Predicting surgical outcomes for mesial temporal lobe epilepsy patients: a novel clinical scoring system with histopathologic and electrophysiologic correlation


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Disclosures

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Temporal lobe epilepsy

• Most common form of focal epilepsy
• Most commonly referred to surgical treatment (50 – 73% of all cases) due to pharmacoresistance¹
  • Hallmark feature – mesial temporal lobe sclerosis (MTS) or Ammon’s horn sclerosis → mesial temporal lobe epilepsy (MTLE)
• Pharmacoresistant MTLE – a major healthcare burden
  • >1 million people in the US with pharmacoresistant epilepsy²,³
  • ~20 years between epilepsy onset and referral to surgery³
• ~20 - 40% of patients continue to have seizures after surgical resection⁴,⁵
• There currently is no widely adopted and effective epilepsy surgical outcome scoring system

¹Tellez-Zenteno et al., Epilepsy Res Treat, 2012
²Zack et al., Center for Disease Control and Prevention, 2015
³Engel, Curr Opin Neurol, 2018
⁴Wiebe et al., N Eng J Med, 2001
⁵Engel et al., JAMA, 2012
Methods

• Consecutive pharmacoresistant MTLE patients undergoing surgical resection of mesial temporal structures between June 2010 and May 2018 were included.

• Resected hippocampi were used for
  • *Ex vivo* for multi-electrode array (MEA) recording of interictal-like activity (IIA) across hippocampal subregions
  • Clinical histopathology evaluation
  • Immunohistochemical assessment of immediate early gene (IEG) expression in the dentate gyrus (DG)

• Retrospective patient chart review was performed to collect relevant clinical parameters including potential surgical outcome predictors.

• Data statistical analysis and surgical outcome risk score calculations were performed.
Results

(1) Electrophysiologic and histopathologic findings

- N=113 cases were included in the analysis
- IIA (activity) was detected in n=51 (45%) of the cases (A-B)
- IIA was most commonly detected in subiculum (SUB) and dentate gyrus (DG) (A)
- Histopathologic diagnosis was available in 86.7% of the cases. Most common site of neuronal loss and gliosis was CA1 while these changes were least common in CA3 (A,C)
Results

(2) Surgical outcome score and predictors

- Engel outcome scores were assigned in 94 of 113 (83.2%) patients. Mean follow-up 3.4±2.1 years
- 79 of 94 (84%) were seizure free at latest follow-up
- Daily seizure frequency (OR: 10.45, p=0.002), disease duration of ≤ 34 years (OR: 10.35, p=0.04) and only simple partial seizure type (OR: 7.32, p=0.02) predicted poor surgical outcome and were included in a multivariable surgical outcome score model (AUC=0.75) (A-B)
- There was a significant difference in post-operative seizure freedom rate among outcome scores 0-2 (no score 3 represented in our cohort) (C). There were significantly more poor outcome cases with score 1 and 2 (D) as compared to 0
Results

(3) Surgical outcome predictor, MEA electrophysiology and histopathology finding associations

- There were significantly less cases with DG neuronal loss (43% vs 71%) when disease duration was ≤ 34 years as compared to > 34 years (p=0.027)
- A trend for less CA1 neuronal loss in cases with seizure frequency 4 as compared to frequency 1-3 (p=0.06) and a small trend for CA1 gliosis being more prevalent in type 1 seizures (p=0.16)

**Explanation:** Frequency 1-3 = 1-6 seizures per week to <1 seizure per month, frequency 4 = daily seizures. Type 2 – 4 = seizures other than simple partial, type 1 = simple partial seizures.
Results

(3) Immunohistochemical assessment of immediate early gene (IEG) expression

- To characterize the cellular origin of IIA in DG; the slices recorded using MEA, or the adjacent slices from n=3 cases where IIA was detected in DG and n=4 cases where IIA was not detected in DG were immunostained for IEGs Arc and c-Fos (A)
- There was higher c-Fos and Arc expression in IIA regions compared to non-IIA regions
- Mean ± SEM 83 ± 8% of Arc High cells (Arc+) and 64 ± 7% of c-Fos High cells (c-fos+) were Prox 1+ suggesting that IIA arises from granular neurons (A-B)
- Higher c-Fos and Arc and Prox 1 expression was observed in IIA regions compared to non-IIA regions (C)
Discussion

- There is currently an unmet need to identify reliable, epilepsy type-specific surgical outcome predictors that could be incorporated in a user-friendly scoring system\(^1\).
- Analysis of easily assessible parameters in our MTLE cohort revealed three significant poor surgical outcome predictors: daily seizure frequency, disease duration of ≤ 34 years and only simple partial seizure type. These were incorporated in a simple bedside surgical outcome prediction score.
- Our MEA recording results revealed SUB and DG as the most common sites of IIA–regions responsible for hippocampus input/output electric activity modulation with potential key role in epileptogenesis and pharmacoresistance\(^2-4\).
- Histopathology analysis revealed lower prevalence of DG neuronal loss to be significantly associated with shorter disease duration and, thus, poor surgical outcome corroborating other researchers’ findings\(^5\).
- Our IHC results suggest that, at a cellular level, IIA regions of the DG granule cell layer correspond to a higher number of highly active granular neurons and that IEG expression could possibly be used as a substitute to MEA in identifying and studying IIA regions and cells.

\(^1\)Gracia et al., Epilepsy Behav, 2019
\(^2\)Cohen et al., Science 2002
\(^3\)Dengler and Coulter, Prog Brain Res, 2016
\(^4\)Xu et al., Ann Neurol, 2019
\(^5\)Jardim et al., Arq Neuropsiquiatr, 2012
Pharmacoresistant MTLE represents a major healthcare burden. While surgery is an effective MTLE treatment, up to 40% of patients continue to have seizures post-operatively.

Our study proposes a simple bedside score to improve epilepsy surgical candidate selection and provides an insight into the ex vivo IIA, histopathologic and IEG expression findings of individual hippocampal sub regions in MTLE.

- A simple surgical outcome score is proposed incorporating three poor surgical outcome predictors: seizure frequency, duration and type.
- Histopathologically, less neuronal loss in DG is associated with disease duration of ≤ 34 years and poor surgical outcome.
- IEG immunoexpression in DG is mapped to the IIA regions detected using MEA and co-localized with granule cell marker Prox1.