Neuropathology of epilepsy

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Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

1. Describe the difference between seizures and epilepsy, and how epilepsy is diagnosed
2. Identify specific histologic patterns that can be observed in epilepsy surgical specimens
3. Outline the appropriate steps for tissue handing in the setting of epilepsy surgery
Outline

• Background
• Hippocampal sclerosis
• Focal cortical dysplasia
• Other lesions
• Practical considerations
Epilepsy

• Recurring, unprovoked seizures
  – At least 2, >24h apart
  – OR single unprovoked seizure if probability of recurrence is >60% over next 10 yrs
  – OR epilepsy syndrome

• 1.2% of US population has active epilepsy

• Can begin at any age, but more people are diagnosed at two distinct phases in life: early childhood and after age 55

Epilepsy is common

• 1 in 26 people will develop epilepsy at some point during their lifetime
• More common than multiple sclerosis, muscular dystrophy, cerebral palsy, and Parkinson’s disease combined
• Impacts the entire family and every activity
• Even seizure free epilepsy patients still report decreased QoL due to stress and uncertainty of when a seizure will occur
Drug-resistant epilepsy

• 65-70% of patients respond to the first or second medication used, with near or complete seizure control.
• Patients who have failed 2 medications have less than ~5% chance of responding to a third
• “medication resistant”
Kids are differentially impacted

- In kids, a window of opportunity to learn key skills means urgency to arrive at accurate diagnosis.

- Longer duration of epilepsy (>5 years) is associated with worse behavioral and psychosocial outcomes:
  - Aggression, self-aggression
  - Attention deficit

Evaluations

Goal is to establish:

Type of epilepsy
- Focal
- Generalized
- Mixed

Underlying cause

- H&P, EEG, MRI, labs, genetic tests
- Drug resistant epilepsy should see an epileptologist
  - Video/EEG monitoring
  - MRI with an epilepsy protocol
  - Neuropsych testing (“thinking and learning”)
  - Genetic testing (WES)
  - PET, SPECT, MEG
ILAE 2017: Updated classification of seizure types

- Focal – start in one spot in the brain
  - Old system
    - complex partial (change in consciousness)
    - simple partial (no change in consciousness)
  - New system:
    - Focal-Aware and Focal-Impaired awareness
    - Motor vs. non-motor
- Any can secondarily become generalized convulsive type
- Generalized
  - Motor
  - Non-motor (absence)
- Determining the type
  - Video/EEG
  - 24 hour increases percent detection into 90s
  - Patients w focal seizures need MRI
ILAE 2017 Classification of Seizure Types Basic Version


__ Focal Onset
  (if focal onset, choose one or leave blank if unknown)
  __ Aware
  __ Impaired Awareness

  (if focal onset, choose one or leave blank if unknown)
  __ Motor Onset
  __ Nonmotor Onset
  __ Focal to bilateral tonic-clonic

__ Generalized Onset
  (if generalized onset, choose one or leave blank if unknown)
  __ Motor
  __ Nonmotor (absence)

__ Unknown Onset
  (if unknown onset, choose one or leave blank if unknown)
  __ Motor
  __ Nonmotor
EEG

Electrical patterns of the brain
- Awake (normal)
- Closed eyes (normal)
- Drowsy (normal)
- Early sleep (normal)
- Deeper sleep (normal)
- REM sleep (normal)
- Some brains don’t make any normal patterns (global disabilities)

Activations
- Flashing lights
- Breathing deeply
- Sleep deprivation
Seizure: mechanism and drug actions

Epilepsy surgery: Pre-surgical evaluation

Phase I
- Non-invasive
- Outpatient monitoring
- Inpatient/video EEG
- Neuroimaging
- Neuropsych testing

Phase II
- Anesthesiology
- Neurosurgery
- Pre-op tests
- Intracranial depth electrodes
- Subdural strip/grid electrodes
- Electrocorticography

www.aboutkidshealth.ca/article?contentid=2056
Electrode tract histology

myelin

GFAP

Zaer H et al. Front Hum Neurosci. 2021; PMID: 33613212
Surgery if indicated after Phase I/II

Phase I
- Workup
- Imaging
- Neuropsych

Phase II
- Intracranial monitoring

Phase III
- Resection
- Disconnection
- Ablation
- Neuromodulation

Phase IV
- Recovery
### Causes of epilepsy

- Migrational anomalies
- Temporal lobe structural abnormalities
- Brain tumors
- Neurocutaneous disorders
- Infections
- Vascular diseases
- Brain injury

#### Table 1: Neuropathological findings in epilepsy surgery

<table>
<thead>
<tr>
<th>Category</th>
<th>Numbers (%)</th>
<th>Age OP</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS</td>
<td>1,908 (32.7%)</td>
<td>33.9 ± 10.4</td>
<td>11.3 ± 7.7</td>
<td>22.7 ± 10.0</td>
</tr>
<tr>
<td>Dual</td>
<td>294 (5.0%)</td>
<td>25.5 ± 12.8</td>
<td>9.5 ± 7.8</td>
<td>15.9 ± 9.9</td>
</tr>
<tr>
<td>LEAT</td>
<td>1,551 (26.5%)</td>
<td>27.9 ± 12.3</td>
<td>16.5 ± 10.1</td>
<td>11.8 ± 8.8</td>
</tr>
<tr>
<td>MCD</td>
<td>930 (15.9%)</td>
<td>18.2 ± 12.0</td>
<td>5.9 ± 5.7</td>
<td>12.3 ± 9.1</td>
</tr>
<tr>
<td>Vascular</td>
<td>328 (5.6%)</td>
<td>36.1 ± 12.3</td>
<td>23.4 ± 11.4</td>
<td>12.7 ± 9.0</td>
</tr>
<tr>
<td>Glial scars</td>
<td>284 (4.9%)</td>
<td>25.6 ± 12.4</td>
<td>10.3 ± 8.0</td>
<td>14.7 ± 8.6</td>
</tr>
<tr>
<td>Ependymitis</td>
<td>96 (1.6%)</td>
<td>20.4 ± 12.6</td>
<td>13.3 ± 9.4</td>
<td>8.2 ± 7.1</td>
</tr>
<tr>
<td>No lesion</td>
<td>451 (7.7%)</td>
<td>29.2 ± 10.8</td>
<td>12.6 ± 7.7</td>
<td>16.1 ± 8.0</td>
</tr>
<tr>
<td>Total</td>
<td>5,842</td>
<td>28.6 ± 12.5</td>
<td>12.4 ± 8.9</td>
<td>16.5 ± 10.1</td>
</tr>
</tbody>
</table>

Data retrieved from the European Epilepsy Brain Bank.

*HS* hippocampal sclerosis, *Dual* dual pathology, *LEAT* long-term epilepsy-associated tumors, *MCD* malformations of cortical development, *Age OP* age of patients at surgery (in years), *Onset* age at onset of spontaneous seizure activity (in years), *Duration* duration of seizure disorder before surgical treatment (in years).
Hippocampal sclerosis

- HS is the pathologic pattern in ~56% of MTLE cases
- Recognized since 1880 (Sommer)
- Overall loss of hippocampal volume
- Surgical resection results in post-op seizure freedom in 60-80%
- Neuronal loss and gliosis involving CA1, CA4/3 subfields
  - Granule cell dispersion
  - Axonal reorganization (mossy fiber sprouting)
ILAE hippocampal sclerosis evaluation

- Dotted lines circumscribe anatomic boundaries between CA sectors
- First detectable neuronal loss by visual inspection ~30-40%
- Quantification should be performed at the center of these regions

Blumcke I Thom M et al. Epilepsia 2013. PMID: 32692496
Hippocampal sclerosis
Hippocampal sclerosis pathology

- Types of HS are distinguished by patterns of pyramidal cell loss
- Highest rate of seizure freedom in Classical HS (type 1)
- Atypical patterns of HS associate with poorer outcomes
- No known genetic susceptibility to HS

Thom M., Neuropathology and Applied Neurobiology (2014), 40, 520–543; PMID: 24762203
### Patterns of neuronal cell loss by sector

<table>
<thead>
<tr>
<th>Sector</th>
<th>HS type 1</th>
<th>HS type 2</th>
<th>HS Type 3</th>
<th>No-HS/Gliosis only</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA1</td>
<td>2</td>
<td>1-2</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>CA2</td>
<td>0-2</td>
<td>0-1</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>CA3</td>
<td>0-2</td>
<td>0-1</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>CA4</td>
<td>2</td>
<td>0-1</td>
<td>1-2</td>
<td>0</td>
</tr>
<tr>
<td>DG</td>
<td>0-2</td>
<td>0-1</td>
<td>0-2</td>
<td>0-1</td>
</tr>
</tbody>
</table>

**ILAE type 1**
- Neuronal loss and gliosis in CA1 > CA4, CA3 with sparing of CA2

**ILAE type 1**
- Classical HS

**ILAE type 2**
- Neuronal loss and gliosis predominant in CA1 subfield
- Extensive neuronal loss (and gliosis) in all subfields including the dentate gyrus

**ILAE type 3**
- Neuronal loss and gliosis in CA4 subfield (endplate/hilus)

**No HS**
- No neuronal loss and no gliosis

**Gliosis only**
- Gliosis only (often involving the subgranular zone)
Which type of HS? Where is the neuronal loss?

Classical HS (ILAE type 1)

CA4-predominant (ILAE type 3)
Which type of HS? Where is the neuronal loss?

No HS/gliosis only

HS ILAE Type 2 (CA1 predominant)
Granule cell dispersion

- Seen in 50% of TLE cases
  - Variably present in HS types 1, 2, and 3
- Abnormal clustering or bi-lamination
- Proposed definition of >10 layers, ill-defined boundary with molecular layer, and ectopic granule cells
  - Important to avoid tangentially cut sections
- Mechanisms proposed
  - Seizures create pro-neurogenic environment
  - Mature neurons migrate due to local effects (reelin deficiency)
- Pediatric series suggest GCD is not specific to seizure-affected brains

Mossy fiber sprouting

- Outgrowth of dentate granule cells’ axons into the inner molecular layer
- Thought to result in aberrant microanatomy which can be epileptogenic
- Animal models with status epilepticus show mossy fiber sprouting
  - Common morphologic marker for hippocampal change/reorganization

TLE case, dynorphin immunoreactivity in inner molecular layer around the dentate gyrus (A) compared to CV (B)

Focal cortical dysplasia

- “microscopically discernable architectural disorganization of the neocortex in patients with focal epilepsies”
- Associated with drug-resistant epilepsy
- Classification has changed several times
  - Challenge of interobserver reproducibility in more subtle lesions
Palmini classification of cortical dysplasias

- Panel of neurologists, neuropathologists, neuroradiologists
- “Malformations due to abnormal cortical development”
  - “cortical dysplasia”/FCD – if malformation restricted to or mostly in the cortex
  - “neuronal migration disorder”
  - “microdysgenesis”
- Mild MCDs
  - with ectopically placed neurons in layer I
  - with abnormalities outside layer I

Dysmorphic neuron  Balloon cell  Giant neuron

Palmini classification of cortical dysplasias

Mild MCD
Type I (ectopic neurons in/adj to layer I)
Type II (microscopic neuronal heterotopia outside layer I)

IA: isolated architectural abnormalities
Dyslamination +/- mild MCD

IB: architectural abnormalities
+ giant or immature neurons

+DN -BC

-DN -BC

MCD: malformation of cortical development
DN: dysmorphic neurons
BC: balloon cells

DNET and Ganglioglioma can be associated with epilepsy and dyslamination in surrounding cortex
### ILAE Diagnostic Methods Commission 2011

<table>
<thead>
<tr>
<th>Palmini et al. 2004</th>
<th>Blumcke et al. 2011 #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild MCD, type I</td>
<td>mMCD type I</td>
</tr>
<tr>
<td>Mild MCD, type II</td>
<td>mMCD type II</td>
</tr>
<tr>
<td>FCD, type IA</td>
<td>Type I</td>
</tr>
<tr>
<td>FCD, type IB **</td>
<td>Type I</td>
</tr>
<tr>
<td>FCD, type IIA</td>
<td>Type IIa</td>
</tr>
<tr>
<td>FCD, type IIB</td>
<td>Type IIb</td>
</tr>
<tr>
<td>Adjacent to LG tumor</td>
<td>Type III (category also includes association with entities other than tumors)</td>
</tr>
</tbody>
</table>

** Not reproducible among 9 North American neuropathologists (Chamberlain et al. 2009)

# 30 international neuropathologists achieved good inter- and intra-observer agreement

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**ILAE classification 2011**

*mMCD: ectopic/heterotopic neurons*

**FCD I:** architectural disorganization without cytologic change

**FCD II:** dysmorphism of neuronal cells
- IIa: no balloon cells
- IIb: with balloon cells

**FCD III:** architectural abnormalities in association with another ‘principal’ lesion (e.g., HS, tumor, vascular, or acquired)

Blumcke I et al. Epilepsia 2011; Najm I et al. Epilepsia 2022
Mild MCD (histo: ectopic neurons in layer 1 and WM)

Dr. C. Jason Liu
FCD 1A and 1B

• 1A
  – Micro-columns
  – “string of pearls”

• 1B
  – Lack of lamination
Loss of laminar pattern (NeuN)
MAP 2: FCD 2A vs. Normal
FCD2b transmantle sign
FCD2b transmantle sign
FCD2b

Variable GFAP expression in BC
FCD 3b (associated with glioneuronal tumor)

Dr. C. Jason Liu (MRI), Blumcke I et al., Epilepsia 2011
• HME: enlargement of one hemisphere
• Structure of the brain on one side may be markedly abnormal or show subtle changes
• PIK3CA variants are more common than mTOR variants (same pathway)
• Spectrum from FCD to HME proposed by recent studies
Relationship of FCD to hemimegalencephaly (HME)

Bottom of sulcus dysplasia

- Focal, epileptogenic cortical malformation
- May be type IIa or IIb
- Maximal abnormalities at bottom of sulcus
- Associated with somatic variants in \textit{MTOR}, \textit{DEPDC5}, \textit{NPRL3}

Studer et al. Epilepsia 2022; PMID: 3592101; Lee et al. Neurology 2020; PMID: 3287954
MOGHE

- Early onset FLE
- Hyperintense cortical lesions (suspected FCD)
- “non-lesional” pathology findings
  - Blurred g/w boundary
  - Increase in subcortical oligodendroglial cells
  - Proliferative cells (Ki-67)
- Proposed mild malformation of cortical development

Schurr et al. Brain Pathol 2017; PMID: 2678554
Whole slide image – case 1

- [https://pathpresenter.net/public/display?token=e027e3c7](https://pathpresenter.net/public/display?token=e027e3c7)
Tuberous sclerosis

- 1:6,000 births in U.S.
- Autosomal dominant
  - TSC1 9q34 or TSC2 16p13.3
  - 1/3 familial, 2/3 de novo
- Loss of function of either TSC gene leads to increased mTOR1 signaling
  - Facial angiofibromas
  - Hypomelanotic macules
  - Shagreen patches
  - Retinal nodular hamartomas
  - Angiomyolipoma of kidney
  - Rhabdomyoma of heart
- Cortical tubers present in utero by 20 weeks gestation (embryonic cortical development)

Roach and Kwiatkowski, Lancet 2016. PMID: 27613522; Dr. D. Agamanolis, neuropathology-web.org
Tuberous sclerosis
Tuber: GFAP
Tuber: neurofilament
Tuber: vimentin
Whole slide image – case 2

• https://pathpresenter.net/public/display?token=af7ee0d6
Sturge-Weber syndrome

- Encephalofacial angiomatosis
- Incidence 1:20,000-50,000 births
- Angiomas of the face, leptomeninges, and eye
- Almost always sporadic, GNAQ mutation
- Leptomeningeal vascular malformation thought to result from incomplete involution of embryonal vasculature, usually unilateral
- Can be associated with FCD 3c
Rasmussen encephalitis

- Focal/multifocal encephalitis
- Drug-resistant epilepsy
- “epilepsia partialis continua”
  - Retained awareness, occur over hours/days/years?
- Cortical pathology can be heterogeneous over disease course
  - Early: T cells and gliosis
  - Late: neuronal cell death, cavitation

Pardo et al. Epilepsia 2004. PMID: 1510833
Tissue handling

- Photography is recommended for en bloc samples
  - Optimal correlation to ECOG and MRI
  - Cortical/subcortical lesions can be macroscopically subtle
  - Track samples procured for research/banking: snap frozen tissue
Sample photography
Tissue handling

• Photography is recommended for en bloc samples
  – Optimal correlation to ECOG and MRI
  – Cortical/subcortical lesions can be macroscopically subtle
  – Track samples procured for research/banking: snap frozen tissue

• Ensure samples available for potential genetic testing
  – Key to sample affected tissue in the setting of mosaicism

2 patients with HME
PIK3CA mosaicism detected from routine frozen tissue
VAF 20-32% in affected brain tissue
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2. Identify specific histologic patterns that can be observed in epilepsy surgical specimens
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Acknowledgments

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• CHLA Neuroradiology
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References


