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Who Gets Epilepsy?  
Etiologies and Risk Factors for Seizures

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Director, OHSU Epilepsy Center  
Portland, OR
Outline

• 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

- Epilepsy
- Acute Symptomatic
- Isolated Seizures
- Febrile Convulsions

Age

% With Seizures
Etiology of Epilepsy by Age

Proportion of cases (%)

0-4 5-14 15-24 25-44 45-64 65+

Others Degenerative Cerebrovascular Brain Tumor Trauma Infection Development

Annegers. 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.

Diagram showing the neurobiological spectrum of epilepsies, with categories including:
- **Inherited channelopathies**
- **Acquired channelopathies**
- **Single-gene epilepsies**
- **Epilepsies with complex inheritance**
- **Trauma Hypoxia Stroke**

The spectrum ranges from **Idiopathic** to **Symptomatic**, with an interaction of genetic and acquired factors via ion channels.
Febrile Seizures

- Ages 3 months to 6 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

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, CHRNB2, CHRNA2</td>
</tr>
<tr>
<td>AD partial epilepsy with auditory features</td>
<td>$K^+$</td>
<td>LGI1</td>
</tr>
</tbody>
</table>

Genetic Testing

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

- Pertussis vaccination has 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

## Factors Causing an Increased Risk of Post-traumatic Epilepsy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Increase in Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating brain injury</td>
<td>40</td>
</tr>
<tr>
<td>Intracranial hematoma</td>
<td>35</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>35</td>
</tr>
<tr>
<td>Early seizure</td>
<td>25</td>
</tr>
<tr>
<td>Depressed fracture of skull vault</td>
<td>15</td>
</tr>
<tr>
<td>Post-traumatic amnesia 24 hours</td>
<td>4</td>
</tr>
</tbody>
</table>

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, hematoma, 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%

Military Trauma

- Afghanistan-Iraq conflict
- Blast injuries
  - Pressure waves
- Increased brain injury
- Increased epilepsy?
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>Overall risk</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>Cumulative risk</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>

# Post-infarct Epilepsy

## Time to First Seizure

<table>
<thead>
<tr>
<th>Seizure Delay</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 wk</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>&gt;2 wk to ≤1 y</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>&gt;1 y to ≤2 y</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

Epilepsy Risk Post Stroke

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

<table>
<thead>
<tr>
<th>Risk Factor</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>

## Risk Factors for Developing Seizures After CVA

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Patients with Seizures (%)</th>
<th>Patients without Seizures (%)</th>
<th>Significance* (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic</td>
<td>(25)</td>
<td>(75)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>(7)</td>
<td>(93)</td>
<td>.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>Patients with Seizures (%)</th>
<th>Patients without Seizures (%)</th>
<th>Significance* (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>(17)</td>
<td>(83)</td>
<td></td>
</tr>
<tr>
<td>Subcortical</td>
<td>(4.7)</td>
<td>(95.3)</td>
<td>.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of Lesion</th>
<th>Patients with Seizures (%)</th>
<th>Patients without Seizures (%)</th>
<th>Significance* (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>(21.2)</td>
<td>(78.8)</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>(5.2)</td>
<td>(94.8)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Chi-square test

## Etiology of Stroke as Predictor

<table>
<thead>
<tr>
<th>Etiology</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>

Predictors of Post Stroke Epilepsy

• 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 Findings as Predictor of Post Stroke Seizures

- 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

Seizures in Patients With Brain Tumors

- Brain tumors and seizures
  - 20%-40% incidence at presentation
  - 20%-45% incidence after diagnosis
  - Primary > metastatic
- Treatment is challenging
  - Relatively refractory seizures
  - Potential interactions with chemotherapy agents
  - High incidence of adverse events
    - 24% adverse effects requiring change or discontinuation
    - Higher than in epilepsy populations due to chemotherapeutic agents and other treatments

# Predictors of Epilepsy in Brain Tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Seizures (%)</th>
<th>No seizures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 glioma</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Grade 3 glioma</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>15</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Seizures (%)</th>
<th>No seizures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical/subcortical</td>
<td>92</td>
<td>75</td>
</tr>
<tr>
<td>Deep white + basal ganglia</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>6</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, gangliogioma</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
- (With delayed diagnosis)

Autoimmune epilepsy -> Tumor detection (MRI, CT, etc.)

- Positive -> Tumor removal
- Negative -> First-line immunotherapy (MP, IVIg, plasma exchange, etc., alone or in combination)
  - Poor response -> Second-line immunotherapy (rituximab, MMF, etc., alone or in combination)
    - Poor response -> Alternative immunosuppressants
    - Good response -> Supportive care, tumor surveillance

Positive response

Negative response
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