CHILDREN WITH DRUG RESISTANT EPILEPSY REFERRED FOR RESECTIVE SURGERY: CHARACTERISTICS DELAYING SURGICAL REFERRAL AND ADVANCED NEUROIMAGING IN IMPROVING OUTCOME

Grace Newell[1,2], Ludovica Corona[1,3], Cynthia Keator[1], Daniel Hansen[1], M. Scott Perry[1], Saleem Malik[1], Christos Papadelis[1,2,3]

1. Jane and John Justin Institute for Mind Health Neurosciences Center, Cook Children's Health Care System, Fort Worth, TX, USA. 2. Burnett School of Medicine at TCU, Fort Worth TX, USA. 3. Department of Bioengineering, University of Texas at Arlington, Arlington, TX, USA.

RESEARCH QUESTIONS

(1) Are there certain characteristics in children with drug resistant epilepsy (DRE) in the US that delay the evaluation for epilepsy surgery despite failing three or more anti-seizure medications (ASMs)?

(2) In children with DRE, does information derived from magnetoencephalography (MEG) advance presurgical localization of the epileptogenic zone (EZ) and improve the surgical outcome in those who have failed prior epilepsy surgery?"

BACKGROUND

- **DRE** is defined as failure of two ASMs.
- **Epilepsy surgery** is often the most promising alternative for children with DRE to become seizure free. **Continued ASM trials may delay surgical treatment** which is associated with **adverse cognitive, developmental, and seizure outcomes**.
- Identifying characteristics that lead to >2 ASM failures prior to surgical evaluation may **help identify opportunities to shorten the duration to surgical evaluation**.

- The gold standard to identify the **EZ** for surgical resection is with **intracranial EEG** (iEEG). However, it is invasive, there is a risk for bleeding and infection, and it is **spatially limited** which may lead to **surgical failure**. **Repeat surgical evaluation** with iEEG is **challenging** due to distorted neuroanatomy from the prior surgery.
- Understanding the utility of MEG, a **noninvasive neuroimaging technique**, in aiding the preoperative evaluation for repeat surgery may help **improve surgical outcomes**.

METHODS

- This **retrospective study** identified 399 children ≤ 18 years of age undergoing epilepsy surgery evaluation from the Pediatric Epilepsy Research Consortium Epilepsy Surgery Database.
- We compared sociodemographic and epilepsy variables of patients failing ≤ and >2 ASMs at the time of epilepsy surgery evaluation.
- For characteristics of significance, we compared seizure outcome (Favorable: Engel 1 or 2; Unfavorable: Engel 3 or 4) after surgery between the two groups.

- Secondly, we retrospectively identified children from Cook Children's who had recurrent seizures after initial epilepsy surgery, underwent a repeat surgical evaluation with the use of MEG, and then underwent a repeat surgery.
- MEG data was analyzed to identify interictal epileptiform discharges (IEDs) that were mapped onto the patient's MRI as dipoles which were used in a dipole clustering method (Fig 1 and 3). Both surgical resections were mapped using the patient's MRI. The distance from both surgical resections to the MEG dipoles and the surgical outcomes characterized by Engel scores were analyzed.
- Statistical analyses was performed with SPSS.

Children failing >2 ASMs prior to surgical referral are younger at seizure onset and have delayed surgical evaluation compared to those failing ≤2 ASMs, additionally, those failing >2 ASMs more often have abnormal neurological exams and daily seizures, which do not impact surgical outcome suggesting delaying surgery for these factors is unnecessary. Finally, the use of MEG augments repeat surgical evaluation and results in better outcomes when the surgical resection is closer to the dipole clusters identified on MEG (Fig 1).

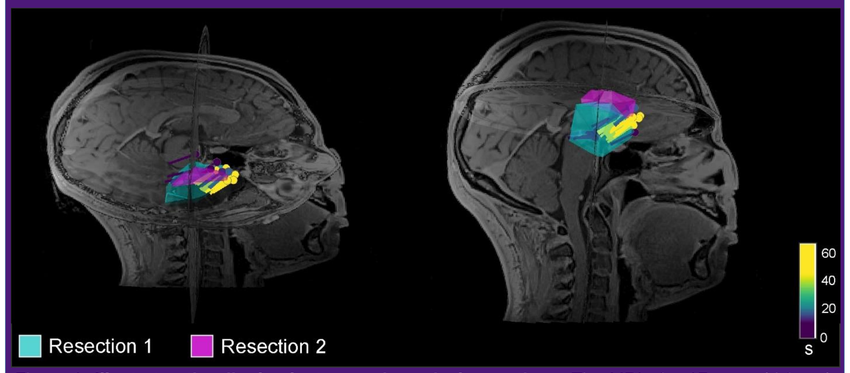

Figure 1. **Illustrates the dipole clusters and surgical resections.** The MRI of a 17-year-old female who had an initial resection in the right temporal lobe (cyan-colored), was not seizure free, then required a repeat surgery (magenta-colored) and was seizure free one year from the repeat surgery. The ECDs are displayed and are color-coded according to their clusterness: from low- (purple) to high-clusterness (yellow) values. Most of the ECDs are covered (resected) by the repeat surgical volume.

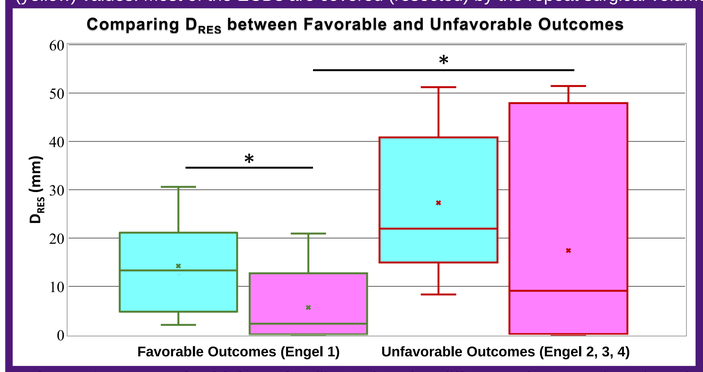

Figure 2. Box and whisker plot illustrating the difference in D_{RES1} (cyan) and D_{RES2} (magenta) between favorable outcomes (green outline) and unfavorable outcomes (red outline). The median of differences of D_{RES} between the favorable outcomes was significant (p=0.012), but was insignificant for unfavorable outcomes (p=0.128). The average D_{RES2} was significantly different between favorable and unfavorable outcomes (p=0.010).

Thesis

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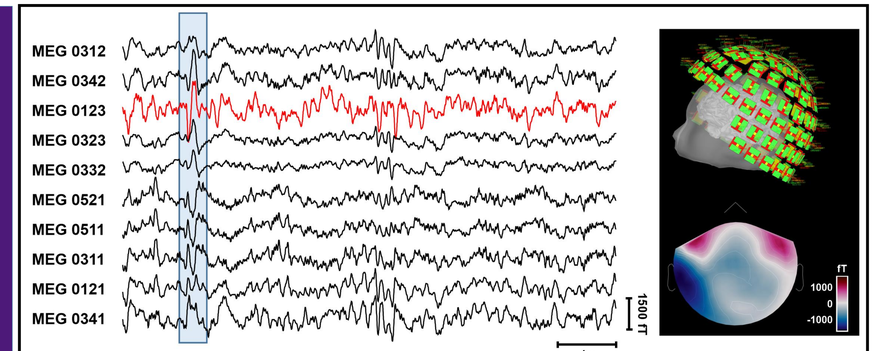

Figure 3: Identification of IEDs on MEG recordings. Data from an 18-year-old female with DRE who failed initial resection guided by iEEG followed by repeat surgical evaluation resulting in seizure freedom after undergoing resection of identified MEG dipoles. The area in the blue box highlights an IED identified on MEG. Topographic maps indicate a possible underlying generator in the left frontal region.

RESULTS

- **Children failing >2 ASMs were younger at seizure onset** (median 3y vs 5.1y; p<0.001), had **longer duration to surgical referral** (median 1.4y vs 0.3y; p<0.001), were more likely to have an **abnormal neurological exam** (p<0.001), **daily seizures** (p=<0.001), **fail other treatments** like dietary treatment or vagal nerve stimulators (p<0.001), were **less often offered surgical treatment** (p=0.02) and more **frequently underwent large resections** (Fig 4; p=0.001) **or palliative procedures** (p=*0.001*).
- **48% of palliative procedures had favorable surgical outcomes** (Engel 1 or 2)
- Abnormal neurological exam, etiology, and number of failed ASMs **did not impact surgical outcome.**
- No significant differences between the two groups were present for gender, ethnicity, race, insurance type, or distance to surgical center

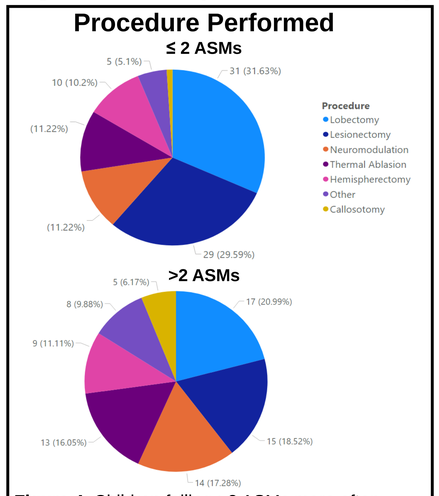

Figure 4: Children failing >2 ASMs more often underwent larger resections (i.e. hemispherectomy)

- **8 patients were seizure free** one year after repeat surgery. D_{RES1} was 14.2 mm ± 9.0 mm compared to 5.6 mm ± 7.6 mm for D_{RES2}. (p=0.012). **7 patients did not have favorable outcomes** (were Engel 2, 3, or 4) one year after repeat surgery. D_{RES1} was 27.3 mm ± 14.5 mm compared to 17.4 mm ± 20.8 mm for D_{RES2} (p=0.128) (Fig 2).
- The **average D_{RES2}** for the **favorable** outcomes was **5.6 mm** compared to **17.4 mm** for **unfavorable** outcomes (p=0.010) (Fig 2).

FUTURE DIRECTIONS

- A study is needed to define characteristics that make good pediatric epilepsy surgical candidates compared to a poor candidates.
- A prospective study is needed to determine if MEG can be the sole neuroimaging technique used for repeat surgical evaluation.