Who Gets Epilepsy? Etiologies and Risk Factors for Seizures

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Audience Response Keypads

- Please utilize the keypad at your table to answer questions throughout the program.
- You will have 10 seconds to answer the question.
- Please leave the keypad at your table at the end of the day.
How to Avoid Epilepsy
The greatest risk for epilepsy occurs in persons who have a history of:

A. Participating in football
B. Alcoholism
C. Positive family history of epilepsy
D. Bacterial meningitis
E. Severe military head trauma
• Epidemiology
• Risk Factors
  • Febrile seizures
  • CNS infection
  • Genetics
  • TBI
  • Stroke
  • Brain tumor
  • Other
Factors Associated with an Altered Risk of Epilepsy

- Family history of seizures: 2.5
- Severe military head trauma: 580
- Severe civilian head trauma: 25
- Moderate head trauma: 4
- Mild head trauma: 1.5*
- Stroke: 22
- Viral encephalitis: 16.2
- Alzheimer’s disease: 10
- Bacterial meningitis: 4.2
- Multiple sclerosis: 3.6
- Aseptic meningitis: 2.3
- Alcohol: 10.1
- Heroin: 2.6
- Marijuana: 0.36
- No adverse exposure: 1

*Not statistically significant.

Risk Factors Guide Epilepsy History

• Birth and developmental history
• Family history of epilepsy
• History of TBI
• History of CNS infection
• History of febrile seizures
• History of stroke
• Other
Seizure and Epilepsy Statistics

- By 75 years of age, 10% have some type of seizure
- Incidence=number of new cases per year
  - 30-50+/100,000
- Active Prevalence=persons being treated or having had a seizure within last 5 years
  - 4-12/1,000
- CDC estimates 3 million US adults and 470,000 children with active epilepsy

Cumulative Incidence of Seizures

Age 2
- Green: Epilepsy
- Yellow: Isolated Seizures
- Blue: Febrile Convulsions
- Pink: Acute Symptomatic

Age 5
- Green: Epilepsy
- Yellow: Isolated Seizures
- Blue: Febrile Convulsions
- Pink: Acute Symptomatic

Age 80
- Green: Epilepsy
- Yellow: Isolated Seizures
- Blue: Febrile Convulsions
- Pink: Acute Symptomatic

% With Seizures
Etiology of Epilepsy by Age

Annegers JF. In: The Epidemiology of Epilepsy: Principles and Practice. 2001.
Acquired vs Genetic Etiologies

- **Acquired**
  - Head trauma
  - CNS infections
  - Stroke
  - Tumors
  - Vascular malformations
  - Neurodegenerative diseases

- **Genetic**
  - >200 single gene defects (1% of epilepsy)
  - Polygenic (Complex genetic factors contribute to ~40% of epilepsy)
Evolving Understanding of Epilepsy Etiologies

Thomas RH, Berkovic SF. Nat Rev Neurol. 2014.
Febrile Seizures

• Ages 6 months to 5 years associated with fever of >38.5°C oral without CNS infection
• 2%-5% of all children
• First may be complex in 30%-40%
• Risk factors:
  • (+) Family history of febrile seizures
  • Developmental delay, birth complications
  • Higher temperatures
  • Low ferritin
• Occurrence after DTP (whole cell) - 6-9/100,000
• Occurrence after MMR vaccination - 25-34/100,000

Febrile Seizures – Link to Epilepsy

- Later risk of epilepsy
  - <5% of all with febrile seizures
  - ~15% of complex febrile seizure
- History of FS in 15% of epilepsy patients
- Risk of developing non-febrile seizures:
  - Abnormal development before 1st febrile seizure
  - Abnormal examination
  - History of family member with afebrile seizures
  - Complex first febrile seizure
- One factor: 3% risk; ≥2 factors: 13% risk

Febrile Status and Intractable TLE

• Febrile status as cause of mesial temporal sclerosis (MTS) and refractory TLE is rare
  • ~1/100,000

Febrile Seizures and Risk of Epilepsy

• National General Practice Study (Family Practice, UK)
• 220 children with FS with 21.6 year follow-up
  • 86% index seizure was the first seizure
  • 12% prior FS
  • 2% multiple prior FS

<table>
<thead>
<tr>
<th></th>
<th>10 years</th>
<th>&gt;20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free</td>
<td>201 (95%)</td>
<td>171 (94%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>12 (5.4%)</td>
<td>14 (6.7%)</td>
</tr>
</tbody>
</table>

• Nearly 10 times increased risk of developing epilepsy

A 29-year-old woman has altered mental status, seizures, and is diagnosed with HSV-1 encephalitis. Which of the following predicts the greatest risk of developing chronic epilepsy?

A. Female sex
B. Abnormal EEG in acute phase
C. Presentation with acute seizures
D. Presence of HLA-B27 allele
E. Presentation with altered mental status
CNS Infections

• Acute seizures and epilepsy
• Risk factors for epilepsy
  • Seizures in acute phase
  • Parenchymal involvement
  • Age at onset
  • Family history of epilepsy
• 20-year risk
  • Bacterial meningitis: 13%
  • Encephalitis: 22%

Bacterial Meningitis

- Up to 50% have acute seizures
- Risk of epilepsy increases 5.4-fold
- Epilepsy risk
  - Early seizures
  - Structural abnormality
  - Persistent neurological or EEG abnormality
  - Low CSF glucose at presentation
  - Strep pneumonia
  - Neonates: Group B Strep
  - (Dexamethasone)

Encephalitis

- HSV-1 most common
  - 50% present with acute seizures
    - Young age
    - Altered level of consciousness
    - Cortical involvement
  - Seizures in HSV-1 associated with poor outcome
- HSV + VZV = 25% of encephalitis cases
  - 50% unidentified etiology
- Most common preventable causes of encephalitis
  - Malaria
  - Neurocysticercosis

Encephalitis: Risk Factors for Epilepsy

- Acute seizures
  - Risk of developing later epilepsy
    - 22% in patients with acute seizures
    - 10% in patients without acute seizures
- Status epilepticus
- Severe altered level of consciousness
- Focal neurological signs
- Neurological deterioration
- Abnormal EEG
- Focal cortical abnormality on imaging

Genetic Causes of Epilepsy

- Single Gene Defects (Ion Channel)
- Genes encoding development (Neuronal Migration)
- Genes encoding cerebral energy metabolism (mitochondrial)
- Genetic neurodegenerative disorders (progressive myoclonus epilepsies)
- Inborn errors of metabolism (lysosomal storage diseases)
- Other genetic syndromes with epilepsy (Down syndrome)
### Genetic Epilepsy Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Channel</th>
<th>Implicated Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign familial neonatal epilepsy</td>
<td>K⁺</td>
<td>KCNQ2, KCNQ3</td>
</tr>
<tr>
<td>Otahara syndrome</td>
<td>Na⁺, K⁺</td>
<td>SCN2A, ARX, CDKL5, STXBP1, PLB1, KCNQ2</td>
</tr>
<tr>
<td>GEFS+</td>
<td>GABA, Na⁺</td>
<td>SCN1A, SCN2A, SCN1B, GABRG2, SCN2A, GABRD</td>
</tr>
<tr>
<td>Severe myoclonic epilepsy of infancy (SMEI; Dravet Syndrome)</td>
<td>GABA, Na⁺</td>
<td>SCN1A, SCN1B, SCN2A, GABRG2</td>
</tr>
<tr>
<td>Doose Syndrome</td>
<td>GABA, Na⁺</td>
<td>SCN1A, SCN1B, GABRG2, SLC2A1</td>
</tr>
<tr>
<td>Migrating partial seizures of infancy</td>
<td>Na⁺</td>
<td>SCN1A</td>
</tr>
<tr>
<td>Childhood Absence</td>
<td>Ca++, GABA</td>
<td>CACNA1A, CACNA1H, GABRA1, GABRB3, GABRG2</td>
</tr>
<tr>
<td>Autosomal Nocturnal FLE</td>
<td>AcH</td>
<td>CHRNA4, CHRN2B, CHRNA2</td>
</tr>
<tr>
<td>AD partial epilepsy with auditory features</td>
<td>K⁺</td>
<td>LGI1</td>
</tr>
</tbody>
</table>

Genetic Mechanisms of Epilepsy

Genetic Testing

• Gap between basic science and clinic
• Area of rapid change
• Search for single gene defect in severe epileptic encephalopathies is high yield
  • Guide treatment
  • Gives parents an answer
  • Avoid unnecessary additional testing
Vaccine Encephalopathy

- Pertussis vaccination had been implicated in severe epileptic encephalopathies
- This condition resembles Severe Myoclonic Epilepsy of Infancy (Dravet)
- Retrospective genetic analysis of 14 patients with first seizure within 72 hours of vaccination
  - 11 of 14 had an SCN1A mutation

Post-traumatic Epilepsy
Etiology: Trauma

- Most common cause of new onset epilepsy in young adults
- 30,000 per year in the US

<table>
<thead>
<tr>
<th>Severity of Injury</th>
<th>Standardized Incidence Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild TBI</td>
<td>1.5 (1.0 – 2.2)</td>
</tr>
<tr>
<td>Moderate TBI</td>
<td>2.9 (1.9 – 4.1)</td>
</tr>
<tr>
<td>Severe TBI</td>
<td>17.0 (12.3 – 23.6)</td>
</tr>
</tbody>
</table>

- Risk Factors from Multivariate Analysis
  - Contusion with SDH
  - Skull fracture
  - LOC >24 hours
  - Age 65 or older

Military Trauma

- **WWI, WWII, Korean**
  - Epilepsy 10 years post injury 50%
- **Vietnam** Head Injury Study, N=520
  - Epilepsy 53%
  - Penetrating injury 92%
  - Risk factors: Brain volume loss, hematomata, retained metal
  - Onset of epilepsy
    - 12 months 58%
    - 1-5 years 21%
    - 5-10 years 9.5%
    - 10-15 years 5.6%
    - 15-35 years 5.6%

Early vs Late Post-Traumatic Seizures

**Early Seizures (< 7 days)**
- Increased with:
  - Severity of injury
  - Young age
- Timing:
  - ¼ in first hour
  - ½ in first day
- Treatment:
  - Short term prophylaxis if high risk
  - Does not reduce risk of epilepsy
- Conflicting data on long-term epilepsy risk

**Late Seizures (> 7 days)**
- Reflects brain reorganization/rewiring
- Presentation of PTE:
  - 86% recurrence rate by 2y
- Timing:
  - 69% by 6 months
  - 82% by 1 year
  - 86% by 2 years
- Risk elevation and severity:
  - Mild: risk persists for ~5 years
  - Moderate: risk persists 10 years
  - Severe: risk persists >/= 20 years

Etiology of Epilepsy in Patients 60 Years and Older: Incident Cases

- Cerebral Infarct: 34.10%
- Arteriosclerosis: 14.9%
- Other: 18.8%
- Head Trauma: 6.9%
- Hemorrhage: 1.7%
- Unknown: 24.6%

# Risk of Seizures after Stroke

<table>
<thead>
<tr>
<th>Seizures</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall risk</strong></td>
<td>8.9</td>
</tr>
<tr>
<td>• Early w/in 2 weeks</td>
<td>4-14</td>
</tr>
<tr>
<td>• Late &gt;2 weeks</td>
<td>3-10</td>
</tr>
<tr>
<td><strong>Cumulative risk</strong></td>
<td></td>
</tr>
<tr>
<td>• 1 year</td>
<td>5.7</td>
</tr>
<tr>
<td>• 5 year</td>
<td>11.5</td>
</tr>
</tbody>
</table>

### Time to First Seizure

<table>
<thead>
<tr>
<th>Seizure Delay</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 wk</td>
<td>24</td>
</tr>
<tr>
<td>&gt;2 wk to ≤1 y</td>
<td>38</td>
</tr>
<tr>
<td>&gt;1 y to ≤2 y</td>
<td>19</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>19</td>
</tr>
</tbody>
</table>

Epilepsy Risk Post Stroke

Risk Factors
- Early seizures
- Cortical involvement
- Large volume
- Hemorrhagic stroke

<table>
<thead>
<tr>
<th></th>
<th>At 1 year</th>
<th>At 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 1 risk factor</td>
<td>4.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>If ≥2 risk factors</td>
<td>33%</td>
<td>58%</td>
</tr>
</tbody>
</table>

# Etiology of Stroke as Predictor

<table>
<thead>
<tr>
<th>Type</th>
<th>% with Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>6 – 8.6</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>10.6 – 27.8</td>
</tr>
<tr>
<td>With cortical involvement</td>
<td>17</td>
</tr>
<tr>
<td>Lobar</td>
<td>32</td>
</tr>
<tr>
<td>Putaminal, thalamic, pontine</td>
<td>2</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>6.3</td>
</tr>
<tr>
<td>Lacunar</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Timing of Stroke as Predictor

- Longer period between stroke and first seizure

Risk of Developing Epilepsy After:

<table>
<thead>
<tr>
<th></th>
<th>Ischemic</th>
<th>Intracerebral Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early seizure</td>
<td>35%</td>
<td>29%</td>
</tr>
<tr>
<td>Late seizure</td>
<td>90%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Acute EEG as Predictor

- EEG findings that have high correlation with clinical seizures:
  - PLEDS, BiPLEDS, focal spikes

- EEG findings that have low correlation:
  - Focal slowing, diffuse slowing, normal record

- Continuous EEG monitoring detected four times more electrographic seizures than clinically evident

Brain Tumors
Seizures in Patients With Brain Tumors

- Brain tumors and seizures
  - 20%-40% incidence at presentation
  - 20%-45% incidence after diagnosis
  - Primary > metastatic
- Treatment may be challenging
  - Relatively refractory seizures
  - Potential interactions with chemotherapy agents
  - High incidence of adverse events
    - 24% adverse effects requiring change or discontinuation
## Predictors of Epilepsy in Brain Tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Hildebrand (%)</th>
<th>Lote (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 glioma</td>
<td>46%</td>
<td>85%</td>
</tr>
<tr>
<td>Grade 3 glioma</td>
<td>30%</td>
<td>69%</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>15%</td>
<td>49%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical/subcortical</td>
<td>92%</td>
</tr>
<tr>
<td>Deep white + basal ganglia</td>
<td>1%</td>
</tr>
<tr>
<td>Both</td>
<td>7%</td>
</tr>
</tbody>
</table>

# Predictors of Epilepsy by Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade glioma, ganglioglioma</td>
<td>60-85</td>
</tr>
<tr>
<td>DNET</td>
<td>100</td>
</tr>
<tr>
<td>High grade glioma</td>
<td>20-40</td>
</tr>
<tr>
<td>Metastasis</td>
<td>15-20</td>
</tr>
</tbody>
</table>

## Location

- Temporal, primary sensorimotor, supplementary cortex
- Epileptic focus did not correlate to tumor location in 33% of patients

What if Etiology Is Not Apparent?

- 29-year-old woman with no historical risk factors for epilepsy
  - Behavioral changes over 2 weeks
  - Explosive onset of seizures multiple times per day
  - Autonomic dysfunction
  - Refractory to traditional anti-seizure medications
  - Normal MRI
  - Negative infectious workup
Autoimmune Epilepsy

Clinical Factors in Autoimmune Epilepsies

- Focal epilepsy
- Risk factors for Ca autoimmunity present
- Subacute onset
- Additional neurologic symptoms
- High seizure frequency
- Nonimmunologic causes excluded

Autoimmune epilepsy work-up warranted
Autoimmune Algorithm

Associated autoantibodies testing (serum and CSF) → Positive

Autoimmune epilepsy

Negative

Alternative diagnosis

Tumor detection (MRI, CT, etc.)

First-line immunotherapy (MP, IVIg, plasma exchange, etc., alone or in combination)

Tumor removal

Positive

(With delayed diagnosis)

Alternative immunosuppressants

Second-line immunotherapy (rituximab, MMF, etc., alone or in combination)

Supportive care, tumor surveillance

Good response

Poor response

Positive

Good response

Poor response

Negative

Etiology Search: Pearls

- In older patient, think stroke (even if no clinical or discrete cortical stroke)
- In explosive, adult-onset epilepsy think autoimmune
- For all “idiopathic” cases, get good imaging and review yourself and with neuroradiology (dysplasias, etc.)
- Consider genetic testing (intellectual disability, autism, dysmorphic features, refractory epilepsy)
- Idiopathic - Unknown
Conclusions

- Epidemiology
- Risk Factors
  - Febrile seizures
  - CNS infection
  - Genetics
  - TBI
  - Stroke
  - Brain tumor
  - Other