Diagnosis and Management of CNS Disorders

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Case 1-Movement Disorders
- A 56 year old man presents with a tremor

Clinical Recognition of Movement Disorder
- Identification of individual signs & symptoms (e.g. tremor, chorea, myoclonus, bradykinesia, …)
- Syndrome recognition (e.g. parkinsonism, …)
- Disease recognition (e.g. Idiopathic Parkinson’s Disease, Essential Tremor, …)

Movement Disorders-Categories
- Hyperkinetic
  - Chorea
  - Ballism
  - Tremor
  - Myoclonus
  - Tics
  - Dystonia
  - Other (stereotypies, akathisia, RLS, moving toes/fingers)
- Hypokinetic
  - Bradykinesia

Tremor
- Repetitive, rhythmic movement that is consistent in time and space

Classification of Tremor
- Rest tremor
- Action tremor
  - Postural tremor
  - Kinetic tremor
  - Task- or position-specific tremor
Causes of Tremor

- Essential Tremor
- Parkinsonism
- Medication Induced
- Physiologic Tremor
- Psychogenic Tremor
- Trauma, Stroke, MS,…

Case 1 - Movement Disorders

A 56 year old man presents with a tremor
- Tremor involves both hands
- Present primarily with activity
- Father had similar tremor
- No associated symptoms

- Neurological examination notable for moderate frequency bilateral postural/intention tremor

Classification of Tremor Based on Relative Frequency (Hz)

<table>
<thead>
<tr>
<th>Frequency in Hz</th>
<th>Typical Etiology</th>
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<tbody>
<tr>
<td>2.4 - 4.0</td>
<td>Cerebellar</td>
</tr>
<tr>
<td>4.0 - 4.5</td>
<td>PD (rest), neuroleptic-induced</td>
</tr>
<tr>
<td>5.5 - 7.0</td>
<td>ET, drug (VPA)</td>
</tr>
<tr>
<td>7.0 - 12.0</td>
<td>Physiological, exaggerated physiologic drug-induced (e.g., epinephrine)</td>
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Core Criteria for Identifying ET

1. Bilateral action (postural and intention) tremor of the hands and forearms
2. Absence of other neurologic signs, with the exception of the cogwheel phenomenon
3. May have isolated head tremor with no abnormal posture
Secondary Criteria for Identifying ET

1. Long duration (>3 years)
2. Family history
3. Beneficial response to ethanol

Treatment of ET

- No treatment
- Weighted Utensils
- Propranolol (prn or scheduled)
- Topiramate
- Primidone
- Gabapentin
- Surgery (Thalamotomy, DBS)

Parkinsonism

- Resting Tremor
- Bradykinesia
- Rigidity
- Masked face, hypophonic speech, swallowing difficulty, micrographia, flexed posture, shuffling gait, gait ignition failure and freezing

Classification of Parkinson Syndromes in a Community

- Idiopathic PD 85%
- Neuroleptic-induced parkinsonism 8%
- Multisystem atrophy 2.5%
- PSP 1.5%
- Vascular parkinson syndrome 3%

Treatment of PD

- No treatment
- Amantadine
- MAO-B inhibitors (e.g. selegiline, rasagiline)
- Dopaminergic agents
  - Levodopa
  - Dopamine agonists
- COMT inhibitors (e.g. tolcapone, entacapone)

Case 2-Spells

- 66 yowm presents with a 2 month history of spells
- Pt is unaware of spells
- Wife notes brief episodes when pt seems to be daydreaming and is slow to respond
- No associated si’s or sx’s
- Returns to baseline quickly
DDx of Spells in the Elderly
- Seizure
- Syncope
- TIA
- Transient Global Amnesia
- REM Behavior Disorder
- Periodic Limb Movements of Sleep
- Vertigo
- Movement Disorders
- Migraine
- Pseudoseizure

Case 2 (continued)
- Normal neurological examination
- Labs (CMP, Mg, Ca, CBC) are normal
- Holter is normal
- Carotid Dopplers show no significant stenosis
- MRI shows scattered white matter changes

MRI: White Matter Changes

Neuroimaging
- MRI is the modality of choice in the non-emergent evaluation of seizure
- Gadolinium contrast should be considered in the elderly to add sensitivity to tumor detection
- Abnormalities should be interpreted with caution
  - Non-specific changes (e.g., atrophy, periventricular white matter hyperintensities, prominent Vircho-Robin spaces) are common
  - 60% of elderly with non-epileptic spells have MRI abnormalities (with >1/3 being focal)

EEG
- Obtain shortly after the initial event
- A single EEG may be normal in many individuals with epilepsy
- Serial EEG’s improve sensitivity
- Sleep deprivation may improve sensitivity
- Video-EEG is the gold standard for seizure diagnosis

Interictal Epileptiform Discharge
Definitions

- A seizure is a temporary disturbance of brain function caused by abnormal electrical activity in the brain.
- Clinically, seizures tend to be brief (1-2 minutes), stereotyped when recurrent, with a wide array of potential manifestations.
- Epilepsy is a chronic condition marked by recurrent seizures.

Classification of Seizures

- Divided into partial vs generalized based on degree of brain involvement.
- Partial seizures are further subdivided based on alteration in consciousness (e.g., simple and complex partial seizures).
- Partial seizures may become secondarily generalized.
- Seizures can also be further subdivided by symptomology (e.g., GTCS, atonic, ...).

Importance of seizures in the elderly

- One of the most common neurological diseases in the elderly.
- Morbidity and mortality associated with seizures are higher in the elderly.
- Incidence of status epilepticus (SE), and resultant mortality, is higher in the elderly.

Treatment of Seizures

- Acute treatment may not be necessary (unless pt is in status epilepticus).
- Only approximately 30% of patients with a normal neurological examination, normal EEG and normal MRI will go on to have recurrent seizures.
- If long-term treatment is necessary:
  - Select a single agent and titrate gradually to maximum tolerated dose before switching medications.
  - Strive for monotherapy.
  - Seizure type, or epilepsy syndrome, might help direct medication choice.

Flowchart of ILAE seizure classification

Age-related incidence of epilepsy

S. LaRoche, 2007
**Recommended AED’s for New Onset Epilepsy**

- Older AED’s
  - Phenytoin (Dilantin)
  - Valproate (Depakote)
  - Carbamazepine (Tegretol)

- Newer AED’s
  - Gabapentin (Neurontin)
  - Lamotrigine (Lamictal)
  - Oxcarbazepine (Trileptal)
  - Topiramate (Topamax)
  - Levetiracetam (Keppra)

**Recommended AED’s for Adjunctive Therapy in Refractory Partial Epilepsy**

- Older AED’s
  - Phenytoin (Dilantin)
  - Valproate (Depakote)
  - Carbamazepine (Tegretol)

- Newer AED’s
  - Gabapentin (Neurontin)
  - Lamotrigine (Lamictal)
  - Oxcarbazepine (Trileptal)
  - Topiramate (Topamax)
  - Levetiracetam (Keppra)
  - Tiagabine (Gabatril)
  - Zonisamide (Zonegran)

*Topiramate can also be recommended for refractory generalized epilepsy*

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**Case 3-Sleep**

- 29 year old man with an 8 year h/o excessive daytime somnolence
- Multiple brief, unexplained awakenings during night-time sleep period
- Sleep is non-refreshing
- No other significant PMH
- No medications

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**Hypersomnia in the U.S.**

- 75% of adults report frequent sleep related problems (with EDS among the most common)
- 60% of adults admit to driving while drowsy
- 4% have had a MVA or near accident related to drowsiness

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**Importance of Hypersomnia**

- >100,000 MVA’s annually in US are caused by driving while drowsy
- Major disasters including Three Mile Island, Exxon Valdez, Bhopal and Challenger were all officially attributed to sleepiness-related impaired judgment in the workplace

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**DDx of Hypersomnia**

- Volitional sleep deprivation (we get 20% less sleep than previous generations)
- Sleep Disordered Breathing (e.g. OSA)
- Narcolepsy
- Idiopathic CNS hypersomnia
- PLMS
- Circadian Rhythm Disorders
- Other (Medications, etc.)
Evaluation of Hypersomnia

- History
- Sleep Diary
- Actigraphy
- Overnight Polysomnography (PSG)
- MSLT and/or MWT

Elements of the History

- Presence/degree of sleepiness (ESS)
- Sleep patterns (onset, continuity, …)
- Amount of sleep per 24 hours
- Naps (refreshing or not?)
- Snoring, witnessed apneas
- Environment during sleep
- Associated sx’s (sleep paralysis, …)

Epworth Sleepiness Scale (ESS)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Score</th>
<th>Chance of falling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smiling and reading</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sitting, yawning</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sitting, reading a book in a moving vehicle</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon or circumstances permit</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sitting quietly after lunch without alcohol</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>In a car, bike, or aeroplane for five minutes without alcohol</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Score: _______

Case 3-continued

- 8-9 hours of uninterrupted sleep per night (approx. 10pm-6:30am)
- Mild-moderate snoring, but no witnessed apneas
- Occasional leg jerks during sleep
- 1-2 episodes of possible sleep paralysis in the past
- No problems noted in the environment
- ESS=21

MSLT

- Mean Sleep Latency = 1.5 minutes
- 4/4 SOREM’s

Toxicology Screen-negative
**Classification of Narcolepsy**  
(ICSD Criteria)  
- Classified by presence or absence of cataplexy  
- EDS almost daily for at least 3 months  
- MSLT testing (following sufficient nocturnal sleep)  
  - Mean sleep latency ≤ 8 minutes  
  - ≥ 2 SOREMP’s  
  - MSLT recommended in all cases, and required in the absence of definite cataplexy  
- Hypersomnia not better explained by another sleep d/o, medical d/o, etc.

**Clinical Manifestations of Narcolepsy**  
- Onset most often in teens/early 20’s  
- Chronic sleepiness  
- Hypnogogic hallucinations  
- Sleep Paralysis  
- Cataplexy  
- Automatic Behavior

**Cataplexy**  
- Sudden muscle weakness brought on by strong emotions  
- May be partial (e.g. affecting only the face)  
- Usually brief (seconds to two minutes)  
- Occurs almost exclusively in narcolepsy  
- 60% of narcoleptics develop cataplexy (usually within 3-5 years of sx onset)

**Narcolepsy-Treatment**  
- Treat other associated sleep d/o’s  
- Scheduled naps  
- Medications  
  - EDS (stimulants, modafinil)  
  - Cataplexy (SSRI’s, TCA’s, γ-hydroxybutyrate)  
  - Disrupted nighttime sleep (zolpidem, γ-hydroxybutyrate)

**Treatment of EDS**  
- Modafinil  
  - 100-400 mg per day (daily or bid dosing)  
  - HA, nausea, insomnia  
- Methylphenidate  
  - Up to 60 mg per day (bid or tid)  
  - Anxiety, insomnia  
- Dextroamphetamine  
  - Up to 60 mg per day (bid or tid)  
  - Insomnia, psychosis  
- Pemoline  
  - Up to 312.5 mg per day (daily or bid)  
  - Hepatic toxicity

**Treatment of Cataplexy**  
- TCA’s  
  - Protriptyline (5-30 mg per day)  
  - Imipramine (50-250 mg per day)  
  - Nortriptyline (50-200 mg per day)  
- SSRI’s  
  - Fluoxetine (20-60 mg per day)  
  - Citalopram (20-40 mg per day)  
- Gamma-hydroxybutyrate (Xyrem)  
  - 4.5-9.0 grams/night in two doses separated by 2.5-4 hours  
  - May also help with EDS
Case 4-Sleep

- 60 year old man dreamed he was working on a loading dock and saw a man running; someone yelled “stop him” and the patient jumped after the man.
- The patient’s wife reports he jumped off the end of the bed and awoke on the floor with a “bloody lip, head, and knee.”
- Initial evaluation revealed facial abrasions and a subdural hematoma.

Parasomnia

- Parasomnias are undesirable movements and behaviors occurring during sleep
- Parasomnias are disorders of arousal, partial arousal, and sleep stage transition

Parasomnias-Evaluation

- History
  - Description of Events
  - Including report of bedpartner
  - Can patient recall events?
  - Timing
- Past Medical History/Medication History
- Physical Exam
  - Obesity
  - Parkinsonism
  - Dementia

Parasomnias-Evaluation (cont.)

- Sleep Diary
- EEG
- PSG
  - Expanded EEG montage
  - Expanded EMG monitoring
  - Video monitoring

Differential Diagnosis

- Sleepwalking
- Sleep Terrors
- REM-Sleep Behavior Disorder
- Nocturnal Seizures
- Hypnogenic Paroxysmal Dystonia
- Obstructive Sleep Apnea
- Rhythmic Movement Disorders
- Nocturnal Psychogenic Dissociative Disorders
- Malingering

Case 4-Sleep

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- The patient’s wife reports he jumped off the end of the bed and awoke on the floor with a “bloody lip, head, and knee.”
- Initial evaluation revealed facial abrasions and a subdural hematoma.
- PSG demonstrated elevated EMG activity during REM sleep
REM Behavior Disorder (ICSD-2)
- REM sleep without atonia
- At least one of the following
  - Sleep related injurious or disruptive behavior
  - Abnormal REM sleep behavior during PSG
  - Awakening short of breath
- Absence of associated epileptiform activity
- Not better explained by another disorder

REM Sleep Behavior Disorder
- A multifaceted parasomnia involving REM sleep and the motor system in which there is problematic behavioral release that is usually experienced by the individual as enactment of distinctly altered, unpleasant, and combative dreams

RBD-Potential Causes
- Withdrawal
  - Alcohol
  - Meprobamate
  - Pentazocine
  - Nitrazepam
- Medications
  - Venlafaxine
  - SSRI’s
  - Mirtazepine

RBD-Epidemiology
- Male predominance (87%)
- Mean age of onset 52-62 years
- Sleep related injuries common (up to 96%)
- Altered dream process and content (more intense, action-filled and violent)
- Preserved sleep architecture (REM/NREM cycling)
- Often associated with parkinsonism (current or future)

REM Sleep (Paradoxical Sleep)
- Defining features
  - REM atonia
  - Rapid Eye Movements (REM’s)
  - Activated EEG
  - High level of brain activity
  - “Paradoxical Sleep”
    - Paradoxical suppression of skeletal muscle tone despite a highly activated brain state

RBD-Paradox Lost
- Loss of the paradoxical atonia in REM sleep
- Dreams are subsequently acted out in reality
RBD-treatment

- Initial trials of REM suppressing TCA’s were unsuccessful.
- Clonazepam was tried next based on its beneficial effect on nocturnal myoclonus, another parasomnia.
  - Clonazepam was found to be immediately effective in approximately 90% of cases.

Clonazepam Suppresses excessive phasic motor activity
Melatonin Restores REM atonia
Sinemet
Anecdotal reports of response to
- L-tryptophan
- Clonidine
- Carbamazepine
- Gabapentin
- MAOIs

Case 5-Head Injury

- 16 yowm brought to office after having “bell rung” at football practice.
- Needs doctor’s permission to return to practice.
- Helmet to helmet contact
- No loss of consciousness, but was dazed for a few minutes
- Headache for a few hours

Concussion in Sports

- Concussion is a trauma-induced alteration in mental status that may or may not involve loss of consciousness.
- Confusion and amnesia are hallmarks.

Concussion in Sports-Evaluation

- Orientation
- Concentration
  - Digits backwards
  - Months of year in reverse order
- Memory
  - 3 words
  - Details of game,…
- Provocative tests (40 yard sprint, push-ups, sit-ups,…)
- Neurologic exam (pupils, coordination, sensation)
Concussion in Sports - Recommendations for Return to Play

- **Grade 1**
  - May return if si’s and sx’s clear in 15 minutes
  - A second concussion eliminates player from competition for at least one week

- **Grade 2**
  - May return if asymptomatic at rest and with exertion for one week, with a normal neurologic exam
  - CT or MRI recommended if sx’s persist
  - Return deferred for at least 2 weeks after a second Grade 2 concussion

- **Grade 3**
  - Consider transport to ER (especially for prolonged LOC)
  - Assess neurologic status daily
  - After a brief (seconds) LOC, may return after asymptomatic at rest and with exertion for 1 week
  - After a prolonged (minutes) LOC, may return after asymptomatic at rest and with exertion for 2 weeks
  - Return is deferred for at least one asymptomatic month after a second Grade 3 concussion