Underwriting Neurologic Diseases in Older Age Applicants

AAIM 124th Annual Meeting

Dave Rengachary, MD
Vice President and Medical Director

October 23, 2015
Outline

I. Alzheimer’s Disease and Cognitive impairment
II. Cerebrovascular Disease
III. Parkinson’s Disease
Alzheimer’s Definitions and Criteria
Alzheimer’s Disease Criteria

Why does it matter?

- 2011 represents 1\textsuperscript{st} time criteria have undergone major revision since 1984
- Represents major (and controversial) undertaking of Alzheimer’s Association and National Institutes of Health
- Critical illness definitions often hinge on these criteria

http://www.alz.org/documents_custom/alz_diag_criteria_faq.pdf\textsuperscript{1}
Alzheimer’s Criteria

- What are the major differences?
  - Previous criteria were entirely clinical. Updated criteria now emphasize consideration of Biomarkers (not necessary to make diagnosis but provide adjunctive support)
  - Identifies 3 stages of cognitive dysfunction 1) Preclinical Alzheimer’s disease 2) MCI due Alzheimer’s Disease 3). Dementia due to Alzheimer’s Disease
Alzheimer’s Dementia

Core Clinical Criteria (All Causes)

- 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
Alzheimer’s Criteria

Probable Alzheimer’s Disease

- Core Clinical Criteria
- Carrier of Causative Genetic Mutation
- With Evidence of AD pathophysiologic process
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
Preclinical Alzheimer's Dementia

- Positive Biomarkers (amyloid imaging, PET, functional MRI, and CSF studies) but *largely asymptomatic patients
Basic Mortality in Cognitive Impairment
Alzheimer’s Mortality

CDC: Percent change in age-adjusted death rates from 2000-2010

Alzheimer’s Mortality

CDC Age Adjusted Death Rates

Some variability in studies but average life expectancy from diagnosis typically quoted as 4-8 years.

Iacovino mortality abstract JIM, 1991:

<table>
<thead>
<tr>
<th>Age Symptom Onset</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Symptom Onset</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>Mortality Ratio</td>
<td>750%</td>
<td>125%</td>
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<tr>
<td>Mortality Ratio</td>
<td>900%</td>
<td>375%</td>
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### Alzheimer’s versus Vascular Dementia

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Interval Year</th>
<th>Mortality Ratio</th>
</tr>
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<tbody>
<tr>
<td>Alzheimer’s</td>
<td>1</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>261</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>511</td>
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<td></td>
<td>4</td>
<td>649</td>
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<tr>
<td></td>
<td>5</td>
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<tr>
<td>Vascular</td>
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<td></td>
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<td>514</td>
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<td>375</td>
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<td>Mixed</td>
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<td>2</td>
<td>278</td>
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<tr>
<td></td>
<td>3</td>
<td>156</td>
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<tr>
<td></td>
<td>4</td>
<td>0</td>
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</table>

Alzheimer’s Mortality

Alzheimer’s Dementia: Morbidity and Mortality, Lisa Duckett, MD

- Reinforced marked difference in mortality ratios comparing early onset to later onset disease
- For disease onset earlier than 65, average length of survival from symptom onset to death was 9.1 years (17.5 in general population)
- When looking at causes of death in Alzheimer’s, infections were markedly over represented (54% in Alzheimer’s cohort versus 1% in general population)

Alzheimer’s Mortality
Mortality Derived From 5-Year Survival in Patients With Alzheimer Disease

- Large (23,000) community based (Washington state) population over age sixty with good extended follow-up
- Overall MR was 142%, low because of average age of patients (80).
- Factors predicting excess mortality included:
  - Dementia Rating Scale > 2.5
  - Gait disturbance/Falls
  - Behavioral change
  - Frontal Release signs
  - Extrapyramidal Symptoms
  - Wandering
  - Incontinence

MCI “Desert Island” Questions

- Rate of AD progression
- Factors predicting progression to AD
- Overall MCI mortality
Rate of progression of MCI to Alzheimer’s Dementia

- Most studies support an adjusted annual conversion rate (ACR) of 5-10% per year

10% per year in specialists setting

5% per year in community based settings
Mortality of Mild Cognitive Impairment

- Mayo Clinic Study of Aging
- 2,154 Olmsted county residents aged 70-89
- Adjusts for age, sex, diabetes, multiple cardiovascular factors, Apoe E4 carrier status,
- Median follow up of 5.8 years
- Overall mortality ratio for any degree of MCI was 203%

Treatments
Results of Phase III, Randomized Placebo controlled, Double blinded Studies

Source: Update on Alzheimer’s Disease Clinical Trials, Laurie Ryan, PhD Program Director, Alzheimer’s Disease Clinical Trials, National Institute on Aging, National Institutes of Health

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Atorvastatin</td>
<td>HMG CoA reductase</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Dimebon</td>
<td>Mitochondrial function</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>LY450139 (Semagacestat)</td>
<td>Gamma Secretase modulator</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Anti-inflammatory</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Phenserine</td>
<td>Cholinesterase Inhibitor</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>PPAR gamma agonist</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>HMG CoA reductase</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Tarenflurbil</td>
<td>Gamma Secretase modulator</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Xaliproden</td>
<td>Serotonin Agonist</td>
<td>NEGATIVE</td>
</tr>
</tbody>
</table>
Medicare Cognitive Screening

- Effective January 1, 2011 as part of the Patient Protection and Affordable Care Act all Medicare beneficiaries are required to undergo a cognitive screening as part of their annual Wellness examination.
- There are 46.4 million part B beneficiaries
- The government did not specify which cognitive tool should be used
- Alzheimer's Association recommends GPCOG, mini-Cog, or MIS for assessment of patients and AD8, GPCOG or short IQCode if informant is primary history giver.
- USPTF recently concluded that the evidence is insufficient to recommend for or against routine screening for dementia in older adults.
Alzheimer’s Association Recommended Cognitive Screens and “Trigger Scores”

**Patient**

<table>
<thead>
<tr>
<th>Test</th>
<th>Score</th>
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<tbody>
<tr>
<td>GPCOG</td>
<td>&lt;8*</td>
</tr>
<tr>
<td>Mini-Cog</td>
<td>≤ 3</td>
</tr>
<tr>
<td>MIS</td>
<td>≤ 4</td>
</tr>
</tbody>
</table>

**Informant**

<table>
<thead>
<tr>
<th>Test</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD8</td>
<td>≥ 2</td>
</tr>
<tr>
<td>GPCOG informant score</td>
<td>≤ 3</td>
</tr>
<tr>
<td>Short IQCODE</td>
<td>≥ 3.38</td>
</tr>
</tbody>
</table>

*GPCOG score less than 8 is considered indeterminate, < 5 is “trigger score”
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
Cognitive Screening
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 teleinterview
- 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
**MMSE and mortality**

*Park et al., 2013⁷*

<table>
<thead>
<tr>
<th>Cognitive Score</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>Mild cognitive dysfunction</td>
<td>1.93</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.66</td>
</tr>
</tbody>
</table>

- Orientation to time and attention were independently predictive of mortality
- Korean population, Average age was 60
- Adjusted for age, gender, socio-demographic factors including education
DWR

- Pros
  - Easy to administer, short, easy to communicate, Free
  - Mortality Data (Vecchione, Journal of Insurance Medicine 2007)\textsuperscript{8}
  - 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)\(^9\)
  - Prone to anxiety
  - Lends itself well to cheating in teleinterviews, or feigning in disability independent medical evaluations
Clock Drawing Test

- Poor interrater reliability!
AD8

- **Pros**
  - Relatively short - 3 minutes (or less)
  - *Function* based with multiple cognitive domains, and identifies *change*
  - Informant based
  - Validated (sensitivity 84% and specificity 84% using 2 hour Clinical Dementia Rating Scale as gold standard) and studied for early cognitive impairment, telephone vs. in person, multiple languages, and settings
  - Easy to administer and interpret (score of 2 or more abnormal)

- **Cons**
  - Informant based (sometimes paired with mini-Cog or other PI based study),
  - Little independent mortality data
  - Entirely subjective (not performance based) and subject to antiselection
AD8 + Performance test

- Mini-Cog – 3 word recall + clock drawing test
- MIS – Memory Impairment Screen – 4 word recall, more points if recalled without any cues (hints) needed.
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) \(^{10}\)
- Data for MCI (sensitivity 86% and specificity 78%) \(^{12}\)
- Have independent mortality data (300,000+ applicants, SMRs 183% year one with predictive value extending 9 years at 129%) \(^{11}\)

**Cons**

- Proprietary
- Length ? (15-20 minutes)
- Developed for LTC
EMST – Enhanced Mental Skills Test

- **Pros**
  - Multiple Domains Tested – Attention, concentration, working memory, abstraction, judgment
  - Based on CERAD 10 word list – immediate recall, interference task, delayed word recall, triadic comparison, cued recognition
  - Independent Mortality Data
  - Able to do by telephone

- **Cons**
  - Proprietary
  - ? Protective value of Additional Testing (in one mortality study 22% death rate screened by EMST vs. 20% by DWR) – but claims data from LTC experience did show a difference between the two screening tests.  #13
  - 20% Cheating rate! (but 94% of these unimpaired)  #14
Biomarkers
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
Biomarkers - Questions

- How soon do these biomarkers become positive?
  - Washington University Dominantly Inherited Alzheimer’s Network
- How frequently will we see these biomarkers in clinical practice?
  - CMS decision regarding reimbursement vs….
  - Marketing by pharmaceuticals
  - Introduction of blood biomarkers
- What are the most common scenario's that we will see biomarkers now?
  - Mild cognitive impairment with equivocal traditional testing
  - Distinguishing dementia from depression and other dementia mimics
  - Cognitive changes in a young individual
  - Asymptomatic but high risk and highly motivated individuals
  - Clinical trials
CSF Biomarkers

- A pattern of low Amyloid B42 and elevated phosphorylated tau
- Available only via lumbar puncture – low rate of complications (1-2%) related to CSF leak (and headaches), infections, and hematoma.
- Commercially available from Athena Diagnostics
- In one published prospective study of MCI: \(^{16}\)
  - Sensitivity 89%
  - Specificity 77%
  - Positive Predictive value 73%
  - Negative Predictive value 91%
- Of the two, phosphorylated tau is more specific (i.e. to distinguish AD from ALS, Parkinson’s, related dementias, Lewy body and Frontotemporal dementia.)
Florbetapir-F18 (Amyvid)

- Florbetapir-F18 is an injectable radiopharmaceutical agent (Amyvid/Eli Lily) developed for PET use. It binds to amyloid plaque and thus can be used in the diagnosis of Alzheimer's Disease.
- FDA approved for the evaluation of cognitive impairment
- Scan sensitivity was estimated at 92% and specificity at 95% in autopsy proven cases
- A second agent, Flutemetamol F18 injection (Vizamyl, GE healthcare) was approved in Fall 2013, and a third agent florbetaben F18 injection (Neuraceq, Piramal Imaging) was approved March 2014
- Side effect profiles generally favorable – hypersensitivity reactions, headaches, dizziness
- Current CMS coverage limited to clinical studies
Flobetapir-F18 (amyvid)

Flobetapir-F18 (amyvid)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number</th>
<th>Number Scans Positive</th>
<th>3/5 Readers Agree</th>
<th>4/5 Readers Agree</th>
<th>5/5 Readers Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>49</td>
<td>38</td>
<td>10</td>
<td>14</td>
<td>76</td>
</tr>
<tr>
<td>MCI</td>
<td>57</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>91</td>
</tr>
<tr>
<td>Cognitively Normal</td>
<td>33</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>90</td>
</tr>
</tbody>
</table>

FDG-PET

- Consistently show decrease glucose metabolism in AD patient, in particular in bilateral parietal and temporal lobes
- Similar sensitivity and specificity rates also published at 80-90%
- One small Italian study of 73 patients with MCI found temporal hypometabolism on FDG-PET to be strongest indicator of progression to Alzheimer's in comparison to other biomarkers
- CMS coverage available to distinguish Alzheimer's from frontotemporal dementia
- Limitations – expense, relatively nonspecific, availability, radiation exposure (low)
The Genetics of Alzheimer's Disease
The Genetics of Alzheimer’s

Deterministic Genes
- Early Onset
- Familial
- Autosomal Dominant

Risk Genes
- Likelihood increases
- Later Onset
- Sporadic
- More Common
Early Onset Alzheimer's

- Before the age of 60
- 5% of all Alzheimer’s Cases
- Autosomal Dominant Mutations
  - Pre-Senilin 1 (PSEN1) = most common and most young
  - Pre-Senilin 2 (PSEN 2) = most rare, onset slightly older
  - Amyloid Precursor Protein = somewhere in between
    - All 3 result in incorrect cleavage of the amyloid precursor protein
Late Onset Alzheimer’s Disease

- Apoe E alleles
- Later age onset (most after 60)
- Account 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 on onset (5 years per allele)
ApoE

1 ApoE e4 allele

- 25% of population
- 4 x Risk

2 ApoE e4 alleles

- 2% of population
- 10 x risk

ApoE e2

- 11% of population
- Slight Protective Effect
Alzheimer’s Conclusions

- In coming decades we will see a significant influx of cognitive information in normal or preclinical Proposed insureds related to multiple factors including: aging of population, changing Medicare requirements, advances in preclinical diagnostics, and failure of current symptomatic treatments.
- Each cognitive screening test will have significant Pros and Cons – Understanding of these Pros and Cons is critical to their interpretation.
- Individual biomarker currently have suboptimal sensitivities and specificities, but combinations of these studies can risk stratify asymptomatic individual prior years prior to any symptoms with high accuracy.
- Once a treatment has even a modest effect on delaying diagnosis of Alzheimer’s in the preclinical state, we will see a significant increase in testing and thus identifying pre-symptomatic individuals.
Cerebrovascular Disease
Basic Mortality in Stroke
Overall Mortality is decreasing

- Stroke has dropped from the third leading cause of death to the fourth\textsuperscript{18}
- From approximately 250 deaths per 100,000 in 1900 to 40 per 100,000 in 2010
- All encompassing pattern – since 1950s around 50% drop in:
  - Recurrent strokes
  - Incidence rates (in higher income countries, globally as well)
  - Case fatality rates
Reduction in Systolic BP by NHANES time period

Systolic Blood Pressure

- 1960-62
- 1971-74
- 1976-81
- 1988-91
- 1988-94
- 1999-04
- 2001-08

SBP mm

NHANES time period

1960-62 130
1971-74 128
1976-81 126
1988-91 122
1988-94 124
1999-04 126
2001-08 132
### Time since Stroke

Morbidity and Mortality Associated With Stroke\(^{19}\)

Robert J. Pokorski, MD, FACP

<table>
<thead>
<tr>
<th>Duration</th>
<th>Age &lt;65 MR%</th>
<th>65-74 MR%</th>
<th>75-84 MR%</th>
<th>&gt;85 MR%</th>
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</thead>
<tbody>
<tr>
<td>6 mo-1 yr</td>
<td>857</td>
<td>380</td>
<td>382</td>
<td>306</td>
</tr>
<tr>
<td>1-2 yr</td>
<td>891</td>
<td>336</td>
<td>285</td>
<td>256</td>
</tr>
<tr>
<td>2-3 yr</td>
<td>489</td>
<td>395</td>
<td>293</td>
<td>274</td>
</tr>
<tr>
<td>3-4 yr</td>
<td>514</td>
<td>237</td>
<td>349</td>
<td>421</td>
</tr>
<tr>
<td>4-5 yr</td>
<td>542</td>
<td>606</td>
<td>75</td>
<td>236</td>
</tr>
</tbody>
</table>
### Age

**Long-term Mortality After Stroke Among Adults Aged 18 to 50 Years**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>640%</td>
</tr>
<tr>
<td>30-39</td>
<td>570%</td>
</tr>
<tr>
<td>40-50</td>
<td>340%</td>
</tr>
</tbody>
</table>
Stroke Severity

Functional Outcome 3 Months after Stroke Predicts Long-Term Survival\textsuperscript{21}

- **MRS 1-2**: Slight to minimal Disability, intact ADLs
  - HR = 1

- **MRS 3**: Requires assistants ADLs, ambulates independently
  - HR = 1.7

- **MRS 4**: Moderately Severe Disability. Requires help with ADLs, able to attend to bodily functions
  - HR = 2.5

- **MRS 5**: Severe disability, Bedridden incontinent
  - HR = 3.8
Clearly highest for cardioembolic and hemorrhagic stroke – Recent study by Stead et al\textsuperscript{23} found 3.4 times mortality for cardioembolic strokes (as compared to small vessel disease) \textit{when controlling for stroke severity}.

Recent article by Dr. Lund\textsuperscript{24} challenges notion of early favorable mortality with lacunar infarction but still overall much less than cardioembolic and appears to mitigate after 10 years

Intermediate values for “atherothrombotic” strokes
Cardiovascular comorbidities

- **Copenhagen Stroke Study**\(^{25,26}\)
  - 31% of death attributed directly to stroke but majority of this was in the first year
  - 21% of death altogether attributed to cardiovascular disease
  - Bronnum study risk of death due to cardiovascular disease twice than expected

- **Atrial fibrillation and DM** independently associated with mortality
Special Topics

I. Endovascular Treatment of Stroke
II. Stroke in the Young
III. Carotid Stenting
IV. Underwriting of Cerebral Aneurysm and AVM
Endovascular Treatment of Stroke
Case Scenario

- Informal inquiry: “I’ve got a guy….”
- 65 year old male whose coming in for 50K
- Very limited info – 2012 had a stroke, was transported by helicopter and underwent treatment with intravenous TPA, interarterial thrombolysis, and required treatment with Merci Stent Retriever
- “Retired”
- Follow up “sparse” since that time – in particular no follow up information on status of stent
- “Willing to take a look?”
2013 Endovascular Therapy

IMS IIII

SYNTHESES

MR. RESCUE
“We have given the strongest recommendation possible – class 1, level of Evidence A – for certain patients to receive Endovascular therapy”
MR CLEAN

Randomized Trial of Interarterial Treatment for Acute Stroke

 Patients:
  - Within 6 hours of symptom onset
  - Occlusion of distal Internal Carotid, MCA or ACA as evidenced by CTA, MRA or angiography
  - NIHSS score of 2 or greater

 Treatment:
  - Usual Care (IV TPA) PLUS:
    - Interarterial Treatment (Interarterial thrombolysis, mechanical treatment or both)
      - 83% received mechanical treatment, 81% Retrievable stent
      - At 90 days there was a 13.5% improvement in rate of functional independence according to modified Rankin Scale (32.6% versus 19.1%)
      - No difference in rates of intracranial hemorrhage
      - No difference in mortality at 90 days (ESCAPE trial with 50% reduction in mortality)
Why the Sudden Change?

- Improved devices (3rd generation vs. 1st generation)
- Better patient selection criteria – Required radiographic documentation of proximal occlusion
- Endovascular therapy was performed more rapidly
Endovascular Therapy – Underwriting Impact

- Initially small – Estimated < 4% of all strokes would receive this therapy
- Increasing usage rates predicted likely driven by reimbursement and marketing
- Familiarity with devices
- Standard of care for relatively minor strokes
Mechanical Thrombectomy

Sussman et al. Creative Commons License Attribution 3.0
Stent Retriever devices

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Stroke in the Young
Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) evaluated stroke incidence between 1993 and 2005.

The proportion of strokes in those less than 55 increased from 13% in 1993 to 19% in 2005. Rates of increase were especially high between 1999 and 2005.

This trend runs counter to an overall decrease in worldwide stroke incidence of 42% between 1972 and 2008.
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

Iancu et al. Creative Commons Attribution 2.0
Dissection

Top 10 things to Remember!

- 1. Very common cause of stroke in the young (10-25%)\(^{31}\)
- 2. Carotid and Vertebral artery dissections are different
- 3. Three main causes – Trauma, Connective Tissue Disease, and “I dunno”\(^{32}\)
- 4. Trauma and idiopathic cases 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)\(^{32}\)
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 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 pay greater emphasis upon remaining stroke deficit.
- 10. Watch for pseudoaneurysm as a complication
Risk of Recurrence?

- Typically quoted as 1% per year but….
- *For traumatic and spontaneous* dissections the majority of dissections are early. In a case series by Bassetti et al there was a single patient with recurrence beyond one year (4 years)
- The risk is much higher in those with a positive family history of dissection of any vessel (? Arteriopathy syndrome) – 50% at 10 years including several late dissections
- Hypertension and tobacco were not risk factors for recurrence
Cerebral Venous Sinus Thrombosis
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 stoke (1%) but 78% of these cases are below the age of 50.\(^{35}\)
- Peak age between 20-40, women outnumbering men 3:1\(^{36}\)
- Primary presenting symptom is headache as a result of increased intracranial pressure. Time course can vary significantly
- Focal symptoms are 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, anti-thrombin III deficiency, antiphospholipid antibody syndrome)
Cerebral Venous Thrombosis

- Risk factors more specific to CVT include local infections (sinusitis, mastoiditis, dental), lumbar puncture, inflammatory bowel disease, head trauma, and central lines (in jugular vein)

- MRI and in particular Magnetic Resonance Venograms – Studies within the first few days can be insensitive

- Treatment – 1) Heparin
  2) Warfarin …. ? Xarelto!
  3) Repeat MRI/MRV in 3-6 months and discontinue anticoagulants if recanalized (or continue indefinitely in those with thrombophilia or prior DVT/PE)
  4) Intravenous lysis or surgical extraction (implies worse presentation)
Cerebral Venous Thrombosis

“Desert” Island Underwriting Questions

- Is there any underlying thrombophilia or systemic disease?
- Any Permanent Symptoms or Complications?
- Did the applicant have infarction or hemorrhage on imaging?
Cerebral Venous Thrombosis

Other Poor Prognostic Factor from International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)\textsuperscript{37}

- Males
- Age > 37
- \textit{Deep} Cerebral Vein Thrombosis
- CNS infection
Carotid Stenting
Case Scenario – Quick hitter

Another informal inquiry…..

- 81 year old woman
- 1 year ago was found to have left carotid stenosis due to bruit
- Instead of open carotid endarterectomy, underwent a carotid stenting procedure.
- “Willing to take a look?”
Carotid Stenting

General Considerations

Is the patient symptomatic?

Why is an endarterectomy not being performed?

Who is doing the procedure?
SAPPHIRE Trial

- Inclusion Criteria (334 high risk surgical patients):
  - Symptomatic stenosis of 50% or asymptomatic stenosis of 80%
  - High risk cardiac disease
    - CHF
    - Abnormal stress test
    - Need for open heart surgery
  - Severe COPD
  - Contralateral Carotid Occlusion
  - Restenosis after CEA
  - Age >80

Gurm et al.\textsuperscript{38}
SAPPHIRE Trial

Results

- Composite endpoint – ipsilateral stroke or periprocedural death, stroke or MI
- Results – at three years carotid stenting (+ and emboli protection device) was noninferior to carotid endarterectomy (24.6% in stenting group versus 26.9% in CEA group)
- Both surgeons and interventionalists were certified with complication rates between 3-5%.
CREST Trial

- 2503 patients followed for an average of 2.5 years
- Enrolled either symptomatic or asymptomatic patients and randomized them to carotid stenting or endarterectomy
- Primary endpoint was a stroke, MI or death

Brott et al.\textsuperscript{39}
CREST Trial

Rate Percentages

- Stroke/Death/MI
- Periprocedural Stroke
- Periprocedural MI

- Stenting
- CEA
Intracranial Atherosclerosis

- WASID trial (Warfarin-Aspirin Symptomatic Intracranial Disease)$^{40}$
  - History of Stroke or TIA and intracranial atherosclerosis
  - Warfarin versus aspirin (1300 mg/day)
  - Trial stopped early because of elevated risk of death, hemorrhage, and myocardial infarctions in warfarin group with no benefit in ischemic stroke prevention
Underwriting of Cerebral Aneurysm and AVM
Cerebral Aneurysm

Background

- Prevalence – 3.2%\textsuperscript{41}
- Risk factors
  - Tobacco
  - Female Sex
  - Family History
  - Polycystic kidney disease (autosomal dominant)
  - Age
  - Atherosclerosis
  - Infections, endocarditis, intravenous drug use
  - Connective Tissue Diseases – Ehlers Danlos, Marfan
- Case fatality rates \textsuperscript{42}
  - 40% mortality within 24 hours
  - 25% additional mortality from complications by 6 months
Most common sites of intracranial saccular aneurysms

incidence

<1 %

10 %

20 %

30 %

artery involved (incidence)

pericallosal artery (4%)

anterior communicating artery (30%)

lateral carotid artery bifurcation (8%)

middle cerebral artery (20%)

posterior communicating artery (25%)

basilar tip (7%)

posterior-inferior cerebellar artery (3%)

Zarosky 43 Creative Commons Attribution License 3.0
Who to Screen and how often?

- **Who to Screen?**
  - Patients with *two* first degree primary relatives
  - PCKD (10-22%), Ehlers Danlos

- **How often to screen?**
  - 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.
Risk of Rupture

Size

From UCAS Japan Investigators\(^4\) (5720 patients, with 6697 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
Risk of Rupture

Other Factors

- *Any* growth - Recent study (Villablanca et al. 2013)\(^48\) showed 12 x rupture rate with growth defined as increase by 5% of volume even for small aneurysms
- Age >70
- Tobacco
- HTN
- Female Sex
How to treat?

A

B

C

Izar et al. Creative Commons Attribution License 3.0
Longest term data available for larger scale trial is from extension of ISAT (International Subarachnoid Hemorrhage Trial)\textsuperscript{50}, 5 year data from 2009:

- Out of 2143 patients there were a total of 24 rebleeds greater than one year after therapy
- The risk of \textbf{rebleeding} overall was higher in the coiling group (17 versus 7 of the bleeds) – This was confirmed in large Meta-analysis published in Stroke of 4 RCTs and 23 observational studies
- The risk of \textbf{death} was lower in the coiling group (RR 0.77)
- The overall Standardized Mortality Rate for any patient with ruptured aneurysm was 1.5
Arteriovenous Malformation
AVM management

ARUBA trial

- Multicenter (39) trial\textsuperscript{52} where patients with \textit{unruptured AVM} were randomized to interventional surgery (any combination of neurosurgery, embolization, or radiosurgery) or medical management.
- The primary endpoint was death or stroke
- Trial was \textit{stopped by the NINDS} after 223 patients had enrolled.
- At time that trial was stopped 30\% had reached primary endpoint in surgical group versus 10\% in medical management group
- A cohort study from Scotland\textsuperscript{53} with 12 years of follow up published in 2014 also supported better outcomes with conservative management.
MARS (Multicenter AVM Research Study)

Kim et al. \textsuperscript{54}

- Largest natural history cohort analysis to date
### MARS (Multicenter AVM Research Study)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.10</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.12</td>
</tr>
<tr>
<td>Associated Arterial Aneurysm</td>
<td>1.68</td>
</tr>
<tr>
<td>Exclusively deep venous drainage</td>
<td>2.14</td>
</tr>
<tr>
<td>Hemorrhage at presentation</td>
<td>3.45</td>
</tr>
</tbody>
</table>
Parkinson’s Disease
Step 1 - Basic entry criteria:
- Bradykinesia and one of:
  - Rigidity
  - 4-6 Hz rest tremor
  - Postural Instability

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

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
## Parkinson’s Disease

### Hoehn and Yahr Scale

<table>
<thead>
<tr>
<th>Hoehn and Yahr</th>
<th>Stage</th>
<th>Modified Hoehn and Yahr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral only; minimal disability</td>
<td>1</td>
<td>Unilateral only</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>Unilateral and axial involvement</td>
</tr>
<tr>
<td>Bilateral or axial but balance intact</td>
<td>2</td>
<td>Bilateral but balance intact</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>Mild Bilateral disease but recovers during pull test</td>
</tr>
<tr>
<td>Bilateral disease, mild to moderate disability</td>
<td>3</td>
<td>Mild to moderate bilateral disease, some postural instability, physically independent</td>
</tr>
<tr>
<td>Severe disability but able to walk or stand unassisted</td>
<td>4</td>
<td>Severe disability but able to walk or stand unassisted</td>
</tr>
<tr>
<td>Restricted to bed or wheelchair</td>
<td>5</td>
<td>Restricted to bed or wheelchair</td>
</tr>
</tbody>
</table>
Parkinson’s disease

- UPRDS (Unified Parkinson’s Rating Disease Scale)
  - 42 point scale with measures of mentation, behavior, mood, activities of daily living, motor exam, dyskinesias, and complications of therapy.
  - A wonderful tool, often little used outside of the ivory towers.
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 which 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

Herlofson et al\textsuperscript{56}

- Overall SMR 1.5
- Higher mortality with younger age of onset (<60, SMR = 1.92)
- SMRs decrease with age
- Clinically definite PD had \textit{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 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
- Axial Rigidity
- Early cognitive changes

Early Autonomic Symptoms
- Vertical Gaze Palsy
- Nonresponsive or hypersensitive to Levodopa
### Causes of death and comorbidities in PD\(^{62}\)

<table>
<thead>
<tr>
<th>Cause of Death/Comorbidity</th>
<th>Parkinson’s (%)</th>
<th>Age Matched Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Stroke</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Cancer</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>CHF</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Injuries, Poisonings</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>COPD</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>
Parkinson’s Disease – Special Topics
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…”
Willing to take a look?
DaTscan

- Developed by GE Healthcare
- Approved by FDA in 2011 (in practice in Europe much earlier)
- Ioflupane iodine-123 (a cocaine analogue) is injected as a contrast agent and followed by single-photon emission computed tomography (SPECT) imaging.
- Ioflupane iodine-123 binds selectively to presynaptic dopamine transporters and is thus shows reduced activity in Parkinsonian Syndromes.
DaTscan

“The Comma turns into a period”

Lord et al. Creative Commons Attribution License 3.0
For the diagnosis of parkinsonian syndrome sensitivity is reported at 91% and specificity at 92%.

- Parkinsonian Syndromes
  - Idiopathic PD
  - PSP
  - MSA
  - Lewy Body
- Non-DA Parkinsonism
  - Essential Tremor
  - Drug induced PD
  - Vascular Parkinson’s
  - Alzheimer’s
63 year old woman carries a diagnosis of IPD for 10 years
Around three years ago required increasing and fairly large doses of levodopa 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.
http://youngandshaky.com/
Deep brain stimulation for PD

- Originally developed by Dr. Jose Delgado in 1952 and utilized for mental illness, pain, and epilepsy
- FDA approved for tremor in 1997, PD in 2002, and Dystonia in 2003
- Targets are typically the subthalamic nucleus (STN) and globus pallidus interna (Gpi)
- Reported complication rates are low: 0-0.4% mortality, 0.4-2% hemorrhages, and 3-5% hardware complications
Deep Brain Stimulation for PD

Appropriate Candidates

- Clearly defined idiopathic PD
- Cognitively normal, no significant psychiatric comorbidities
- Remain responsive to L-Dopa
- Good for those with wide motor “on/off” fluctuations
- Age < 75,
- Free of significant cardiovascular comorbidities

But….. Also includes those who:

- Have symptoms that interfere with ADLs
- Have had PD for at least five years… typically longer
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\(^6\)
- Does not typically benefit falls and balance
- Elevated suicide rates after surgery have been reported (4.3\%)\(^67\)
- 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
Genetics of Parkinson’s

- Those with first degree relative have just 4-9% likelihood of disease
- Single gene mutations (either dominant or inherited) account for 3-5% of sporadic cases and 30% of familial cases
- Reduced penetrance and phenocopies are common
- LRRK2 – most common mutation associated with familial PD, late onset autosomal dominant
- SNCA – less common, younger onset (<50), rapid progression and increased dementia
- Parkin – autosomal recessive, youngest onset (<40), juvenile PD
6 genes monogenic PD

Autosomal Dominant

SNCA (PARK 1-4)
LRRK2 (PARK 8)

Autosomal Recessive

Parkin (PARK 2)
PINK1 (Parkin 6)
DJ-1 (PARK 7)
ATP13A2 (PARK 9)
Name: Sergey Brin
Location: Palo Alto, CA
2006 XI FINA World Masters Championships
2006 Dive Statistics

<table>
<thead>
<tr>
<th>Dive Height</th>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>3M</td>
<td>Forward Dive Pike</td>
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<tr>
<td>1M</td>
<td>Forward 1 1/2 Somersault Pike</td>
<td>22.95</td>
</tr>
<tr>
<td>3M</td>
<td>Forward Flying 1 1/2 Somersault Pike</td>
<td>13.50</td>
</tr>
<tr>
<td>1M</td>
<td>Back 1 Somersault Straight</td>
<td>25.50</td>
</tr>
<tr>
<td>3M</td>
<td>Back 1 1/2 Somersault Straight</td>
<td>18.00</td>
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<tr>
<td>1M</td>
<td>Back 1 1/2 Somersault Tuck</td>
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<td>1M</td>
<td>Reverse Dive Tuck</td>
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<td>1M</td>
<td>Inward Dive Pike</td>
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<td>3M</td>
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</tr>
<tr>
<td>1M</td>
<td>Inward 1 1/2 Somersault Tuck</td>
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<tr>
<td>3M</td>
<td>Inward 1 1/2 Somersault Tuck</td>
<td>31.35</td>
</tr>
</tbody>
</table>

Questions or Comments?

drengachary@rgare.com
(636) 736-5827
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References (continued)


References (continued)


