Evolving Paradigms of Localization for Resective Pediatric Epilepsy Surgery

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- Epilepsy (Greek- “to be taken hold of, seized, attacked”)
  - 2nd most common neurologic affliction
  - 50 million people worldwide affected; highest incidence in the third world
  - 2 million people in the United States- 1/3rd don’t respond to medicines
- Epilepsy in children
  - Epilepsy affects 0.5-1% of all children through 16
  - Median age of seizure onset is 6-10; majority of active epilepsy cases are of childhood onset

Epilepsy

scope of problem

- Epilepsy- recurrent seizures
- 2 million people in US
- 1% of all children

Alabama

Population: 5 million

Alabama's Children: 1,250,000

12,500 with epilepsy
Epilepsy in Children-intractability

- Kwan and Brodie- 50% control with first med and another 50% with second med. Likelihood of control after 2 med failure exceeds 95%
- Intractability- “satisfactory seizure control cannot be achieved with antiepileptic medications alone or in combination at subtoxic levels”-Bourgeous
- straightforward definition- yet can only represent an ideal
- working concept emerges- failure of second med

Antiepileptic drugs
"newer drugs" since 1993

- Clobazam
- Felbamate
- Gabapentin
- Lamotrigine
- Topiramate
- Vigabatrin
- Oxcarbazepine
- Zonisamide
- Levetiracetam
- Pregabalin
- Rufinamide
- Lacosamide
- Coming attractions: 
  - Brivaracetam
  - Eslicarbazepine
  - Engilskine
Refractory Epilepsy

• 1 of every 3 children continue having seizures.
• Besides seizures, many also have depression, inattention, and anxiety.
• These children need a referral to an epilepsy center for further assessment.

case study

1.) realization that primary pathology in pediatric epilepsy are malformations of cortical development (MCDs) or cortical dysplasias

2.) assessment and treatment of MCD requires aggressive approach to localization and mapping
   - large subcortical grids with precise stimulation and mapping
   - aggressive surgical resection of precisely mapped cortex

technologic
   - improved imaging, optics, illumination, frameless stereotaxy, functional imaging
Substrates of Pediatric Intractable Epilepsy

- Classification of MCDs:
  - I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
    - A. Decreased Proliferation / Increased Apoptosis: Microcephalies
    - B. Increased Proliferation/ Decreased Apoptosis (normal cell types): Megalencephalies
    - C. Abnormal Proliferation (abnormal cell types)
      - 1. Non-neoplastic
        - a. Cortical Hamartomas of Tuberous Sclerosis
        - b. Cortical Dysplasia with balloon cells
        - c. Hemimegalencephaly (HMEG)
  - II. Malformations due to abnormal neuronal proliferation or migration
    - A. Decreased Cell Proliferation / Increased Apoptosis
      - 1. Decreased Proliferation / Increased Apoptosis (abnormal cell types): Anencephalies
    - B. Increased Cell Proliferation/ Decreased Apoptosis (normal cell types):
      - Megalencephalies
  - II. Malformations due to abnormal neuronal migration
    - A. Lissencephaly/Subcortical Band Heterotopia Spectrum
    - B. Cobblestone complex
      - 1. Congenital muscular dystrophy syndromes
      - 2. Syndromes with no involvement of muscle
    - C. Heterotopia
      - 1. Subependymal (periventricular)
      - 2. Subcortical (other than Band Heterotopia)
      - 3. Marginal glioneuronal
    - II. Malformations due to abnormal neuronal organization (including late neuronal migration)
      - A. Polymicrogyria and schizencephaly
        - 1. Bilateral polymicrogyria syndromes
        - 2. Schizencephaly (polymicrogyria with clefts)
        - 3. Polymicrogyria with other brain malformations or abnormalities
        - 4. Polymicrogyria or schizencephaly as part of Multiple Congenital Anomaly/Mental Retardation syndromes
      - B. Cortical dysplasia without balloon cells
      - C. Microdysgenesis
Surgical Evaluation is individualized YET has 5 standardized components:
1. History/Semiology (syndrome, phakamatosis etc.)
2. vEEG in EMU
3. MRI
4. Functional Imaging Modality (often 2)
   • Ictal SPECT/SISCOM/ISAS
   • PET
   • MEG
5. Intracranial electrode investigation
   • Grid and depth electrodes

CONCORDANCE OF ABOVE COMPONENTS DICTATES SURGICAL RESECTION

Pre-Surgical Assessment-clinical

• Clinical
  – History and Physical Examination
  – Detailed seizure history
  • Semiology
  • Stereotypic nature
• Pattern recognition of the child’s epilepsy (immediate clue as to procedure candidacy)
  1. Localization related epilepsy (partial)
     • Generalization/spread, characteristic postures, MRE
  2. Catastrophic generalized epilepsy
     • Drop events, high seizure burden, accelerating
     • Epileptic syndromes
       – Infantile spasms/West Syndrome
       – Lennox-Gastaut Syndrome
  3. Multi-focal epilepsy MRE (mild-moderate-severe)

Video/EEG in monitoring units

Epilepsy Monitoring Unit (EMU):
• Inpatient unit with specialized personnel
• Continuous video and EEG recording
• When?
  National Association of Epilepsy Centers (NAEC) recommendation:
  - Treatment failure of 1 year
  - Failure of 2-3 AEDs
• Why?
  - Differentiate between epileptic and non-epileptic spells
  - Identify unrecognized seizures
  - Record seizures for pre-surgical evaluation
MRI

- Perhaps the greatest single cause for advances in epilepsy surgery
- Remarkable sensitivity for the substrates of epilepsy
- Prior to MRI the two most common substrates for epilepsy (MTS and MCDs) were *post mortem* diagnoses
- 1.5 or 3 Tesla

Ictal/Interictal SPECT

- Principle: injected radionuclide tracer follows blood flow - ictal regions hot
- Ictal SPECT significantly more localizing
- Given during video-EEG—allows correlation of clinical activity and SPECT pattern
- SISCOM—allows digital subtraction of interictal from ictal
**PET**

- Noninvasive measure of cerebral metabolic rate
- Area of ictal activity hypoperfused interictally becomes hyperperfused during seizure
- Important role in identification of underlying MCD in infants demonstrating infantile spasms

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**Basic Principles of Biomagnetism**

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**UAB MEG**
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CONCORDANCE OF ABOVE COMPONENTS DICTATES SURGICAL RESECTION

Pediatric Epilepsy Case Conference

• Wednesday 12pm-1 pm
• Attendees:
  – Neurosurgeons (2)
  – Epileptologists (3)
  – Nurse Coordinator for program
  – Nurse Pract, Nurses (6)
  – EEG Technicians (6-8)
  – Neuropsychologist (1)
• Standardized format- semiology, EEG, MRI, functional imaging- DISCUSSION

Figures courtesy of Drs Iskander and Ramirez- UW-Madison.
Invasive monitoring

- Allows detailed cortical mapping including stimulation
- Risks
  - infection
  - CSF leak
  - mass effect - ICP problems
  - tearing of draining veins
Intraoperative MEG co-registration
Depth electrodes

Inter-hemispheric electrodes
Image composite demonstrating utility of grid / depth strategy

Sagittal projection demonstrating interhemispheric placement of grids
Anterior coronal projection demonstrating broad hemispheric coverage in post trauma case with depth and grid electrode strategy.

CURRY based superimposed layering of images showing:
- MEG dipoles
- Ictal SPECT regions of activity
- Depth electrodes (black/dark-gray)
- Grid electrodes (red, orange, yellow)

Highly unusual bilateral sampling with superimposed functional imaging (gray/black). Note black/red interhemispheric electrode engineered to record trans-falx from both sides simultaneously.
Depth electrode placement to augment grid based strategy using Vertek component of Stealth Frameless Navigation

Grid based strategy augmented by Vertek guided placement of supplemental depth electrodes

Allows multi-dimensional functional investigation of epileptic cortex to define epileptogenic networks
Take Home Points

• Medical therapy controls 2/3rds- patients who fail to control should be recognized and evaluated early
• Much MRE arises from fundamental structural abnormalities in brain tissue
• Conceptual and technologic advances have made surgery safer and more central
• Surgical candidates fit one of three patterns
  – Localization related
  – Catastrophic generalized
  – Multifocal MRE

Evolution of Epilepsy Treatment

• Antiquity
  – Hopelessness, despair- mortality and profound disability
  – Supernatural- spiritual “witches”
• Early Organized Medicine- 18th/19th Century
  – Understanding of Epilepsy as an Electrical /Brain Phenomenon-Calabri/Galvani
  – Early ideas of hyper-excitability and spread/“march” early classification of seizures (Hughlings-Jackson)
  – Concept of epilepsy surgery-1886 (Horsley)
• Preliminary successes- 19th-20th Century
  – Bromides, barbiturates, Phenytoin (Merrit-Putnam)
  – With advent phenobarb surgery FORGOTTEN for 50 years!
Evolution of Epilepsy Treatment

- Medical
  - Meticulous approach of Merrit-Putnam set bar
    - Trimethadione
    - Carbamazepine
    - Valproic Acid
  - Later 20th Century
    - More meds/fewer side effects

- Surgical
  - Pioneers
    - Krause, Foerster
    - Krayenbuhl, Yasargil
    - Penfield, Jasper, Rasmussen
    - Schwartz, Goldring
    - Talairach, Bankaud-SEEG
  - Procedures
    - Temporal Lobectomy
    - Hemispherectomy
    - Invasive Recordings- very late

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“newer drugs” since 1993

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- Gabapentin
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- Topiramate
- Vigabatrin
- Oxcarbazepine
- Zonisamide
- Levetiracetam
- Pregabalin
- Rufinamide
- Lacosamide
- Coming attractions:
  - Brivaracetam
  - Eslicarbazepine
  - Ezogabine

Evolution of Epilepsy Treatment - Later 20th and Early 21st Century

- Improved functional imaging capacity
- Conceptual awareness of MCD
- Technologic improvements intra-op
  - Magnification
  - Illumination
  - Navigation
  - Depth electrodes to supplement grids
- Surgery grows safer and more effective
  - Still vastly underused
  - Remains largely only in centers of excellence
  - Increasing awareness late failures
- Even the newest of medications improve side effects and cannot control ~1/3rd of pts.
Emerging Concepts of Resective Surgery

- Minimally invasive strategies
  - SEEG
  - Laser interstitial thermal-ablation therapy (LITT)
  - Endoscopic procedures: ECC, E hemispherectomy
  - SRS
- Repeat smaller procedures may be better than larger single procedure
  - Perhaps recurrent network/circuitry inherently more fragile than the initial epileptogenic network
  - Smaller repeated lesioning may be more effective and less invasive and inherently risky
- Merging of multiple modality imaging to optimize planning and outcomes

Concepts of SEEG utilizing ROSA Robot

1. Hypothesis of abnormal network generated based on pre-op EMU evaluation
2. Strategy of Depth Electrode based investigation planned
3. ROSA robot assists in efficiently and accurately defining trajectories for electrodes
4. Intracranial monitoring and mapping
5. Electrode removal
6. Delayed resection targets pathologic network
Advantages of SEEG

• Allows better investigation of deep structures poorly sampled with grid
  – Insula
  – Operculae
  – Cingulum
• New insights into important epileptogenic network patterns
  – e.g. insular-cingulum network
• Better tolerated
  – Less pain, emesis, shorter stays
  – Anchor bolts secure electrodes firmly

Disadvantages of SEEG

• Field of reach of depth electrodes still limited to 2 mm
• Mapping cortical planes not possible
• Thin skull in little children does not hold anchor bolt- minimal AB thickness=25 mm
• Can create challenging/difficult resection strategies
• Potential for complications
  – Hemorrhage
  – Misdirected electrodes-tangential, epidural etc.
Learning ROSA SEEG Methods

Courses and seminars
Relatively few exist
- May 2016 - Cleveland Clinic
- October 2016 - Montreal, North America SEEG Meeting

Visit/ Collaborate with Existing Program
- European programs
- Cleveland Clinic
- UAB
- Houston, Miami

Visit Cleveland Clinic X 2 to observe and learn their paradigms, techniques and protocols
May 2015
June

Observe UAB (Dr. Kristen Riley)
SEEG cases X 4
SEEG Protocol- pre-op

- Conference to determine SEEG candidacy
- Epileptologist forwards map of implicated network
- Neurosurgeon develops depth electrode based plan on ROSA computer
  - Upload/cross reference CT with, MRI with, Functional Imaging Studies
  - Target Desired Areas- entry point and target point
  - Use software to trace trajectory and avoid vessels/hyperdensities
**SEEG Protocol- *intra-op***

- ROSA robot registered to anesthetized patient head
  - Laser registration
  - Skull fiducials
- ROSA calculates and efficiently establishes trajectories for electrode placement
- Neurosurgeon
  - Anesthetize, incise skin, Drive robot to periosteum
  - Twist hole through robot arm; Anchor bolt
  - Measure/calculate distance to target
  - Dura opened, Stylet, Electrode to target
  - Secure to anchor bolt
  - Repeat

**SEEG Protocol- *post-op***

- Awaken in PACU; CT en-route to PICU
- PICU overnight- EMU for remainder of stay
- Monitor and map for 5-7 days
- Motrin and Tylenol for pain
- Return to OR for electrode removal
  - Brief LMA based anesthetic
  - Anchor bolts loosened, electrodes removed, A8 removed and sutured.
  - Home next day
- Return electively for surgery after planning and review of findings at conference
Composite image showing MRI tractography co-registered with post SEEG CT showing electrodes to define trajectory for focal insular and motor strip resection for medically resistant epilepsy in 9 year old boy.

**UAB/COA SEEG Experience**

- **UAB**
  - N= 15 patients
  - 13 Resection
  - 1 hemorrhage requiring evacuation
  - 2 tangential electrodes
  - Too early to conclude seizure efficacy - all seizure free at present

- **COA**
  - N= 6 patients
  - 4 Resection
  - No hemorrhage
  - 1 electrode aborted
  - 2 tangential electrodes
  - Too early to conclude seizure efficacy - all seizure free at present

**Disadvantages of SEEG**

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- Mapping cortical planes not possible
- Thin skull in little children does not hold anchor bolt - minimal AB thickness=25 mm
- Can create challenging/difficult resection strategies
- Potential for complications
  - Hemorrhage
  - Misdirected electrodes-tangential, epidural etc.
Mapping

Leg tonic - ZB 7-9
Hand/arm tonic - Z9-12

Proposed resection includes

X 1-5
Y 1-9
ZA 1-7
Z1-7
ZB1-6
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Conclusions

• Surgery is a crucial option for the 1/3rd of patients with epilepsy who do not control with medications
• Advances in localization include better imaging software capabilities and new strategies in intracranial electrode placement
• ROSA based SEEG strategies
  – offer promise for meaningful investigation of medically resistant epilepsy
  – appear in early experience to be safe, effective and less invasive than traditional grid based strategies
Questions, comments and discussion...???

Thank you!