Clinical severity of seizures
Hot Topics Symposium
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Disclosure

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• Eisai Pharmaceuticals

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Type of Financial Relationship

• Institutional sponsorship of clinical trials

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• Consultant
Learning Objectives

• Understand concepts of seizure severity and their relationship to medication treatment, and diagnostic tests such as EEG and MRI
Overview

• Severity of epileptic seizures vary widely between individuals

• Current clinical diagnostic tools are limited in measuring and predicting seizure severity
  – EEG
  – MRI

• Improved definition of seizure severity and progression will provide a framework for staging of seizures
III. Improve treatment options for controlling seizures and epilepsy-related conditions without side effects.

A. Understand the initiation, propagation, and termination of seizures at the network level in different forms of epilepsy.

B. Identify biomarkers for assessing or predicting treatment response, including markers that may identify specific populations that are likely to have good outcomes or develop adverse responses.

C. Develop or refine models that are aligned with etiologies and clinical features of human epilepsies, especially treatment resistant forms, to enable improved understanding of ictogenesis and preclinical development to improve seizure control with fewer side effects. Establish the sensitivity and specificity of these models with regard to current therapies.

D. Identify, develop, and improve interventions to detect, predict, prevent, or terminate seizures, including approaches suitable for use in the home and other non-medical settings.

E. Identify, develop, and improve anti-seizure therapies that target (either alone, or in combination) novel or multiple seizure mechanisms.

F. Develop, improve, and implement interventions for effective self-management, including treatment adherence.

G. Develop and validate objective patient-centered outcome metrics for clinical studies.
Case 1

- 18 year old woman with a history of a single episode of loss of consciousness, preceded by an unusual epigastric sensation, progressing to a secondarily generalized tonic-clonic seizure
- She presented on a dose of levetiracetam 250 mg twice daily
- She reported intolerable side effects (lethargy) to levetiracetam at higher doses.
Case 1

• Evaluation:
  – EEG showed right temporal epileptiform discharges
  – MRI was normal

• After 6 months of AED therapy on levetiracetam 250 mg twice daily, she had a repeat seizure 3 days after abrupt self-discontinuation of her medication

• After restarting levetiracetam 250 mg twice daily, she has remained seizure free for one year.
Case 2

• Development of complex partial epileptic seizures after an episode of encephalitis at age 7
• Treatment with multiple AEDs, left anterior temporal lobectomy, and vagal nerve stimulator
• Typical seizures with onset of a feeling of nausea and lightheadedness followed by loss of consciousness continue on a weekly basis at age 67
Epileptic seizure severity

- Both patients presented with complex partial seizures, due to temporal lobe epilepsy
- The severity of seizures differed markedly between the two cases
- What are the factors responsible for the differences between the subjects?
Concepts of seizure severity

Therapeutic antiepileptic drug levels

- 84 patients followed prospectively, on monotherapy phenytoin, phenobarbital, and carbamazepine
- All studied patients were seizure free for one year
- AED levels were recorded after patients had their last seizure and following control for one year
- Medications increased until clinical toxicity if necessary

AED levels required for complete seizure cessation
(Schmidt D, Haenel F, 1984)

Figure. Therapeutic plasma concentrations of phenytoin, phenobarbital, and carbamazepine in 84 patients receiving single-drug treatment. Complete cessation of all seizures occurred at these therapeutic plasma concentrations.
Therapeutic antiepileptic drug levels

• Comparison of clinical features of patients with levels in the upper range. Patients with greater seizure frequency before treatment required higher levels for control.

• Taking therapeutic range of PHT of 10-20, 21% of pts. controlled with low levels, 30% of patients controlled with high levels.

ILAE defined drug-resistant epilepsy, with 2 “hierarchical” levels.

- **Level 1**
  - Assessment of adequate trial of AED for efficacy in treating seizures

- **Level 2**
  - Drug-resistant epilepsy as a failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used antiepileptic drug regimens to achieve freedom from seizures.
  - If complete seizure control is not achieved with trials of two appropriate antiepileptic drugs, the likelihood of success with subsequent regimens is much reduced.
  - While drug resistance may “remit” over time (at a rate of 4% per year among adults and a higher rate among children), seizure relapse is common, suggesting a fluctuating course.

Measuring seizure severity

- **EEG**
  - Clinical and electrographic seizure monitoring
  - Better EEG techniques to measure seizure severity
- **MRI**
  - Structural lesions as a measure of seizure severity
  - Progression of structural lesions in chronic epilepsy
- **Longitudinal studies are necessary to better measure seizure severity**
Prevalence of interictal epileptiform discharges in epileptic patients

- Initial EEG demonstrates an epileptiform discharge in 29-55% of patients.
- Serial EEGs performed over time capture epileptiform discharges in 80-90% of patients.
- Repeat studies, with sleep deprivation and more extended recording times, help increase the chances of recording epileptiform discharges in patients with epilepsy.

“Dry electrode” EEG system

- Low power, ultra-high input impedance EEG recording system
- Similar performance to “wet” electrode recordings
- Advantages of ease of application of electrodes, minimal scalp preparation, and portability

Dry Electrode

Dry Electrode EEG system

Dry Electrode EEG system

- Wireless transmission of data opens the possibility of acute and longer-term/prn monitoring of EEG data
- Home monitoring of EEG
  - Recording of infrequent seizures
- Status epilepticus
  - Monitoring of EEG data in the emergency medical setting to guide initiation and monitoring of treatment

Measuring disease burden: Clinical seizure counts

- EMU-based studies show most patients vastly underestimate seizures (patients typically remember about 50% of seizures)
- Left hemispheric onset seizures are associated with greater loss of awareness of seizures
- Clinical seizure counts are overall a suboptimal measure of seizure severity

Awareness of seizures in the EMU

- Questioning every evening about awareness of seizures during the previous 24 hours.
- Patients assessed according to TLE or ETLE seizures (comparison of TLE and ETLE found no significant difference in self-reporting of events)
- Right TLE aware of 31/43 seizures (72.1%), left TLE aware of 17/50 seizures (34%) (P < 0.001)

Awareness of TLE seizures

Seizure counts in clinical research and practice

- Patient reported outcomes have implications in research and care for patients
- Method of acquisition of information influences findings
  - Paper seizure diary
  - On-line electronic diary
  - Linking to other sources of information (i.e. biosensors)

Long-term intracranial EEG

• Study showed feasibility of long-term intracranial EEG in ambulatory patients
• Seizure predictability with sensitivities ranging from 65% to 100% in 11/15 patients, enabling acute treatment
• Correlation of electrographic and clinical seizures

Long-term intracranial EEG

Components of long-term intracranial EEG system with seizure advisory system

Long-term intracranial EEG

Monthly seizure rates-reported seizures versus clinical seizures captured by intracranial electroencephalography

Structural brain changes in epilepsy

“Each fit does some amount of damage to the brain: in the interval the brain recovers itself to a great degree, when a new fit comes on, and new mischief is done; and so the repetition of the paroxysms leaves the brain altered as I have described it. [shrinking of the convolutions, alterations in the color and consistency of the grey and white matter].”

MRI-based hippocampal volume loss and TLE

• Asymmetry of hippocampal volumes in TLE correlates well with:
  – Lateralization of EEG onset of seizures
  – Post-surgical pathological verification of MTS
  – Good outcome after epilepsy surgery

Severity of seizures and MRI-detected MTS

- MRI-detectable MTS in benign TLE (rare or no seizures > 2 years follow-up)
- 39/100 (38.6%) of patients had MRI evidence of unilateral MTS (based on volume loss and/or signal intensity alteration)
- MRI-detected mesial temporal sclerosis is often present in patients with sporadic benign temporal lobe epilepsy.

Progressive structural changes in TLE

Progressive changes in mesial temporal structures

- Subregional trajectories of progressive hippocampal, entorhinal, and amygdalar atrophy using cross-sectional and longitudinal designs
- Progressive atrophy in hippocampal CA1, anterolateral entorhinal, and amygdalar laterobasal group bilaterally
- Convergent longitudinal and cross-sectional patterns of subregional mesiotemporal atrophy emphasize the progressive nature of TLE

Bernhardt BC, Kim H, Bernasconi A, Bernasconi N. Subregional mesiotemporal patterns of disease progression in temporal lobe epilepsy. Epilepsia 54 [Suppl. 3], 11-12. 2013.
Comparisons of stages of structural changes in AD

Summary

• Seizure severity varies widely between patients
• Improved measures of seizure severity will aid in research and treatment
  – Longitudinal studies with EEG and MRI
• Defining seizure severity and progression will allow for staging of seizures, as in other disease models (i.e. Alzheimer Disease)