Multiple Sclerosis
Parkinson’s Disease
Epilepsy
Peripheral Nervous System
Cerebrovascular Disease
Cognitive Impairment
Multiple Sclerosis
Background

- Around 400,000 people in the U.S. with the disorder, prevalence of 33 per 100,000 (2.3 million people worldwide)\(^1\)

- Average age of onset is 30, with a 2:1 female-to-male ratio

- The basic pathology centers on repeated autoimmune demyelinating attacks on the axons of the brain and spinal cord, followed by remyelination and corresponding clinical improvement, almost certainly partial in nature

- While classically thought of as T-cell-mediated disease affecting white matter, we are finding increasing evidence of both B-cell and gray matter
### McDonald Criteria

**“Dissemination in Time, Dissemination in Space”**

<table>
<thead>
<tr>
<th>Clinical Episodes</th>
<th>Objective Clinical Lesions</th>
<th>Additional Requirements to Satisfy Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2 or more</td>
<td>Dissemination in Space (either by MRI or CSF or second clinical attack)</td>
</tr>
<tr>
<td>2 or more</td>
<td>1</td>
<td>Dissemination in Time (either by MRI or second clinical Attack)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Dissemination in Space and Time (either by MRI or second clinical attack)</td>
</tr>
</tbody>
</table>
| 0/Progressive at Onset | N/A                      | • One year of disease progression and 2/3 of the following:  
  o DIS in brain  
  o DIS in spinal cord  
  o positive CSF |
McDonald Criteria

- Dissemination in Space: one or more characteristic MS lesions in at least two of the following locations:
  - Periventricular
  - Juxtacortical
  - Infratentorial
  - Spinal cord

- Dissemination in Time
  - A new, characteristic enhancing or non-enhancing lesion on MRI in comparison with a baseline scan
  - Any combination of non-enhancing and asymptomatic enhancing MRI lesions on the same scan
Kurtzke Expanded Disability Status Scale (EDSS)

Functional scores
Kurtzke Expanded Disability Status Scale (EDSS)

- Normal neurologic exam
- No disability, minimal signs in one FS
- No disability, minimal signs in > one FS
- Minimal disability in one FS
- Minimal disability in two FS
- Moderate disability in one FS or mild in 3 or 4 FS
- Fully ambulatory but moderate disability in one FS + other milder FS scores
- Fully ambulatory without aid, up 12 hours per day, FS of 4 or combo of milder FS
- Fully ambulatory without aid, some assistance ADLs
## Kurtz Expanded Disability Status Scale (EDSS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>Ambulatory up to 200 meters without aid, impaired ADLs</td>
</tr>
<tr>
<td>5.5</td>
<td>Ambulatory up to 100 meters, impaired ADLs</td>
</tr>
<tr>
<td>6.0</td>
<td>Intermittent/unilateral assistance (e.g., cane, brace) required to walk 100 meters</td>
</tr>
<tr>
<td>6.5</td>
<td>Constant bilateral assistance required to walk 100 meters</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk 5 meters without assistance, usually in wheelchair</td>
</tr>
<tr>
<td>7.5</td>
<td>Essentially restricted to bed or wheelchair, retains many self-care functions</td>
</tr>
<tr>
<td>8.0</td>
<td>Essentially restricted to bed or wheelchair but out of bed for much of day</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed, retains some self-care functions</td>
</tr>
<tr>
<td>9.0</td>
<td>Can communicate and eat but helpless and bedbound</td>
</tr>
<tr>
<td>9.5</td>
<td>Bedbound, helpless, unable to communicate or eat</td>
</tr>
</tbody>
</table>

Modified from Kurtze⁴
Mortality and Multiple Sclerosis

Based on initial presenting symptoms

- **Favorable**
  - Younger age at diagnosis
  - Male
  - Shorter disease duration
  - **Optic neuritis in women**

- **Unfavorable**
  - Older age at onset
  - Female
  - **Cerebellar symptoms** (gait difficulties, ataxia, tremor)
  - Longer disease duration
Prognosticating Multiple Sclerosis

Other favorable factors

- Sensory rather than motor symptoms
- Intact cognition
- Course and imaging over first year
- Long latency before second attack
- Absence of brainstem pathology
Causes of Excess Mortality in MS

- Aspiration pneumonia
- DVT and pulmonary embolism
- Urosepsis
- Sepsis from pressure sores
- Accidents
- Suicide
Clinically Isolated Syndrome (CIS)

- CIS refers to a single clinical demyelinating event which then places the patient at higher risk for future development of clinically definite multiple sclerosis (CDMS).

- Underwriters should be aware of the overall risk of progression to clinically definite multiple sclerosis as well as the prognostic factors that may significantly alter this risk.

- Estimates of the overall risk of developing multiple sclerosis vary widely depending upon cohorts and timeframes studied, but is generally quoted at 50% within the next five years.
Clinically Isolated Syndrome

Predictive Power of MRI – National MS Society

If the MRI of brain is normal at time of CIS, the risk of MS is 20%

If the MRI of brain is abnormal at the time of CIS, the risk is 60-80%
## Progression of CIS to CDMS

### Favorable and unfavorable factors

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal MRI</td>
<td>• “Positive” MRI at presentation</td>
</tr>
<tr>
<td>• Isolated optic neuritis</td>
<td>• Motor symptoms</td>
</tr>
<tr>
<td>• Isolated sensory symptoms</td>
<td>• Excess oligoclonal bands</td>
</tr>
<tr>
<td>• Normal CSF</td>
<td>• Abnormal evoked potentials</td>
</tr>
<tr>
<td>• Caucasian</td>
<td>• Age &lt;30</td>
</tr>
<tr>
<td>• Age &gt;30</td>
<td>• Multifocal symptoms at onset</td>
</tr>
<tr>
<td>• Unifocal symptoms at onset</td>
<td>• Smokers</td>
</tr>
<tr>
<td>• Low EDSS at presentation</td>
<td>• Positive EBV titers</td>
</tr>
</tbody>
</table>

- CIS: Clinically Isolated Sclerosis
- CDMS: Clinically Definite Multiple Sclerosis
- MRI: Magnetic Resonance Imaging
- CSF: Cerebrospinal Fluid
- EDSS: Expanded Disability Status Scale
- EBV: Epstein-Barr Virus
Neuromyelitis Optica

Key distinguishing features

Specific antibody
- NMO-IgG: antibodies to aquaporin-4 proteins
- Located on the foot processes of astrocytes
- 70% sensitive, 90% specific

Different treatment
- No benefit with traditional MS disease-modifying therapies (DMTs)
- Worsens with interferon beta
- Imuran, mycophenolate, rituximab often used

Worse prognosis
- For typical relapsing form, 68% survival at 5 years
- For rarer monophasic subtype, 90% survival at 5 years has been reported
Acute Disseminated Encephalomyelitis (ADEM)

Risk factors for progression to MS

- No confusion or EEG changes
- No viral illness
- Abnormal CSF immune profile
- No fever
Parkinson’s Disease
Parkinson’s Diagnostic Criteria

UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria

- Step 1: basic entry criteria
  - Bradykinesia and one of:
    - Rigidity
    - Postural instability
    - 4-6 Hz rest tremor

UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria

Exclusion criteria
- Multiple strokes
- Head injury
- Neuroleptic treatment
- Strictly unilateral features after three years
- Early severe dementia
- Babinski sign
- Early severe autonomic signs

Supportive criteria
- Unilateral onset still affecting side of onset predominantly
- Progressive disorder
- Response to levodopa
- Hyposmia
- Levodopa-induced chorea
- Visual hallucinations
Prognosis in Parkinson’s

AAN Practice Parameter: Diagnosis and Prognosis of PD

- Older age of onset (variably defined as over age 57-78 years) (two Class II and one Class III studies) and rigidity/hypokinesia as a presenting symptom (two Class II studies) are factors that are probably useful in predicting a more rapid rate of motor progression of PD

- The presence of associated comorbidities (one Class II study), features of PIGD (postural instability and gait disturbance) (one Class II and one Class III studies) and male gender (one Class II study) are factors that are possibly useful for predicting a more rapid rate of motor progression of PD

- Tremor as the initial presentation is a factor that is possibly useful in predicting slower progression and a longer response to levodopa therapy (one Class II and one Class III studies)

- Older age of onset and initial manifestations of hypokinesia/rigidity are factors that are probably useful in predicting earlier development of cognitive decline and dementia (two Class II and one Class III studies)

- Older age of onset, dementia, and decreased dopamine responsiveness are factors that are possibly useful in predicting an increased risk for nursing home placement and shorter survival after diagnosis (one Class II study)
Basic Mortality in Parkinson’s

- Overall SMR 1.5
- Higher mortality with younger age of onset (<60, SMR = 1.92)
- SMRs decrease with age
- Clinically definite PD had lower mortality than possible PD
- Increased SMR with MMSE <23
Basic Mortality in Parkinson’s

What else matters

- Gait disturbance
- Severity of disease (e.g., Hoehn and Yahr >2)
- Duration of disease
- Lack of tremor
- Symmetric disease
# Parkinson’s Plus Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Reported Survival Times (yrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive Supranuclear Palsy</td>
<td>5.6</td>
</tr>
<tr>
<td>Multiple Systems Atrophy</td>
<td>9</td>
</tr>
<tr>
<td>Lewy Body Disease</td>
<td>7.3</td>
</tr>
<tr>
<td>Corticobasal Ganglionic Degeneration</td>
<td>7.9</td>
</tr>
<tr>
<td>Parkinsonism-dementia-amyotrophic lateral sclerosis complex</td>
<td>3-5</td>
</tr>
</tbody>
</table>
Red Flags for Parkinson’s Plus Syndromes

Symmetric Onset

- Early postural instability
- Early cognitive changes
- Axial rigidity
- Vertical gaze palsy
- Nonresponsive or hypersensitive to levodopa
Case Scenario

- Informal inquiry ("I’ve got a guy....")

- 59-year-old man “with Parkinson’s disease. He was developing some funny features. They thought he might have had PSP so they did one of these new DaTscans. Turns out he just has Parkinson’s.”

- Wiling to take a look?
DaTscan

“The comma turns into a period”
DaTscan

- For the diagnosis of Parkinsonian syndrome sensitivity is reported at 91% and specificity at 92%\(^\text{11}\)

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**Parkinsonian Syndromes**

- Idiopathic PD
- PSP
- MSA
- Lewy Body

**Non-DA Parkinsonism**

- Essential Tremor
- Drug-induced PD
- Vascular Parkinson’s
- Alzheimer’s
Case Scenario

Deep brain stimulation (DBS)

- 63-year-old woman carries a diagnosis of IPD for 10 years
- Around three years ago required increasing and fairly large doses of Sinemet and still had unsatisfactory control of motor symptoms
- Two years ago underwent DBS at local academic center without post-operative complication
- Did well in the following year; had mild depression treated with SSRI; was able to greatly reduce but not eliminate PD meds
- Now fully independent ADLs, able to work part-time from home
Deep Brain Stimulation for PD

- Most common benefit is to improve “off state” and reduce dyskinesias, thus reducing (but typically not eliminating) the amount of medication.

- In pivotal NEJM trial, outcomes measured in mean improvements in UPRDS and PDQ-39 of 19.6 and 9.5 points\textsuperscript{12}

- Does not typically benefit falls and balance.

- Elevated suicide rates after surgery have been reported (4.3\%)\textsuperscript{13}

- Very limited mortality data shows survival rates of 94\% and 99\% at 3 and 5 years respectively, with some suggestion of decreased survival in those with pre-surgical cognitive deficit and less post-surgical motor improvement.
Definitions

Absence (Petit Mal) seizures*

- International League Against Epilepsy (ILAE) Commission 1989: inclusion criteria for childhood absence epilepsy
  - Children of school age (peak manifestations at 6 to 7 years)
  - Very frequent (several to many per day) partial seizures
  - EEG with bilateral, synchronous, and symmetrical spike-waves, usually at 3 Hz
  - Development of generalized tonic-clonic seizures often occurs during adolescence

*incorrectly used interchangeably with complex partial seizures
Absence vs. Complex Partial Seizures

Absence

- Onset typically in childhood
- No aura
- Usually last <20 seconds
- 3 Hz spike and wave discharge
- Begin and end abruptly – but often confused for inattentiveness
- Better prognosis

Occur in all age groups

- Often preceded by aura
- Last from 15 seconds to 3 minutes
- Variable EEG (often arise from temporal lobe)
- More gradual onset/end
Mortality in Epilepsy

General principles

- Overall SMR in mortality studies varies from 1.6 to 3.0 in studies with 7 to 29 years of follow-up\textsuperscript{14}

- SMRs tend to be higher in children (given overall lower mortality rates) and in the elderly (because of comorbidities)

- Mortality tends to be highest within the first few years of diagnosis; however, excess mortality is still seen 20+ year after diagnosis

- Mortality rates are not significantly changing

- People with epilepsy do not tend to die from seizures
1. Is the brain otherwise normal? (both radiographically and clinically)

- A key factor relates to differentiation between idiopathic/cryptogenic vs. symptomatic; there are some studies which suggest little to no increased risk in idiopathic epilepsy
  - National General Practice Study in UK prospective study in a cohort of 1,000 patients followed from mid-'80s to 2009
    - Life expectancy for idiopathic epilepsy reduced by 2 years compared to 10 years for symptomatic epilepsy
  - “Seizure control (>1 year without seizure) was achieved in 82% of patients who had idiopathic generalized epilepsy, 35% of those with symptomatic partial epilepsy, 45% of those with cryptogenic partial epilepsy, and 11% of those with partial epilepsy associated with hippocampal sclerosis (HS).”\textsuperscript{15}
2. Are the seizures controlled?

- Prospective study in Finland followed a cohort of 245 children for 40 years; 15% of deaths occurred in those who were in remission (no seizures x 5 years) vs. 85% of deaths with active seizures; a history of status epilepticus predicted higher chance of SUDEP\textsuperscript{16}

- In 583 patients with who had received epilepsy surgery, 18 deaths observed in patients with recurrent seizures (mortality rate = 11.4 per 1,000 person-years) and 1 death in patients with no recurrent seizures (mortality rate = 0.85 deaths per 1,000 person-years)\textsuperscript{17}

- Event rates as rare as >1 seizure per year are associated with increased mortality\textsuperscript{18}

- SUDEP strongly associated with seizure frequency

- Little specific data on correlating number of seizures with frequency (most define “control” as no seizures in last year and remission as 5 years)
3. What type(s) of seizures are present?

- Generalized tonic clonic seizures generally accepted as associated with higher mortality risk

- In a prospective study of 4,578 patients (16,463 patient-years) GTC seizures were the single highest risk factor for SUDEP

<table>
<thead>
<tr>
<th>Attained Age</th>
<th>Recent GTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-14</td>
<td>420%</td>
</tr>
<tr>
<td>15-24</td>
<td>423%</td>
</tr>
<tr>
<td>25-34</td>
<td>419%</td>
</tr>
<tr>
<td>35-44</td>
<td>245%</td>
</tr>
<tr>
<td>45-65</td>
<td>152%</td>
</tr>
<tr>
<td>5-65</td>
<td>293%</td>
</tr>
</tbody>
</table>

Day et al. 20
Epilepsy syndromes with a potentially favorable prognosis

- Rolandic epilepsy or benign epilepsy with centrotemporal spikes (BECTS) has a very favorable prognosis
  - Onset between age 2 and 13, partial motor or sensory seizure with clusters of generalized seizures, often at night
  - Characteristic central or temporal spikes on EEG
  - Excellent prognosis – 50% in remission by age 6 and 99.8% by age 18\(^2\)

- Childhood absence epilepsy
  - Reported rates of seizure freedom (70-80%)
  - 10% transform to GTC or juvenile myoclonic epilepsy
4. Has the applicant ever had status epilepticus?

- Defined by ILAE as, “seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur”

- Can be convulsive or nonconvulsive; traditionally 30 minutes, but as low as 5 minutes of seizure activity is recognized as meeting criteria

- Mortality from single episode is quite high (around 20%) – one of the key risk factors for status epilepticus is….status epilepticus!
  - Children have SE more frequently, but mortality rate of each episode much lower at 3%22

- 43% mortality at 10 years (!) after first episode of status epilepticus excluding those that died within the first 30 days (Rochester Epidemiology Project)23

- Well-described risked factor for SUDEP
5. Is there evidence of active psychiatric disease?

- Rate of depression varies between 20% and 55% in uncontrolled seizures (and 3-9% in controlled seizures)\textsuperscript{22}

- 3-fold increase of suicide overall, particularly high within first six months of diagnosis\textsuperscript{24}

- Temporal lobe epilepsy is associated with greater degrees of depression and suicide rates\textsuperscript{25}

- Exercise great caution in cases of post-surgical seizures (SMR for suicide 13.9 for TLE and 6.4 for other epilepsy surgeries)\textsuperscript{26}
6. Are there any other synergistic comorbidities?

Most people with epilepsy do not die from epilepsy

- Alcohol
- Stroke
- Malignancy
- Central and Obstructive Sleep Apnea
- Pneumonia*
7. Is the applicant at particular risk for injury?

- Overall, accidents account for 6% of fatal epilepsy cases
- Is the applicant driving? Should they be?
  - Driving restrictions vary by state, typically six months; some states have mandatory reporting; some physicians allow driving if seizures are exclusively nocturnal or partial
  - Risk is probably higher than other conditions (eg., 2.3 x CV risks, DM) but low overall (0.2%)
- Any occupational exposures?
- Risk for drowning? Scuba?
  - 60% in unsupervised baths
- Risk is especially high in those with comorbid neurologic insult
- History of injury itself is a risk factor for future mortality (OR 1.4)
8. Are there any EEG abnormalities?

- EEG abnormalities are an independent risk factor for mortality – risk of death 3.7 times higher\(^{27}\)

- Value of EEG is in prognosticating chance of recurrence

- Normal *single routine* EEG has little predictive value
  - 3 normal EEGs effectively rule out electrographic abnormalities

- In the event of a single seizure, the risk of recurrence by two years is 58% if the EEG is abnormal compared to 27% if normal\(^{28}\)

- Identify particular syndromes (with both positive and negative ratings implications)

- Identify subclinical seizures (e.g., child with declining grades)
9. Is the applicant adherent with regimen?

- Patients nonadherent to medication regimen have SMRs of >3, and also at higher risk for MVAs, fractures, ER visits \(^ {29}\)

- Priming: if a patient has been nonadherent with frequent seizure, seizure control becomes more difficult long-term

- Again, be aware of synergy between epilepsy, depression and nonadherence

- Levels of newer medications (leviracetam, lamotrigine, topiramate gabapentin) more helpful in ensuring adherence rather than guiding therapy; frequent AED level checks may be akin to attending physician criticism

- Paradoxically, refractory epileptics associated with better degrees of adherence

- Medication adherence drops dramatically with frequency of dosage; paradoxically, those with complex, multidrug regimens more adherent \(^ {30}\)
10. Are there any associated mortality risks with treatment?

- Overall mortality risks related to medication effect are quite low
- FDA estimates 1/50,000 risk of fatal exposure
- Even less often with newer medications (more even pharmacokinetics)
## Mortality Risks with Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Mortality Risk</th>
<th>Antiepileptic Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens Johnson</td>
<td>Phenytoin, Lamotrigine, Carbamazepine most commonly</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>Carbamazepine, Divalproex Sodium, Phenytoin, *Felbamate</td>
</tr>
<tr>
<td>Metabolic Acidosis, Nephrolithiasis</td>
<td>Topiramate, Zonisamide</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Carbamazepine, Oxacarbazepine</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>Phenytoin (hypersensitivity syndrome), Carbamazepine</td>
</tr>
<tr>
<td>Arrhythmia, Toxicity</td>
<td>Phenytoin, Fosphenytoin, Divalproex Sodium</td>
</tr>
<tr>
<td>Suicidality</td>
<td>All</td>
</tr>
<tr>
<td>?? Cancer</td>
<td>All</td>
</tr>
</tbody>
</table>
Peripheral Nervous System
Peripheral Neuropathy

*It is fairly common for us to see applicants with either sensory or motor neuropathies as determined by either clinical history or EMG reports. Which ones should we worry about, and which ones are less concerning?*
“Normal” Loss of Sural Nerve with Aging

- 23% of patients aged 70-79\textsuperscript{31}
- 40% of patients over 80\textsuperscript{31}
- Bottom line: isolated absence of sural nerve likely of little consequence in terms of morbidity and mortality, especially in the elderly
Red Flag Indicators in NCT/EMG Reports

NCT

- “Demyelinating” or “significant slowed conduction velocities”
- “Conduction Block”
- “Asymmetric”

EMG

- “Acute,” “Fibrillations,” “Positive Sharp Waves” – these latter two are indicators of an active recent process very much analogous to contrast enhancement on MRI
- Myopathy
Diabetic Peripheral Neuropathy

- Incidence is roughly 50% for both diabetics and non diabetics\textsuperscript{32}
- Can cause a wide variety of neuropathy patterns (axonal, demyelinating, small fiber, autonomic, cranial, treatment-related)
- Glucose control can prevent the complications, probably more so for type I than type II diabetes (annualized risk = -1.84% for tight type I control versus -0.58% for type II)\textsuperscript{33}
Diabetic Autonomic Neuropathy

- The 5-year mortality rate in patients with diabetic autonomic neuropathy is three times higher than in diabetic patients without autonomic involvement

- Silent cardiac ischemia a particular concern
Myasthenia Gravis

- Prototypical autoimmune neuromuscular disease process
- Basic pathology is of abnormal T cell-mediated production of antibodies against the post-synaptic acetylcholine receptor antibody (Anti-AChR antibodies)

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Myasthenia Gravis – Presenting Symptoms

• Dysarthria
• Dysphagia
• Dysphonia

• Fluctuating weakness
• Neck extensors
• Hip flexors

• Fluctuating weakness
• Neck extensors
• Hip flexors

• Dyspnea
• “Myasthenic crisis”

Ocular
Limb
Respiratory
Bulbar
Myasthenia Gravis

Treatment

- Pyridostigmine and relatives
  - Do not affect underlying pathology

- Chronic immunosuppressants
  - Steroids
  - Azathioprine
  - Mycophenolate

- For rapid treatment exacerbations
  - IVIG
  - Plasmapheresis

- Thymectomy
# Underwriting of Myasthenia Gravis

## A few pearls....

<table>
<thead>
<tr>
<th>Conceptualize similar to asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exacerbations</td>
</tr>
<tr>
<td>• ER/hospitalizations</td>
</tr>
<tr>
<td>• Intubations (status asthmaticus similar to myasthenic crisis)</td>
</tr>
<tr>
<td>• Medication burden</td>
</tr>
<tr>
<td>• Exam between flares</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ocular myasthenia generalizes in roughly 50% of patients most (85%) within the first 2 years[^35]</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anti-Musk antibodies highly predictive of non-ocular disease (but lower thymic disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Be skeptical of thymectomy data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nonrandomized</td>
</tr>
<tr>
<td>• Surgical groups tend to be younger, with fewer comorbidities and less severe disease</td>
</tr>
<tr>
<td>• Looked for recurrent thymic tissue in failed remissions</td>
</tr>
</tbody>
</table>

[^35]: Ocular myasthenia generalizes in roughly 50% of patients most (85%) within the first 2 years.
Myopathies – Risk Stratification

Five questions – 1) Is the myopathy inherited or congenital?

- **Congenital**
  - Hypotonia
  - Head lag
  - Poor suck, feeding
  - Failure to gain weight
  - Dyspnea, frequent infections

- **Childhood**
  - Difficulty running
  - Toe walking
  - Cramps
  - Gowers’ sign

https://en.wikipedia.org/wiki/Gowers%27_sign#/media/File:Gower%27s_Sign.png
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Myopathies

2) Is the myopathy paraneoplastic?\textsuperscript{36,37}

Dermatomyositis
- Heliotrope rash
- Gottron’s sign
- Proximal muscle weakness
- Elevated CK, positive myositis antibodies

- Malignancy risk increases with age (not typically seen in children)
- Diagnosis temporally distributed in normal fashion with median at the time of diagnosis (and great majority within first 2 years)
Myopathies

3) Is the myopathy associated with respiratory failure?

- Inflammatory
  - Anti-Jo-1 myopathy
  - Sarcoidosis
  - Dermatomyositis/polymyositis

- Congenital
  - Central core
  - Nemaline/rod
  - Cushings (glucocorticoid excess)
  - Acromegaly

- Traumatic/Crush injury

- Metabolic
  - Acid Maltase/Pompe disease

- Muscular Dystrophies
  - Becker
  - Duchenne
  - Myotonic
## Myopathies

4) Is the myopathy associated with systemic end organ disease?

<table>
<thead>
<tr>
<th>Myopathy</th>
<th>Other organs involved/disease processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid</td>
<td>Renal, MGUS, myeloma</td>
</tr>
<tr>
<td>MELAS</td>
<td>Strokes</td>
</tr>
<tr>
<td>Myotonic, Duchenne</td>
<td>Cognitive</td>
</tr>
<tr>
<td>Thyroid, parathyroid, Cushing, acromegaly</td>
<td>Various</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Paget’s disease of the bone</td>
</tr>
</tbody>
</table>

MELAS = mitochondrial encephalopathy lactic acidosis and stroke
5) Is the myopathy associated with cardiac involvement?
Cerebrovascular Disease
“We often receive attending physician statements where we have difficulty telling whether an individual had a TIA. We already know what TIAs are and how to apply ratings for these events. We need some guidance on situations where it is not entirely certain that a person had an actual TIA or whether it might be another condition like migraine.”
## Causes of TIA Mimics

<table>
<thead>
<tr>
<th>Diagnosis of Mimic</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>44</td>
</tr>
<tr>
<td>Migraine</td>
<td>23</td>
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<tr>
<td>Psychogenic</td>
<td>7</td>
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<tr>
<td>Hypertensive encephalopathy</td>
<td>4</td>
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<tr>
<td>Transient global amnesia</td>
<td>4</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
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<tr>
<td>Hypoglycemia</td>
<td>2</td>
</tr>
<tr>
<td>Benign paroxysmal vertigo</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>2</td>
</tr>
<tr>
<td>Brain neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral nerve lesion</td>
<td>1</td>
</tr>
<tr>
<td>*Syncope</td>
<td>??</td>
</tr>
</tbody>
</table>
Symptoms Predictive of TIA mimic

- Headache – no mechanism whereby TIA should cause headache
- Memory loss (*see below!)
- Blurred vision (as opposed to loss of vision or diplopia)
- Syncope
- Recurrent stereotyped episodes with negative workup
- Symptoms that do not conform well to a single artery – generalized symptoms with a gradual or hazy onset rather than focal sudden onset symptoms (“weak all over,” “dizzy”)
- Lack of other vascular risk factors
Transient Global Amnesia

- One of the most interesting neurologic phenomena – happens in entirely normal people with little medical history
- Pathogenesis unknown
- Key feature is sudden and profound inability to form new memories, repetition of questions lasting on the order of hours without focal symptoms
- Often follows exercise
- Workup typically normal (MRI, ECHO, carotids, EEG)
- Entirely different prognosis
  - Low rate of recurrence (6%)
  - Lower rate of stroke, myocardial infarction or death
Case Scenario

Carotid dissection

- 41-year-old male, hypertension, + tobacco
- 3 years ago, left carotid dissection presenting with headache, Horner’s syndrome, right hemiparesis, dysarthria
- Workup included – MRI, MRA of the brain and carotids, echo, PT, PTT, ESR, homocysteine, alpha1 antitrypsin, ANA/ENA
- REFUSED oral anticoagulation, would take ECASA 81 mg
- Good recovery – right hand clumsiness, decreased right toe taps, independent ADLs, back to work
Carotid Dissection
Dissection

Top 10 things to remember!

1. Very common cause of stroke in the young (10-25%)\textsuperscript{40}

2. Carotid and vertebral artery dissections are different

3. Three main causes – trauma, connective tissue disease, and “I dunno”

4. Trauma and “I dunno” have the best prognosis; connective tissue disease has the worst prognosis but is the most rare

5. In roughly 15% of cases multiple arteries are involved (and multiple artery involvement indicates underlying connective tissue disease)\textsuperscript{41}
Dissection

Top 10 things to remember!

6. Nobody knows how to treat dissection

7. The gold standard of diagnosis is changing

8. There is an increasing association with infections (but is it the infection or is it the cough?!)

9. The time frame for recanalization is 3-6 months (this corresponds well with permanency of any stroke deficit); when rating, place greater emphasis on remaining stroke deficit

10. Watch for pseudoaneurysm as a complication
Case Scenario

Cerebral venous thrombosis

- 67-year-old woman with history of allergies, hypothyroidism
- Advised in 1998 to take Lovenox because of extensive travel history
- 2008 DVT, 2009 DVT
- December 2012, after picking up an intestinal virus she had a syncopal event and then a concussion
- After the concussion developed double vision requiring Fresnel prism
- 1 month later found to have transverse sinus thrombosis
- At time of application on chronic anticoagulation with Warfarin, no residual symptoms, full resolution of flow radiographically, but still travels extensively
Cerebral Venous Thrombosis

- Overall a rare cause of stroke (1%), but 78% of these cases are below the age of 50\(^42\)
- Peak age between 20 and 40, women outnumbering men 3:1\(^43\)
- Primary presenting symptom is headache as a result of increased intracranial pressure; time course can vary significantly
- Focal symptoms are a concerning prognostic indicator as they implicate focal infarction and hemorrhage
- Risk factors are very similar to other sources of venous thrombosis: *hormonal*, pregnancy, oral contraceptives, cancer, dehydration and various thrombophilias (Factor V, protein C and S deficiency, antithrombin III deficiency, antiphospholipid antibody syndrome)
Cerebral Venous Thrombosis

“Desert island” underwriting questions

- Is there any underlying thrombophilia or systemic disease?
- Did the applicant have infarction or hemorrhage on imaging?
- Any permanent symptoms or complications?
Cerebral Aneurysm

- Whom to screen?
- How to treat?
- Whom to treat?
Whom to Screen and How Often?

- **Whom to screen?**\(^44\)
  - Patients with *two* first-degree primary relatives
  - PCKD (10-22%), Ehlers-Danlos

- **How often to screen?**\(^45\)
  - For high-risk category every 5 years is recommended
  - 20% had an aneurysm by 10 years after negative initial screen

- **How to screen?**
  - CTA and MRA are fairly equivalent with high sensitivity and specificity above 3 mm\(^46\)
Risk of Rupture

Size

From UCAS Japan Investigators\textsuperscript{47} (5,720 patients, with 6,697 aneurysms studied for 3 years)

<table>
<thead>
<tr>
<th>Size</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 mm</td>
<td>Reference</td>
</tr>
<tr>
<td>5-6 mm</td>
<td>1.13</td>
</tr>
<tr>
<td>7-9 mm</td>
<td>3.35</td>
</tr>
<tr>
<td>10-24 mm</td>
<td>9.09</td>
</tr>
<tr>
<td>&gt;25 mm</td>
<td>76.26</td>
</tr>
</tbody>
</table>
# Risk of Rupture

## Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Risk of Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle Cerebral</td>
<td>Reference</td>
</tr>
<tr>
<td>Internal Carotid</td>
<td>0.43</td>
</tr>
<tr>
<td>PICA/Vertebral Junction</td>
<td>0.68*</td>
</tr>
<tr>
<td>Basilar/Superior Cerebellar Junction</td>
<td>1.49*</td>
</tr>
<tr>
<td>Posterior Communicating/Internal Carotid</td>
<td>1.0</td>
</tr>
<tr>
<td>Anterior Communicating Artery</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Not statistically significant

PICA = Posterior inferior cerebellar artery
Cognitive Impairment
Alzheimer’s Dementia

Core clinical criteria (all causes)\textsuperscript{48}

- Interfere with the ability to function at work or at usual activities
- Represent a decline from previous levels of functioning
- Are not explained by delirium or major psychiatric disorder
- Cognitive impairment is diagnosed through a combination of (1) history-taking and (2) an objective cognitive assessment
- The cognitive or behavioral impairment involves a minimum of two of the following domains:
  - Impaired ability to acquire and remember new information
  - Impaired reasoning and handling of complex tasks, poor judgment
  - Impaired visuospatial abilities
  - Impaired language functions
  - Changes in personality or behavior, or comportment
Mild Cognitive Impairment Criteria

- Cognitive concerns or complaints
- Objective cognitive deficits
- Absence of other psychiatric or systemic disorder that would explain the cognitive deficit
- Preservation of activities of daily living
Lawton Instrumental Activities of Daily Living

- Telephone
- Shopping
- Cooking
- Housekeeping
- Laundry
- Transportation
- Medication administration
- Finances
Clinical History

What clinical factors should be considered when assessing potential progression to dementia?

- Age
- Who is noticing the cognitive complaint? *Depression?*
- Is there a documented change from baseline?
- Abrupt or gradual?
- Any loss of activities of daily living? Executive dysfunction?
- Deficits of language?
- Medication effect or systemic disease
- Smell and taste difficulties
Limitations of Cognitive Screening

- Over 100 cognitive screens have been developed (and this will only increase given Medicare wellness requirements)
- Time to administer
- Expense (many proprietary)
- Expertise to administer
- Priming
- Cheating in tele-interview
- Technology impediments
- Many are not validated
- Specificity decreases with multiple examinations
MMSE

Pros
- Ubiquitous
- Fairly easy to administer
- Independently predictive of mortality

Cons
- Education and culturally dependent (reduces sensitivity in insured population)
- Age dependent
- Less sensitive for MCI
- Priming
- Proprietary
DWR

- **Pros**
  - Easy to administer, short, easy to communicate, free
  - Mortality Data (Vecchione, Journal of Insurance Medicine 2007)\(^{49}\)
  - Expected mortality based on 2001 Smoker Distinct Valuation Basic Tables
DWR

- Cons
  - Limited scope limits specificity (e.g., 1997 study by O’Carroll et al. found poor ability of DWR to differentiate between depression and cognitive impairment)\textsuperscript{50}
  - Prone to anxiety
  - Lends itself well to cheating in tele-interviews, or feigning in disability-independent medical evaluations
MCAS – Minnesota Cognitive Acuity Screen

Pros

- Multiple domains tested (9): orientation, attention, delayed word recall, comprehension, repetition, naming, computation, judgment and verbal fluency
- Validated in detecting dementia in the context of insurance screening and telephone interviews (97% sensitive, 98.5% specific) \(^{51}\)
- Data for MCI (sensitivity 86% and specificity 78\%) \(^{52}\)
- Have independent mortality data (300,000+ applicants, SMRs 183\% year one with predictive value extending 9 years at 129\%) \(^{53}\)

Cons

- Proprietary
- Length ? (15-20 minutes)
- Developed for LTC
AD Biomarkers

Markers of amyloid accumulation
- Decreased CSF amyloid beta
- PET amyloid studies

Markers of neuronal injury
- Increased CSF phosphorlyated tau
- FDG-PET and fMRI
The Genetics of Alzheimer’s

**Deterministic Genes**
- Early onset
- Familial
- Autosomal-dominant

**Risk Genes**
- *Likelihood* increases
- Later onset
- Sporadic
- More common
Late Onset Alzheimer’s Disease

- Apoe E alleles
- Later-age onset (most after 60)
- Accounts for 20-25% of all Alzheimer’s cases
- While most are sporadic, around 40% have first-degree relative with the disease

- Apolipoprotein E gene – 3 different alleles: Apoe E2, E3, and E4
  - The number of Apoe E4 alleles both increases the likelihood of Alzheimer’s disease and reduces the age of onset (5 years per allele)
ApoE

- 1 ApoE e4 allele: 25% of population, 4x Risk
- 2 ApoE e4 alleles: 2% of population, 10x risk
- ApoE e2: 11% of population, Slight protective effect
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References


References


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Questions?

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