An Epileptic Seizure

Excessive neuronal discharges

Clinical seizures

Incidence of Epilepsy

Incidence/100 000/year

PROPOSED DIAGNOSTIC SCHEME FOR PEOPLE WITH EPILEPTIC SEIZURES AND WITH EPILEPSY

Axis 1
Ictal phenomenology
Detailed description of symptoms during the seizure

Axis 2
Seizure type or types
According to ictal phenomenology and EEG

Axis 3
Syndrome
List of syndromes, syndromic diagnosing is not always possible

Axis 4
Etiology
Genetic defects, or specific pathological substrates for symptomatic focal epilepsies

Axis 5
Impairment
Disability caused by epilepsy

Epilepsy Classification: ILAE1981

1. Partial (Focal, Local) Seizures
   A. Simple partial seizures
   B. Complex partial seizures
   w/ cons. impairment at onset
   SPSe= CPS
   C. Partial seizures (A,B) evolving into GTC.

2. Generalized Seizures
   Convulsive vs Non-convulsive

3. Unclassified Epileptic Seizures

Incidence Chart

Age (years)

0 5 10 20 30 40 50 60 70 80

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Generalized seizure

PROPOSED DIAGNOSTIC SCHEME FOR PEOPLE WITH EPILEPTIC SEIZURES AND WITH EPILEPSY

Axis 1
- Ictal phenomenology: detailed description of symptoms during the seizure

Axis 2
- Seizure type or types: according to ictal phenomenology and EEG

Axis 3
- Syndrome: list of syndromic diagnoses is not always possible

Axis 4
- Etiology: genetic defects, or specific pathological substrates for symptomatic focal epilepsies

Axis 5
- Impairment: disability caused by epilepsy

Epileptic Syndromes
A collection of:

- **Sidioptic epilepsy syndrome**: A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms. Etiology presumed to be genetic. Usually age-dependent.

- **Symptomatic epilepsy syndrome**: Epileptic seizures are result of an identifiable structural lesion.

- **Probably symptomatic epilepsy syndrome**: Epileptic seizures believed to be symptomatic, but no etiology has been identified.

- **Benign epilepsy syndrome**: Epileptic seizures are easily treated or need no treatment and remit without sequelae.

Etiology of epilepsy

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>0-9 yrs</th>
<th>10-19 yrs</th>
<th>20-29 yrs</th>
<th>30-39 yrs</th>
<th>&gt;50 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>60%</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Birth injury</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Infections</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Head trauma</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Stroke</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Epilepsy Syndromes

- **Benign Neonatal Convulsions (+/- familial)**
- **Benign myoclonic epilepsy in infancy**
- **Childhood absence epilepsy**
- **Juvenile absence epilepsy**
- **Juvenile myoclonic epilepsy**
- **Epilepsy with GTCs on awakening**
- Some reflex epilepsies
- **Benign Rolandic epilepsy (Benign childhood epilepsy with centro-temporal spikes)**
- **Benign occipital epilepsy of childhood**
- **Autosomal dominant nocturnal frontal lobe epilepsy**
- **Primary Reading Epilepsy**

ILAE Classification of Epilepsy

<table>
<thead>
<tr>
<th>Type</th>
<th>Localization-Related (named by location)</th>
<th>Generalized (named by disease)</th>
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<tbody>
<tr>
<td>Idiopathic</td>
<td>Absence epilepsy, myoclonic epilepsy, symptomatic epilepsy</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Absence epilepsy, myoclonic epilepsy, symptomatic epilepsy</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>Absence epilepsy, myoclonic epilepsy, symptomatic epilepsy</td>
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</tbody>
</table>
### Idiopathic vs Symptomatic Generalized Epilepsies

<table>
<thead>
<tr>
<th>1. Etiology</th>
<th>Symptomatic</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Acquired/Genetic</td>
<td>Genetic</td>
</tr>
<tr>
<td>2. Seizure types</td>
<td>Atyypical absences, Myoclonic</td>
<td>Absence, Myoclonic, Tonic-clonic</td>
</tr>
<tr>
<td></td>
<td>Tonic, atonic</td>
<td></td>
</tr>
<tr>
<td>3. Exam</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Intellectual disability</td>
<td></td>
</tr>
<tr>
<td>4. EEG</td>
<td>Normal background, Spike-wave 3 Hz</td>
<td>Background, Spike-wave 2.5 Hz</td>
</tr>
<tr>
<td></td>
<td>Background</td>
<td></td>
</tr>
<tr>
<td>5. Imaging</td>
<td>Normal (cortical abnormality)</td>
<td>Normal</td>
</tr>
<tr>
<td>6. Prognosis</td>
<td>Good</td>
<td>Poor</td>
</tr>
</tbody>
</table>

### Early Infantile Epileptic Encephalopathy with Suppression-Bursts (EIEE, Ohtahara’s Syndrome)
- **Incidence:** no data
- **Age of onset:** within first 3 months
- **Etiology:** cerebral dysgenesis, anoxia, cryptogenic
- **Seizures:** tonic, spasm, focal motor, hemiclonal, generalized seizures
- **Background EEG:** suppression-burst
- **Ictal EEG:** diffuse synchronization, cluster of fast activity
- **Therapy:** ACTH, B6-vit., VPA, other AEDs, surgery
- **Prognosis:** static impairment to severe mental retardation, quadraplegia and bedridden, evolution to West and Lennox Gastaut syndrome, high incidence of death

### Early (Neonatal) Myoclonic Encephalopathy (EME)
- **Incidence:** no data
- **Age of onset:** neonatal
- **Etiology:** inborn errors of metabolism, familial, cryptogenic
- **Seizures:** erratic or fragmentary myoclonus, massive myoclonus, simple partial seizures, infantile spasms, tonic suppression-burst
- **EEG:** suppression-burst
- **Therapy:** ACTH ineffective, pyridoxine may be tried
- **Prognosis:** progressive impairment to vegetative state, infantile spasms, high mortality in infancy

### Non Ketotic Hyperglycinemia
Nonketotic Hyperglycinemia (NKH)

- **aka glycine encephalopathy**
  - Autosomal recessive hereditary metabolic disorder
  - affects the breakdown of the amino acid glycine in infants
  - Characterized by abnormally high levels of the amino acid glycine in the blood, urine, and the cerebrospinal fluid.
  - cause extensive neuronal damage in neonatal brain
  - via N-methyl-D-aspartate glutamate receptor-mediated

What is affected?

- **Glycine Cleavage System**
  - mutation in the GCS
  - inadequate supply of the enzymes necessary to the break down of glycine causing a build up of glycine in the body.

- **AMT and GLDC genes**

Fig. Infant brain with NKH
Symptoms and Effects

Four forms of this disorder:

• Neonatal form
  - seen in the first few days after birth
  • low muscle tone (hypotonia), and drowsiness
  • seizures and mental retardation

• Infantile form
  - six months of seemingly normal development
  • with the exception of occasional feeding difficulties & seizures
  • varying degrees of mental retardation become evident.

• Mild-episodic form
  - appears during childhood episodes of delirium; involuntary, jerky movements (chorea); inability to look upward (vertical gaze palsy)
  • fever and mild mental retardation

• Late-onset form
  - during childhood with progressive stiffness in both legs and degeneration of the optic nerve, leading to loss of sight.
  • Neither seizures nor mental retardation are associated

How common is NKH?

• Rare metabolic disorder that usually affects infants soon after birth.
  - Estimated 1 in 60,000
• Males & females appear to be affected in equal proportions.
• Both parents are carriers
  - 25% chance child will be born with the disease
  - 50% chance child will be a carrier for the gene defect.

Can it be treated? How?

• At this time there are no existing treatments.
  - Rarely children grow out of NKH and go on to live normal lives.
• For some individuals glycine levels have decreased but mental retardation and seizures may still persist.

West syndrome

(infantile spasms, psychomotor deterioration, hypsarrhythmia)

- Incidence: 3-5/10,000 live births
- Age of onset: 50-77% between 3-7 months, 93% up to 2 yrs
- Etiology: Malformations, 15-20% cryptogenic
- Seizures: Tonic spasms in clusters, partial seizures preceding or associated with spasms
- EEG: Ictal generalized fast activity, interictal hypersrhythmia
- Therapy: VGB, ACTH
- Prognosis: mortality 5-31%, mental retardation 80%, epilepsy 60-80%, Lennox-Gastaut 40-60%
Lennox Gastaut syndrome

- **Prevalence:** 2-3% of childhood epilepsies
- **Age of onset:** 1-8 years (peak 3-5 yrs)
- **Etiology:** malformations, neurectodermal disorders, infections, 20-30% cryptogenic
- **Seizures:** tonic-axial, atonic and atypical absence seizures
- **EEG:** abnormal background activity, generalized slow spike-waves <3 Hz and, often multifocal abnormalities. During sleep, bursts of fast rhythms (∼10 Hz) appear
- **Therapy:** VPA, LTG, TPM, LEV, benzodiazepines
- **Prognosis:** mental retardation 78-96%, resistant epilepsy
Acquired epileptic aphasia  
(Landau-Kleffner)

**Incidence:** rare, exact numbers not available  
**Age of onset:** 2-8 years (peak 5-7 years)  
**Etiology:** epileptogenic functional lesion in the speech cortex  
**Seizures:** present in 70-80%: atypical absences, myoclonic seizures, focal seizures w/ 2° generalization, variable prognosis  
**Clinical:** verbal auditory agnosia → acquired aphasia → behavioral and psychiatric problems  
**EEG:** bilateral symmetrical/asymmetrical multifocal spikes and slow waves in temporal and parieto-occipital regions, sleep enhances spiking up to CSWS (85% of slow wave sleep)  
**Therapy:** VPA, BZDs, ESM, TPM, (steroids, surgery, immunoglobulin)  
**Prognosis:** aphasia usually improves w/ EEG normalization before adulthood, 10-20% may achieve complete normalization, others are left with permanent sequelae

**Epilepsy & malformations of the cerebral cortex**

- abnormal proliferation of neurons and glia  
  - hemimegalencephaly  
    - focal cortical dysplasia  
    - schizencephaly  
- abnormal neuronal migration  
  - gray matter heterotopia  
  - bilateral periventricular nodular heterotopia  
  - classical lissencephaly and subcortical band heterotopia  
- abnormal cortical organization  
- syndromes resulting from regional polymicrogyria

**Hemimegalencephaly**

- A five month old girl who started having clonic jerking of the right arm at age four months  
- NSVD, Uneventful prenatal history  
- G+D Regrad face 2 m, Follow 3 m, Sit with support 5 m  
- Med: Phenobarbital 20 mg/kg/day, BI level > 130 uG/ml  
  - PHT, CBZ, Vigabatrin, Topiramate  
  - B6 100 mg trial  
- Video-EEG monitoring:  
  - Interictal: > 90% Lateralized left hemisphere 10% Rt C4 P4  
  - Ictal EEG: > 90% Lateralized Lt Hemisphere
Diagnosis

Severe cortical dysplasia and hemimegalencephaly.

STURGE-WEBER SYNDROME:

- Encephalotrigeminal angiomatosis
  - 1) leptomeningeal angiomatosis
  - 2) skin of face
  - typically the V1 and V2 portions of the Facial Nerve
- LA may be unilateral or bilateral
- Functional Neuroimaging:
  - may demonstrate a greater area of functional than anatomic abnormality
Neurologic Manifestations

• 1) Seizures
• 2) Focal deficits, such as hemiparesis and hemianopia
• 3) Stroke-like episodes
• 4) Headaches
• 5) Developmental delay
  – more common with bilateral hemangiomas

Classification

• Complete SWS: both brain and eye
• Incomplete: when only one area is affected
  • Roach Scale:
    – I: Both facial and leptomeningeal angiomas
      • may have glaucoma
    – II: Facial angioma alone
      • may have glaucoma
    – III: Isolated LA;
      • usually not with glaucoma

Age of Presentation

• Typically presents at birth with facial angiomas
• However, not all children with PWS have SWS
• “Incomplete forms” occur without cutaneous features (Type III)
  – May have no suspicion until seizure or other neurologic problem occurs
• Klippel-Trenauney-Weber: hemangiomas, hemihypertrophy

Seizures in SWS

• Incidence: 75 - 90%
• May have dual pathology: microgyria
• Survey SWF: seizures in 136/171
• Median age onset 6 months, range birth to 23 years
• Age of Sz onset:
  – 75% onset during first year
  – 86% before two years
  – 95% before 5 years
• Sz in 71% with unilateral and 87% with bilateral lesions

Seizures in SWS

• Majority focal
• SWF survey: 50% complete control, 39% had only partial control
• Later seizure onset: lower incidence dev delay, fewer special needs
• Roach: onset < 2 years: greater chance refractory epilepsy and MR
• Earlier onset with bilateral disease

Predictors Poor Outcome

• Early Sz onset
• Extensive LA
• Refractory Sz
• Relapsing/permanent motor deficits
• HA, trauma with transient deficits
• Progressive neurologic disorder
• Focal Sz with II Genl
• Increasing Sz frequency, duration or post-ictal deficits
• Focal or diffuse atrophy
• Progressive atrophy and calcification
• Hemiparesis
• Intellectual regression
Sturge-Weber Syndrome: MRI

STURGE-WEBER SYNDROME:
Large Area of Mild Glucose Hypometabolism Associated with Poor Cognitive Outcome

Tuberous Sclerosis
A 3 year old girl, presented with giggling!
Tuberous Sclerosis

- CNS pathology: Multiple cortical tubers / SEGA -> Hydrocephalus
- CCF:
  - Not all the tubers are epileptogenic,
  - Interictal EEG/Video EEG monitoring and ictal SPECT can elucidate the tuber which is “epileptogenic”
  - Good Surgical outcome -> significantly improved seizure control

Tuberous Sclerosis

- Epiloia or Bourneville’s disease.
- 1:5000-1:10000
- Damage of one of two genes which regulate growth.
- Hamartomas in variety of organ.
- Most common - brain, kidneys, skin.
- Can present at any age.
- Variation in severity

Tuberous Sclerosis: Genetics

- AD transmission, variability in symptoms.
- Mutation on either TSC1 (Tuberous sclerosis) gene (chromosome 9) or TSC2 gene (chromosome 16).
  - Gross deletion/insertions and micromutations.
- 60-70% are sporadic (new mutations).

Ash-leaf Spots

- Cutaneous Manifestations
  - Cafe-au-lait spots (7-16%)
  - Fibromas: flattened and can appear on the trunk, gingivae, periungual region, and along the hairline or eyebrows.
  - Koenen’s Tumors (20%): Subungual or periungual fibromas, usually first appear in adolescence, toes>fingers.

Adenoma Sebaceum

- Neurologic Manifestations

  - Cortical tubers
    - Focal, gray-white matter interface
    - Microscopically - loss of normal cytoarchitecture, abnormal neurons and glial cells.
    - MRI > CT
    - Number and size correlate with seizures and mental retardation.
**Neurologic Manifestations**

- **Subependymal nodules**
  - Usually line the third ventricle. Large, irregular cells that are more densely aggregated and more uniform in appearance compared with the cortical tubers.
  - Some will grow > than 3 cm in diameter => called subependymal giant cell astrocytomas (5%).
  - Histologic features similar to cortical nodules.
  - Histologic features similar to cortical nodules.
  - Later in life, subependymal nodules often calcify.

- **Seizures (60-90%)**
  - Most common symptom of TS.
  - Risk of sudden epileptic death.
  - Initially may present as infantile spasms:
    - 25-50% of patients with infantile spasms later develop signs of TS.
    - Can appear as early as 1 week of age.
    - Later develop other types of generalized seizures.

- **Mental health**
  - Very common, very difficult.
  - More in children with epilepsy.
  - May be associated with tubers in temporal area.
  - Autism (25%) and autism spectrum disorders (50%).
  - Sleep disturbances.
  - ADDH +/- hyperactivity.
  - Anxiety and depression.

- **Development and learning disorders**
  - Developmental delay (40-60%).
  - Learning difficulties (40-60%).
  - More in children who present with infantile spasm and epilepsy.
  - The earlier the onset of seizures the greater the likelihood of mental retardation (if seizures begin <1 year of age a 92% chance of MR).

**Rasmussen’s Encephalitis**

- A 9 year old girl with a 2-3 years Hx of Rt arm jerking.
- Initially controlled with CBZ for 1-2 months
- Progressively worsen to the face / leg with right hemiparesis
On April 20, 2008, I met a spunky little girl named Jessie Hall. I had no idea that on this day, my life would never again be the same. I fell in love with the most darling little girl. Let me tell you a bit about Jessie and her impact on me.

Imagine being told that your child has a very cruel and extremely rare brain disease, and the only hope for survival was the removal of half their brain. Cris and Kristi didn’t know what to do, nor whom to speak with. Having access to a referral list of fellow parents going through this same nightmare, would have meant the world to them.

There was no foundation or charity in place to seek for organized support or the distribution of educational materials.