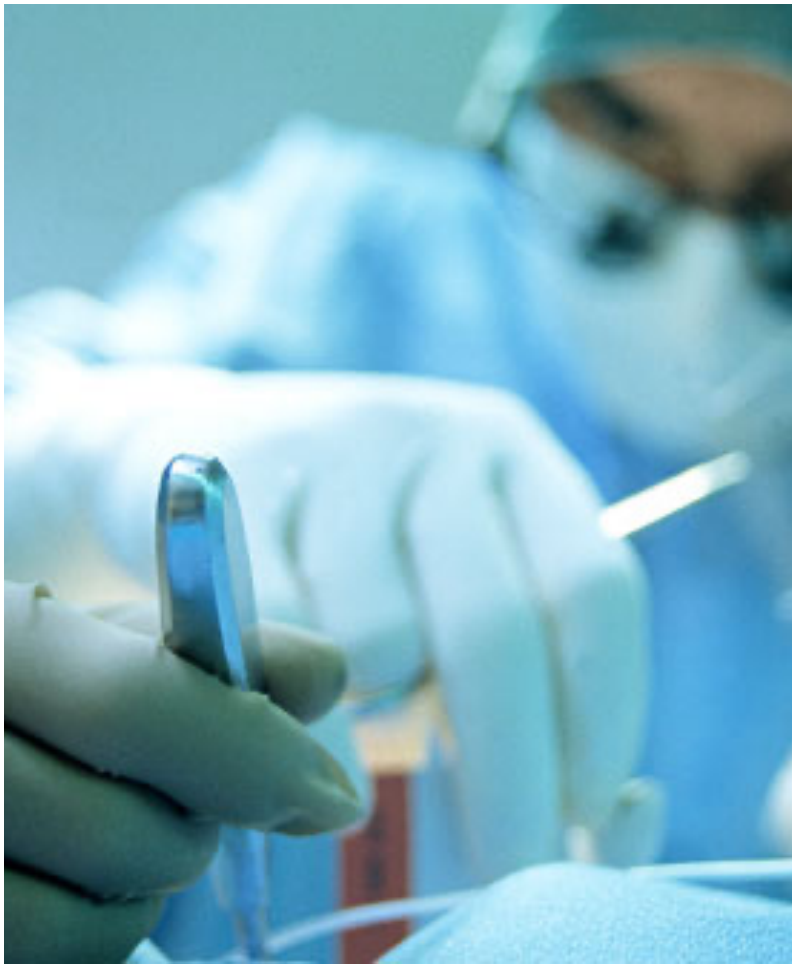
Treatment: VNS



- VNS stands for vagus nerve stimulation, a treatment that is sometimes called a "pacemaker for the brain." It uses a small surgically implanted device to send electrical pulses to the brain. The pulses travel via the vagus nerve, a large nerve in the neck. VNS is an option for people who don't do well with medication.

SURGICAL TREATMENT OF REFRACTORY EPILEPSY

- Approximately 20–30% of patients with epilepsy are resistant to medical therapy despite efforts to find an effective combination of antiepileptic drugs. For some, surgery can be extremely effective in substantially reducing seizure frequency and even providing complete seizure control. Understanding the potential value of surgery is especially important when, at the time of diagnosis, a patient has an epilepsy syndrome that is considered likely to be drug-resistant.



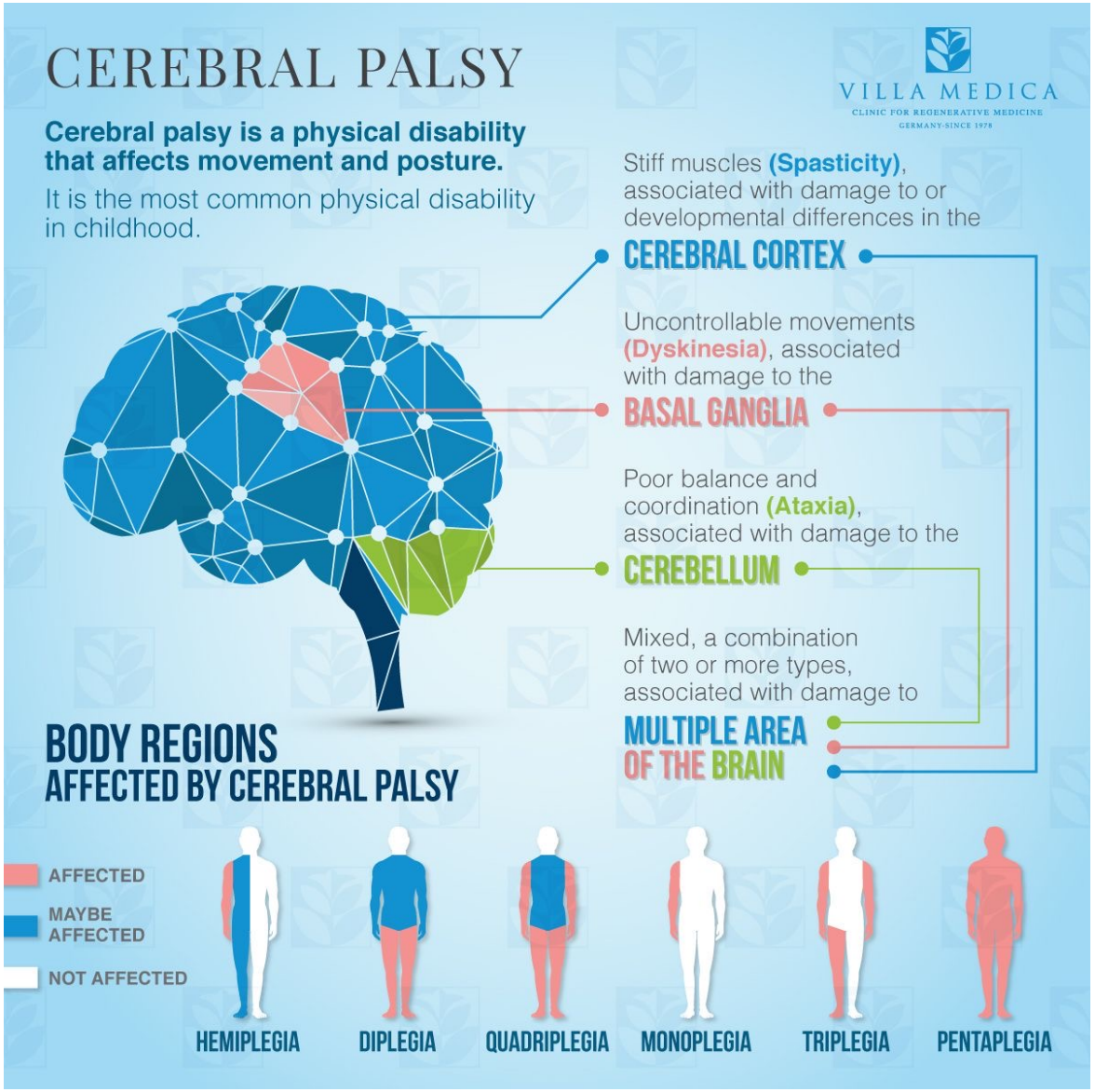
CEREBRAL PALSY

Mihail Iosif GAVRILIUC

Definition

„Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy and by secondary musculoskeletal problems."

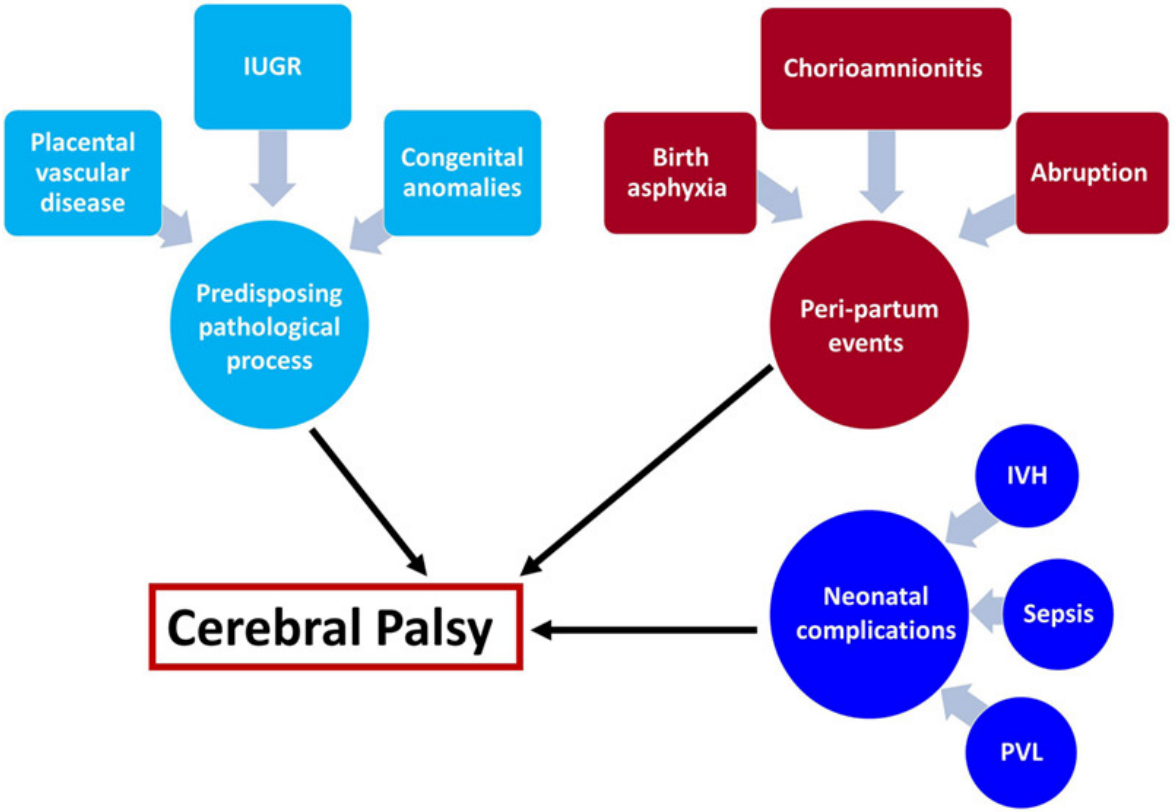
Rosenbaum et al, 2006: Definition and classification of CP.



Causes

- Cerebral palsy is due to abnormal development or damage occurring to the developing brain.
- This damage can occur during pregnancy, delivery, the first month of life, or less commonly in early childhood.

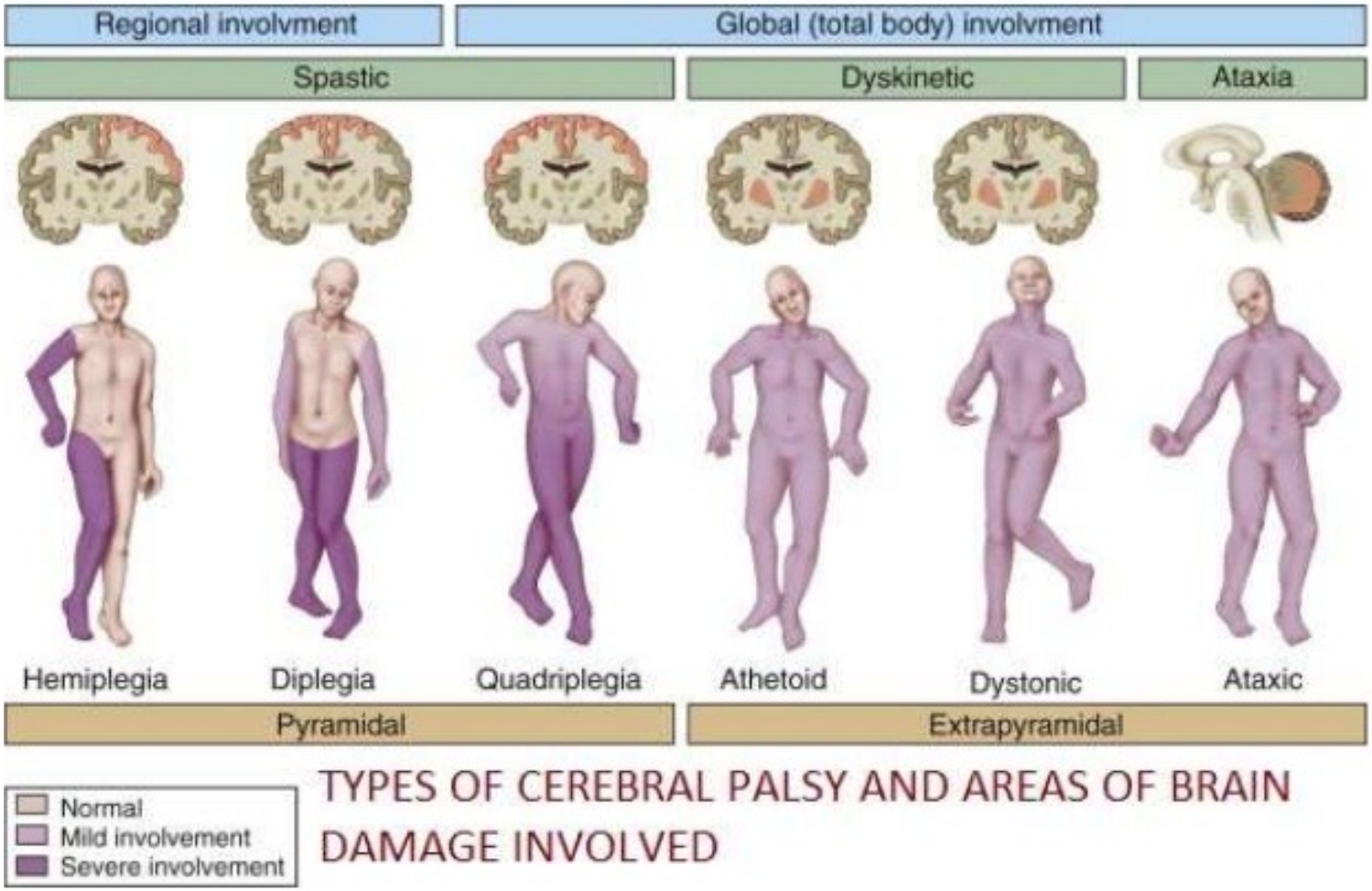
Typical causes include problems in intrauterine development (e.g. exposure to radiation, infection, fetal growth restriction), hypoxia of the brain (thrombotic events, placental conditions), birth trauma during labor and delivery, and complications around birth or during childhood.



IUGR – intrauterine growth restriction
IVH – intraventricular hemorrhage
PVL – periventricular leukomalacia

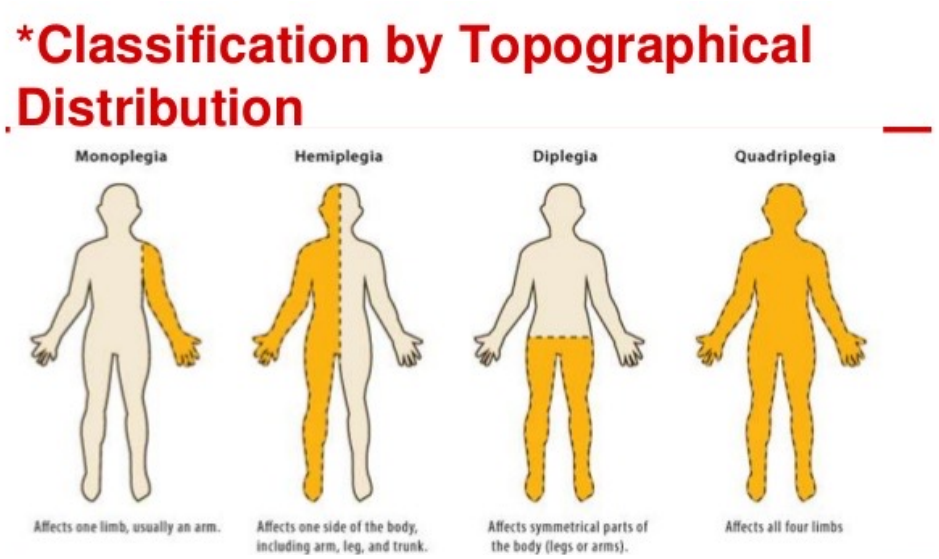
Classification

There are three main CP classifications by motor impairment: spastic, ataxic, and athetoid/dyskinetic. Additionally, there is a mixed type that shows a combination of features of the other types. These classifications reflect the areas of the brain that are damaged.



Spastic cerebral palsy

- Spastic CP is the most common type of overall cerebral palsy, representing about 80% of cases.
  - spastic monoplegia,
  - spastic hemiplegia,
  - spastic diplegia, and
  - spastic quadriplegia.



Ataxic cerebral palsy

- Ataxic cerebral palsy is observed in approximately 5-10% of all cases of cerebral palsy, making it the least frequent form of cerebral palsy.

- patients with ataxic cerebral palsy experience problems in coordination, specifically in their arms, legs, and trunk; ataxic cerebral palsy is known to decrease muscle tone.

- the most common manifestation of ataxic cerebral palsy is intention (action) tremor.

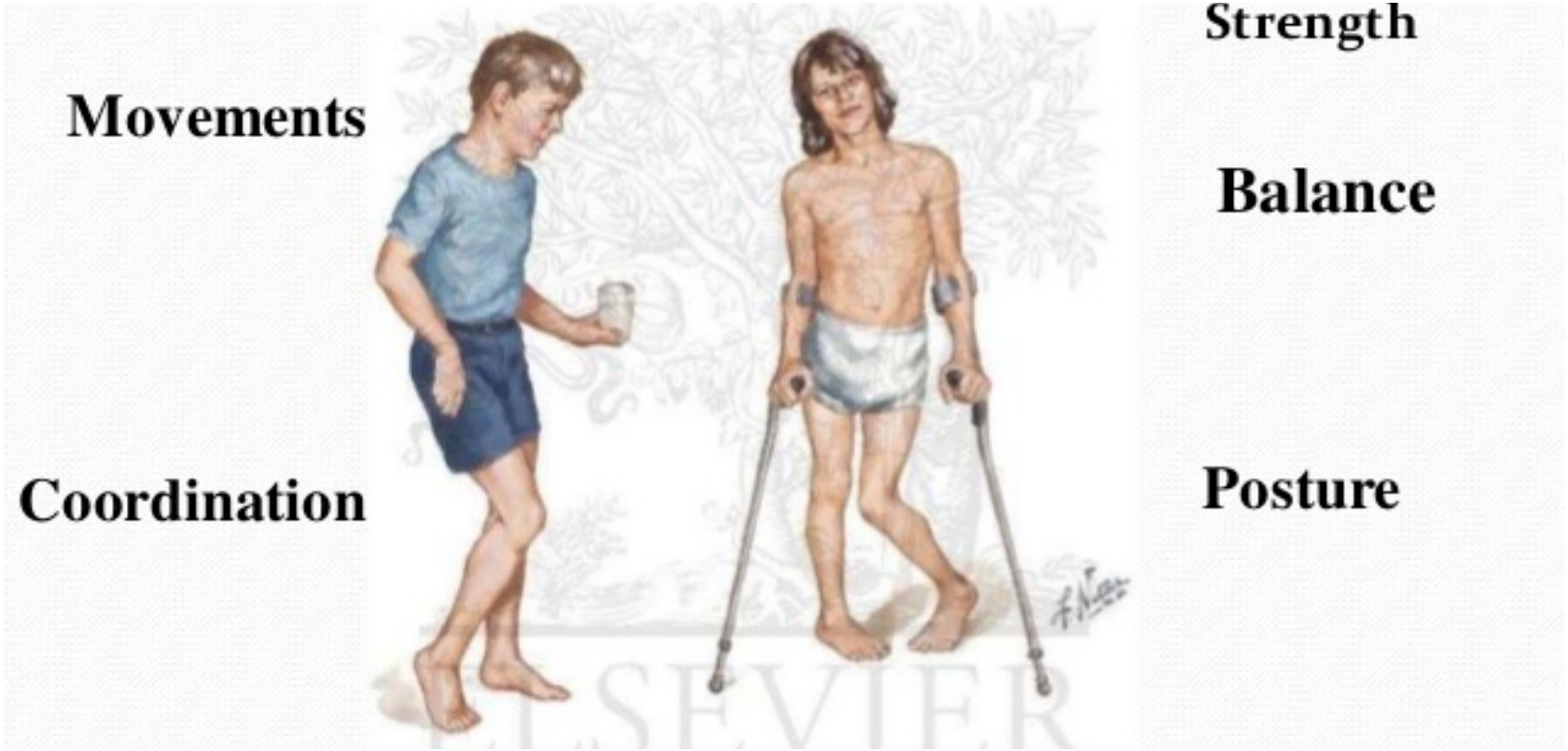
Athetoid cerebral palsy

- Athetoid cerebral palsy or dyskinetic cerebral palsy is primarily associated with damage to the basal ganglia and the substantia nigra in the form of lesions that occur during brain development due to bilirubin encephalopathy and hypoxic-ischemic brain injury.

  - choreoathetoid,
  - dystonic.

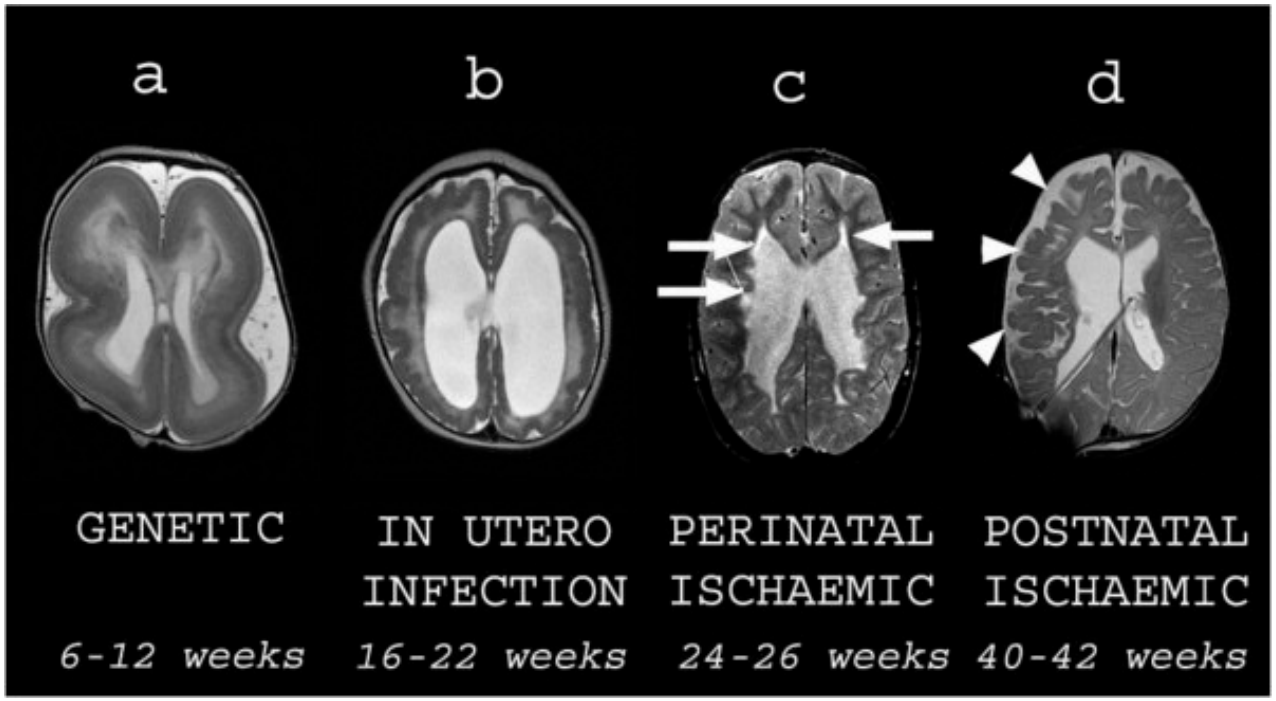
Mixed cerebral palsy

- Mixed cerebral palsy has symptoms of athetoid, ataxic and spastic CP appearing simultaneously, each to varying degrees, and both with and without symptoms of each.



Diagnosis of cerebral palsy

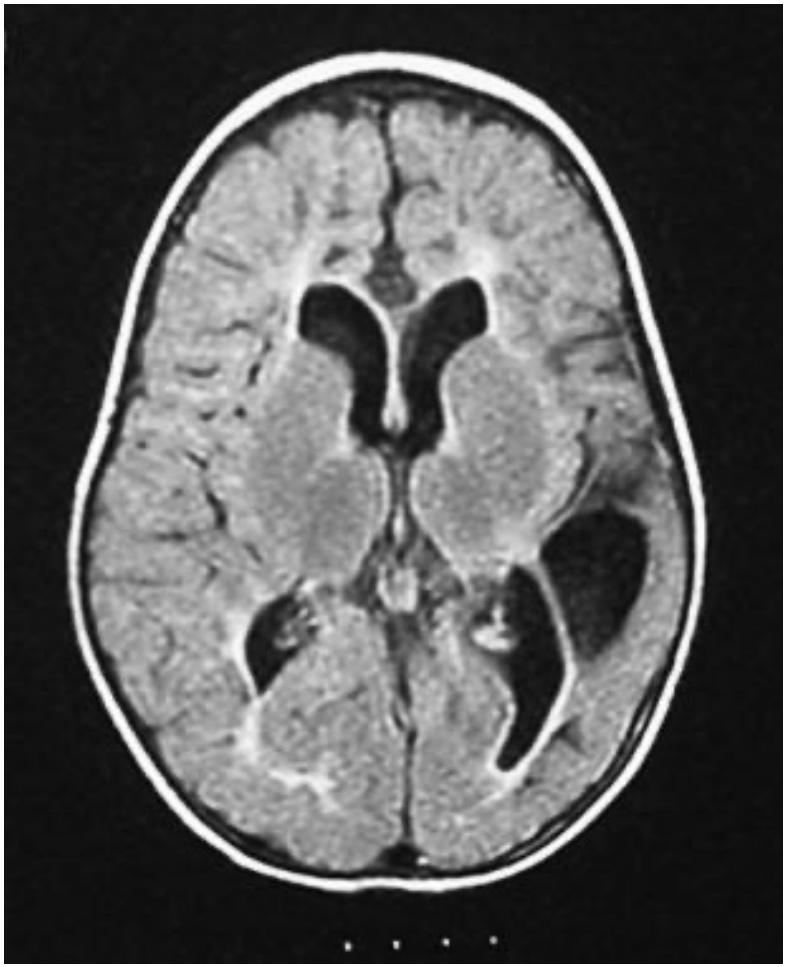
- The diagnosis of cerebral palsy is based on the person's history and physical examination.
- Neuroimaging with CT or MRI is warranted when the cause of a person's cerebral palsy has not been established.



Diagnosis of cerebral palsy

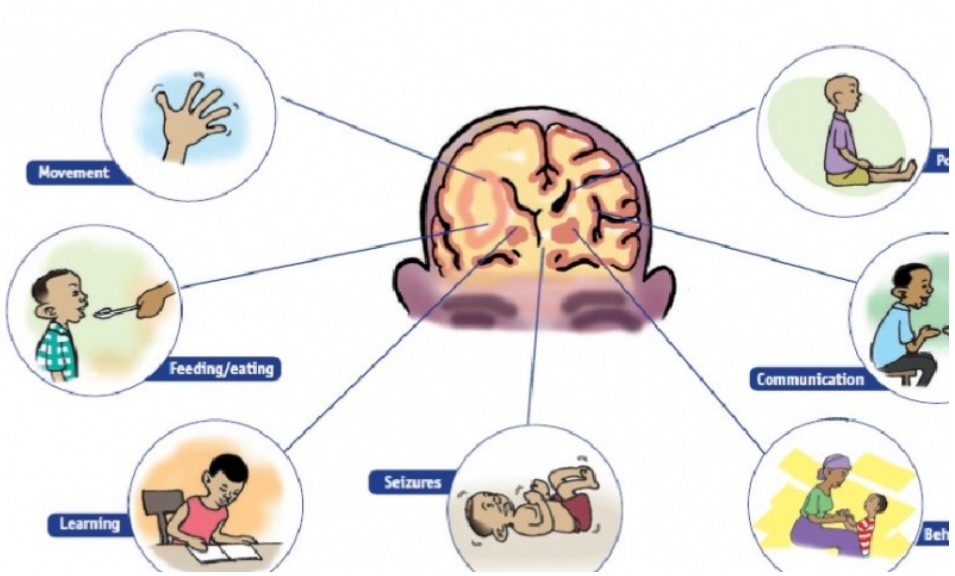
MRI of a 16-month-old boy who was born at term but had an anoxic event at delivery. Examination findings were consistent with a spastic quadriplegic cerebral palsy with asymmetry (more prominent right-sided deficits).

Cystic encephalomalacia in the left temporal and parietal regions, delayed myelination, decreased white matter volume, and enlarged ventricles can be seen in this image. These findings are most likely the sequelae of a neonatal insult (eg, periventricular leukomalacia with a superimposed left-sided cerebral infarct).



Management of cerebral palsy

- A multidisciplinary approach for cerebral palsy management is recommended, focusing on "maximizing individual function, choice and independence".
- The team may include a paediatrician, a health visitor, a social worker, a physiotherapist, a speech and language therapist, an occupational therapist, a teacher specialising in helping children with visual impairment, an educational psychologist, an orthopaedic surgeon, a neurologist and a neurosurgeon.



THE END
QUESTIONS ???