Memory and Cognitive Impairment in Epilepsy

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Disclosures
- Financial relationships that could bias discussion
  - None
- Will discuss research involving use of medications that have been tried in the treatment of epilepsy-associated memory loss but which are not approved for this use
- Generic drug names are used; may mention the brand name equivalent in discussion to aid drug recognition

Objectives
- What kinds of cognitive problems do people with epilepsy (PWE) have?
- What are the symptoms?
- How common are they?
- What causes them?
  - My meds? My seizures? My condition?
- What can I do about it?

Patient stories from my practice

AG 39 year old woman, attorney
- 15 year history of temporal lobe seizures
  - Aura, trance, can answer some questions
  - Seizures – auras and simple partial 3-4 per month
- Progressive problems with memory
  - Has to re-read contracts, can’t remember statutes or routine legal processes, errors
- Oxcarbazepine → Lamotrigine → Levetiracetam
- Donepezil
  - No improvement in memory
- Unable to work as attorney, disabled

AM 25 year old woman
- Age 1 – Brain tumor (surgery, radiation), complicated by hydrocephalus (shunt)
  - Excellent recovery, honors student
- Age 14 – seizures – complex partial (right and left temporal) and generalized tonic-clonic (grand mal)
- Several medications, vagus nerve stimulator
- Seizures: 6-12 per month, increasing duration, falls
- Last 1-2 years – progressive memory problems
  - Asks same questions again and again, disoriented, repetitively asks about appointments, anomia (e.g. calls “can of soup” a “thing”)
ML 54 year old woman, court clerk

- Temporal lobe seizures, 5 years
- Phenytoin ➔ Carbamazepine ➔ valproic acid
- Seizure-free, but has memory loss (forgot well known meals), mistakes at work, left brownies in oven, slowed movements, poor energy, unsteadiness, tremors
- Parkinson's? Dementia – unable to work
- Valproic acid ➔ Keppra
- Significant improvement in cognitive status, some return of seizures (simple partial temporal), able to work, extremely grateful

What kinds of cognitive problems do patients with epilepsy (PWE) have?

Cognitive problems – epilepsy type

<table>
<thead>
<tr>
<th>Epilepsy/Seizure type</th>
<th>Cognitive problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe epilepsy</td>
<td>Learning, memory, word finding</td>
</tr>
<tr>
<td>Absence epilepsy</td>
<td>Attention, executive</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>Memory, attention, executive</td>
</tr>
<tr>
<td>Lennox-Gastaut/Dravet's/Spasms</td>
<td>Global cognitive abnormalities</td>
</tr>
<tr>
<td>Left hemispheric</td>
<td>Verbal skills, word finding</td>
</tr>
</tbody>
</table>

Cognitive problems in epilepsy - Symptoms

- Memory
  - forget appointments, forget meds but wrongly think took meds, mistakenly convinced they need to take meds already taken, repeat stories/questions
- Attention
  - Unable to sustain focus, have to re-read paragraphs/sentences, failure to complete tasks
- Executive
  - Planning, organizing, multi-tasking

Frontal Lobe

- "CEO"/foreman
- Secretary
- Parent
- Fine/gross Motor Coordination

Courtesy of Dr. Michael Zaccariello, Ph.D., L.P.
Left Temporal Lobe
- Production of language
- Comprehension of language
- Auditory learning/memory
- With parietal lobe—sight word reading and comprehension

Right Temporal Lobe
- Interprets musical patterns
- Prosody
- With frontal lobe—spatial organization
- Visual/spatial memory

Parietal/Occipital Lobe
- Occipital
  - Characteristics of visual objects
  - Interpretation of visual objects
- Parietal
  - Interpretation of sensory information
  - Math operations
  - Written expression

What causes cognitive symptoms in epilepsy?
- Is it...
  - Underlying condition also causing the epilepsy?
  - Seizure burden?
  - Treatment?

It’s not just the meds
Cognitive loss can precede treatment

- 247 untreated newly diagnosed epilepsy
- 30% had significant deficits in memory
- 30% significant deficits in attention/executive
- Half of affected were unaware of deficits
- Greatest risk –
  - generalized tonic-clonic (grand mal) seizures
  - Epilepsy due to underlying brain disease
  - Lower educational level

Witt & Helmstaedter. J of Neurol 2012; 259:1727-31

Baseline cognitive scores in people with epilepsy before treatment


It’s not just the seizures

Attention deficits - precede treatment and may not resolve with seizure freedom

- N = 446 children newly diagnosed with absence
- Completed neuropsychologic testing prior to meds
- 36% had evidence of attention deficits on the Continuous Performance Test (CPT) at baseline
  - 4 times higher than expected
- Did not go away with successful treatment of absence seizures
  - Suggests seizures not only reason for deficits in attention in absence (petit mal) epilepsy


Abnormalities of brain structure are being found in epilepsy

Lin et al. Epilepsia 2013; 3: 663-72

2013

2002
11/17/13

However, sometimes it can be the meds

- Difficult to sort out the independent effects of medications, seizure burden, underlying brain lesions on cognition in PWE
- However -
  - Certain meds have worse track record than others
  - Individual responses to certain medications may be more prominent than can be appreciated in studies of large groups of patients (dilution effect)

Cognitive effects of specific meds

- Valproic acid more likely to worsen attention more than ethosuximide, lamotrigine\(^1\)
- Fetal exposure in offspring of mothers treated with valproic acid had lower IQ (\(= 97\)) compared to fetal exposure to other drugs (IQ = 105-108)\(^2\)
- Topiramate associated with cognitive decline in non-epilepsy persons (35% compared to 5%)\(^3\)

Cognitive effects of specific meds (cont’d)

- Lamotrigine associated with fewer cognitive side effects compared to topiramate\(^1\)
- Topiramate tolerated slightly less than valproic acid\(^2\)
- Lamotrigine tolerated better than carbamazepine\(^3\)
- Gabapentin tolerated better than carbamazepine\(^4\)
- Phenobarbital negative effects on attention, processing speed, IQ\(^5\)

Cognitive effects of specific meds (cont’d)

- Phenobarbital, phenytoin, valproic acid all associated with cognitive deficits, phenobarbital greatest\(^1\)
- Levetiracetam shows favorable cognitive profile\(^2\)
- Levetiracetam favorable cognitively in children\(^3\)
- Levetiracetam fewer cognitive effects than carbamazepine\(^4\)
- Zonisamide – 6% discontinuation related to cognition\(^5\)


Seizure medications - cognitive profile

<table>
<thead>
<tr>
<th>Relatively favorable</th>
<th>Less favorable</th>
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<tbody>
<tr>
<td>Levetiracetam</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Gabapentin/pregabalin</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Zonisamide</td>
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What can I do to maintain and improve my cognition?

Factors that affect cognition in epilepsy

- Seizure frequency – clinical and subclinical
  - Cognitive decline can be caused by uncontrolled seizures
  - Are all nighttime seizures controlled?
- Continuous spike-wave during sleep (CSWS) in children
- Generalized tonic-clonic seizures
  - Compliance with meds
  - Ensure dosages are sufficient - consider drug levels
- Concurrent conditions
  - Thyroid
  - Depression
  - Sleep apnea
  - Other medications

What else can I do?

- Cognitive exercises
  - www.Lumosity.com
  - www.happy-neuron.com
  - Unproven, and there is a cost, but probably harmless
- General health and fitness
  - Advocated by specialists in treating other chronic neurologic disorders
  - Daily walk, safe exercise in gym
  - Get off the sofa, hide the TV clicker, eat smart

Medication therapies for memory

- Donepezil (approved for Alzheimer’s) - increased number of words remembered in small epilepsy group, no overall increase in seizure rate
- Clinical trial of donepezil showed no benefit
- Other Alzheimer drugs – no data
- Ginkgo biloba – not advised if taking seizure drugs metabolized by the liver – can lead to reduced levels and worse seizures