Pediatric Epilepsy: A Clinician’s Perspective

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Objectives

- To review
  - Epilepsy management in 2017
  - Types of epilepsy surgery
  - Challenges in identification of patients who will benefit from surgery
  - Importance of brain imaging in the investigation of epilepsy
Key Messages

- Epilepsy is common and if uncontrolled has high morbidity and mortality
- Surgery is under utilized to treat epilepsy
- High quality structural and functional neuroimaging is of critical importance to identify lesions and eloquent networks
Epilepsy

- Epilepsy affects ~3% of population
- 2/1000 in first 3 years of life
- Is treatment resistant in 30%
- Cognitive and neuropsychiatric co-morbidity in 1/3 of patients
- Negative impact on quality of life
- 5X increased mortality with uncontrolled seizures
Epilepsy and Learning

- Berg et al., Neurology 2012
- Prospective cohort of children with epilepsy diagnosed < 8 years
- Early age at seizure onset and pharmaco-resistance resulted in lower IQ
- Pharmaco-resistance had most profound impact in 0-3 year group
Treatment of Epilepsy in 2017

- Anti-seizure medications
- Dietary therapies
- Surgery
- Brain Modulation
  - Vagus nerve stimulation, Deep brain stimulation
- Thermocoagulation
- Personalized treatment guided by genomics
Causes of Epilepsy

Types of Epilepsy Surgery

- Resective:
  - Lesionectomies, Cortical resections, amygdalo-hippocampectomy
- Disconnective surgeries:
  - Hemispheric, multilobar, MSTs, corpus callosotomy
- Vagus nerve stimulation
- Deep Brain stimulation:
  - Anterior or centromedian nucleus of thalamus, hippocampus
Surgery vs Medical Treatment in Temporal Lobe Epilepsy

- Wiebe et al., NEJM 2001 RCT
  - Seizure free outcome at 1 year: 58% v 8%
  - Improvement in QOL, employment and school attendance in surgical group

- Engel et al., JAMA 2012 RCT
  - Early surgical vs medical management in TLE
  - Seizure free at 2 years: 11/15 treated surgically vs 0/23 in medical group
Pre-Surgical Work-Up

- **Phase 1:**
  - High resolution MRI
  - Video-EEG monitoring
  - Neuropsychological testing
  - Functional neuroimaging
    - SPECT, PET, fMRI, MEG
- **Phase 2:**
  - Invasive EEG monitoring Grids, Stereo-EEG
Case 1:

- 16.5 year old right handed male
- Seizure onset at 14 years
- No aura, arrest of activity, staring, rapid breathing, yawning, oral automatisms, +/- manual automatisms, may turn in a circle, confusion
- Duration 10-45 seconds, 2-3 sz weekly
- Bilateral convulsive seizures 1/month
Case 1

- Seizures unresponsive to 5 medications
- Neuropsychology:
  - Verbal IQ 50th Centile, Performance 63rd C
  - Mild dysfluency and inattention
- Interictal EEG:
  - Left frontal delta + anterior frontal spikes
  - Bilateral frontal temporal spike wave L>R
- Ictal EEG: Left frontotemporal changes
Subtraction Ictal SPECT coregisterd with MRI
Summary: Pre-Surgical Work-Up

- Seizure semiology: temporal
- No MRI lesion
- Ictal EEG non-localizing at seizure onset
- MEG: cluster of left frontal spikes
- Subtraction Ictal SPECT: left frontal hyperperfusion
- Decision: Electrocorticography and if negative leave subdural grid electrodes in place
Electro-corticography: Left Frontal.
Electrographic Seizures x4
Case 1

- Pathology: Focal cortical dysplasia type IIa
- Seizure free since surgery (7.5 years)
- Key Points:
  - Lateral frontal lobe seizures may have similar clinical features to temporal lobe seizures
  - SISCOM and MEG: Left frontal abnormalities
  - Surgery performed in one stage
  - Invasive EEG and associated morbidity avoided
Case 2

- 12 year old R handed girl with seizure onset at age of 11 years
- Seizure type #1:
  - Aura: +/-feeling in abdomen, or mouth
  - Right arm/leg extension, left hand to mouth, giggling, speech arrest, aware, last < 20 seconds
  - Clusters, multiple seizures per day, hour,
- Failed 5 anti-seizure medications
Seizure Onset L mid Central
Left Lateralized (Typical) Language Organization

Laterality

LI

-1

-0.8

-0.5

-0.3

0

0.3

0.5

0.8

1

FDR

0.1

0.05

0.01

0.005

0.001

Left

Right

Laterality

FDR

p < 0.001
Phase 1 Evaluation

- 3T MRI negative
- Interictal and ictal EEG left mid central (frontal)
- Neuropsychology: executive dysfunction
- Ictal SPECT not done as seizures so short
- fMRI: Left hemisphere language

**Recommendation:**
- Phase 2 evaluation with subdural electrodes covering left frontal, parietal lobes including medial surface (SMA, cingulate)
Seizures

1G 8x8

4G 2x5

3G 1x6

2G 1x4

5G 1x4
Phase 2: Ictal Onset
SEIZURE #9 GRIDS: 2G 1x4, 3G1x6, 4G2x5, 5G1x4
Case 2: Follow-up

- Left mesial frontal resection
- Pathology: Focal cortical dysplasia type IIa
- No complications
- Seizure free at 16 months
- On 2 anti-seizure medications
Epilepsy Surgery in Tuberous Sclerosis Complex

cortical tubers

cytomegalic neurons

and balloon cells

mTOR pathway
Tuberous Sclerosis Complex (TSC)

- 90% develop epilepsy
- Onset often in 1st year of life
- Uncontrolled epilepsy: high risk of Autism and intellectual impairment
- Advances: Biomarkers of epilepsy and treatment prior to seizure onset
- mTOR inhibitors effective for epilepsy
Epilepsy Surgery in TSC

**Challenges:**
- Multiple tubers
- Multifocal EEG abnormalities
- Ictal EEG often non-localizing
- SISCOM, AMT-PET and MEG very useful to identify the epileptogenic tuber(s)
Depth Electrode in Tuber
• Seizure-Free: 47%
• Rare Seizures: 26%
• 50-90% Decrease: 16%
• < 50% Decrease: 5%
• Unchanged: 8%

• Median F/U 2.4 years (range 0.2-16.2)
• Median current AEDs 2 (range 0-5)
• Median duration seizure-free 2.5 years (range 1-9)
• Seizure-free off medication: 1
Epilepsy Surgery in TSC

- Epilepsy surgery results in good outcomes in carefully selected patients
- Surgery should be considered early
- Earlier surgery may improve developmental outcomes
mTOR Inhibitors and Epilepsy

- **TSC mouse models:**
  - Rapamycin reversed astrogliosis/neuronal disorganization
  - mTOR inhibitors:
    - Prevent development of seizures
    - Improve learning and attention

- **Clinical trials:**
  - Rapamycin reduced seizure frequency
  - Everolimus Phase 1/2 and EXIST-1 SEGA trials showed reduction of seizures in some patients
  - EXIST 3 trial: Everolimus effective in reducing seizures
Management of Gelastic Seizures and Hypothalamic Lesions
Gelastic Seizures

- Classically with hypothalamic lesions
- LASER thermocoagulation is currently preferred treatment
- Radiosurgery and resection also options
Hemispheric Surgery

- Sturge-Weber syndrome
- Infarction
- Malformations
  - Cortical dysplasia
  - Hemimegalencephaly
- Rasmussen’s encephalitis
- Hemispheric tumors
Anatomical hemispherectomy

Functional Hemispherectomy
Sturge - Weber syndrome
Functional Neuroimaging in Hemispheric Disorders

- Allow assessment of extent of disease in affected hemisphere
- Allow assessment of function of contralateral hemisphere
- May not be necessary in some cases
Conclusions

- Epilepsy Surgery in children
  - At best can result in a complete cure
  - Is not a treatment of last resort
  - Should be considered earlier
  - Opportunity to improve developmental outcome and long term economic impact
  - Extratemporal more common than temporal
Unique Challenges in Children

- Identification of brain malformations may be difficult to detect due to brain maturity
- Effects of seizures and inter-ictal epileptiform activity on brain development
  - Epileptic encephalopathy
  - Malformations of brain development
  - Tuberous Sclerosis complex
  - Hypothalamic tumors
Why is Epilepsy Surgery Underutilized?

- Lack of knowledge about efficacy
- Fear about surgical morbidity
- Lack of knowledge about eligibility criteria for surgery
- Lack of understanding about negative impact of uncontrolled epilepsy on brain development
SAM Question 1

Video-EEG monitoring during ictal and interictal SPECT studies is

A. Unhelpful

B. Necessary for accurate determination of whether the patient is having a seizure

C. Adds unnecessary expense
SAM Question 2

For accurate ictal SPECT studies the tracer injection should be administered

A. Within 20 seconds of seizure onset
B. Within 30 seconds of seizure onset
C. > 30 seconds of seizure onset
D. As soon as seizure is over

SAM Question 3

The accuracy of ictal SPECT is highest with
1. Visual analysis of ictal scan alone is used
2. Visual analysis of ictal and interictal scans
3. Voxel based co-registration techniques such as Subtraction ictal SPECT coregistered to MRI

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References


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