First seizure...

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Objective

• Review seizures and other differential diagnosis
• Discuss AAN guidelines on investigations and management in adults presenting with first unprovoked seizure
• Highlight evidence based studies on AED use in adults with seizures.
Differential Diagnosis (top)

- Syncope (all causes)
- TIA
- Migraine
- Transient global amnesia
- Sleep disorder
- Movement disorder
- Psychiatric (anxiety, panic etc)
- Psychogenic non epileptic events – ex conversion, dissociative etc.
A Venn diagram example

- Pure “cardiac” Syncope
- Our typical patient with LOC
- “Ideal seizure”
Definitions

• Seizure – sudden discharge of neuronal activity in synchrony producing electrical or clinical manifestations

• Epilepsy – chronic disease marked by recurrent unprovoked seizures*
  – Can be defined based on >2 seizures or > 1 seizure with > 60% risk of having subsequent seizure
Classification of Seizures

Seizures

Generalized
- Tonic-Clonic
- Myoclonic

Absence

Focal (partial)
- Simple Partial
- Complex Partial
  - “Dyscognitive”

*Can secondarily generalize

ILAE 2010
Focal Seizure

Primary Generalized Seizure
Seizure types - typical

- Stereotyped semiology, last approx 1-2 minutes
- Focal
  - Simple partial – aura, motor, sensory – preserved awareness
  - Complex partial “dyscognitive” – loss of awareness, automatism, unresponsive, “glossy eye”
- Generalized
  - Can be preceded by focal seizure
  - Stiffening (tonic) +/- clonic
- Ictal tongue biting / incontinence
- Post ictal sleepiness / confusion
Seizures – atypical features

- Seizure semiology – bizarre behaviours, hypermotor, hallucinations, spitting/laughing
- Jacksonian march
- Todd’s paresis – “stroke like” post seizure
- Status epilepticus – seizure > 5-15 minutes
  - Generalized
  - Focal - epilepsia partialis continua (EPC) w/ awareness or complex partial status
Seizure as a symptom...

- **Structural**
  - Tumor, Ischemia / hemorrhage

- **Drug induced toxic/metabolic encephalopathy**
  - Illicit drug use
  - Alcohol / Benzo withdrawal
  - Rarely other medication

- **Metabolic** – hypo/ hyperglycemia, electrolyte (Na, Mg, Ca, Phosphate)

- **Infection: Abscess; meningoencephalitis**

Avila & Graber, 2010
Seizures and Epilepsy

• Seizures are common – incidence approximately 8% of single seizure
  – Cause variable

• Epilepsy defined as >2 unprovoked seizures
  – Affects approximately 1% of population
  – 47% can become seizure free on single antiepileptic (AED); 14% after 2\textsuperscript{nd} or 3\textsuperscript{rd}, 3% after taking >2 AED

• Refractory – failure of properly chosen 2 AEDs

• Approx 1/3 of patients diagnosed with epilepsy will be refractory to medical treatment

Potschka and Brodie 2012, Wiebe and Jette 2012
# AAN Guideline for Evaluating first Seizure

1. **EEG**

   **Good evidence supports**
   - An EEG should be considered as part of the routine neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure (Level B).*
   - An EEG should be considered as part of the routine neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure because it has value in determining the risk for seizure recurrence (Level B).*

2. **Imaging**

   **Good evidence supports**
   - Brain imaging using CT or MRI should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B).*

3. **Lab**

   **Inadequate evidence to support or refute**
   - In the adult initially presenting with an apparent unprovoked first seizure, blood glucose, blood counts, and electrolyte panels (particularly sodium) may be helpful in specific clinical circumstances, but there are insufficient data to support or refute routine recommendation of any of these laboratory tests (Level U).*

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Krumholz et al., Neurology 2007
What’s better a CT or MRI?
CT initially reported as normal
Urgent MRI requested...
Pathology...

- Part of lesion was Grade I glioma
- However, second biopsy sample was Grade III anaplastic astrocytoma
Does a normal EEG “rule out” epilepsy or seizures?
EEG

- A test that assesses brain electrical activity at that point in time over ~ 30 minutes
- Should be used as a risk stratifying tool and supportive
- Not commonly “diagnostic” – unless patterns (ex. infantile spasms) or ictal events are captured
  - Assesses for interictal epileptiform discharges (IED)
- Highest yield within 24 hours (51 vs 34%) to capture IED
- Range of IED is 12-27%
- Sleep deprivation increases yield to 23-50%

- Yield seems to be higher in patients < 16 yo (59 vs 39%)

Pohlmann-Eden and Newton, Epilepsia 2008
FIG. 2. Operational curve for new interictal epileptiform activity (IIEA) detection by serial EEGs. Points are based on percentage of yield of new IIEA for each EEG, applied to the group undergoing EEG (corrected for patient attrition). A full explanation is given in the text.
AAN Guideline

• What is the risk of recurrence?

Strong Evidence

Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first two years after a first seizure (21 percent to 45 percent) (Level A).

Clinicians should also advise such patients that clinical factors associated with an increased risk for seizure recurrence include a prior brain insult such as a stroke or trauma (Level A) and an EEG with epileptiform abnormalities (Level A).

Moderate Evidence

Clinicians should also advise such patients that clinical factors associated with an increased risk for seizure recurrence include a significant brain-imaging abnormality (Level B) and a nocturnal seizure (Level B).

Krumholz et al., Neurology 2015
Figure 1  Percentages of patients with first seizure experiencing a recurrent seizure over time

Krumholz et al., Neurology 2015
Patient with Juvenile Myoclonic Epilepsy
Cumulative probability of second seizure

**Years since first seizure presentation**

<table>
<thead>
<tr>
<th>Years since first seizure presentation</th>
<th>idiosyncratic (EEG positive)</th>
<th>remote symptomatic</th>
<th>idiosyncratic (EEG negative)</th>
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<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>253</td>
<td>461</td>
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<td>1</td>
<td>47</td>
<td>137</td>
<td>318</td>
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<tr>
<td>10</td>
<td>6</td>
<td>21</td>
<td>55</td>
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</tbody>
</table>

Patients at risk:

Lawn et al., 2015
AAN Guideline

Moderate Evidence

Clinicians should advise patients that immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk for a seizure recurrence in the two years subsequent to a first seizure (Level B).

Moderate Evidence

Clinicians should advise patients that over the longer term (> 3 years) immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (Level B).

Krumholz et al., Neurology 2015
Immediate treatment of seizures reduces chance to second seizure so early remission (~2 years), but at 5 years both have same rate of seizure freedom

Krumholz et al., Neurology 2015
What’s the perfect drug?

....the one that works!
Show me the evidence...

• Standard and New Antiepileptic Drug-trial (SANAD) – compared lamotrigine (LTG), carbamazepine (CBZ), Oxcarbazepine (OXC), Gabapentin (GBP), Topiramate (TPM)
  – Unblinded study over 12 mths – LTG had lowest incidence of treatment failure compared to all except OXC (started later in study)

• LaLimo trial – LTG vs Levetiracetam (LEV) – superiority trial (26 weeks)
  – Partial and generalized epilepsy
  – No difference in seizure freedom between two
Primary generalized epilepsy

- SANAD Trial #2 – Time to treatment failure and to 12 month remission Valproic acid (VPA) was better than TPM and to LTG

- Avoid Carbamazepine, Oxcarbazepine, Dilantin, Gabapentin

Marson et al., Lancet 2007
But...

- Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study (2013)
  - Largest prospective study examining IQ and other cognitive domains after exposure to AED
- At 6 yo IQ of children exposed to VPA was lower (~-8-12 pts) compared to CBZ, LTG, and PHT on verbal and non verbal tests
- This was a dose dependent effect and was improved if mothers were given pre-conceptual folate
NEAD Study (2013)

Dashed lines (no folate); solid lines (with folate)

Meador et al., Lancet Neuro 2013
<sigh>...Driving...
Driving

• As drivers we are bound by Ontario highway Traffic Act to obey laws
• Driving is a privilege not a right
• As physicians we are bound by law to report patients >16 yo who we feel is “suffering from a condition that may make it dangerous for the person to operate a motor vehicle.”
• Mandatory reporting: MD, Optometrist, Police
• Nurse practitioner: no definite legislation yet but can complete forms for reinstatement
Risk of seizures and driving

• Seizures are unpredictable, unprovoked*
  – Increased risk with sleep deprivation, alcohol
• risk is assumed to be frontloaded - length of time being seizure free correlates to reduced accidents
• One study suggests 85% reduced chance of accident after 6 months and 93% after 12 months seizure free (but this is self reported)
  – no good pooled data

Naik et al., Epilepsy Behav 2015
Why report? Are all seizure same?

• Overall seizure with LOA / LOC risk of accident
  – Generalized tonic clonic; Absence; Complex partial / “dyscognitive”

• Nocturnal – less risk in itself, but some patients convert to diurnal so need period of stability

• Aura – some patients quickly turn to CPS
  – Need to see stability because auras are seizures
  – No auras of forced head / eye deviation
Billing code - $36.25 – allowed at 1 per 12 months PER physician
CMPA and the Law / Colleges

• CMPA reviewed 67 cases from 2005-2009 and described three main themes
  – Allegations of physicians who failed to report
    • Need to discuss with patient duty to report and explain the process
  – Complaints that a report was made
    • Ontario legislation protects against legal action
    • College supports physician if report was made in “good faith.”
  – Complaints relating to refuse application to restore driving privilege
Driving pearls...

- Don’t assume someone else sent MTO form
- 1\textsuperscript{st} seizure generally 3 months with
  - Assessment, imaging, EEG
- Epilepsy > 2 sz - 6 months no driving
- Commercial drivers (A/Z) usually stricter
- Be careful of just “CC” to the MTO of your letter
- Structural lesion ~ 6 mth
- Alcohol withdrawal seizure – still need EEG to r/o epileptiform discharges
  - Need proof of enrolment in program ~ 6 vs 12 mths
Summary

• Everyone who had a first seizure should be investigated with imaging and EEG (routine or sleep deprived)

• If suspicion of mimick, other investigations needed

• Careful discussion of driving

• Many choices for antiepileptic drugs; but the choice depends also on situation
# Mass General Epilepsy Registry

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>1812</td>
<td>2.0</td>
<td>(1.4 to 2.8)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>1078</td>
<td>3.1</td>
<td>(2.1 to 4.3)</td>
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<tr>
<td>Levetiracetam</td>
<td>648</td>
<td>2.2</td>
<td>(1.2 to 3.6)</td>
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<tr>
<td>Topiramate</td>
<td>425</td>
<td>4.5</td>
<td>(2.7 to 6.9)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>420</td>
<td>2.9</td>
<td>(1.5 to 5.0)</td>
</tr>
<tr>
<td>Valproate</td>
<td>333</td>
<td>9.0</td>
<td>(6.2 to 12.6)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>211</td>
<td>1.9</td>
<td>(0.5 to 4.8)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>201</td>
<td>6.0</td>
<td>(3.1 to 10.2)</td>
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<td>Gabapentin</td>
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<td>(0.02 to 4.4)</td>
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<tr>
<td>Zonisamide</td>
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<td>0.0</td>
<td>(0.0 to 3.3)</td>
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<td>Clonazepam</td>
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<td>External Control</td>
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<td>(1.5 to 1.7)</td>
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