Pearls and Pitfalls in the Management of Neurological Disease

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Disclosures

none

Outline

• Seizures
  – New classification scheme
  – Management of new onset seizures
• Parkinson Disease
  – Initial medical management
• Headaches
  – New and emerging therapies

Seizures

Classification and initial management

Images from Wikimedia Commons
What are we talking about?

- **Seizure:** paroxysmal synchronized electrical activity in the brain.
  - 10% of people have a seizure at some time in their lives

- **Epilepsy:** tendency toward recurrent unprovoked seizures
  - 0.5-1.0% prevalence of epilepsy

Seizure Classification

- **Partial Seizures:**
  - Simple Partial (motor, sensory, psychic-cognitive)
  - Complex Partial (psychic-cognitive)
  - Partial Seizures Secondarily Generalized

- **Generalized Seizures:**
  - Clonic
  - Tonic
  - Tonic-Clonic
  - Absence
  - Myoclonic
  - Atonic

New Seizure Classification

- **Focal**
  - Without impairment of consciousness/responsiveness
  - With impairment of consciousness/responsiveness
  - Evolving to a bilateral, convulsive seizure

- **Generalized**
  - Clonic
  - Tonic
  - Tonic-Clonic
  - Absence
  - Myoclonic
  - Atonic

New Epilepsy Classification

- Symptomatic Temporal Lobe Epilepsy
  - Epilepsy with focal seizures due to HSV encephalitis
  - Epilepsy with focal seizures due to neurocysticercosis

Berg et al, Epilepsia Feb 2010
Case #1: First unprovoked seizure

- A 25 year-old otherwise healthy man comes to your clinic to establish care after presenting to the ED one week earlier with his first seizure. He had convulsions for one minute followed by post-ictal confusion. A workup in the ED including basic labs, a non-contrast head CT and a lumbar puncture was negative. His neurological examination is normal.

Do you treat?

- Seizure
- 40% 2-year recurrence risk
- History Exam
- EEG
- MRI
- Abnormal: 50-65% recurrence risk
- Normal: 25% recurrence risk
- 2nd seizure: 75% recurrence risk

Treatment reduces 2-year recurrence risk to 25-32% but does not prevent epilepsy

Berg, Epilepsia 2008

Question 1

What AED do you choose?

1. Phenytoin (Dilantin)
2. Carbamazepine (Tegretol)
3. Oxcarbazepine (Trileptal)
4. Lamotrigine (Lamictal)
5. Levetiracetam (Keppra)
6. Divalproex (Depakote)
7. Gabapentin (Neurontin)
8. Pregabalin (Lyrica)
9. Topiramate (Topamax)
10. Zonisamide (Zonegran)
Choose based on seizure type

**Focal seizures**
- Lamotrigine
- Divalproex
- Carbamazepine
- Oxcarbazepine
- Gabapentin*
- Topiramate
- Phenytoin

**Generalized seizures**
- Lamotrigine*
- Divalproex
- Topiramate

*Not FDA-approved for monotherapy

French et al, Neurology 2004

**SANAD: focal seizures**

![Graph showing seizure freedom over time for different medications for focal seizures.](image)

Marson et al, Lancet 2007

**SANAD: generalized seizures**

![Graph showing seizure freedom over time for different medications for generalized seizures.](image)

Marson et al, Lancet 2007

**Newer is not necessarily better**

- **Levetiracetam (Keppra)**
  - 6 randomized trials vs. placebo as add-on therapy
  - 1 randomized trial vs. carbamazepine as monotherapy
  - 73% in each group achieved a 6-month seizure free period

- **Lacosamide (Vimpat)**
  - 2 randomized trials vs. placebo as add-on therapy

Brodie et al, Neurology 2007; image from Wikimedia commons
Women with Epilepsy

- OCPs are only 94% effective (especially carbamazepine, oxcarbazepine, phenytoin, topiramate, and phenobarbital)
- Teratogenicity
  - Highest risk with valproic acid and polytherapy
- Folic acid supplementation
  - 0.4 mg daily for all women of childbearing potential

Bone Density

- Bone mineral density declines at a faster rate in patients on AEDs than controls
- Likely more profound in patients on enzyme inducing AEDs (phenytoin, carbamazepine, phenobarbital) although not all studies confirm this
- Vitamin D and calcium supplementation for all seizure patients should be considered

Long Term Side Effects

- Dilantin: neuropathy, cerebellar degeneration, gingival hyperplasia and dental problems, osteoporosis

Epilepsy Monotherapy

**Focal seizures**
- Lamotrigine
- *Divalproex*
- Carbamazepine
- Oxcarbazepine
- Gabapentin*
- Topiramate
- Phenytoin

**Generalized seizures**
- Lamotrigine*
- *Divalproex*
- Topiramate

*Not FDA-approved for monotherapy
Case #2: New onset Parkinson disease

A 65 year-old man comes to your clinic complaining of a tremor. It bothers him the most when he is sitting in business meetings. He also notes that he can’t keep up with his grandkids like he used to. His exam shows a rest tremor on the right, with cogwheeling rigidity in the right arm, and a slightly shuffling gait.

Question 2
What is the next step diagnostically?

1. Brain MRI
2. Head CT
3. Cervical Spine MRI
4. Trial of levodopa/carbidopa
5. Trial of a dopamine agonist
6. Referral to a neurologist

Parkinson Disease

- Differential Diagnosis
  - Secondary Parkinsonism:
    - Antipsychotics, anti-emetics
    - Vascular parkinsonism
    - Head trauma
    - Toxins (manganese)
    - Structural lesions (hydrocephalus, tumor, chronic subdural)
    - Metabolic (hypoparathyroidism, chronic liver disease)
  - Parkinson plus syndromes:
    - Dementia with Lewy bodies
    - Multiple system atrophy
    - Progressive supranuclear palsy
    - Corticobasal degeneration
Hydrocephalus
Presented in this patient purely as a gait disorder mimicking parkinson disease

PD: Treatment

- **L-dopa vs. dopamine agonists:**
  - Well known that the longer one is exposed to L-dopa, the higher the risk of motor complications (dyskinesias, wearing off, on-off fluctuations, freezing)
  - Often dopamine agonists are used first in order to delay the use of L-dopa
  - Whether this truly delays the onset of motor complications is debated

<table>
<thead>
<tr>
<th>PD: Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Starting levodopa:</strong></td>
</tr>
<tr>
<td>- Combine with carbidopa to prevent conversion to dopamine outside of the CNS</td>
</tr>
<tr>
<td>- Need at least 75 mg of carbidopa per day (e.g. Sinemet 25/100 TID)</td>
</tr>
<tr>
<td>- Can prescribe extra carbidopa</td>
</tr>
<tr>
<td>- Titrate up to 3 tablets TID before calling a patient unresponsive</td>
</tr>
<tr>
<td>- Taken on empty stomach</td>
</tr>
</tbody>
</table>

CALM-PD 2009

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Pramipexole</th>
<th>Levodopa</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS (mean change from baseline)</td>
<td>2</td>
<td>-4.5</td>
<td>-9.2</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.2</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>First dopaminergic motor complication</td>
<td>2</td>
<td>28%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>52%</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>50%</td>
<td>78%</td>
</tr>
<tr>
<td>Quality of Life scores (mean change from baseline)</td>
<td>2</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>~4</td>
<td>~4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7.1</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Parkinson Study Group, JAMA 2000, Arch Neurol 2004 and 2009
PD: Treatment

• Carbidopa/Levodopa
  – Avoid use of CR formulation except at bedtime

• Dopamine agonists
  – Use with caution in the elderly (>70 years old):
    • Daytime somnolence
    • Hallucinations
    • Obsessive behaviors (pathologic gambling)
  – Use ropinerole or pramipexole; older ergot derived agonists such as pergolide can lead to cardiac valve fibrosis

Image from Wikimedia Commons

Neuroprotection?

• Selegiline: neuroprotective?

DATATOP: Parkinson Study Group, Ann Neurol 1996

Neuroprotection?

• Rasagiline: neuroprotective?

Parkinson Study Group, Arch Neurol 2004

Neuroprotection?

• Rasagiline: neuroprotective?

ADAGIO, NEJM 2009
Question 3
Your patient desires treatment for his tremor and slow gait. How would you treat him?

1. Levodopa/carbidopa
2. Pramipexole or ropinerole (dopamine agonist)
3. Rasagiline

Case #3: Cluster headache

- A 53 year-old man comes to your office with a severe, right sided, retro-orbital, piercing headache. It occurs once a day, reliably at 6pm, and lasts for 45 minutes. During the headache he paces the floor, unable to bear the pain. It has been going on for a week. A similar episode happened 6 years earlier. His exam is normal except for a mild right ptosis and miosis.

Question 4
Which of the following CAN NOT be used as a treatment for BOTH cluster and migraine headaches?

1. Verapamil
2. Sumatriptan (Imitrex)
3. High flow oxygen
4. Valproic acid
5. Ergotamine
Cluster treatments

Abortives
- Sumatriptan 6mg subcutaneously
- High flow oxygen

Preventives
- Lithium 600 – 900 mg daily
- Prednisone 60 mg for 7 days followed by rapid taper
- Verapamil
- Valproic Acid
- Ergotamine prior to attacks

Oxygen in cluster headache
- 100% O₂ at 12L/min by face mask
- 4 attacks treated in 109 patients
- Primary end-point: pain free at 15 minutes

<table>
<thead>
<tr>
<th>% of Attacks</th>
<th>Air</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain free at 15 min</td>
<td>20%</td>
<td>78%</td>
</tr>
<tr>
<td>Pain free at 30 min</td>
<td>24%</td>
<td>72%</td>
</tr>
<tr>
<td>Need for rescue med</td>
<td>53%</td>
<td>28%</td>
</tr>
<tr>
<td>Good or excellent response to treatment</td>
<td>15%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Cohen et al, JAMA 2009; image from Wikimedia commons

Trigeminal Autonomic Cephalgias

<table>
<thead>
<tr>
<th></th>
<th>Cluster Headache</th>
<th>Hemicrania Continua</th>
<th>Paroxysmal Hemicrania</th>
<th>SUNCT/SUNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attacks per day</td>
<td>1 – 8</td>
<td>Constant</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Length of attacks (in minutes)</td>
<td>30 – 180</td>
<td>Constant pain, waxing/waning</td>
<td>2 – 30</td>
<td>1 – 10</td>
</tr>
<tr>
<td>Triggers</td>
<td>Alcohol, nitroglycerin</td>
<td>Alcohol, nitroglycerin</td>
<td>Cutaneous stimulation</td>
<td></td>
</tr>
<tr>
<td>Episodic:Chronic</td>
<td>90:10</td>
<td>35:65</td>
<td>10:90</td>
<td></td>
</tr>
<tr>
<td>Circadian/ circannual periodicity</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

| Treatment         | Oxygen or Sumatriptan | Indomethacin | Indomethacin | Lamotrigine or Topiramate |

Goadsby et al, Semin Neurol 2010; image from Wikimedia commons

Migraine treatments

- Abortives:
  - NSAIDs
  - Aspirin/acetaminophen/caffeine
  - Triptans
  - Ergots: cafergot, DHE nasal spray
  - Anti-emetics: compazine, phenergan, reglan
  - Acetaminophen/butalbital/caffeine (Fioricet)
  - Acetaminophen/dichloralphenazone/isometheptene (Midrin)

Silberstein, Neurology 2000
The CGRP Antagonists: Cagepants

- CGRP receptors are found on trigeminal nerve pathways involved in migraine
- 1854 subjects randomized to telcagepant 150 mg or 300 mg, zolmitriptan 5 mg, or placebo

Telcagepant Trial

<table>
<thead>
<tr>
<th></th>
<th>Telcagepant 150 mg</th>
<th>Telcagepant 300 mg</th>
<th>Zolmitriptan 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain free at 2 hours</td>
<td>17%*</td>
<td>27%</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>Pain relief at 2 hours</td>
<td>50%</td>
<td>55%</td>
<td>56%</td>
<td>28%</td>
</tr>
<tr>
<td>2-24 hours sustained pain freedom</td>
<td>11%*</td>
<td>20%</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>2-24 hours total migraine freedom</td>
<td>8%**</td>
<td>17%</td>
<td>16%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*p<0.05 compared to zolmitriptan
† NS compared to placebo

Ho et al, Lancet 2008

Transcranial Magnetic Stimulation

- 201 patients with migraine with aura
- Primary endpoint: pain free at 2 hours

Lipton et al, Lancet Neurology 2010; image from Wikimedia commons

Summary

- Seizures
  - New classification scheme
  - Reasonable first line agents: carbamazepine for focal seizures and valproic acid for generalized seizures (except in women of childbearing age)
- Parkinson Disease
  - Initiate therapy with L-dopa, rasagiline, or dopamine agonists
  - Rasagiline may be neuroprotective
- Migraines and Cluster headache
  - High flow oxygen proven efficacious for cluster
  - Cagepants: a new therapeutic option in migraine?
  - Transcranial magnetic stimulation