Epilepsy Surgery Genetics

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History of “Epilepsy” surgery

*Trepanation:*
To relieve the brain from demons
To decrease pressure from depressed skull fractures

*The skull was found in a dolmen in France by Pruniéres (Wellcome Library, London)*
Transition from skull surgery to Epilepsy surgery

Late 1800’s

The transition from skull surgery to modern brain surgery was prompted by:
1) An increasingly critical view of trepanation
2) The emerging localization theories of the brain
3) The introduction of antisepsis and better pain treatment.
Late 19th Century: Resection of cortical lesion

Sir Victor Horsley:

Successful cortical resections with significant reduction in epileptic seizures in 3 patients (Horsley, 1886)
first association of epilepsy localization and “etiology” for the success of epilepsy surgery

“...local commencement of the fit suggests that the disease causing them is at the surface of the brain...”

*Sir William Gowers, 1881*
Late 19th Century: Pathology (lesion) a possible cause of Epilepsy as a clinical “disease”

Pathology (lesion)

Sir Victor Horsley, J.H. Jackson and D. Ferrier: Macroscopic lesion (pathology) and/or cortex area which, on stimulation, reproduced the initial symptoms of the clinical seizure (semiology).

Direct cortical stimulation

Seizure Semiology

Epilepsy Surgery
Mid 20\textsuperscript{th} Century: Pathology a possible cause of Epilepsy as an electrical “disease”
Second half of 20th Century: Epilepsy Surgery helped in the microscopic characterization of Epileptic pathologies

- Pathology (lesion)
  - Hippocampal Sclerosis
  - Cortical Dysplasia
  - Tumors
  - Trauma
- Epilepsy Surgery
Pathology of Temporal lobe Epilepsy

Penfield reported “incisural sclerosis” in 100 out 157 patients he operated on for temporal lobe epilepsy. He called the lesion probably ischemic and involving at times the anterior part of the “first temporal convolution” in the remaining 57 cases: tumors or the sequelae of head injury or infection.
temporal lobe epilepsy. It had been found by
in 100 out of 157 patients (63%) submitted to
operation. The extent of this sclerosis ranged from
involvement of a single gyrus to involvement of the
whole temporal lobe, but the mesial and inferior
sections of the lobe (uncus, hippocampal gyrus) in
first temporal gyrus were the areas most fre-
have already been reviewed by Hill, Falconer, and
Pampiglione (1953). Several other cases of tempo-
lobe epilepsy due to large structural lesions, such
as readily recognizable tumours, porencephalic
cysts, and angiomias, were also operated on during the
same period, but these were excluded as the opera-
tion intervention in them was limited to an excision

Hippocampal Sclerosis
Focal dysplasia of the cerebral cortex in epilepsy

D. C. Taylor, M. A. Falconer, C. J. Bruton, J. A. N. Corseuil

Neurosurgical Unit of Guy's, Maudsley, London
King's College Hospitals, London
Department of Neuropathology, Runwell Hospital, Wickford, Essex

Abstract

An unusual microscopic abnormality has been identified in the lobectomy specimens removed surgically from the brains of 15 epileptic patients. The abnormality could seldom be identified by palpation or with the naked eye. Histologically, it consisted of congregations of large, bizarre neurones which were littered throughout all but the first cortical layer. In most, but not in all cases, protoplasmic cells, probably of glial origin, were also present in the depths of the affected cortex and in the subjacent white matter. This kind of abnormality appears to be a malformation. The picture is reminiscent of tuberous sclerosis but too many distinguishing features, both in the clinical and in the pathological aspects, make this diagnosis undesirable. The cases are therefore listed provisionally (since all but one are still alive) as comprising a distinct form of cortical dysplasia in which localized, exotic populations of nerve cells underlie the electrical and clinical manifestations of certain focal forms of epilepsy.

Main features:

1. Architectural disorganization
2. Dysmorphic cells
3. Giant cells in white matter and cortex
4. Gliosis
Late 20th Century: Epilepsy Surgery helped in microscopic sub-characterization of Epileptic pathologies

Pathology (lesion)

- Hippocampal Sclerosis subtypes
  - Blümcke et al, Epilepsia. 2013
- FCD subtypes
  - Palmini et al, Neurology. 2004
  - Blümcke et al, Epilepsia. 2011
- Tumor subtypes
- Dual pathologies

Epilepsy Surgery

Late 20th Century: Pathology helped in imaging characterization of epileptic lesions

Pathology (lesion)

- Hippocampal Sclerosis subtypes
- FCD subtypes
- Tumor subtypes
- Dual pathologies

Epilepsy Surgery
Localization of the epileptic region in the 21st Century

- SCALP EEG
- MRI
- FDG-PET
- ICTAL SPECT
- MEG
- INVASIVE
EEG does not adequately localize the Epileptic region

Ristic et al, Epileptic Disorders, 2012
MRI in Epilepsy

...but up to 25% of patients with medically intractable epilepsy do not show 'lesions' on MRI!
FDG-PET scan:
High sensitivity, low specificity, not a good predictor of pathology
Ictal SPECT:
Maps network of ictal activation

...but does not point to the epileptogenic zone
MEG may localize the interictal focus and its spread

…but does not always accurately localize the Epileptogenic Zone or may be negative

*Wang et al, Hum Brain Mapp. 2012*
Invasive evaluations with SEEG or Subdural grids fail to localize the ictal onset in up to 15% of the cases.
Localization of the epileptic region in the 21st Century

<table>
<thead>
<tr>
<th>SCALP EEG</th>
<th>Regionalizes… but may mislocalize Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Identifies most lesions, predicts pathology… but may be negative</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Identifies areas of dysfunction… but is non specific</td>
</tr>
<tr>
<td>Ictal SPECT</td>
<td>Maps networks of ictal activation</td>
</tr>
<tr>
<td>MEG</td>
<td>Localizes some epilepsies (convexity, perisylvian…)... But may be negative</td>
</tr>
<tr>
<td>Invasive</td>
<td>Invasive, expansive… high failure rates in MRI negative epilepsies</td>
</tr>
</tbody>
</table>
Does Technology help? Improvement in Frontal Lobe Surgical Outcomes over the Years (N = 324) Cleveland Clinic 1997-2010

- Seizure-free (%)
- Years from Surgery

<table>
<thead>
<tr>
<th>Years from Surgery</th>
<th>1 Year</th>
<th>2 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Seizure-free - 2000 or After</td>
<td>65%</td>
<td>58%</td>
<td>47%</td>
</tr>
<tr>
<td>% Seizure-free - Before 2000</td>
<td>53%</td>
<td>48%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Why do we fail?

The main reason for the failure of the modern medical science is that it is dealing with results and not causes. Nothing more than the patching up of those attacked and the burying of those who are slain, without a thought being given to the real strong hold.

— Edward Bach —

1886-1936
Focal lesions (when completely resected) have best outcome
HS failures: early and late
FCD type 1 and TS have the worst outcome
Hemimegalencephaly and Rasmussen’s encephalitis fail early

Najm et al, 2013
The role of genetics in Epilepsy Surgery

• Predict the pathology before surgery
• Predict the outcome
• Highlight opportunities for preventing failures
Can Genetics Predict Epileptic Pathologies?
Why predicting pathology?

Hippocampal sclerosis

- Large number of patients with pathologically confirmed HS have normal MRI
- Early Detection of hippocampal sclerosis increases the likelihood of surgical intervention and improved seizure freedom
- Patients with HS continue to fail over time
### Why predicting pathology?

**Hippocampal sclerosis**

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Epilepsy Duration</th>
<th>SEEG Indication</th>
<th>SEEG seizure onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>17</td>
<td>Normal MRI</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>14</td>
<td>17</td>
<td>Basal occipital encephalomalacia (s/p Ganglioglioma resection, new seizures)</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>13</td>
<td>8</td>
<td>Frontal encephalomalacia (s/p LGG resection F2/F3/opercularis, new seizures)</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>32</td>
<td>11</td>
<td>Parietal lesion (IPL, post-traumatic lesion)</td>
<td>Hippocampus/Amygdala</td>
</tr>
<tr>
<td>47</td>
<td>3</td>
<td>Visual and auditory auras</td>
<td>Hippocampus/entorhinal gyrus/Temporal pole</td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>Normal MRI</td>
<td>Hippocampus/Amygdala</td>
</tr>
<tr>
<td>35</td>
<td>10</td>
<td>Left HS and Right temporal seizures</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>16</td>
<td>33</td>
<td>Bilateral HS on MRI</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>MRI abnormality anterior insula and posterior perisylvian semiology</td>
<td>Hippocampus/Amygdala/Temporal pole</td>
</tr>
<tr>
<td>15</td>
<td>18</td>
<td>Bilateral hip atrophy on MRI</td>
<td>Hippocampus/PHG</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>Hemispheric congenital abnormalities</td>
<td>Hippocampus</td>
</tr>
</tbody>
</table>

In a large number of patients, MRI does not uncover HS or may point to other pathologies.
Genetics of Hippocampal sclerosis

...but why patients with HS exhibit seizure recurrence years after successful epilepsy surgery
Why predicting pathology?

Malformations of cortical development

- Surgical outcomes depend on the type and subtype of FCD: *The type of FCD is confirmed after surgical resection... no presurgical diagnosis*
- A large number of patients with FCDs have normal MRIs: *This leads to surgical resection for some patients who could have been excellent candidates*
Outcome of surgery with patients with FCD following invasive implantation

- **139 patients** (1999-2011)
- **Baseline characteristics:**
  - Mean age at onset: 11 y (0.1-55 y, median: 9 y)
  - Mean age at surgery: 27 y (4-66 y, median: 25 y)
  - Mean duration of epilepsy: 16 years (0-55 y)
  - Mean follow-up: 2 y (0.5-13, median 1 y)
  - MRI: Non lesional in 40% of patients

*Pinheiro Martins et al, In Preparation*
## Four Predictors of Early Surgical Failures

Multivariate analysis (whole model logrank test <0.0001)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Adjusted p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathology</strong>: FCD type I or IIA</td>
<td>3.99</td>
<td>1.52-12.97</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Semiology</strong>: More than one type</td>
<td>2.35</td>
<td>1.07-5.07</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Size</strong> of the ictal onset zone</td>
<td>2.17</td>
<td>1.04-4.61</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Function</strong>: Overlap with eloquent cortex</td>
<td>2.74</td>
<td>1.09-6.60</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Pinheiro Martins et al, In Preparation*
Pathological Subtype:
FCD Type IIB and Type III have the best Outcome

\[ p=0.004 \]

\textbf{Pinheiro Martins et al, In Preparation}
Somatic mosaicism and neurodevelopmental disease

Alissa M. D’Gama$^{1,2,3}$ and Christopher A. Walsh$^{1,2,4,*}$

Normal
Low mosaic
$DCX$ mutation
10% mutant cells

High mosaic
$LIS1$ mutation
~50% mutant cells

Germline
$DCX$ mutation (M)
or $LIS1$ mutation
(M and F)
100% mutant cells

PMG germline mutation
PMG-1 $MTOR$ Ms (100% of cells)

HME germline mutation
HME-11 TSC2 Ms (100% of cells)

HME somatic mutation
HME-11 TSC2 Fs (~6.9% of cells)

HME somatic mutation
HME-22 $PIK3CA$ Ms (~32% of cells)

FCD somatic mutation
FCD-6 $MTOR$ Ms (~4.9% of cells)
80 children subjected to surgery for the treatment of drug-resistant epilepsy at the Rothschild Foundation Hospital (Paris, France) between 2015 and 2018
Why predicting pathology?
Glioneuronal tumors

Glioneuronal tumors: gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumors (DNTs), represent a well-recognized cause of intractable epilepsy. Histologically, they are characterized by mixed neuroepithelial cell types, including aberrantly shaped neuronal cells and glial elements, in coexistence with cortical dysplasia.
The presence of BRAF is a predictor of worse post resection outcome in patients with glioneuronal tumors.
Can Genetics Predict Surgical Outcomes?
Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review

Remi Stevelink¹, Maurits WCB. Sanders¹, Maarten P. Tuinman¹, Eva H. Brilstra², Bobby PC. Koeleman¹, Floor E. Jansen¹, Kees PJ. Braun¹

Meta-analysis of 24 articles of 82 patients who underwent surgical resection for medically intractable epilepsy and had genetic studies:

Three types of gene mutations were reported:
1. Channel function and synapses
2. mTOR pathway
3. Other genetic mutations

Table 1A. Success rates of epilepsy surgery for patients with different genetic causes (germline mutations) of epilepsy.

<table>
<thead>
<tr>
<th>Genetic cause</th>
<th>MRI-positive seizure-free/total</th>
<th>MRI-negative seizure-free/total</th>
<th>Total group seizure-free/total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenic variants of genes related to ion channel function and synaptic transmission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN1A</td>
<td>FCD: 0/2</td>
<td>0/2</td>
<td>0/8</td>
</tr>
<tr>
<td>SCNTB8</td>
<td>HS: 1/1</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>HS: 0/2</td>
<td>0/1</td>
<td>0/3</td>
</tr>
<tr>
<td>STXBP1</td>
<td>-</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1/9</td>
<td>1/5</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td><strong>Pathogenic variants of mTOR pathway genes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEPDC5</td>
<td>FCD: 3/6</td>
<td>2/3</td>
<td>5/9</td>
</tr>
<tr>
<td>PTEN</td>
<td>HME: 1/1</td>
<td>-</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>5/8</td>
<td>2/4</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td><strong>Other genetic causes of epilepsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microdeletions</td>
<td>HS: 9/10</td>
<td>0/2</td>
<td>9/12</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>FCD: 2/2</td>
<td>1/1</td>
<td>12/21</td>
</tr>
<tr>
<td>Fragile-X syndrome</td>
<td>HS: 2/2</td>
<td>-</td>
<td>2/2</td>
</tr>
<tr>
<td>Mitochondrial mutations</td>
<td>HS: 1/3</td>
<td>-</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>23/35</td>
<td>1/3</td>
<td>24/38 (63%)</td>
</tr>
<tr>
<td>Total</td>
<td>29/52 (56%)</td>
<td>4/12 (33%)</td>
<td>33/64 (52%)</td>
</tr>
</tbody>
</table>
Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review

Remi Stevelink¹, Maurits WCB. Sanders¹, Maarten P. Tuinman¹, Eva H. Brilstra², Bobby PC. Koeleman², Floor E. Jansen¹, Kees PJ. Braun¹

Meta-analysis of 24 articles of 82 patients who underwent surgical resection for medically intractable epilepsy and had genetic studies:

Three types of gene mutations were reported:
1. Channel function and synapses
2. mTOR pathway
3. Other genetic mutations

Table 1B. Success rates of epilepsy surgery for patients with different genetic causes (somatic mutations) of epilepsy.

<table>
<thead>
<tr>
<th>Genetic cause</th>
<th>MRI-positive seizure-free/total</th>
<th>MRI-negative seizure-free/total</th>
<th>Total group seizure-free/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>HME: 3/5</td>
<td>-</td>
<td>6/6</td>
</tr>
<tr>
<td></td>
<td>FCD: 1/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathogenic variants of mTOR pathway genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKT3</td>
<td>HME: 1/3</td>
<td>-</td>
<td>2/4</td>
</tr>
<tr>
<td></td>
<td>FCD: 1/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR</td>
<td>HME: 1/1</td>
<td>-</td>
<td>7/8</td>
</tr>
<tr>
<td></td>
<td>FCD: 6/7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15/18 (83%)</td>
<td>-</td>
<td>15/18 (83%)</td>
</tr>
</tbody>
</table>
Long Term Seizure Freedom in Adult and Pediatric Patients Following Epilepsy Surgery
Cleveland Clinic (N = 1,594)

Seizure-free (%)

Years from Surgery

<table>
<thead>
<tr>
<th>Years from Surgery</th>
<th>1 Year</th>
<th>2 Years</th>
<th>5 Years</th>
<th>10 Years</th>
<th>12 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Seizure-free (overall group)</td>
<td>76%</td>
<td>71%</td>
<td>62%</td>
<td>50%</td>
<td>44%</td>
</tr>
<tr>
<td>% Seizure-free (adult epilepsy)</td>
<td>72%</td>
<td>66%</td>
<td>56%</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>% Seizure-free (pediatric epilepsy)</td>
<td>80%</td>
<td>76%</td>
<td>67%</td>
<td>50%</td>
<td>44%</td>
</tr>
</tbody>
</table>
Can genetics play a role in some epilepsy surgery failures?

Early recurrences are due to failure in epilepsy localization.

Late recurrences are due to failure to understand epileptogenesis.

Najm et al, 2013
Genetic Susceptibility for seizure recurrence?

Polygenic burden in focal and generalized epilepsies

Costin Leu,1,2,3 Remi Stevelink,4 Alexander W. Smith,2 Slavina B. Goleva,5,6 Masahiro Kanai,2,7,8,9,10 Lisa Ferguson,11,12,13 Claran Campbell,14,15 Yoichiro Kamatani,16,18 Yukinori Okada,10,17,18 Sanjay M. Sisodiya,3,19 Gianpiero L. Cavalleri,14,15 Bobby P.C. Koeleman,4 Holger Lerche,26 Lara Jehi,11,13 Lea K. Davis,5,6 Imaad M. Najm,11,13 Aarno Palotie,7,21 Mark J. Daly,2,7,21 Robyn M. Busch,11,12,13 Epi25 Consortium and Dennis Lali,2,11,22

[Graph showing polygenic burden in different cohorts]

GE-PRS
FE-PRS
T2D-PRS

Cohort Cleveland Clinic Epilepsy Center Epi25-EUR Population controls


PRS 0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9 2.1

Geometric mean odds ratio


Conclusion

• Recent genetic observations show promise in the presurgical diagnosis of various epileptic pathologies, and in the possible prediction of surgical outcome.

• There is a need for large multicenter/multinational studies to address the challenges through the inclusion of large number of patients.
Cleveland Clinic

Every life deserves world class care