

Epilepsy: The Basics

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Lecture Outline

- Definitions of seizures and
- What are seizures from a physiological viewpoint
- Epidemiology - How big of a problem is this?
- How do we classify seizures and epilepsy syndromes
- What do the different types of seizures look like
- How do we diagnose seizure disorders and epilepsy
- What are the causes
- How do we investigate for a cause
- What other conditions can be confused with seizures
- How do we treat seizures
- What is likelihood patients will comply
- How do we medically follow seizures
- What do we do when the patient does not respond
- Intractable Epilepsy
- Alternative therapies – ketogenic diet, VNS, Epilepsy Surgery
- First Aid for Seizures

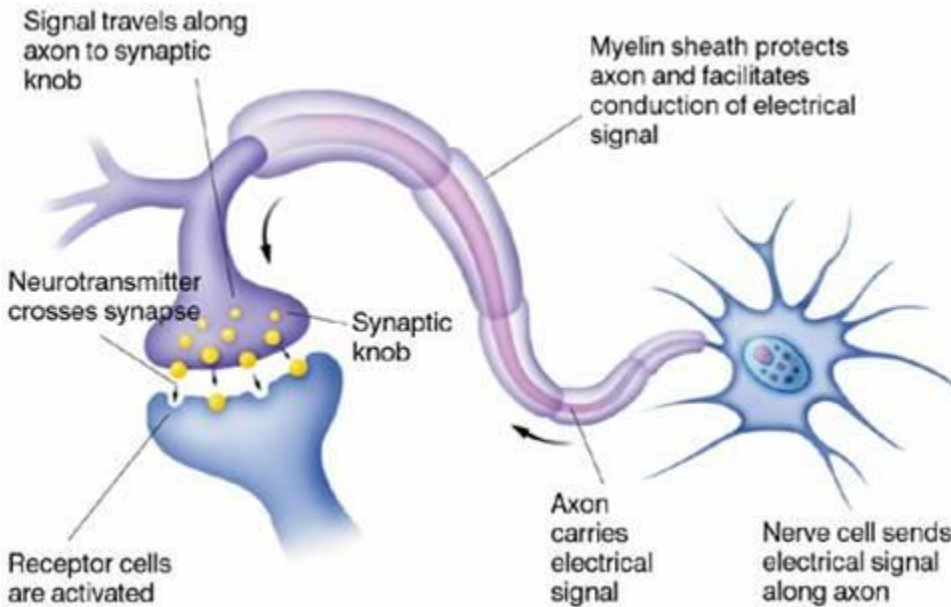
Some Definitions

- A **SEIZURE** is the clinical manifestation of abnormal, synchronous and excessive activity of a set of cortical neurons.
- We define **EPILEPSY** as recurrent, unprovoked seizures
- One definition of epilepsy is occurrence of multiple unprovoked seizures separated by more than 24 hours.
- **STATUS EPILEPTICUS** is defined as a seizure that goes on continuously for 30 minutes or multiple seizures that recur for > 30 minutes without regaining consciousness

What are Seizures Biologically?

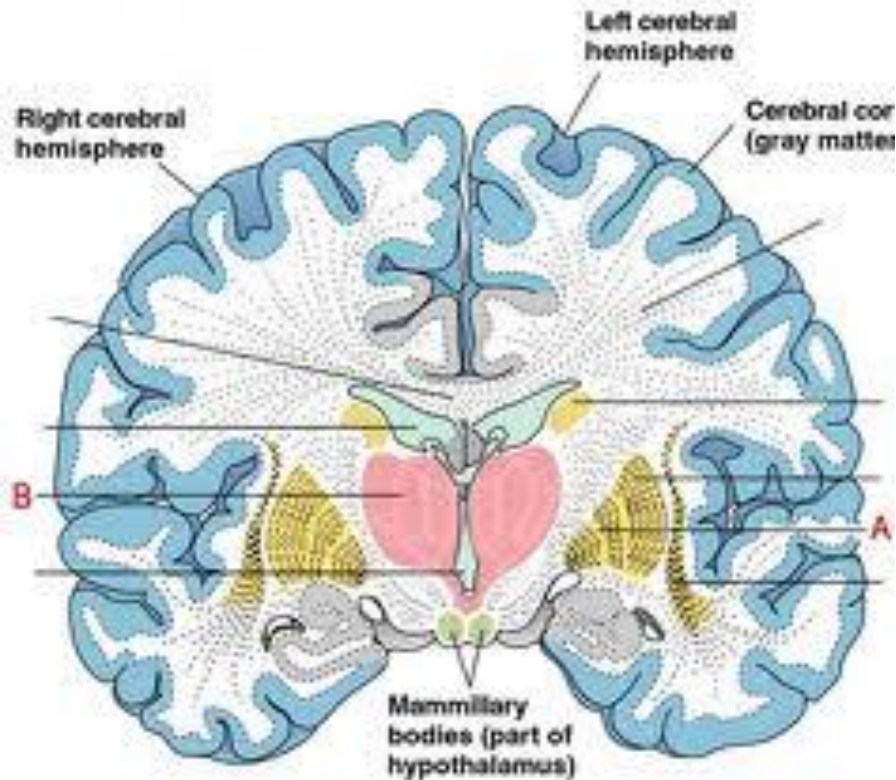
- Anyone can have a seizure under the right set of circumstances

Neurophysiology 101



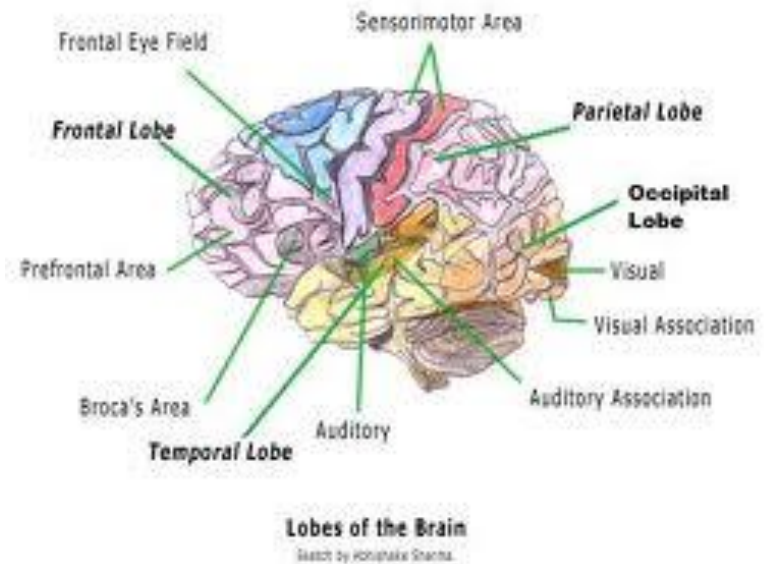
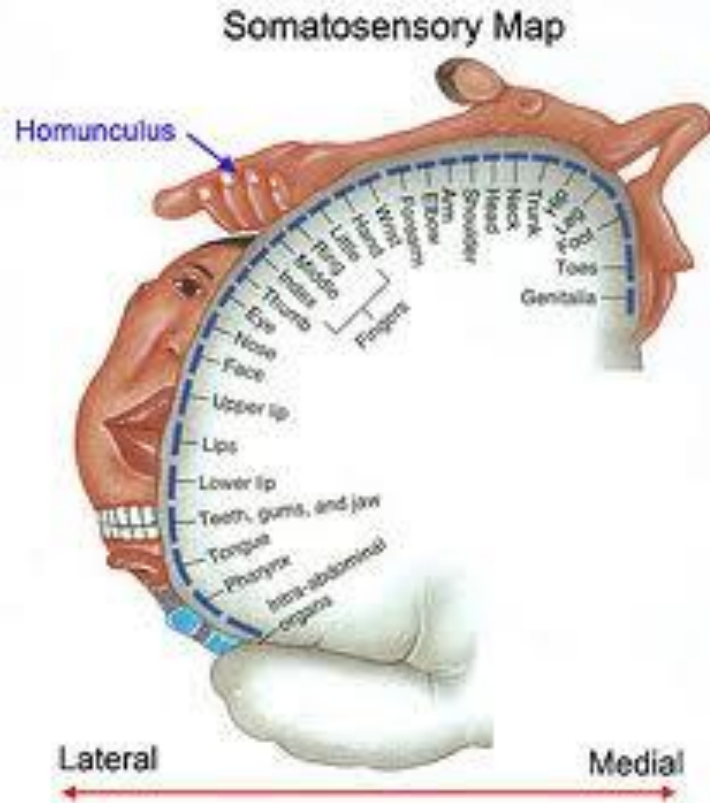
- Brain is comprised of about 10 billion individual nerve cells called neurons – these are arranged in layers on the outside of the brain and called the grey matter
- These cells are connected by “wires” that are the axons of neurons which when packed together make up the white matter of the brain
- Neurons communicate with each other by secreting chemicals called neurotransmitters

Neuroanatomy

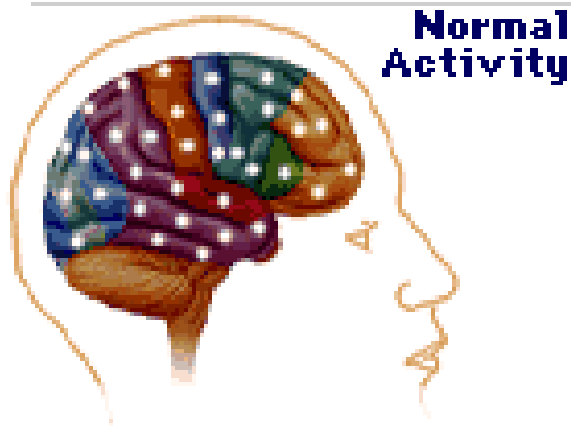


- Neurons are on the outside of the brain – the convolutions allow for more cells
- The axons of neurons comprise the white matter

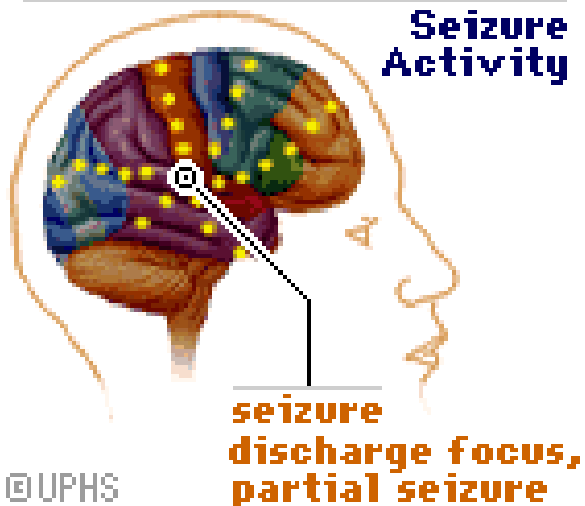
Cortical Localization



Seizure Physiology



- Neurons are inherently excitable – if they were not your brain wouldn't work
- When a group of neurons fire synchronously and out of control one has a seizure
- The symptoms of the seizure depend on where the seizure discharge starts and where the discharge spreads

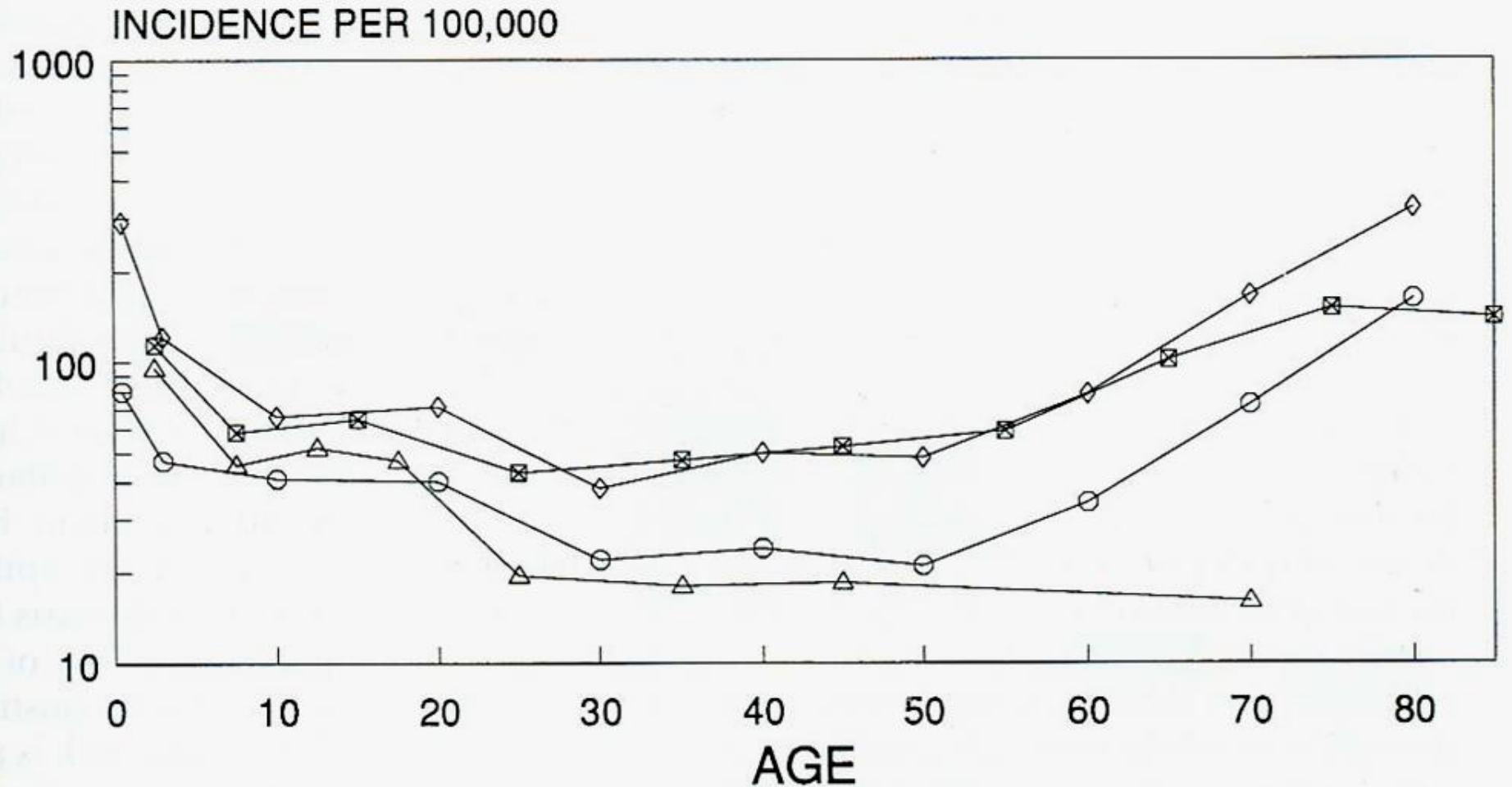


Epidemiology

How big is the problem?

- Looking at total populations the reported incidence seems to be
 - lowest in the United Kingdom and Canada
 - intermediate in the United States and Japan
 - higher in Scandinavia and Italy.
- The incidence in developing countries appears to be 20 to 50% higher than in developed countries.

INCIDENCE RATES OF AFEBRILE SEIZURES



○ ROCHESTER EPILEPSY 1975-84

1975-84

△ DENMARK EPILEPSY 1960-72

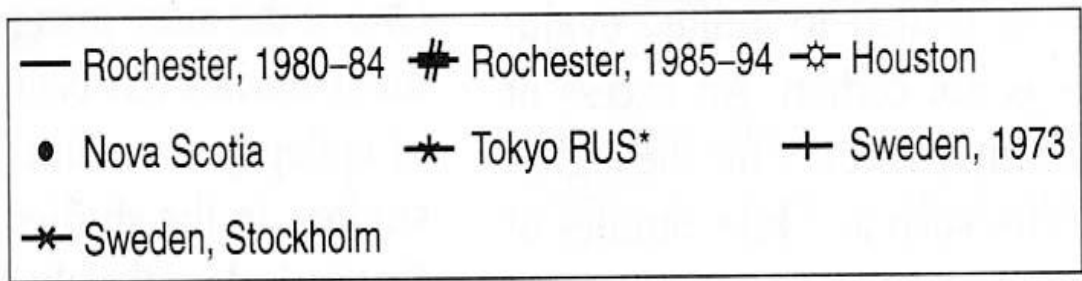
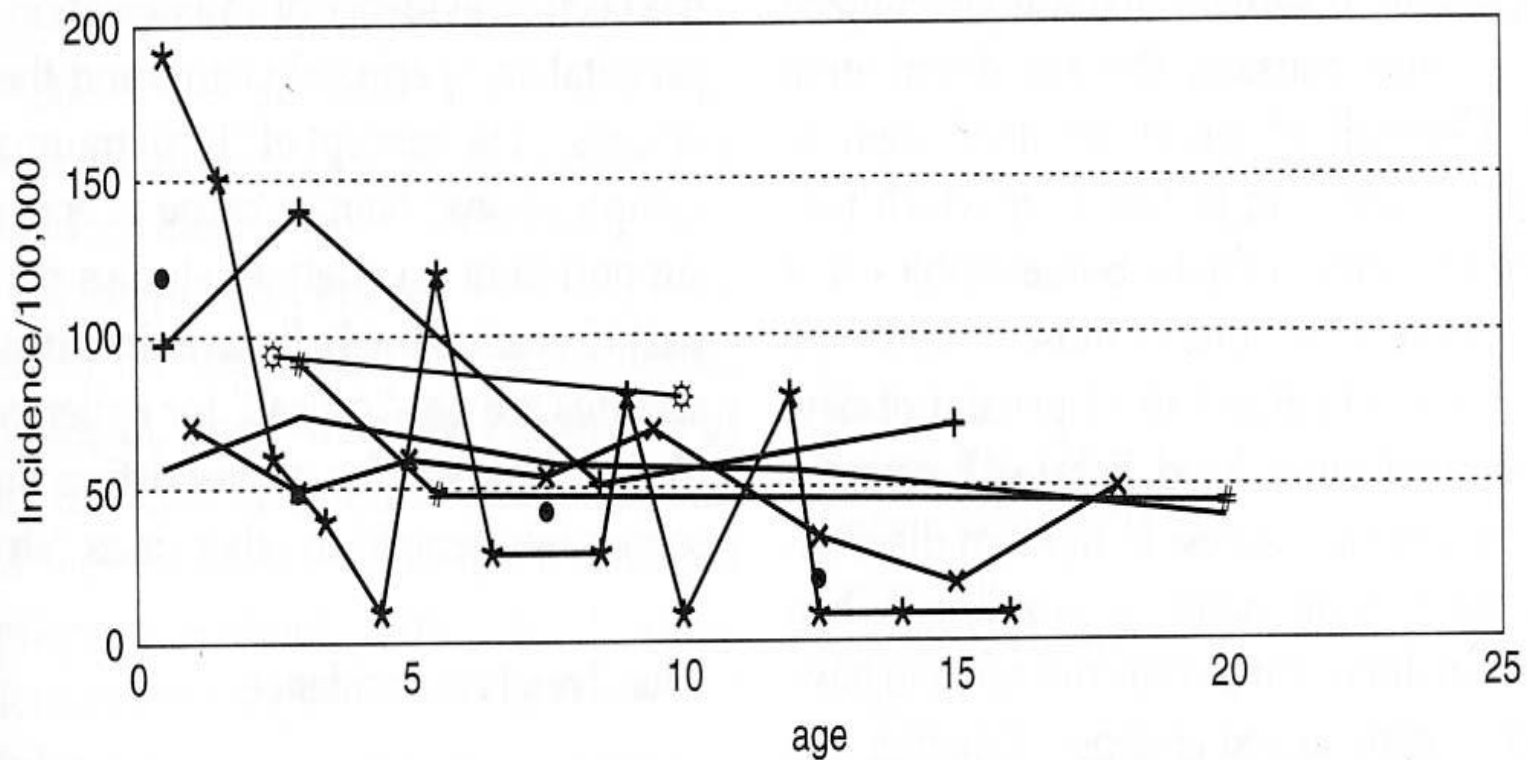
1960-72

◇ ROCHESTER AFEBRILE 1975-84

1975-84

⊠ FRANCE AFEBRILE 1984-85

1984-85



*RUS = recurrent unprovoked seizures.

Figure 7-1. Incidence of epilepsy* in children in developed countries.

Cumulative incidence

- The risk of developing a convulsive disorder through a specific age.
- In Rochester Minnesota
 - The cumulative incidence through age 20 for seizures of any type is approximately 4%
 - The cumulative incidence of epilepsy is approximately 1%
 - The cumulative incidence for all afebrile seizures is about 2%.

How are seizures classified

Definitions

- Semiology – the branch of linguistics concerned with signs and symptoms
- Epileptic seizure – manifestation of epileptic (excessive and or hypersynchronous) usually self-limited activity of neurons in the brain
- Ictus – a sudden neurologic occurrence such as a stroke or seizure

Definitions

- Epilepsy - A chronic neurologic condition characterized by recurrent epileptic seizures
- Epileptic Syndrome – a combination of one or more seizure types with other features that occur as a package – such as EEG, age of onset, semiology specifics etc
- Focal (synonym partial) – a seizure whose initial semiology indicates, or is consistent with, initial activation of only part of one cerebral hemisphere
- Generalized (synonym bilateral) - a seizure whose initial semiology indicates, or is consistent with, more than minimal involvement of both cerebral hemispheres

Definitions

- Versive – sustained, forced conjugate ocular or cephalic rotation
- Astatic – loss of erect posture that results from an atonic, myoclonic or tonic mechanism = drop attack
- Oroalimentary – lip smacking, lip pursing, chewing, licking, tooth grinding or swallowing
- Gestural – often unilateral, fumbling, resemble movements intended to lend further emotional tone to speech

Seizure Classification History

- Tissot(18th century) -defined epilepsy as the liability to unprovoked seizures
- Reynolds (19th century) differentiated provoked seizures such as febrile convulsions from epilepsy
- Sachs – divided childhood epilepsy into eclamptic (febrile or otherwise provoked) and epileptic
- French
 - Grand Mal
 - Petit mal
- Localization Era – early 20th century; Hughlings Jackson, the advent of EEG and the beginning of epilepsy surgery
- ILAE Seizure Classification – 1981
- ILAE Epilepsy Syndrome Classification - 1989
- ILAE Revision – 2001, a 5 axis system
- “Cleveland School” Seizure Semiology Classification
- Current Trends
 - Genetic factors such as the evolving channelopathies

Why Classify

- Alters treatment – points to drugs that may work, ones that probably won't and ones that may exacerbate
- Integral to picking candidates for epilepsy surgery
- Helps with predicting prognosis
- Clarity and communication
- Uniformity for research purposes

Ways to classify epileptic syndromes

- Seizure type(s)
- Age of onset
- Etiology
- Anatomical localization
- Precipitating factors
- Severity
- EEG findings – ictal and interictal
- Duration of epilepsy
- Associated clinical features
- Chronicity
- Diurnal and circadian cycling
- Prognosis

Seizure Classification - 1981

- Partial Onset
 - Partial simple
 - Partial complex
 - Evolving to generalized tonic clonic
- Generalized
 - Absence seizures (formerly called petit mal)
 - Myoclonic seizures
 - Clonic seizures
 - Tonic seizures
 - Tonic clonic seizures (formerly called grand mal)
 - Atonic seizures (drop attacks)
- Uncertain as to whether partial or generalized
 - Infantile spasms

Epilepsy Syndrome Classification - 1989

- Localization-related epilepsies and syndromes
 - Idiopathic with age-related onset
 - Benign childhood epilepsy with centrotemporal spikes
 - Childhood epilepsy with occipital paroxysms
 - Symptomatic
 - Mesial Temporal Lobe Sclerosis
- Generalized epilepsies and syndromes
 - Idiopathic with age-related onset
 - Benign neonatal familial convulsions
 - Benign neonatal convulsions
 - Benign myoclonic epilepsy of infancy
 - Childhood absence epilepsy (pyknolepsy)
 - Juvenile absence epilepsy
 - Juvenile myoclonic epilepsy (JME)
 - Epilepsy with grand mal seizures on awakening
 - Idiopathic and/or symptomatic
 - infantile spasms
 - [Lennox-Gastaut syndrome](#)
 - Epilepsy with myoclonic atstatic seizures
 - Epilepsy with myoclonic absences
 - Symptomatic

2001 Revision

- Axis 1: Descriptive ictal terminology
- Axis 2: Seizure type, from the List of Epileptic Seizures with specific brain location, if known
- Axis 3: Syndrome, from the List of Epilepsy Syndromes, not always possible
- Axis 4: Etiology, including specific genetic defects or pathologic substrates
- Axis 5: Impairment, optional but useful parameter can be derived from the WHO ICDH-2 impairment classification

2001 Revision

- also discussed the abandonment of the terms partial-onset or localization-related seizure or epilepsy for the term focal. In addition, the task force recommended that the term “cryptogenic” be replaced by the more precise wording of “probably symptomatic”
- critics complain that this system is unnecessarily complex and its reliability, accuracy, and clinical use are uncertain.

Problems

- Seizure classification changed significantly between pre-and post monitoring in more than a third of patients
- A semiological classification may be better suited for every day clinic use
- Complex partial seizure is the most common designation, often without clear evidence of altered consciousness and many events turned out to be not partial or even epileptic

Cleveland School Semiological Classification

- Auras
 - Somatosensory
 - Visual
 - Auditory
 - Gustatory
 - Olfactory
 - Autonomic
 - Abdominal
 - Cyclic

Cleveland School Semiological Classification

- Autonomic seizure
- Dialeptic Seizure (isolated alteration of awareness)
- Motor seizures
 - Simple motor
 - atonic, tonic, tonic-clonic, epileptic spasm, myoclonic, versive
 - complex motor
 - automotor, hypermotor, gelastic
- Special seizures (negative)
 - aphasic, astatic, atonic, akinetic, hypo-motor, negative myoclonic

History Taking

- Before seizure onset
- At the beginning of the seizure
- During the seizure
- Post ictal phase

Before seizure onset

Features	Significance
Prodrome	May precede GTC seizure – can be hours
Environment of occurrence	To exclude syncope or pseudoseizures
Time of day	Myoclonic or primary generalized on awakening
Precipitants or triggers	Reflex or photosensitive
Association with sleep	Rolandic or frontal lobe

An onset of the seizure

Features	Significance
Aura	Lobe of origin
Focal Onset	Lateralization and/or localization

During the seizure

features	significance
Progression	Identify the involved brain regions
Aphasia	Dominant hemisphere
Awareness and consciousness	Simple versus complex partial or generalized
Duration	Status epilepticus

Postictal Phase

Feature	Significance
Confusion/amnesia	Suggest complex partial or generalized
Unilateral headache	Ipsilateral seizure origin
Todd's Paresis	Contralateral hemispheric origin
Visual field defect	Occipital lobe involvement
dysphasia	Dominant hemisphere involvement

Examination of patient during the seizure for semiologic characteristics

Examination	Significance
Response to communication	Level of awareness
Speech (naming, reading)	Dominant hemispheric involvement
Memory (presenting words or phrases for later recall)	Temporal lobe involvement
distractibility	Frontal lobe involvement
Response to passive eye opening	To exclude pseudoseizure (tight closure)
Response to physical stimulation	Attention, motor dysfunction
Weakness or lack of motor control	Contralateral seizure origin
Plantar extensor response	Post ictal paresis

CLASSIFICATION OF SEIZURES

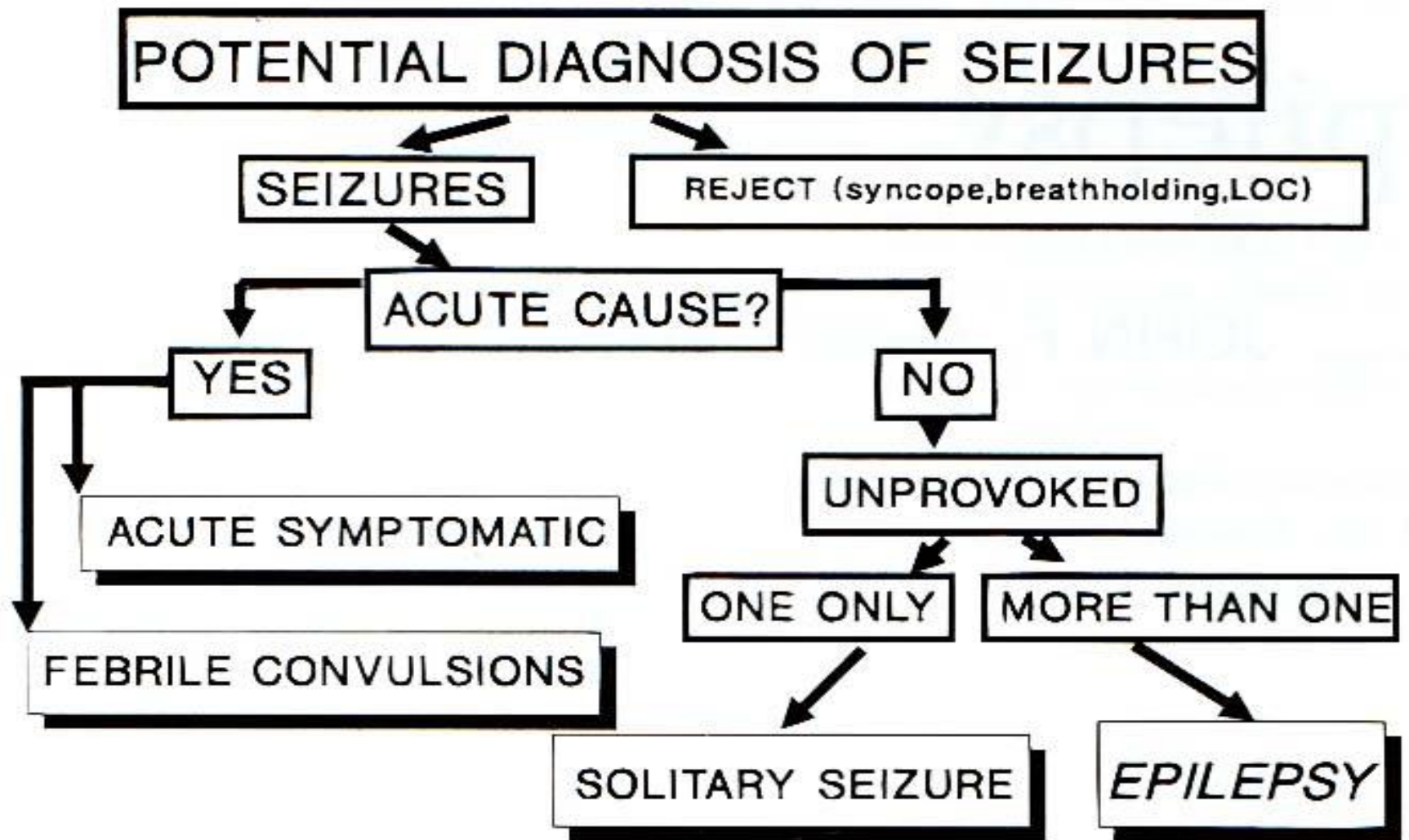


Fig. 11-1. Classification of Seizures.

What are acute symptomatic seizures?

- “Occur in close a temporal association with a systemic or central nervous system insult”
- Approximately 5% of children with infections of the nervous system have acute symptomatic seizures.
- Approximately 10% of children with traumatic brain injury experience early seizures.
- By age 20, 1% of all children may have experienced an acute symptomatic seizure
- As they are counted as epilepsy this may confuse the actual count of patients with true epilepsy. It is thought this may double the actual reported incidence of epilepsy in children.

What are febrile seizures?

- A convulsive episode occurring in association with an acute febrile illness
- In the U.S. and northern Europe about 2-4% of all children can be expected to have a febrile seizure by 5 years of age.
- There seems to be a much higher incidence in Japan.

What are unprovoked seizures?

- No identified acute cause
 - Idiopathic – usually means genetically determined
 - Remote symptomatic means probably due to an old insult
 - Cryptogenic – cause is unknown
- ~ 25% of newly diagnosed unprovoked seizures in children are single events which will never reach criteria for epilepsy
- ~60% of patients have had more than one seizure before reaching a physician
- Of those 40% who have not, only about 1/3 will have a recurrent seizure
- In Japan and Spain half of newly identified unprovoked seizures did not recur

Videos

- Understanding Epilepsy
 - <http://www.epilepsy.com/node/989624>
- Partial Seizures
 - http://www.epilepsy.com/video/types/understanding_partial
- Generalized Seizures
 - http://www.epilepsy.com/video/types/understanding_generalized
- Absence Example
 - <http://www.youtube.com/watch?v=H3iLQi6wt94>
- Example drop seizure
 - <http://www.youtube.com/watch?v=qo-TEuiblU>
- Example of an Infantile Spasm
 - <http://www.youtube.com/watch?v=vpgj3vs-zx4>
- Seizure Imitators
 - <http://www.epilepsy.com/video/diagnosing/seizure>
- Psychological Imitators
 - <http://www.epilepsy.com/video/diagnosing/psychological>

What causes seizures/epilepsy?

- A seizure is a symptom of brain dysfunction – like a cough in the respiratory system
- Any lesion/disorder of the brain can cause seizures
- Between 60 and 80% of all new cases in children have no apparent cause
- Approximately 20% of cases are associated with neurological handicaps presumed present from birth such as mental retardation or cerebral palsy
- These later conditions are usually of unknown etiology so that overall etiology is unknown in as many as 97%

Is it a seizure?

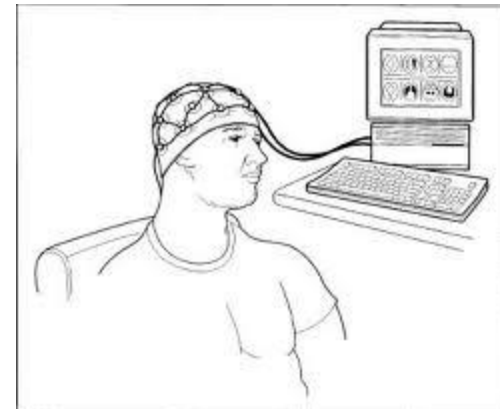
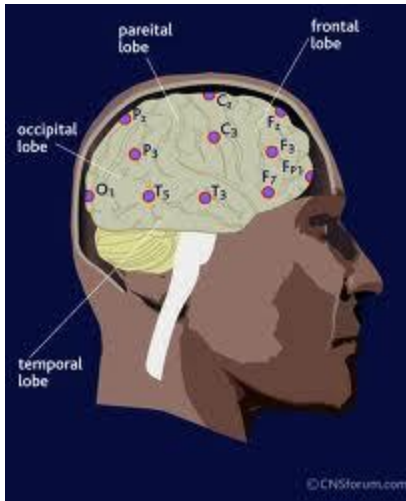
Differential Diagnosis

- Vascular
 - Migraine
 - Stroke/TIA
 - Transient Global Amnesia
- Movement Disorders
 - Tics
 - Paroxysmal Choreoathetosis
- Stereotypy
 - Self-Stimulation
 - Autistic or MR
 - Excitement Responses
- Psychiatric Disorders
 - Hyperventilation
 - Panic
 - Rage
 - Dissociative
- Airway/Anoxic
 - Breath-holding
 - Cardiac Syncope
 - Convulsive Syncope
 - Vasovagal/vasodepressor
- Structural Disorders
 - Craniocervical Junction
 - Colloid Cyst
- Toxic/Drug
 - Medication Toxicity
 - Oculogyric crisis
- Sleep
 - Narcolepsy/cataplexy
 - Parasomnias

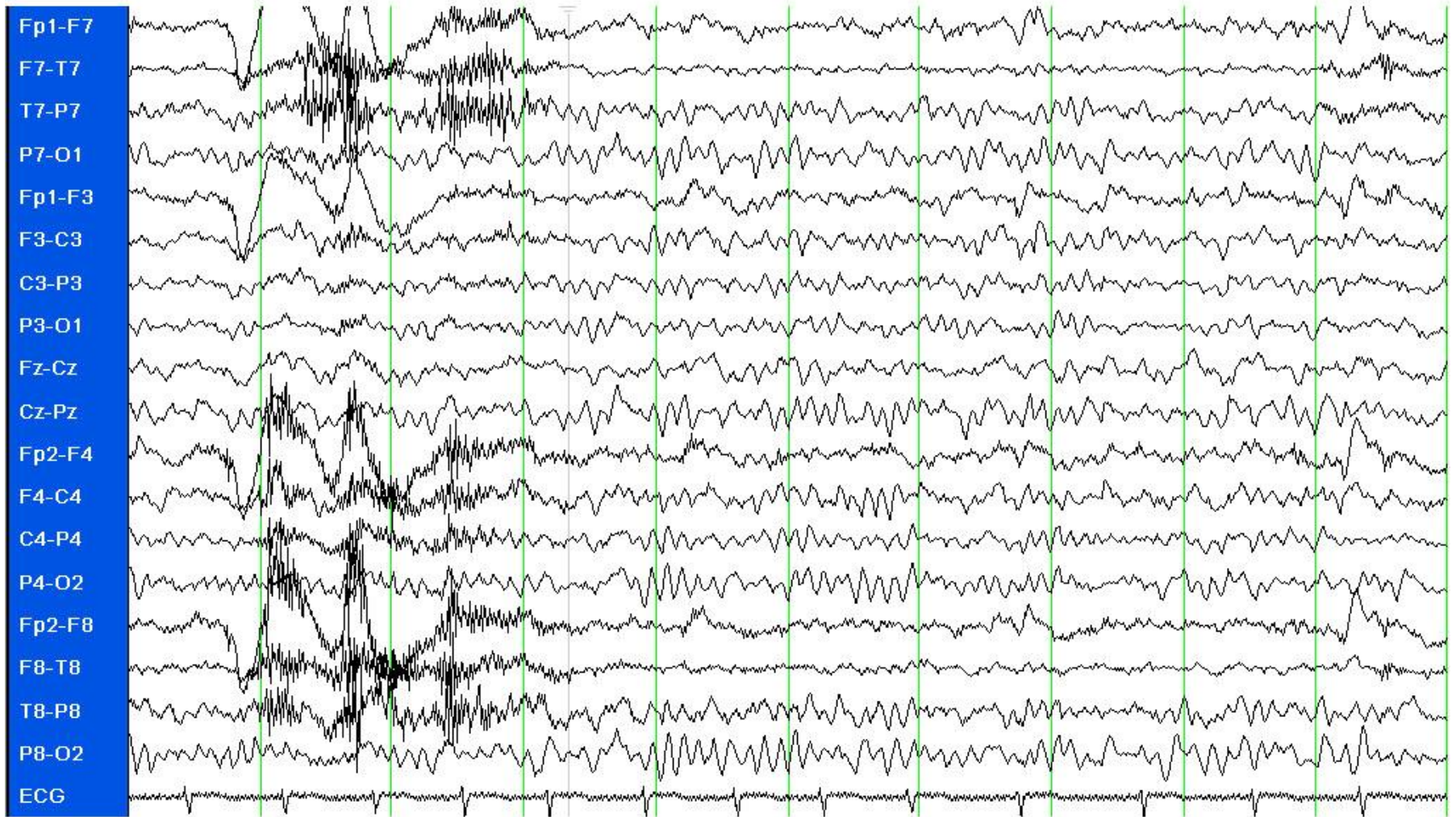
How are seizures investigated?

- History and PE
- EEG
- Imaging – CT and MRI
- Spinal Tap if infection likely
- Blood Chemistries
 - Na⁺, Ca⁺⁺, glucose, BUN, O₂, Drugs
- Home Video
- Prolactin Levels

EEG



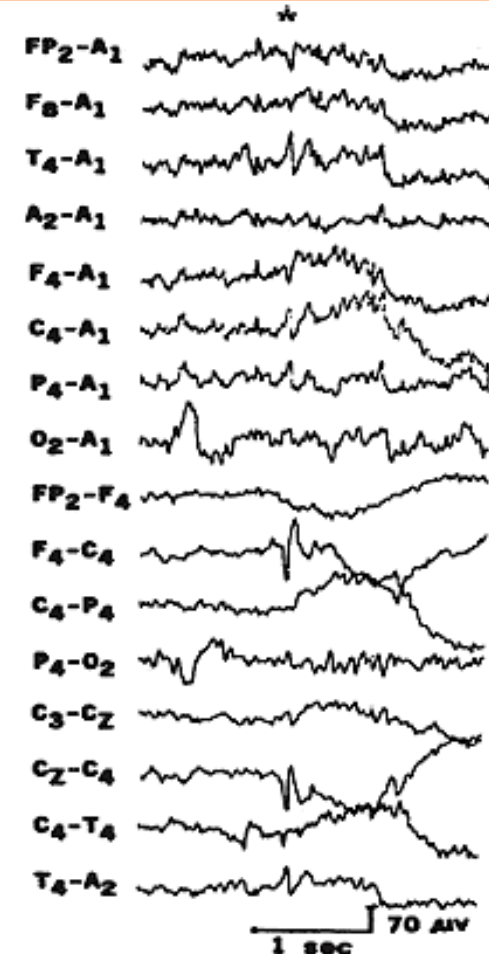
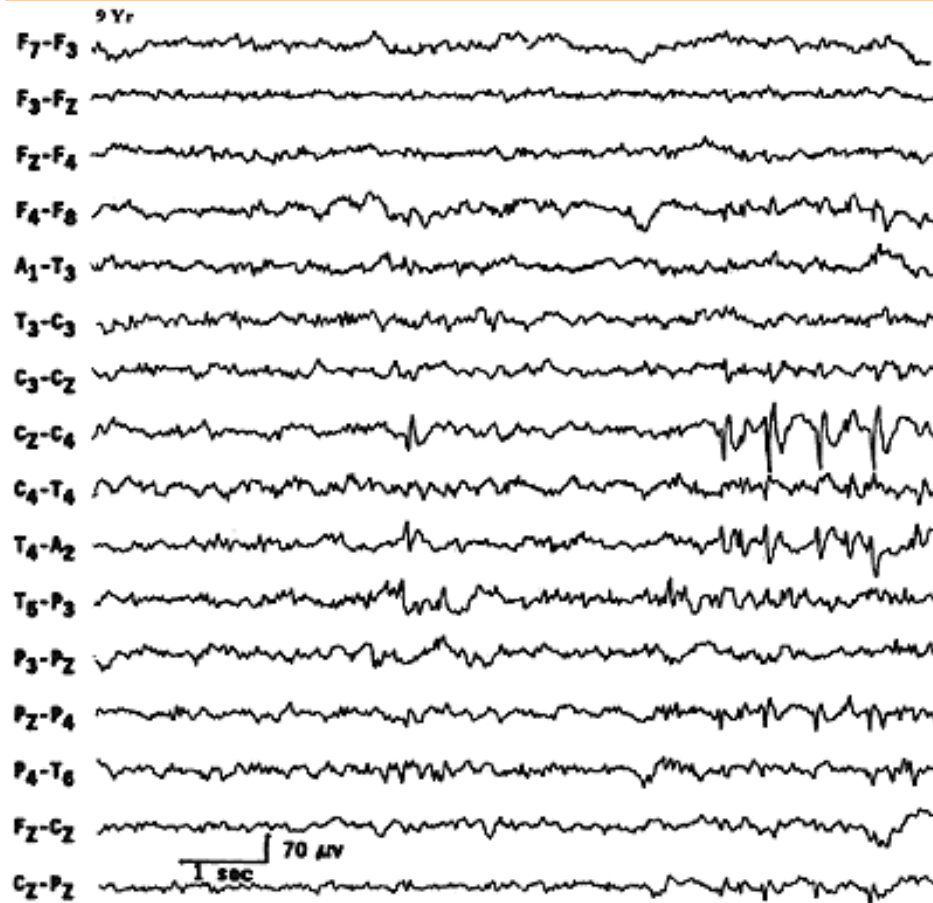
EEG Normal 9 y/o



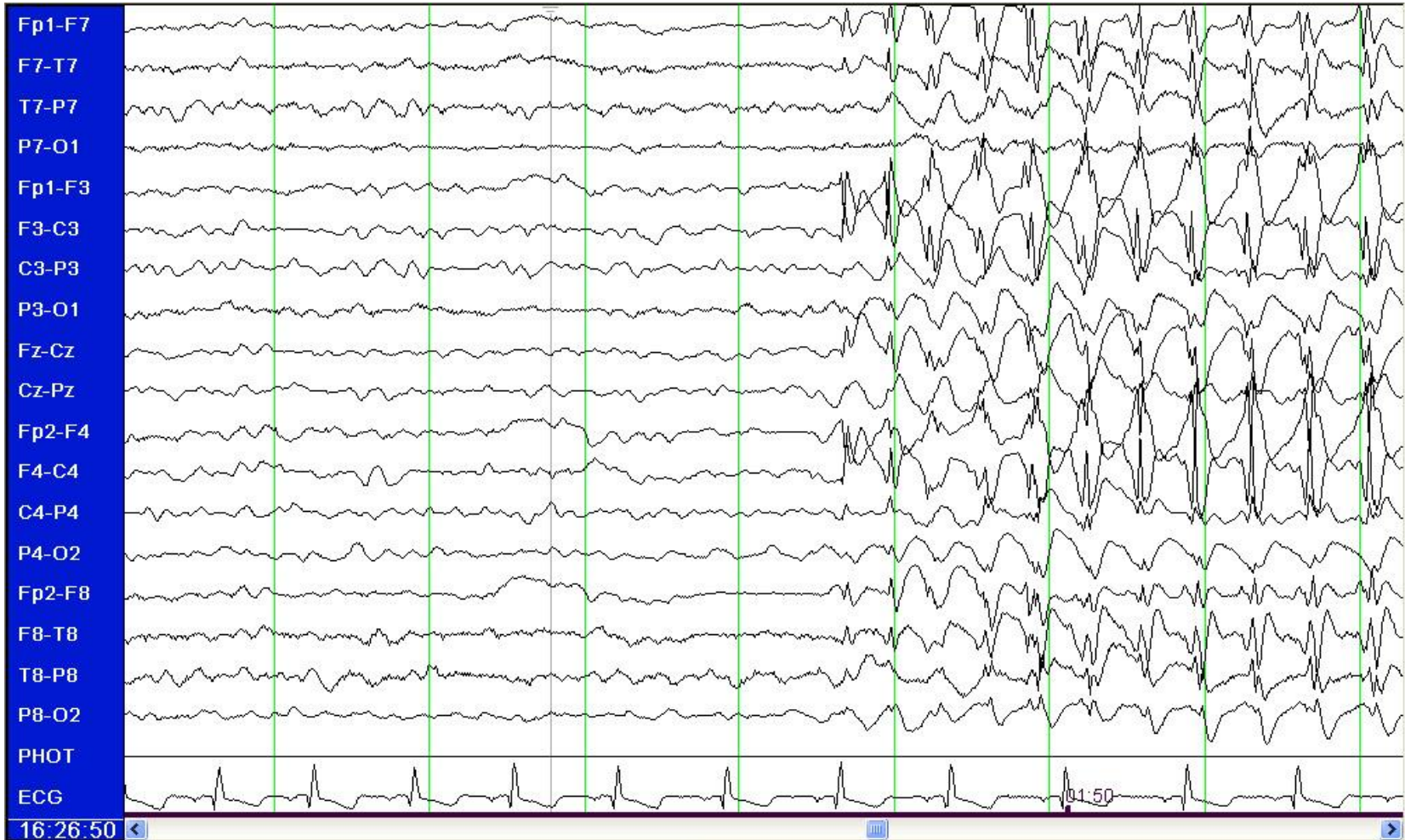
EEG Benign Rolandic

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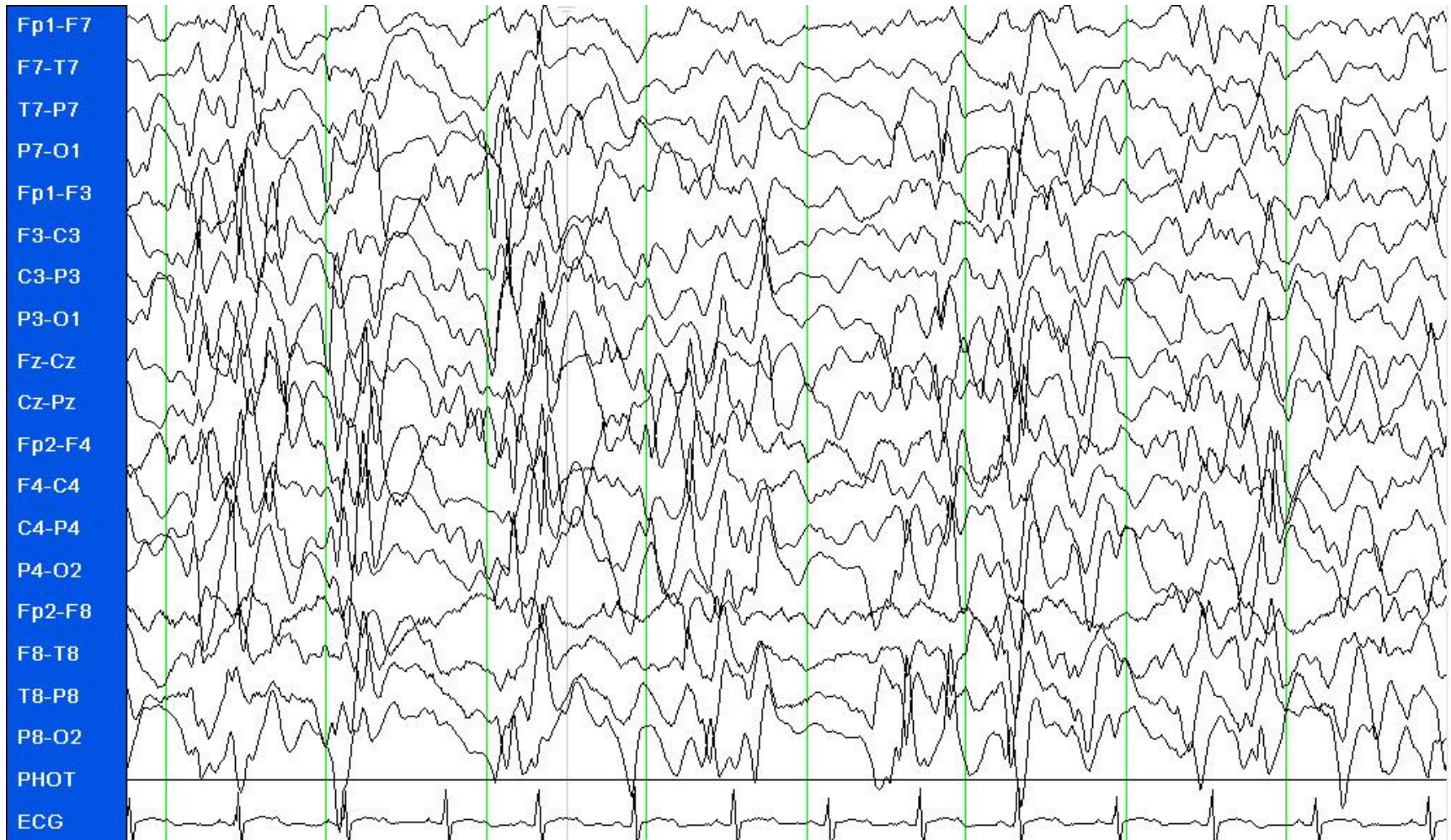


Juvenile Myoclonic Epilepsy EEG



13 y/o male

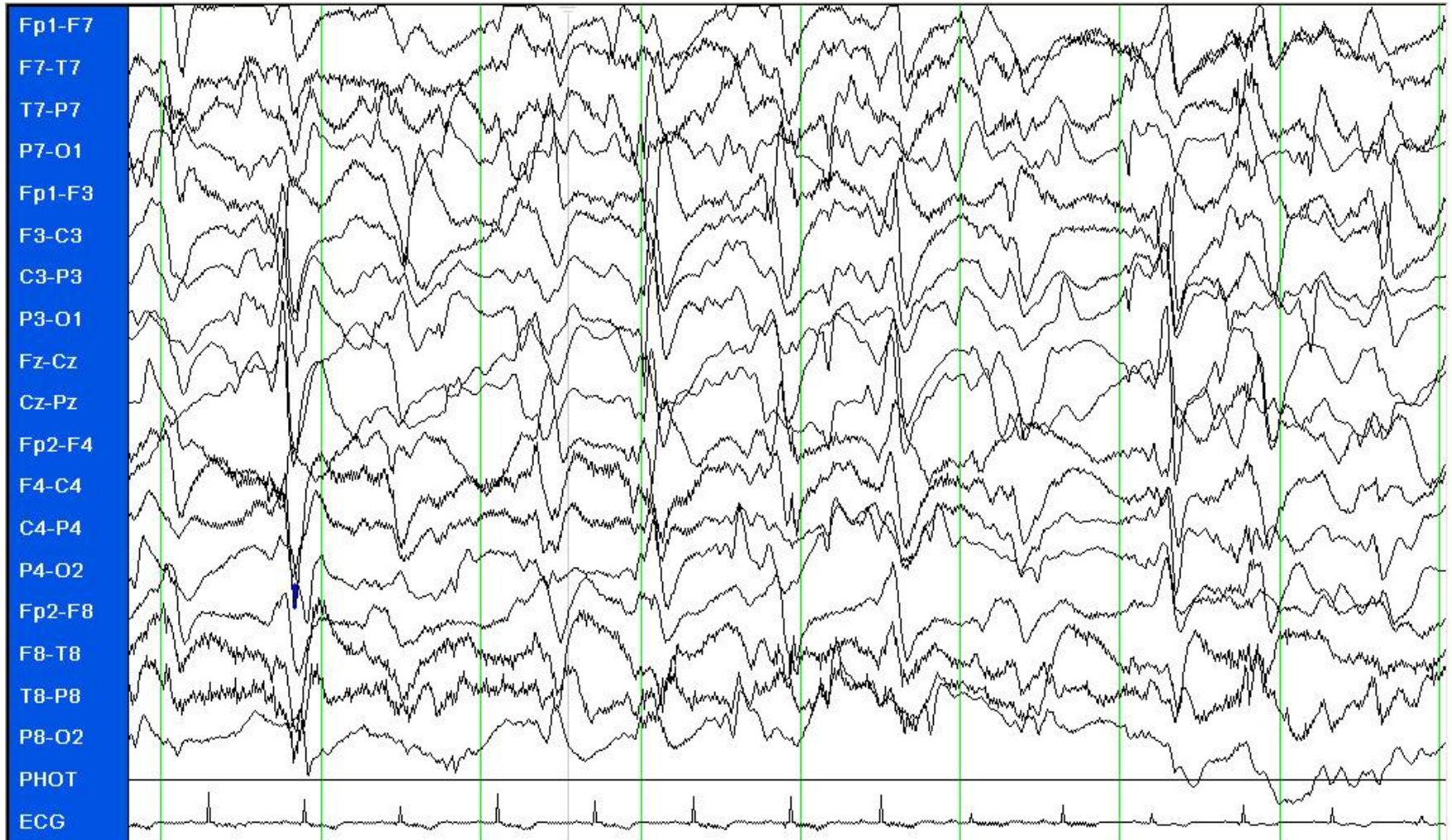
Infantile Spasms EEG



1 y/o with Lissencephaly

Sensitivity 30 $\mu\text{v}/\text{mm}$

Lennox Gastaut EEG

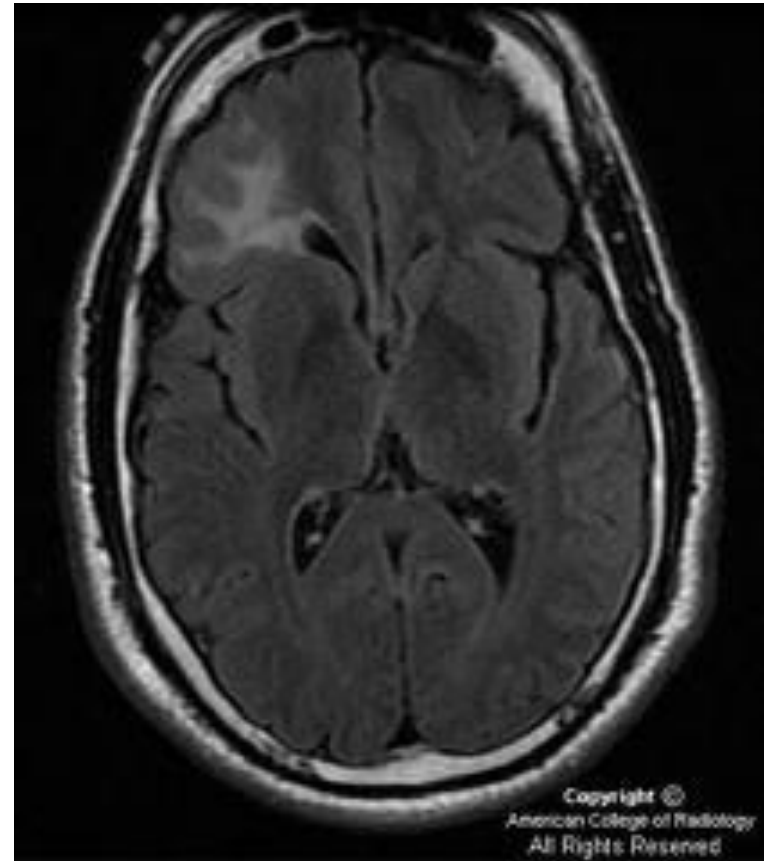


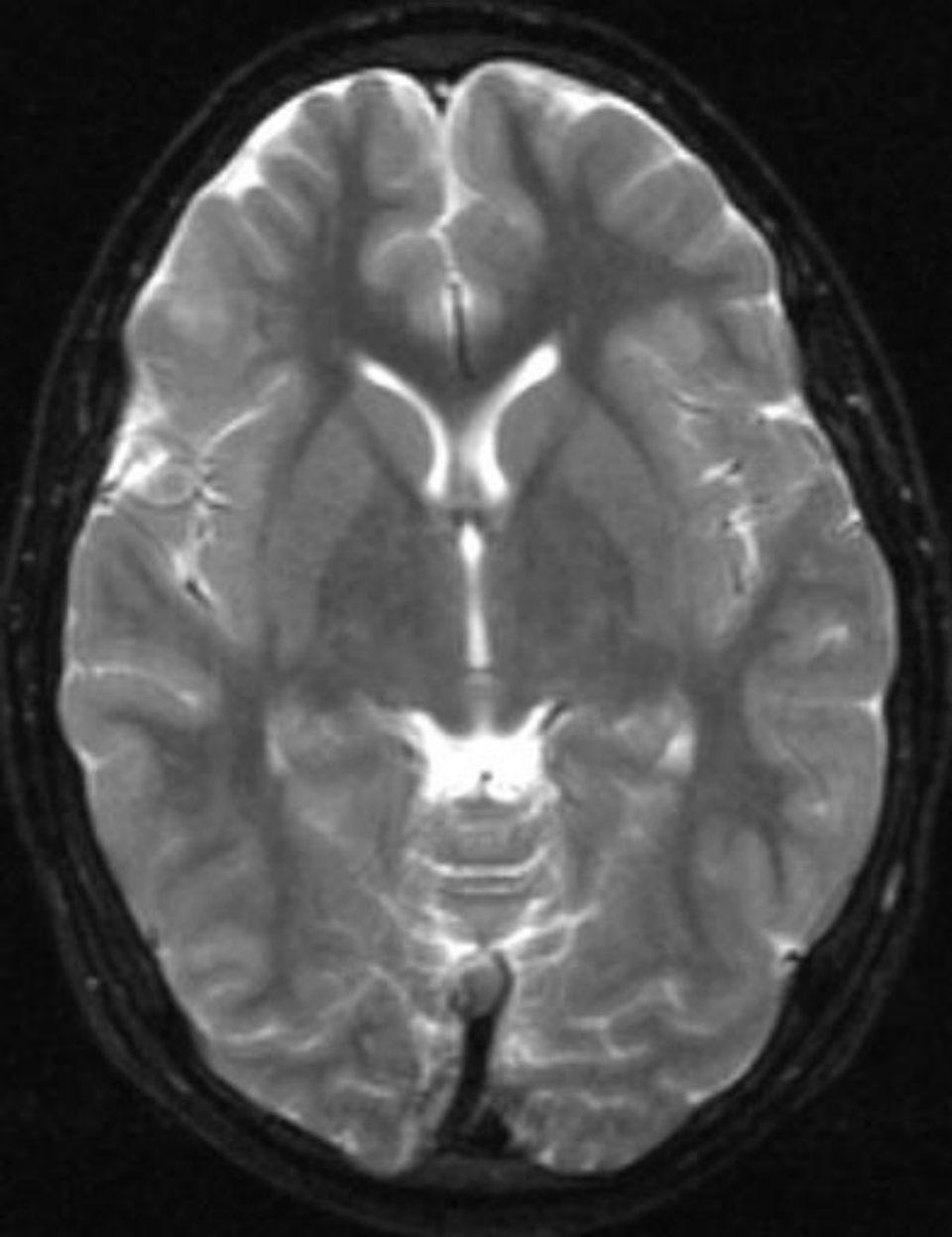
13 y/o female

Sensitivity 20 $\mu\text{v}/\text{mm}$

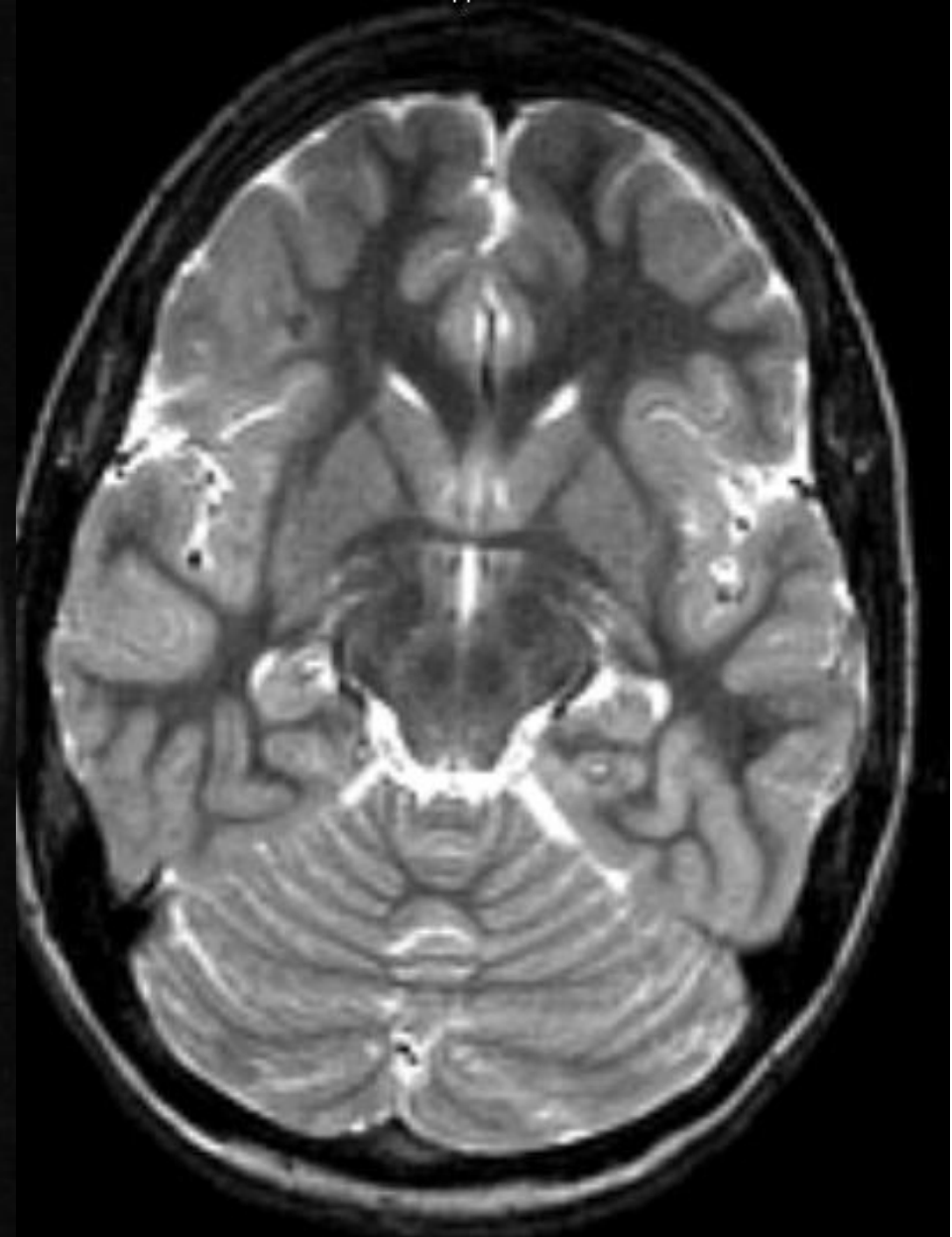
MRI

- Example of focal cortical dysplasia which may lead to intractable epilepsy that can be cured with surgery





1.5T



3T

Epilepsy

Reasons to treat

- Seizures are unpleasant
- Social consequences
- Physical Injury
- Status Epilepticus
- Adverse effect on cognitive function
- Adverse effect on behavior
- ? Kindling risks
- Sudden Unexpected Death

Epilepsy

Reasons not to treat

- Adverse effects of medications
- Uncertain long-term risks
- Expense
- Hassle
- Stigma

The Goals of Therapy

- Eliminate all seizures
- Produce no side effects with treatment
- Do it as soon as possible

Would you want treatment?

- What if the risk of recurrence was 1/5000?
- What if the risk of death was 90% with the next one?
- What if the medications work about 5% of the time
- What if you are going to vomit daily and lose all your hair?

What you want to know

- How likely is another seizure?
- What are the risks of another seizure?
- How likely are the medications to work?
- What are the risks of the medications?

After one seizure, how likely is the second?

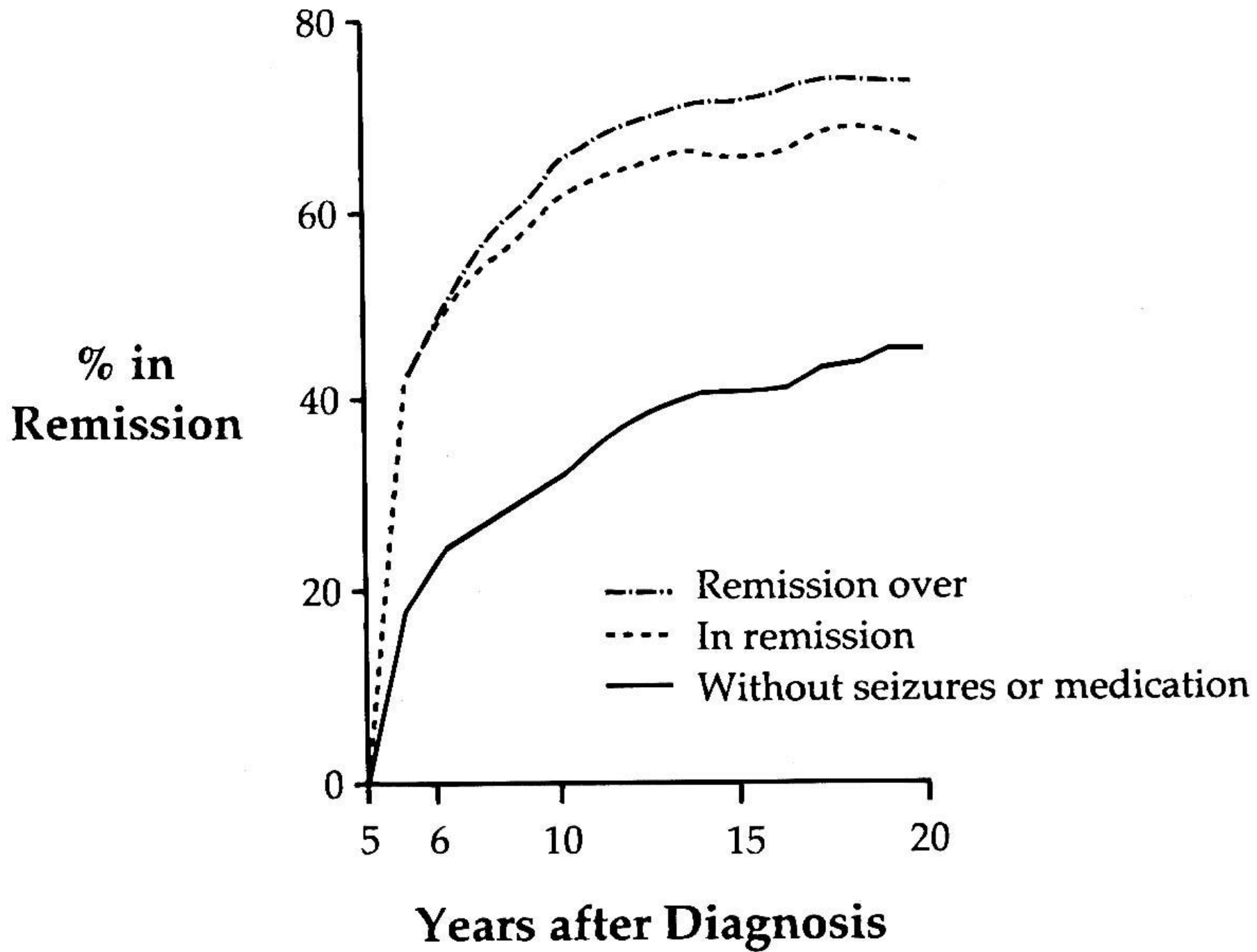
- Hauser: risk about 1/3
- Predictors that make more likely
 - Prior Neurological Insult
 - Partial seizure type
 - Abnormal EEG
 - Prior acute seizures including febrile seizures
 - Status Epilepticus
 - Multiple seizures at onset
 - Todd's paralysis
- After two, the third occurs in ~75%
- After 3 the fourth occurs in about 75-80%

How dangerous are seizures?

- It is very unlikely an individual seizure will kill or seriously harm the patient
- There is a risk of sudden unexpected death in epilepsy but that does not occur early
- Risk of physical harm including drowning – water safety is very important
- Aspiration, hypoxia, bite tongue or cheek

How likely are seizures to be controlled?

- 60-80% of patients with a diagnosis of epilepsy will go into remission on treatment
- At least ½ will do so in the first year after diagnosis
- 75% of patients with epilepsy will go into at least a 5 year remission of seizures
- About 30-50% of patients will never have another seizure after starting AED treatment
- 60-70% of children seizure free for 2-4 years will successfully come off medication
- Likelihood varies of course depending on underlying etiology and seizure type.



What is the likelihood meds will hurt?

- Rather high probability of some adverse effect
- Very low probability of serious adverse effects
- Risks vary with different medications

How are seizures treated?

- No treatment in some cases
- Medications to prevent - we don't have any drugs that are "anti-epileptic", that fix the problem. Medications simply help the brain suppress seizures
- Medications to treat individual seizures – rescue meds
- Ketogenic diet
- Epilepsy Surgery
- Vagal Nerve Stimulator

Medications

- Phenobarbital
- phenytoin
- Primidone
- Carbamazepine
- Valproate
- Clonazepam
- ACTH
- acetazolamide
- ethosuximide
- Felbamate
- Gabapentin
- Lamotrigine
- Tiagabine
- Oxcarbazepine
- Levetiracetam
- Zonisamide
- Pregabalin
- Lacosamide
- Rufinamide
- Vigabatrin
- clobazam

What is likelihood patients will comply?

- Cultural anthropologist came to our clinic and interviewed patients after a visit
- 50% were not truthful with the physician
- Lots of reasons to not comply
 - Adverse effects – sometimes reluctant to tell the physician
 - easy to forget
 - Denial of the problem

How do we follow treatment

- Monitor labs for toxicity
- Monitor levels
- Role of follow-up EEG
- Role of repeating imaging

What do we do when patient does not respond?

- Reconsider Diagnosis of epilepsy
- Reconsider seizure classification
- Consider compliance
- Consider drug pharmacokinetics
- Trial of a new drug

Predictors of Remission from time of Diagnosis

- More Likely to have remission
 - Young age onset
 - Young age diagnosis
 - Generalized onset seizures
 - Normal neurological exam
 - Idiopathic/cryptogenic etiology
- Less Likely for Remission
 - Known symptomatic etiology
 - Partial seizure type
 - MR or CP
 - Primary or secondarily generalized seizure
 - Abnormal EEG – especially generalized S&W
 - Number and duration of seizures inversely correlated
 - More than 3 seizures in the second 6 months of treatment

Predictors of Remission During Epilepsy

- Multiple seizure types
- Frequent GTC seizures
- Time to control
 - Uncontrolled after 1 year – 60% reach remission
 - Uncontrolled > 4years – only 10% reach remission
 - Seizures persist 10 years – 5% reach remission

What is Intractability?

- The child has failed trials of appropriate Antiepileptic Drugs for their seizure type – but how many?
- What if seizures are rare or of minimal consequence? We expect the epilepsy to be incapacitating to be called intractable.
- Only 5-10% of all incident cases of epilepsy become truly intractable
- Adults who have epilepsy surgery have had epilepsy for an average of 20 years
- 10 of those years were consumed determining the patient is intractable – How long should it take?
- Why the further 10 year delay?

What makes Intractability more likely?

- Frequent seizures – daily or weekly
- Clustering
- Early seizure onset, especially in infancy (<2 years old)
- Children with brain damage and a structural brain lesion

Biological Basis of Intractability

- Probably multifactorial
 - Severity of underlying problem in the brain
 - Abnormal reorganization of neuronal circuitry
 - Alteration in neurotransmitter receptors
 - Ion channelopathies
 - Reactive autoimmunity
 - Impaired AED penetration to seizure focus
- Are some of these a consequence of recurrent seizures – i.e. is the epileptic condition progressive?
 - Animal data suggest it is a progressive disease
 - Human data as well

Definitions of Intractability

<p>Arts et al</p>	<p>A. Seizures in last 6 mo B. at least 2 years since Diagnosis</p>
<p>Kwan et al</p>	<p>Any seizures in last year</p>
<p>Berg et al</p>	<p>A. ≥ 1 seizure/month for 18 months B. No more than 3 months seizure free in 18 months</p>

When can you say epilepsy is Intractable?

- Berg et al
- 333 patients at 7 surgical centers
- 26% had a 1 year seizure remission
- 8.5% had a 5 year remission
- They conclude that it may take a number of years for intractability to occur and possibly we can find ways to prevent this from occurring

How many drugs do you have to fail?

Glasgow

- Began 1982, 525 adolescent and adult patients
- 64% achieved long-term remission
- 9% developed refractory epilepsy after initial good response
- 35% never attained adequate control
- 31% never had another seizure after their first dose medication
- 92% who entered remission did so in the first 3 years of treatment
- 47% responded to first drug, 90% on moderate doses
- 14% responded to second or third drug
- 3% responded to two drug therapy

How many drugs do you have to fail? Canada

- Camfield et al, J Peds 1997; 131:821-4
- 417 children new onset epilepsy
- Treated with PB, CBZ, PHT
- 61% eventually off of medications in remission
- 17% had inadequate seizure control with first drug and received a second
- Only 42% of these had a complete remission
- They recommend trying at least 2 drugs before considering invasive or complex therapies

What is the benefit of more drug trials?

- Gilman looked at 21 children referred for epilepsy surgery who had significant treatment omissions – only 2 benefited from additional medication trials
- Most agree that after 2 or 3 failures, the likelihood of success with future drugs is low
- There are always exceptions we work for

What are the consequences of Intractability?

- Quality of Life
- Behavioral Regression and Dysfunction
- Cognitive Impairment, Memory Dysfunction
- Educational Attainment
- Employment Status
 - Unlikely to be an independent adult
- Morbidity and Mortality Risk
- Driving
- Marital Status

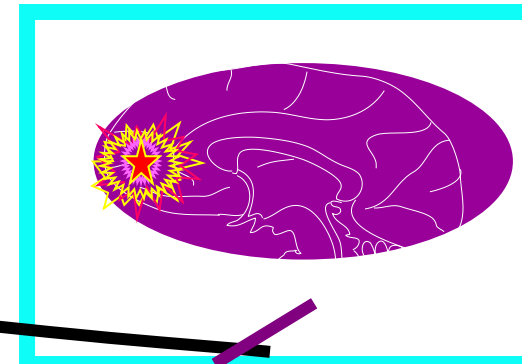
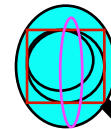
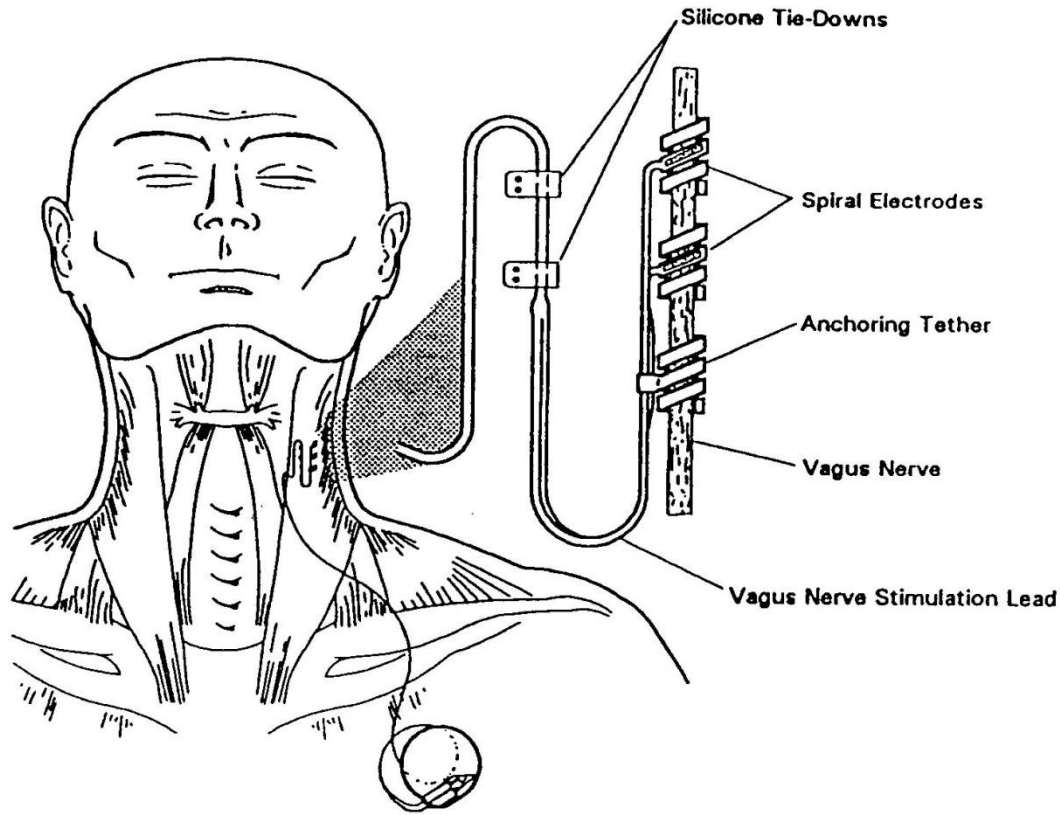
So What do we do if medications fail?

- More trials of medication combinations
- Ketogenic Diet
- Evaluate for epilepsy surgery
- Vagal nerve stimulator

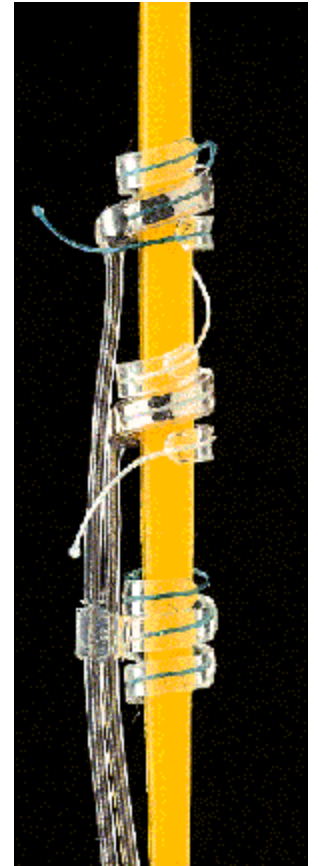
Ketogenic Diet

- High ratio of fat to protein and carbohydrate
- Most effective in children
 - Not typically used in adults
- No comparative or controlled studies of the ketogenic diet.
- Appears to be effective for most seizure types
 - More than half of patients experience $\geq 50\%$ seizure reduction at 6 months
 - A 47% continuation rate at 1 year
 - Only one out of ten have seizure freedom at 1 year

Vagal Nerve Stimulation Therapy for Epilepsy



VNS Device



VNS Patient Outcome Cyberonics Registry (90 patients)

- QUALITY OF LIFE ASSESSMENT AT 2 YEARS - %
Improvement

– Alertness	64 %
– Verbal Skills	52 %
– Mood	46 %
– Achievements	43 %
– Memory	44 %

VNS Patient Outcome

Cyberonics Registry (90 patients)

- **AFTER 3 MONTHS**

- $\geq 50\%$ seizure reduction 46%
- $\geq 90\%$ seizure reduction 18%

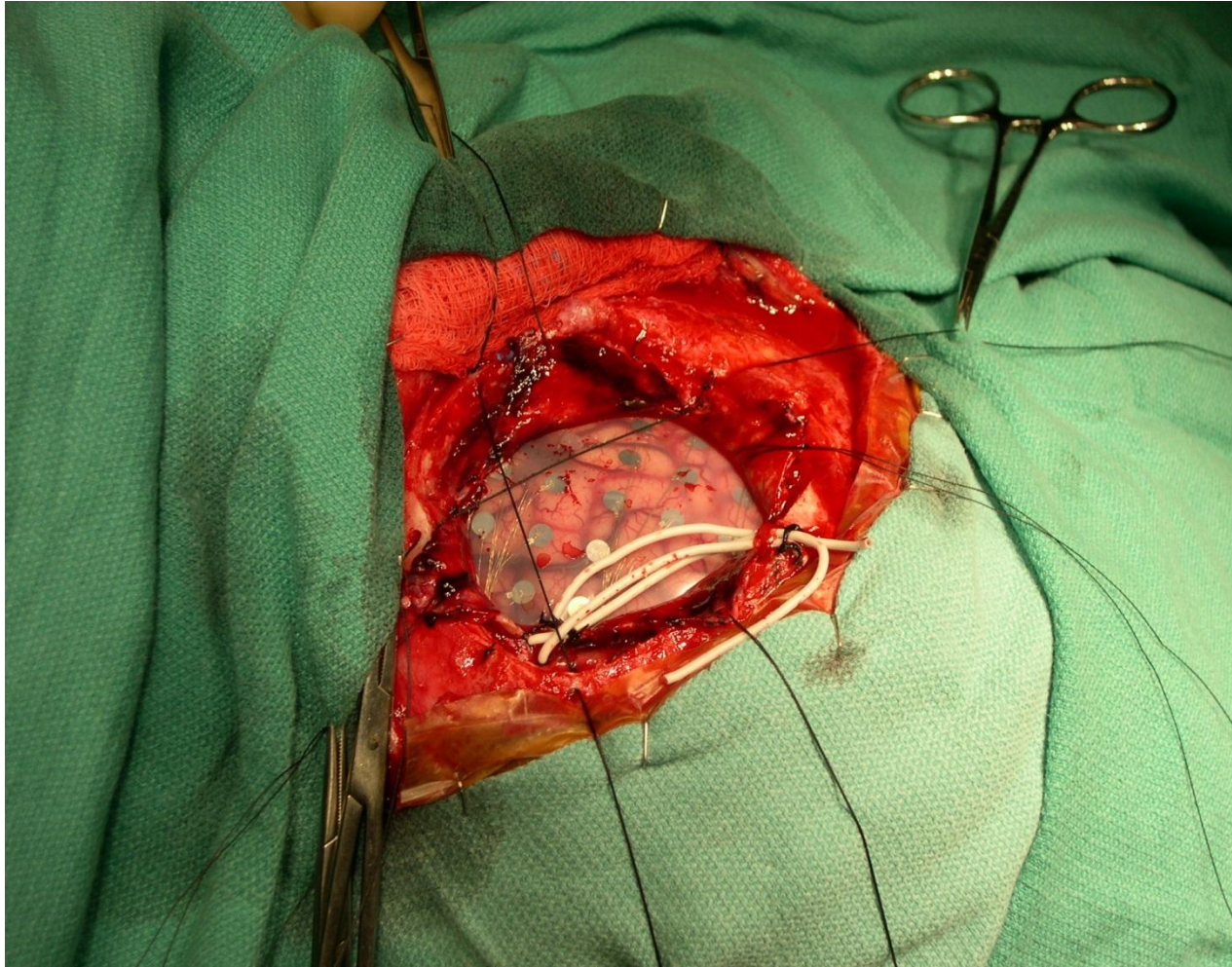
- **AFTER 2 YEARS**

- $\geq 50\%$ seizure reduction 68%
- $\geq 90\%$ seizure reduction 26%

Epilepsy Surgery

- Phase I
 - Scalp EEG recording of 3-5 seizures
 - PET
 - Ictal SPECT
 - Wada
 - Neuropsychological testing
- Phase II
 - Intracranial electrode placement and record seizures
 - Cortical stimulation to identify “eloquent” cortex
- Phase III
 - Resect brain tissue felt to be source of seizures

Grid Placement to Guide Surgery



Outcome of Epilepsy Surgery

Engel's classification

Classes I-IV

- I: No seizures or few auras
- II: More than 90 % seizure reduction
- III: 50-90 % seizure reduction
- IV: less than 50 % improvement, or seizure worsening

I and II: successful surgery

III and IV: unsuccessful

Single Randomized Trial of Surgery

- 80 patients (40 surgical treatment)
- At 1 year 58% of surgical group seizure-free vrs 8% of medical group
- 10% adverse effects of surgery – 1 small CVA, 1 wound infection, 2 memory decrement
- Other series <10% morbidity, rarely debilitating
- 1 death in medical group

Surgical Outcomes in Children

- Temporal Lobectomy
 - 72 patients
 - 78% Class I
- Extra-Temporal Resections
 - 48 Patients
 - 54% Class I
 - 32% Class II

Prognostic Factors

- Pathology
 - Neoplastic 75% Class I
 - Dysplasia 50% Class I
- MRI
 - Lesional 56% Class I
 - Normal 33% Class I

First Aid

- Don't Panic – “take your own pulse”
- Note the time to establish duration
- Make observations of the patient's symptoms
- Role onto side – protect airway, suction if available
- Prevent physical harm – e.g. fall, remove objects from mouth
- Do not force anything into the mouth, especially your fingers
- Call for help if more than a transient event
- Call 911 if seizure >10 minutes