Basic Mechanism of Epilepsy

- Focal seizure activity:

- can begin in a very discrete region of cortex and then spread to neighboring regions, i.e.,

- there is a seizure initiation phase and a seizure propagation phase.

- The initiation phase is characterized by two concurrent events in an aggregate of neurons: (1) high-frequency bursts of action potentials (which involve influx of extracellular Ca^{++} & Na^{+}) and (2) hypersynchronization.

- Normally, the spread of bursting activity is prevented by intact hyperpolarization and a region of "surround" inhibition created by inhibitory neurons (inhibitory GABA play important role).

- With sufficient activation there is a recruitment of surrounding neurons via a number of synaptic and nonsynaptic mechanisms.

- There are many intrinsic & extrinsic factors control neuronal excitability.

- Origin of *absence epilepsy* me be related to oscillatory rhythms normally generated only during sleep by circuits connecting the thalamus and cortex.
- Origin of *other idiopathic generalized epilepsies* is less clear.

Mechanism of Anti-epileptic Drugs:

- anti-epileptic drugs appear to act primarily by blocking the initiation or spread of seizures. The mechanisms include:

- inhibition of Na+-dependent action potentials (e.g., phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide),

- inhibition of voltage-gated Ca2+ channels (phenytoin, gabapentin, pregabalin),

- attenuation of exitatory glutamate activity (lamotrigine, topiramate, felbamate),

- potentiation of inhibitory GABA receptor function (benzodiazepines and barbiturates),

- increase in the availability of GABA (valproic acid, gabapentin, tiagabine),

- modulation of release of synaptic vesicles (levetiracetam).

- The two most effective drugs for absence seizures, ethosuximide and valproic acid, probably act by inhibiting T-type Ca2+ channels in thalamic neurons.

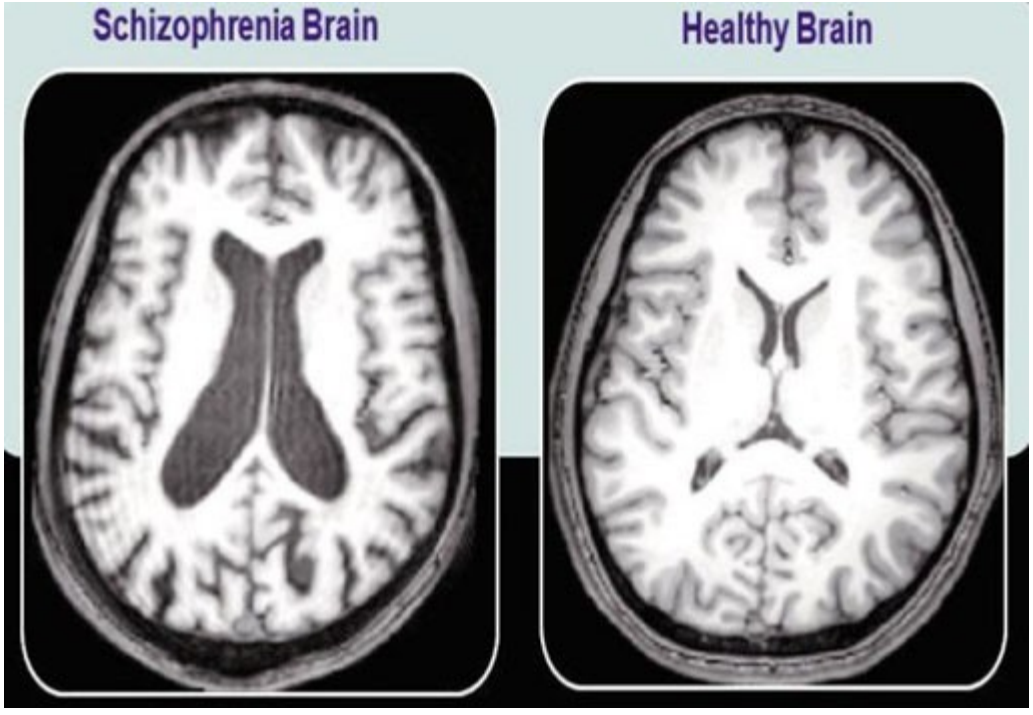
Differential diagnosis of epilepsy:

- Syncope
- Psychological causes:

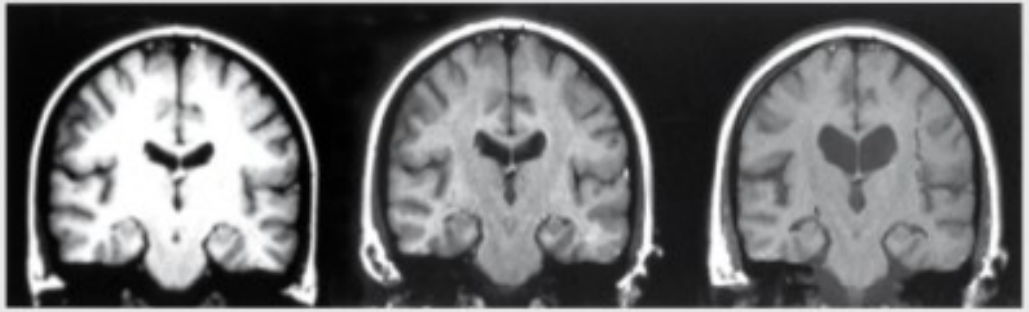
- conversion disorders (pseudo fits): no injury to self, no tongue biting, no cyanosis, no sphincter disturbances, always in-front of others, tend to full on others, longer duration of attack, no post-ictal state, patient continue listening but can not replay, existence of primary & secondary gains, positive psychiatric history & psychological tension.

- 1/3 of temporal lobe epileptics are schizophrenics & 1/3 of schizophrenics are temporal lobe epileptics (common effection on temporal lobes)

- Frontal lobe epilepsy should considered in any case of atypical psychosis.


Schizophrenia Brain
Healthy Brain

10-year MRI follow-up
34-year-old female with chronic schizophrenia



Feb. 1990
1st episode

Feb. 1995
5 years later

Jan. 2000
10 years later

- Metabolic disturbances: alcoholic blackouts, delirium tremens, hypoglycemia, hypoxia.
- Psychoactive drugs (e.g., hallucinogens).
- Migraine with aura (focal epilepsy): spreading of aura over 10 – 25 minutes.
- T.I.A (usually loss of functions)
- Sleep disorders: narcolepsy/cataplexy (atonic epilepsy), benign sleep myoclonus (JME), night terrors (frontal lobe epilepsy), sleep walking (TLE)
- Other movement disorders (never occur during sleep): tics, nonepileptic myoclonus, paroxysmal choreo-athetosis

Investigations

- Serum glucose & electrolytes like calcium, magnesium.
- hepatic & renal function tests.
- Blood and urine for toxicology should also be obtained from all patients in appropriate risk groups, especially when no clear precipitating factor has been identified.
- Full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Chest X-ray
- Serology for syphilis, HIV, collagen disease
- A lumbar puncture is indicated if there is any suspicion of meningitis or encephalitis, and it is mandatory in all patients infected with HIV, even in the absence of symptoms or signs suggesting infection.

- EEG studies:

- Up to 15% of non-epileptics have epileptic EEG, while 4% of epileptics have persistently normal EEG (good prognosis)

- So EEG not diagnostic test, & normal EEG does not exclude diagnosis of epilepsy.

- Show epileptic discharges in the form of spikes, sharp waves, polyspikes-wave complexes, slow waves, phase reversal.

- These could be focal or multi-focal or generalized; symmetrical or asymmetrical, depending on type of epilepsy.

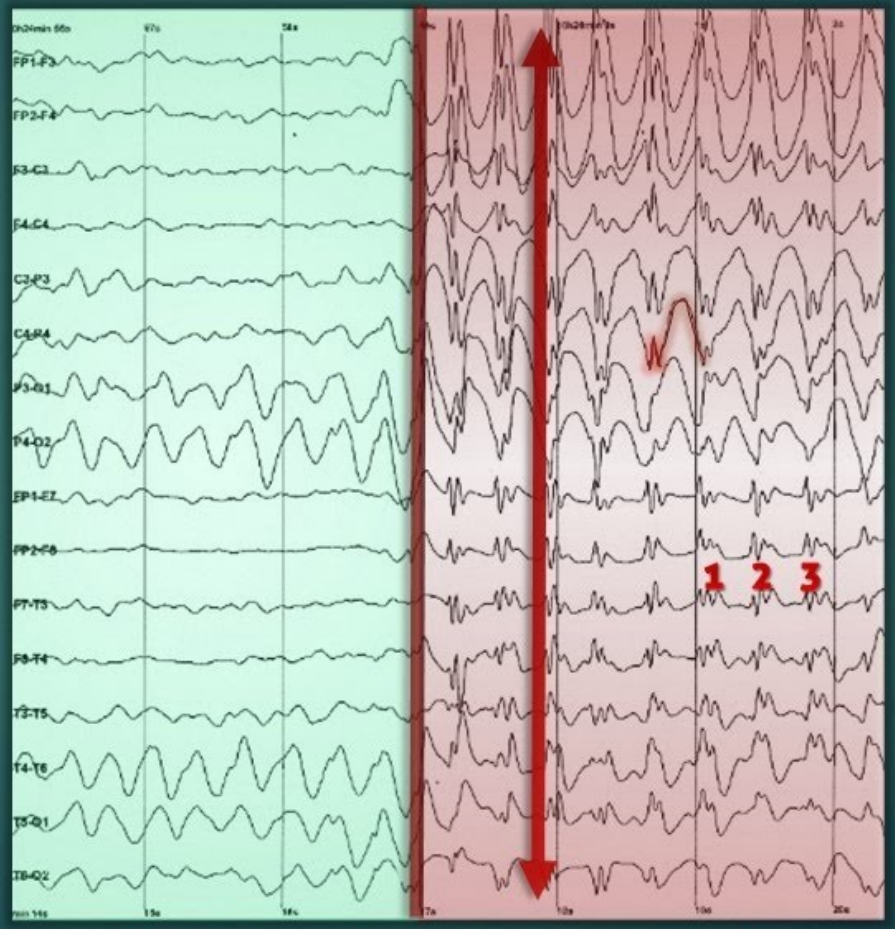
- 3 Hz generalized spike-wave complexes symmetrical discharge is diagnostic for *typical absence* epilepsy *providing clinically relevant*.

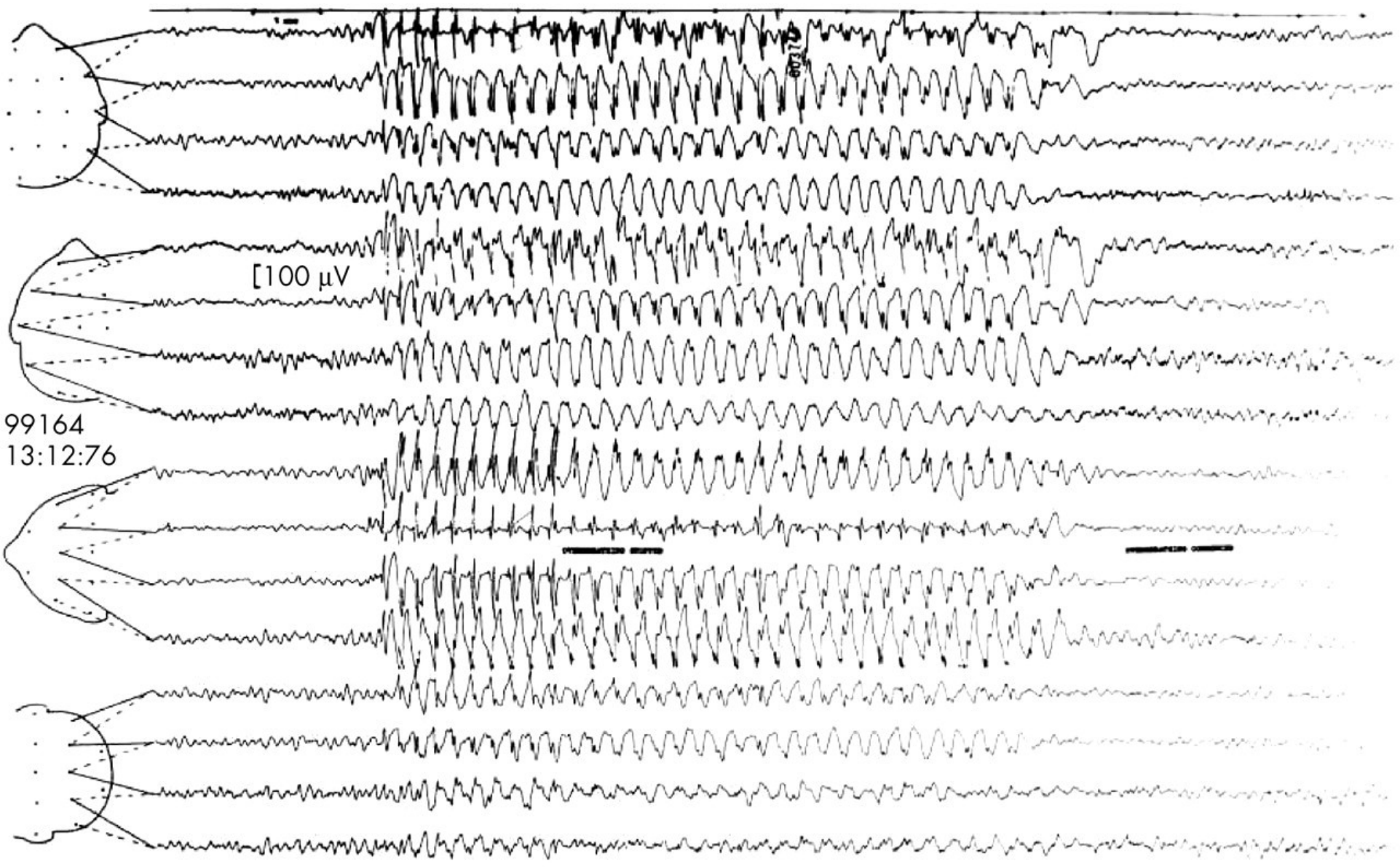
- Video monitoring & sleep EEG is useful for frontal lobe type of complex partial epilepsy.

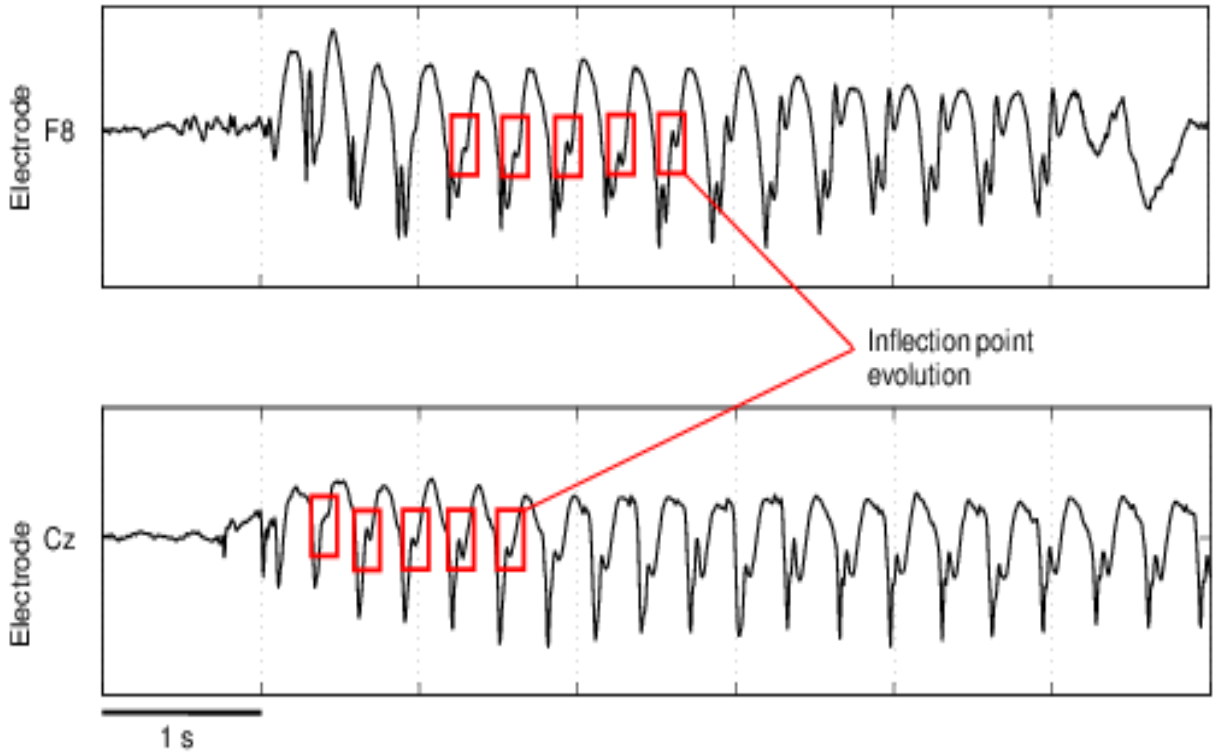
Absence Seizures

Generalized 3 Hz Spike-and-Wave Complexes

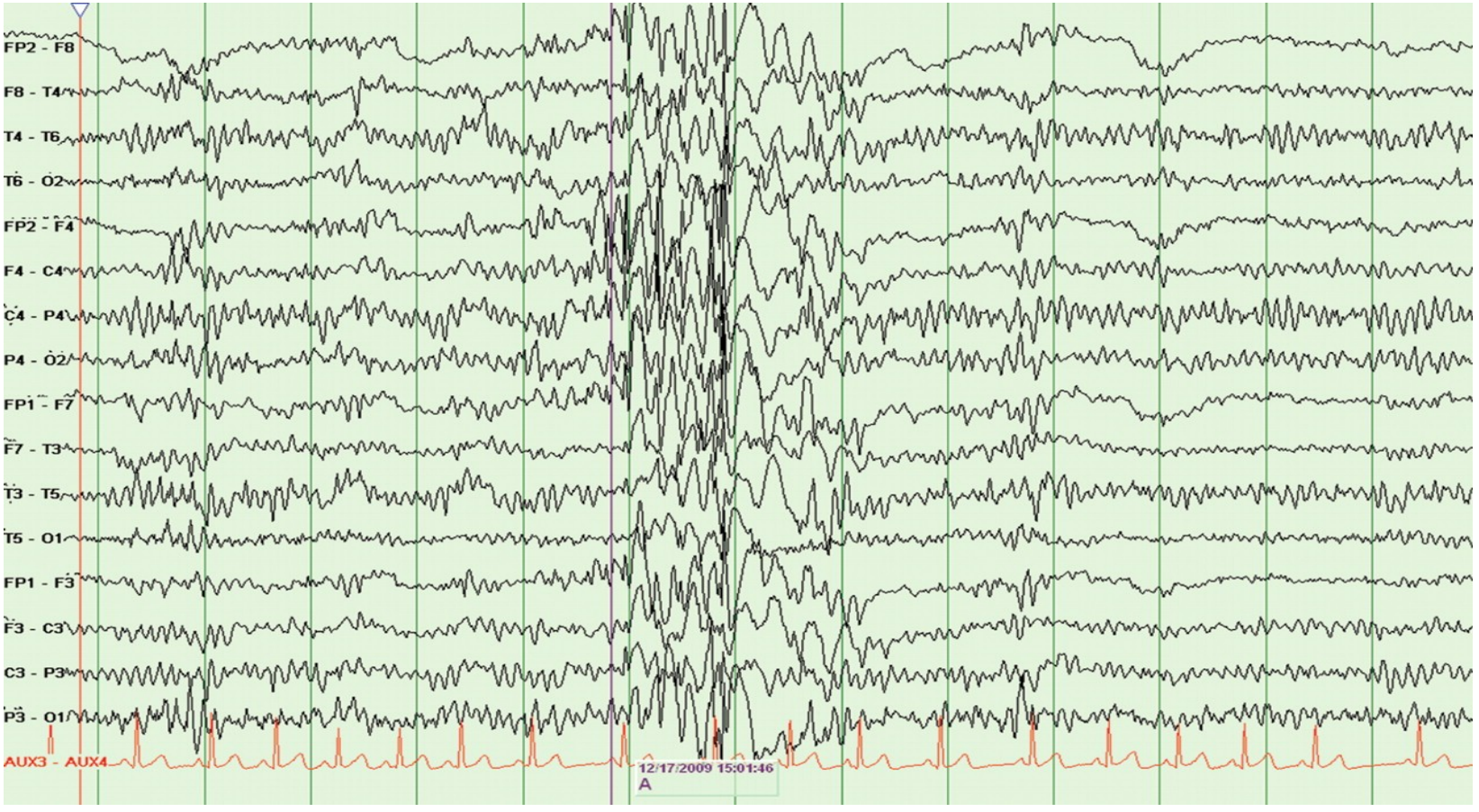
- Sudden Onset
- Generalized
- Spike and Wave Complexes
- Three per second



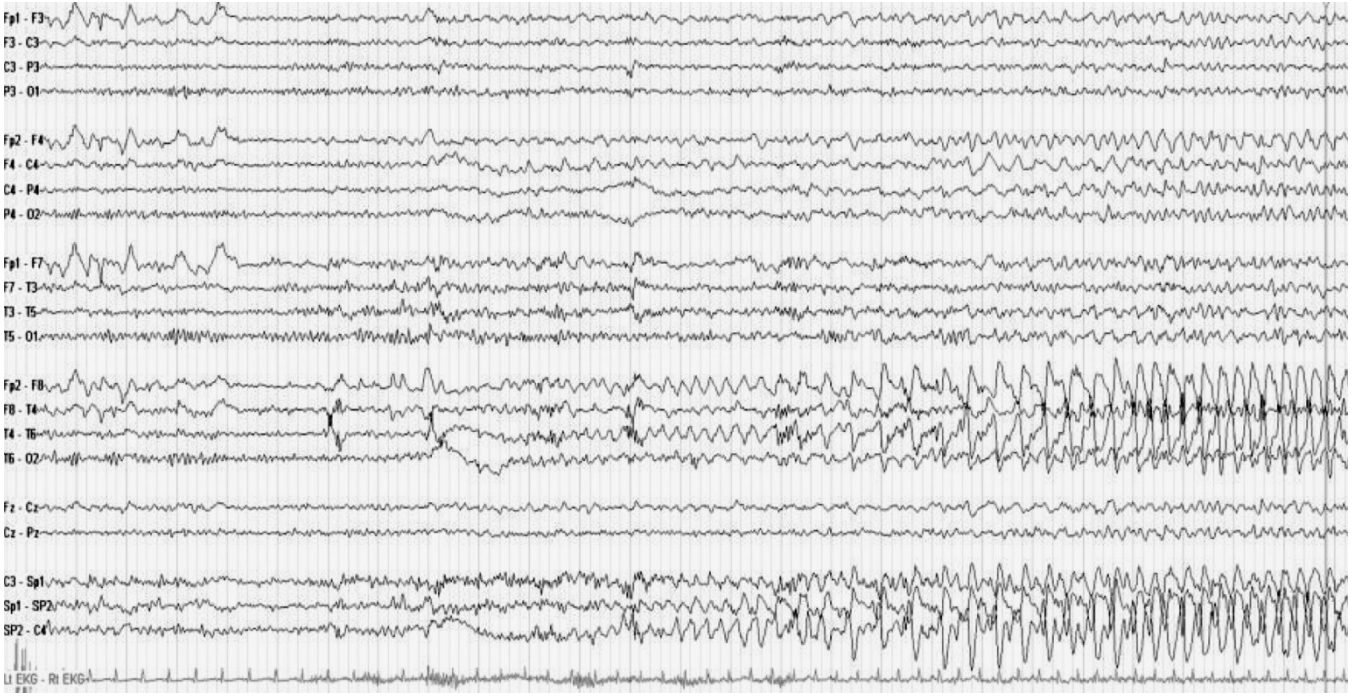

[100 µV
99164
13:12:76


Electrode
F8
Inflection point
evolution
Electrode
Cz
1 s

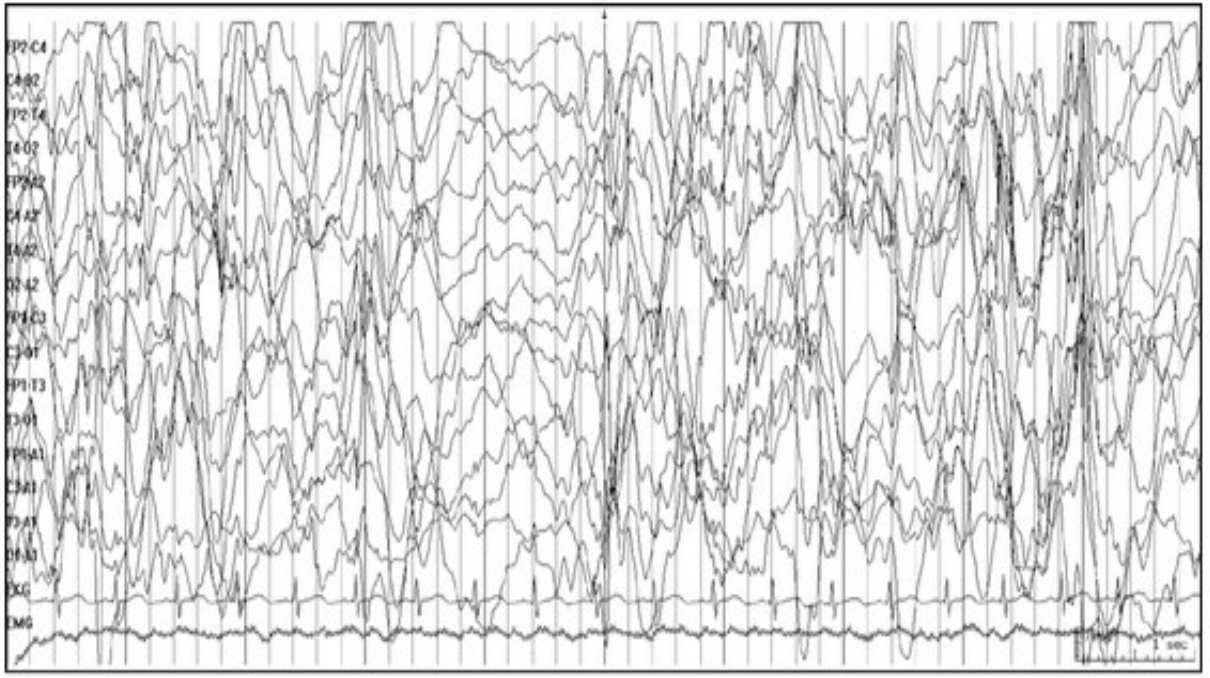
Juvenile myoclonic epilepsy



Temporal lobe epilepsy



Hyps-arrhythmia



Timebase = 30 mm/s; sensitivity = 7 μV/mm; high cut = 70 Hz and low cut = 1 Hz

- CT brain scan & MRI of brain:

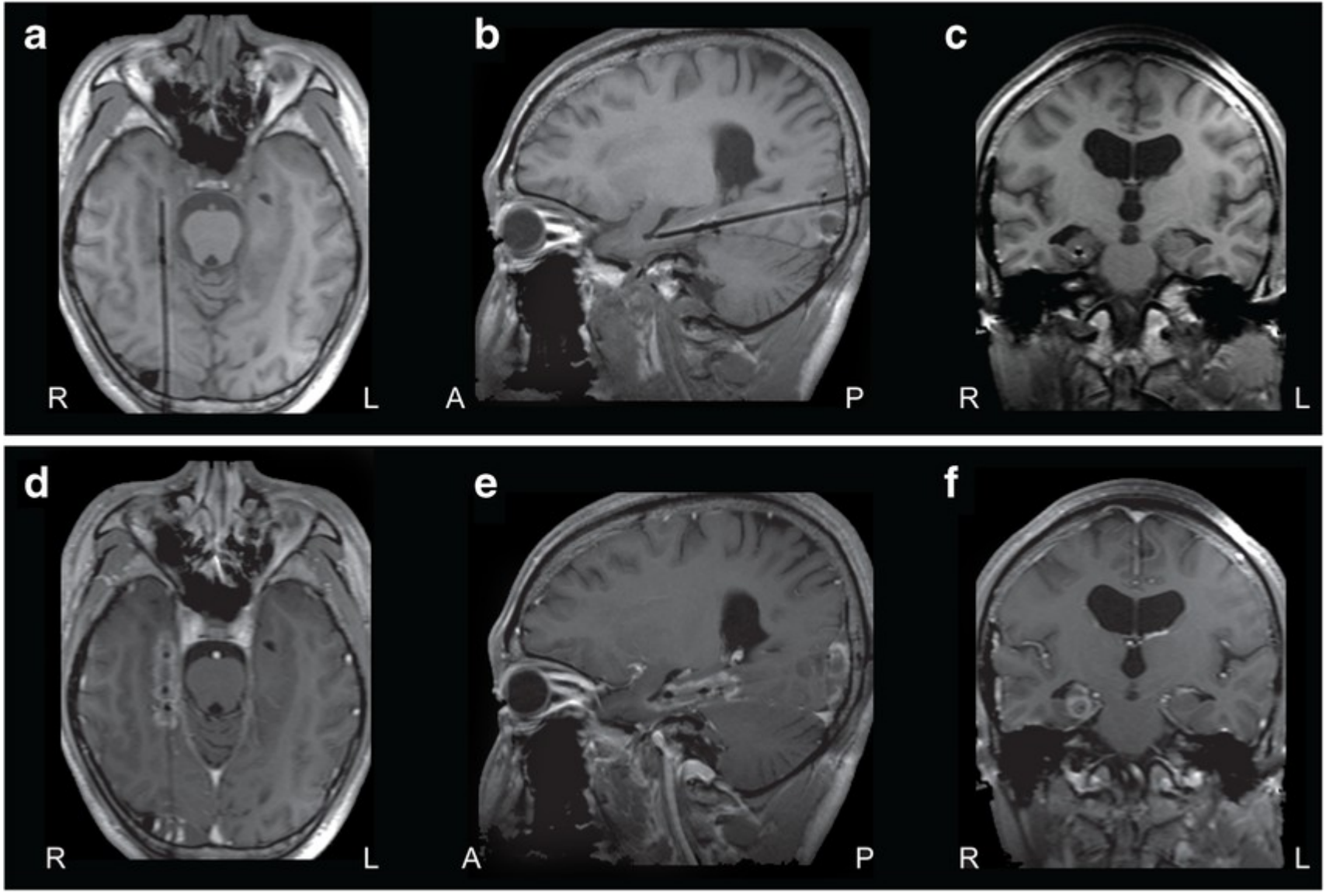
- Almost all patients with new-onset seizures should have a brain imaging study to determine whether there is an underlying structural abnormality that is responsible.

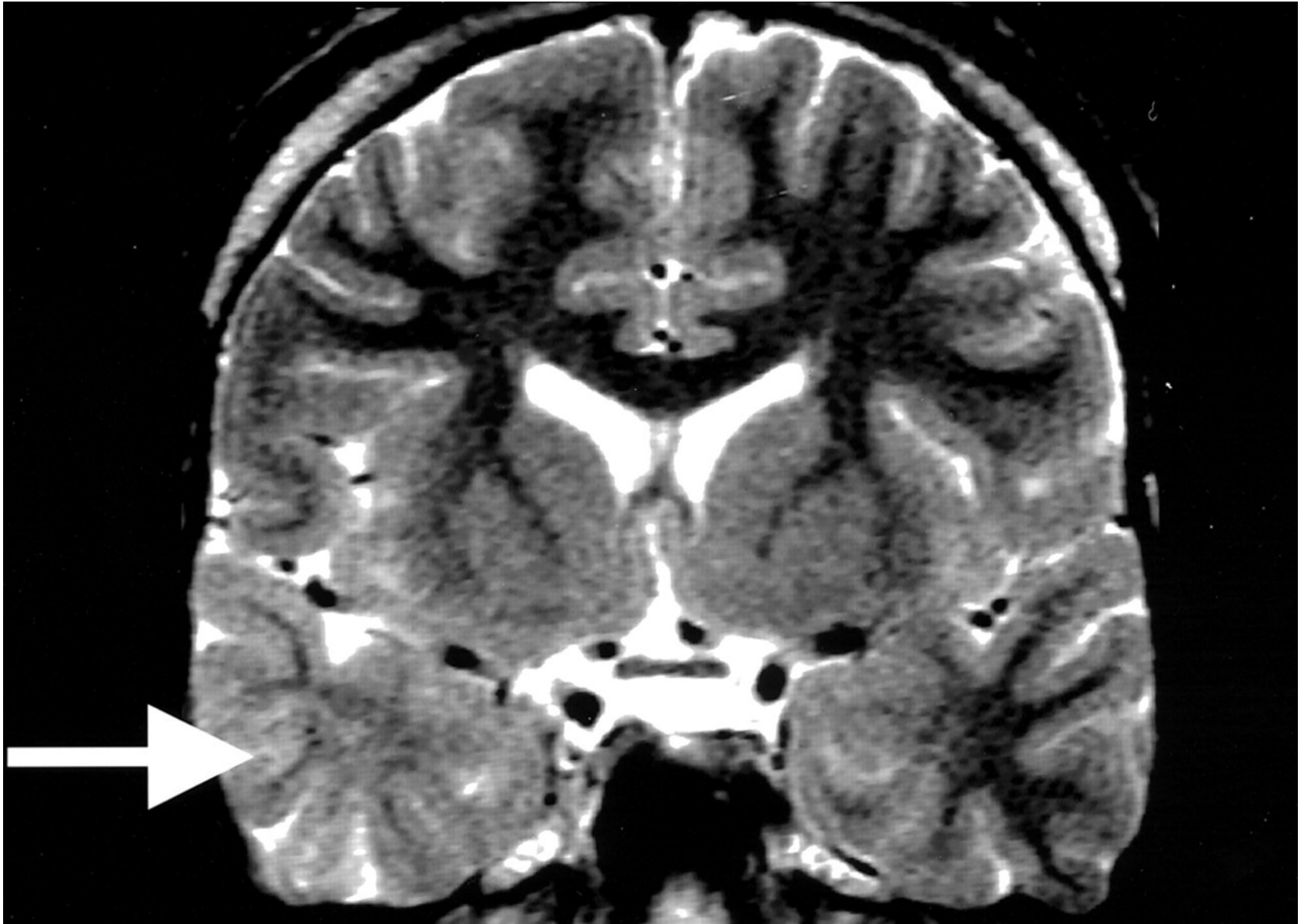
- The only potential exception to this rule is children who have an unambiguous history and examination suggestive of a benign, generalized seizure disorder such as absence epilepsy.

- Brain MRI *(with thin slides & coronal sections)* has been shown to be superior to CT for the detection of cerebral *cortical* lesions associated with epilepsy.

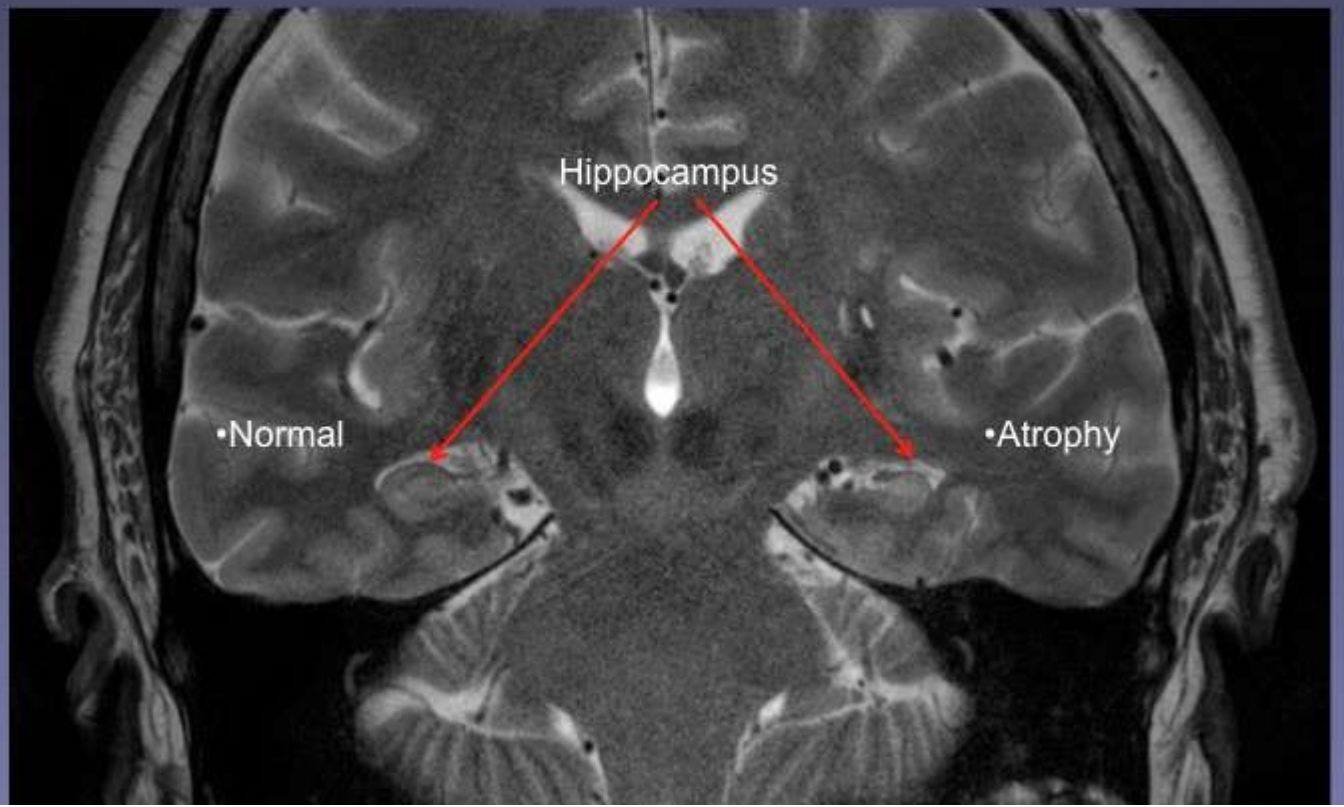
- In some cases MRI will identify lesions such temporal lobe sclerosis. Also, can detects tumors, abscess, vascular malformations, or other pathologies that need immediate therapy.

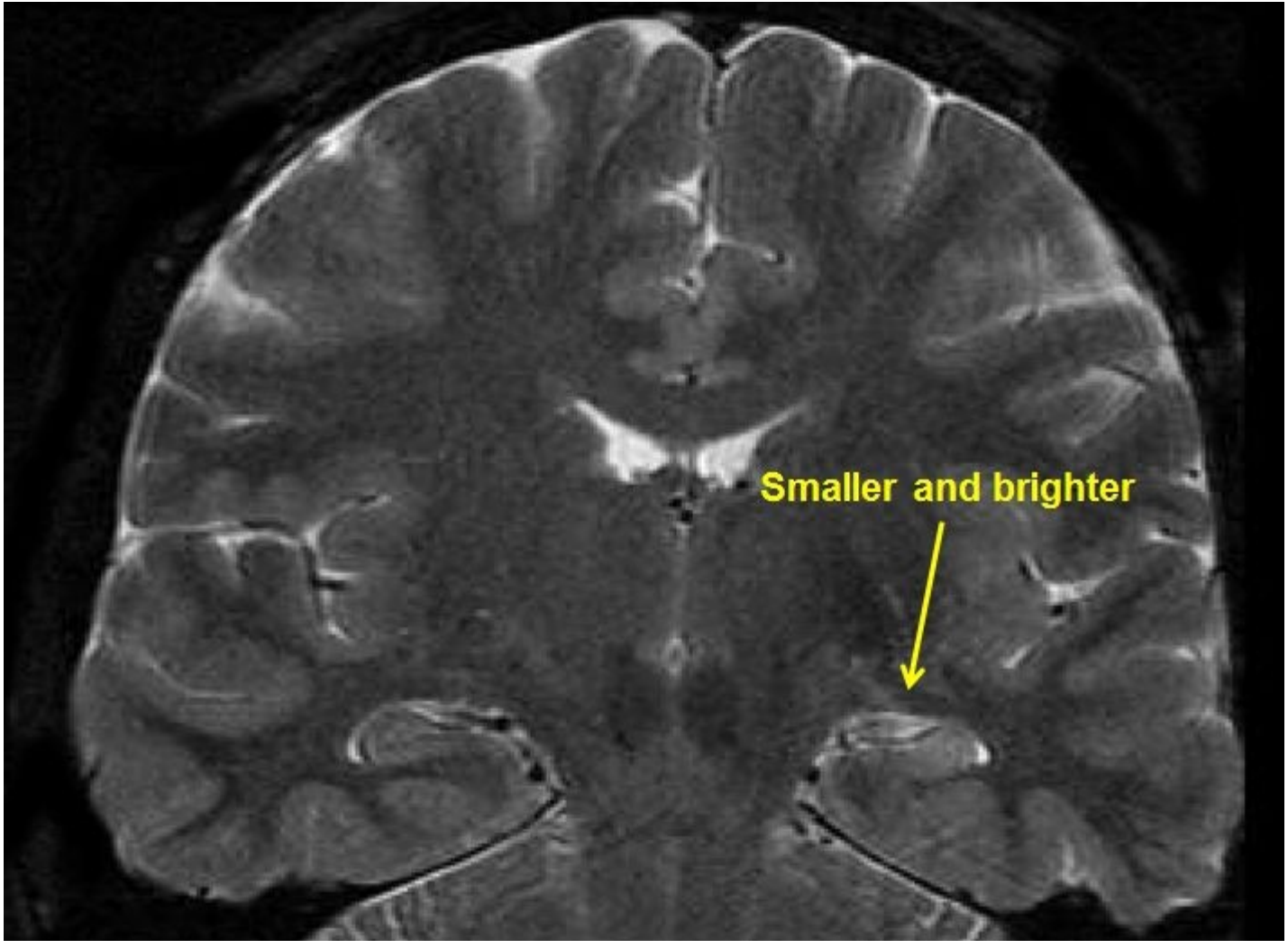
- Brain image should repeated in well controlled epileptic who show recent unexplained deterioration, even if previous one was normal.

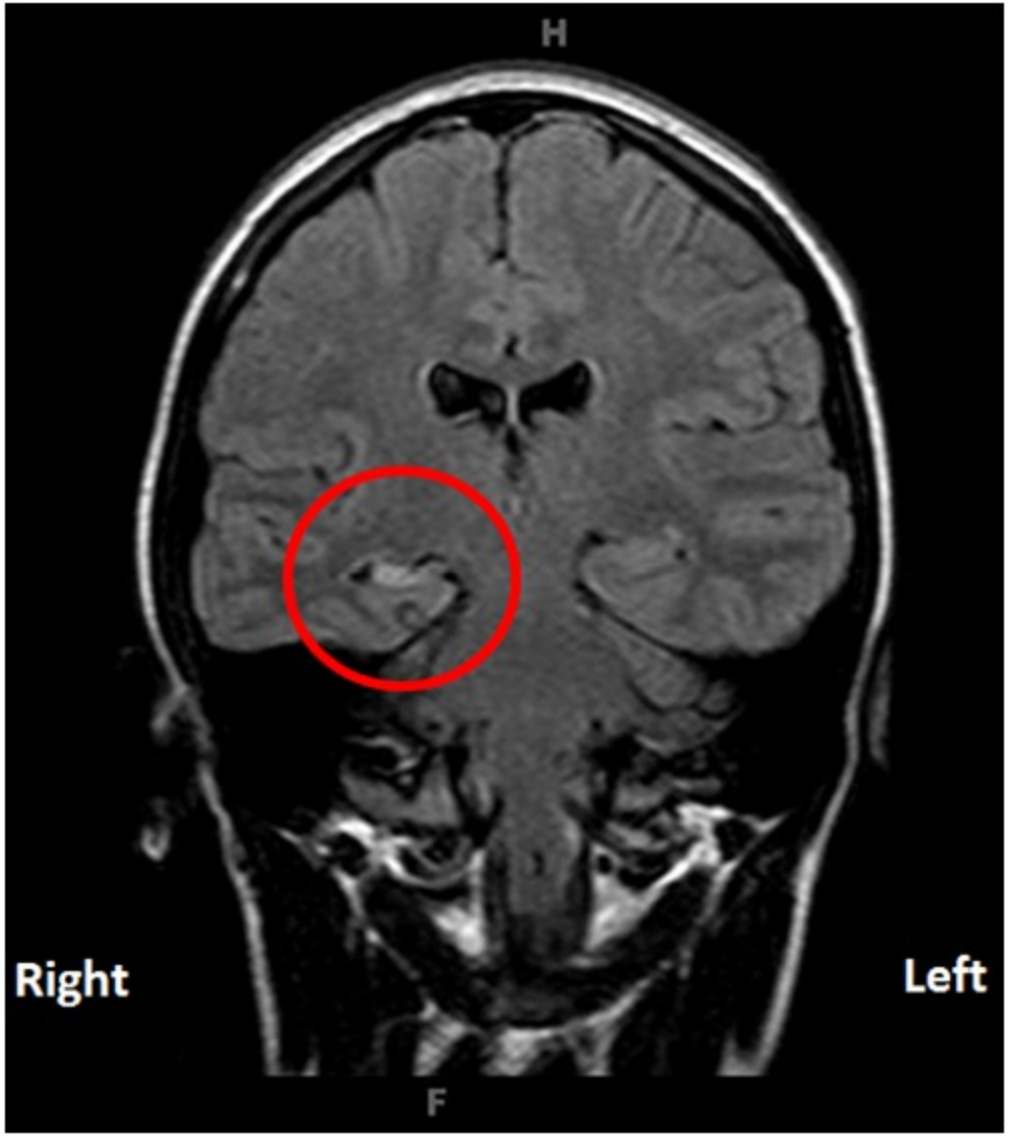

a
R
L
b
A
P
c
R
L
d
R
L
e
A
P
f
R
L



Temporal Lobe Epilepsy: An Acquired form of Epilepsy in adults caused by Hippocampal Sclerosis




Smaller and brighter


H
Right
Left
F

Treatment of epilepsy

- Immediate management of seizures

- Ensure airway is patent. Put patient in lateral decubitus position to prevent aspiration.

- Get patient away from dangerous things & sites

- Do not put something inside patient mouth in the aim to prevent tongue biting because you may injures heir/his teeth (irreversible)

- Give oxygen to overcome cerebral hypoxia

- Give intravenous anticonvulsant (e.g. diazepam 10 mg) ONLY if convulsions are continuous or repeated (if so, manage as for status epilepticus)

- Take blood for anti-epileptic levels (if patient is known epileptic)

- Try to investigate cause & treat it if correctable

Drug treatment of epilepsy

- Try to use smallest therapeutic possible dose
- Aim should targeted to achieve clinical rather than EEG control
- Try to limit treatment to single drug whenever it is possible
- In about 1/3 of epileptics, initial drug failed at maximum dose. Here we should consider switch to 2nd drug while 1st drug at it's therapeutic level, then when 2nd drug being at therapeutic level discontinue 1st drug gradually. 2nd drug should tried as monotherapy, before considering drug combinations.

Selection of suitable anti-epileptic drug:

- If selection was wrong, but patient respond well, then NEVER change drug.
- *1st line treatment for focal epilepsy with or without secondary generalization are:*

- Phenytoin 300 – 400 mg/day in single dose

- Carbamazepine 400 – 1600 mg/day in 2 – 3 divided doses

- Oxcarbazepine 600 – 2400 mg/day in 2 divided doses

- Levetiracetam 1000 – 3000 mg/day in 2 divided doses

- Lamotrigine start 25 mg at bed time daily for 14 days then increased to 25 mg X 2 for further 14 days, then increased to 50 mg X 2. (100 – 700 mg/day)

- *2nd line drugs for focal epilepsy with or without secondary generalization:*

- Topiramate start 25 mg at night daily for 14 days then increased to 25 mg X 2. If no response, increased by 25 - 50 mg every 14 days, up to 400 mg

- Valproic acid 750 – 3000 mg/day in 2 – 3 divided doses

- Gabapentin 900 – 4800 mg/day in 2 - 3 divided doses

- Primidone 750 – 1000 mg/d in 2 – 3 divided doses

Idiopathic generalized tonic clonic:

- *1st line drugs are:*

- Valproic acid (S.E: tremor, weight gain, hair loss, hepatic dysfunction, thrombocytopenia)

- Lamotrigine (S.E: ataxia, diplopia, insomnia, skin rash, Stevens-Jonson syndrome)

- Topiramate (S.E: anxiety, depression, suicide, renal stones, glaucoma)

- *2nd line drugs are:*

- Phenytoin (S.E: diplopia, ataxia, hirsutism, polyneuropathy, osteoporosis, megaloblastic anemia, gingival hyperplasia, facial disfigurement)

- Carbamazepine [excreted from liver] (S.E: diplopia, ataxia, osteoporosis, hyponatremia, blood dyscrasia, hepatic dysfuction, irreversible importance & sperm deficiency)

- Oxcarbazepine [excreted from kidney] (no blood dyscrasia, no oteoporosis or sexual dysfuction)

- Phenobarbital (S.E: sedation, insomnia, diplopia, ataxia, dizziness, confusion, behavioral disturbances, decrease libido, skin rash)

- Primidone (S.E: same of Phenobarbital apart from skin rash)

Typical Absence

- 1st line:

- Valproic acid

- Ethosuximide 15 – 40 mg/kg/day in 2 – 3 divided doses (S.E: ataxia, gastric upset, blood dyscrasia, skin rash, headache)

- 2nd line:

- Lamotrigine

- Clonazepam 1.5 – 8 mg/day in 2 – 3 divided doses (S.E: sedation, ataxia, diplopia, behavioral disturbances, hyper-salivation)

Myoclonic epilepsy

- *1st line:*

- Valproic acid
- Lamotrigine (occasionally cause deterioration)
- Topiramate

- *2nd line:*

- Clonazepam
- Felbamate

- Valproic acid & Carbamazepine need periodic – 6 monthly – follow up by:

- complete blood picture, &

- total serum bilerobin

- Periodic serum drug level monitoring is needed with most anti-epileptic drugs (Gabapentin & Pre-gabalin are not established)

Treatment of Status Epilepticus (S.E)

- The time point t_2 (30 minutes) should not considered in mind in treating major status epilepticus.
- Treatment of major S.E should started when:

1) any convulsion continue for 5 minutes (operational dimension 1 time "t_1") or more, or

2) when 2 succesive convulsions happened without regaining of normal consciousness in between them within 5 minutes

- This because, at this point; "t_1"; the likely-hood of continuation *[[or repetition without conscious recovery in between attacks]]* of convulsion for 30 minutes or more will be high, & such continuation associated with high probability of serious brain damage & life threatening complications.

- Ensure airway is patent, give oxygen to prevent cerebral hypoxia, and secure intravenous access
- Draw blood for glucose, urea and electrolytes (including Ca and Mg), and liver function, and store a sample for future analysis (e.g. drug misuse)
- Give diazepam 10 mg slow I.V. injection (or 0.2 mg/kg rectally) or lorazepam 4 mg I.V. - can be repeated once only after 10 - 15 minutes
- Transfer to intensive care area, monitoring neurological condition, blood pressure, respiration and blood gases, intubating and ventilating patient if appropriate

- You *must proceed* to I.V. infusion (with cardiac monitoring) with one of:

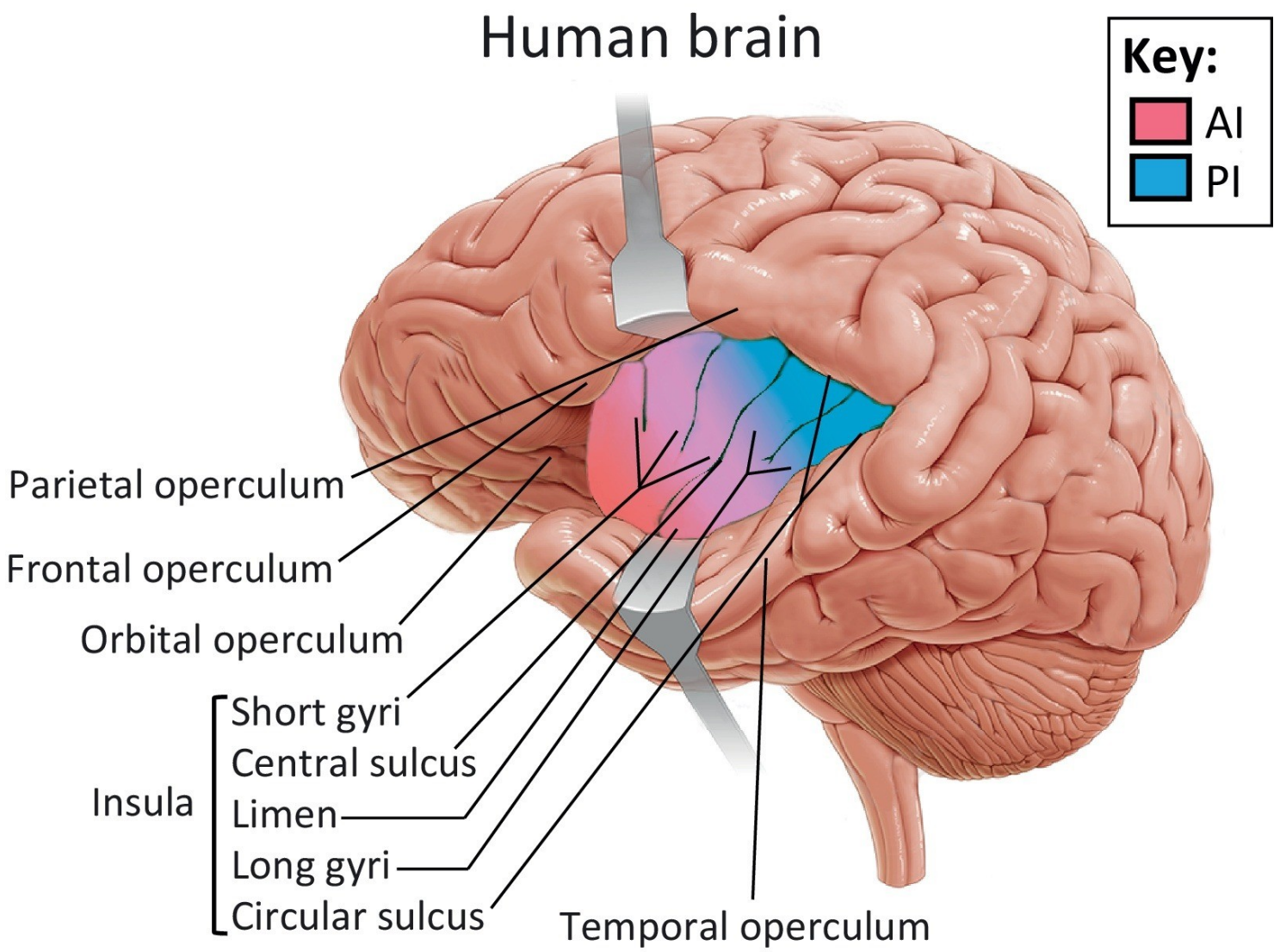
- Phenytoin: 20 mg/kg at 50 mg/min in N/S (never use G/W or G/S because drug will crystallized)

- Fosphenytoin: 20 mg/kg at 150 mg/min

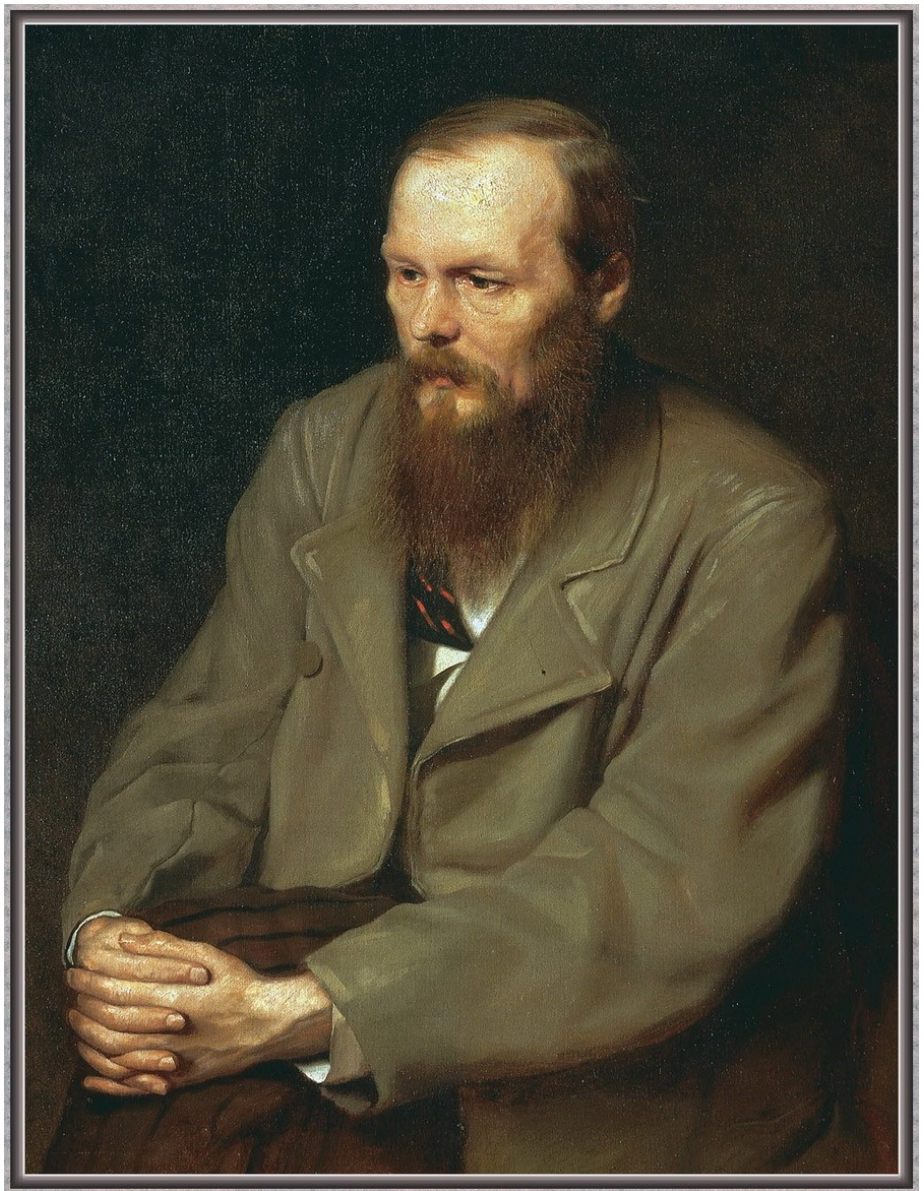
- If no response add additional 10 mg/kg of any of the above 2 drugs at same given rate of infusion
- If no response use Phenobarbital 20 mg/kg at 50 – 100 mg/min I.V infusion
- If no response then general anesthesia at induction stage using propofol or thiopental or pentobarbital or medazolam

Life style changes:

- Patient with temporal lobe epilepsy should avoid advanced (deep) philosophical readings (whether religious or atheistic) due to abnormal activation of insular structures (mythic area of brain) within defected temporal lobe.
- Avoid nocturnal jobs
- Avoid stressful jobs & situations
- Avoid jobs with dangerous machines that can cut patient if loss control
- No swimming at all
- Avoid sites when critical body balance is needed
- Driving not allowed until at least 1 year passed on drug treatment without any fit or fits exclusively happening during sleep only.
- Avoiding precipitating factors like fastening & flash lights.



Trends in Neurosciences



Drug discontinuation

- Providing the brain image of patient is normal (good prognosis), pharmacological treatment can be discontinued at lest 2 years after it's start if no fit happened during this period.
- However, if brain image is abnormal (bad prognosis), then drug discontinuation should not attempted unless after 5 years from start pharmacological treatment.
- Drug discontinuation must done gradually (over 3 weeks for example)
- E.E.G should done before discontinuation to assess % of success (if normal it is optimistic *but not absolute*), & final decision whether to discontinue drug or not is to the patient not to the doctor.

Woman & epilepsy:

- *Contraception:*

- Many anticonvulsant drugs, including carbamazepine, phenytoin, topiramate and barbiturates, induce hepatic enzymes and accelerate the metabolism of oestrogen, causing breakthrough bleeding and contraceptive failure.

- The safest policy is to use an alternative contraceptive method.

- sometimes it is possible to overcome the problem by giving a higher-dose preparation of oestrogen.

- Lamotrigine and oxcarbazepine have little interaction, and sodium valproate has no interaction with oral contraception.

- ***Pregnancy:***

- Anticonvulsent drugs associated with risks of fetal anomalies like cleft lip, spina bifida and cardiac defects, microcephaly, mental retardation, & increased risk of stillbirth & epilepsy in children born to epileptic woman.

- So, patient should consult heir neurologist 2 months before *planned* pregnancy so as to shift heir to a relatively safe anti-epileptic medication (Levetiracetam > Lamotrigine) over 1 month & insure enough dose over 2nd month. ***If patient become pregnant, you must never change heir anti-epileptic drug because risk on heir life & life of heir fetus will be more if undergo convulsion during switch process.*** Also, start folic acid 5 mg daily for 2 months before conception will reduce risk.

- They also increase risk of haemorrhagic disease of the newborn. So,give oral vitamin K 20 mg daily to the mother during last month. Give i.m. vitamin K 1 mg to the neonate at birth.

- Pregnancy by itself increases frequency of seizure due to decrease drugs plasma level as a result from enhanced drug metabolism.

-Status epilepticus during pregnancy should treated as described above (life threatening condition)

- *Lactation:*

anti-epileptic drugs excreted in breast milk in neglected small amount that bear no risk to feeding baby.

- *Catamenial epilepsy:*

- Some women show marked deterioration around time of menses.

- This due to either the effects of oestrogen and progesterone on neuronal excitability or changes in antiepileptic drug levels due to altered protein binding or metabolism.

- Some patients may benefit from increases in antiepileptic drug dosages during menses. Adding acetazole amide around & during time of menses is helpful.