Of Plaques & Tangles: Dementia Care

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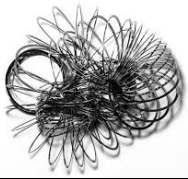
Objectives

- What are the different types of dementia
- Identify biomarkers of dementia
- Discuss treatment and care strategies

Neurodegeneration

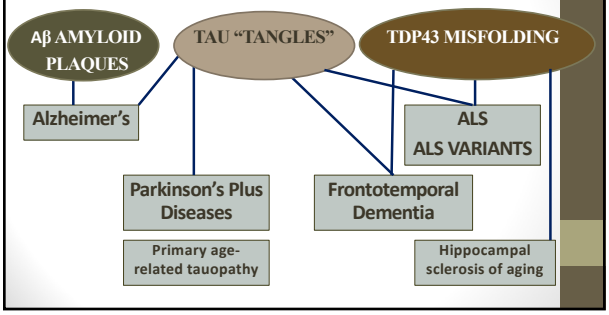
- "Neurodegeneration" – a progressive disease, or degeneration, of nerve cells (neurons) - **cascade of events**
- Process often starts **years** before symptoms are noticed
- Protein misfolding is the hallmark of neurodegeneration
- We still know relatively little about how they develop or how to treat them.



Neurodegenerative Diseases

- Alzheimer's Disease
- Parkinson's Disease
- Frontotemporal Dementia
- Lewy Body Dementia
- ALS (Lou Gehrig's Disease)
- Huntington's Disease
- Ataxias

A Spectrum of Dementia: Overlapping Pathology



Parkinson's variants

An Aging Population…

- Alzheimer's disease affects 6 million American's in 2017; 15 million by 2060
- Alzheimer's is 6th leading cause of death
- Cost of dementia:
  - Total payments in 2015 for health care & long-term care and hospice services for dementia in persons >65 years: $226 billion
  - Family members & unpaid caregivers provided an estimated 17.9 billion hours in 2014 (= lost productivity)

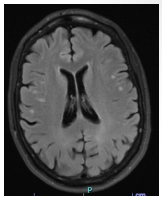
Brookmeyer et al 2017

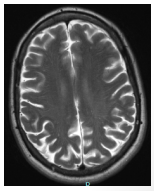
- Mild Cognitive Impairment (MCI)
  - Able to function independently
  - 15-20% of persons >age 65
- Dementia
  - Cognitive decline interferes w/ independent function

Case

- 52 y/o nurse brought in by husband who is noticing cognitive problems over past year
- Trouble at work: slower, rechecking things.
- Home: grandkids notice w/playing games
- Went to optometrist – sometimes has trouble finding things on the counter top in front of her, thought her vision was off.
- Exam: very tearful, distressed, appears depressed.
- Initial exam: recalls 2/5 items, difficulty with calculations, fluency, clock draw, TRAILS-B test. Very anxious during test.
- 4 months later: MMSE: 26/30 but still significant difficulty at work, taking leave.

What do you do next?





Alzheimer's Dementia

Early onset: age<64

~5% of AD cases

- Genetic predisposition
  - 10% autosomal dominant; many are polygenic, ↑ APOE- Є4)
- Faster deterioration
- More likely to have h/o TBI
- ↓↓ ASCVD, DM, obesity
- Language, visuospatial, dysexecutive fx
- Parietal lobe deterioration
- Can have other sx: myoclonus, seizures, gait abnormalities,

Late onset: ≥age 65

5.7 million Americans

- Mostly polygenic, 60-80% genetic predisposition
  - APOE-Є4 allele is common
- Gradual decline over years
- ↑↑Risk factors for cardiovascular disease
- ↑↑ Sleep disorders, OSA/insomnia
- ↓↓Semantic memory
- 5 A's: Amnesia, Aphasia, Anomia, Agnosia, Apraxia
- Hippocampal/temporal lobe deterioration

Alzheimer's

- Progressive loss of short term memory, visuospatial capability, language
- "5 A's"
- Slowly progressive

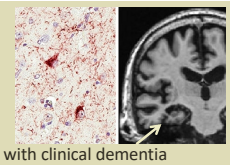
Mimickers of Alzheimer's

Vascular Dementia

Stepwise progression; treat vascular risk factors

Diseases of the "oldest old"

- **Hippocampal Sclerosis of aging (TDP-43)**
- **Argyrophilic Grain Disease**
- **1' Age-related Tauopathy**



Found in 20% of normal controls, 50% with clinical dementia (amnestic) in patients >85yrs

"Pure" forms or in combination with other neurodegenerative d/o.

MRI: temporal lobe/hippocampal atrophy

Source: Jicha & Nelson. Hippocampal Sclerosis, Argyrophilic Grain Disease, and Primary Age Related Tauopathy. Continuum, Feb 2019.

Frontotemporal Dementia

- Peak age 50's-60's; behavioral variant = 50%
- Triad: Apathy, disinhibition/loss of social graces, loss of compassion
  - Marital disputes, estranged from friends/family, job loss
  - Alzheimers: usually no loss of compassion
- Repetitive, ritualistic, or compulsive behaviors.
  - Hyperorality, overeating, dietary changes
  - Memory loss may occur if there is hippocampal involvement
- Can eventually develop motor sx (parkinsonism or ALS)
- MRI imaging may be relatively normal

Amyotrophic Lateral Sclerosis (ALS)

- Weakness, "wasting" of muscles, cramps, difficulty speaking & swallowing
- Similar to cancer:
  - Develops late in life
  - Short life expectancy (2-5 years)
  - Genetics contribute, but + gene ≠ disease
  - Only ~10% of cases are familial

- Can co-occur with FTD (genetic, c9orf72)
- Sporadic ALS is likely caused by **genetic susceptibility** + multiple **environmental exposures**

Clinical Approach to Progressive Cognitive Decline

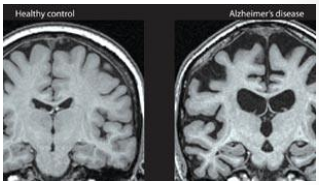
- Thorough history!!
- Earliest symptoms can be most helpful
- Determine level of functional impairment (ADLs, iADLs)
- Address psychiatric symptoms
  - may need to treat before a formal diagnosis can be made

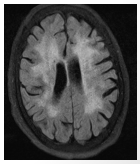
DOMAINS OF MEMORY:

- Episodic memory
- Visuospatial/navigation
- Language
- Executive function
- Difficulties w/devices/technology
- Psychiatric sx
- Motor sx: falls, tremor
- Sleep: RSBD

Work up of Dementia

- Labs: B12, TSH
- Imaging: CT or **MRI**
  - PET scan: FTD vs AD
  - DaT Scan: DLB/PD
  - Amyloid scan: clinical trials only
- LP for tau/amyloid, autoimmune causes (younger pt)



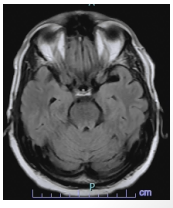


The Lewy Body Dementias

- Two disease entities: → Parkinson disease dementia
  → Dementia w/Lewy bodies (DLB)
- DLB Core Clinical Features:
  - Fluctuating cognition
  - Visual hallucinations
  - REM sleep behavior d/o
  - Parkinsonism
- DLB Supportive features:
  - Repeated falls
  - Syncope or episodes of unresponsiveness,
  - autonomic dysfx, orthostasis,
  - depression/apathy

Rapidly Progressive Dementia

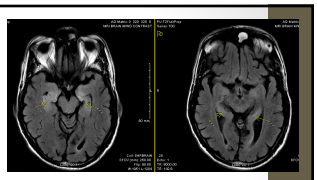
- 65 y/o professional w/several weeks of increasing forgetfulness
- Initially saw PCP for transient stereotypical "trail of flashes" in vision, thought to be migraine aura. ↑ frequency. MRI normal.
- Memory trouble at work – has to think about procedures, had trouble running payroll.
- Mood changes – more irritable, sometimes tearful.
- Wife brings him to ED after developing severe confusion while driving to work.

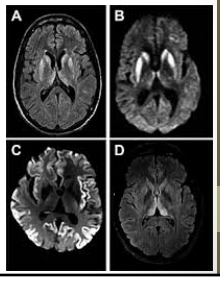


Rapidly Progressive Dementia

- Vascular: SDH, multifocal stroke, vasculitis
- Autoimmune/paraneoplastic encephalitis (all ages!!)
- Infections, including HIV, PML, Prion disease/Creutzfeldt-Jacob
- Toxic/metabolic: heavy metals, vitamin deficiency, hepatic
- Malignancy: lymphoma, metastases, paraneoplastic
- Pseudodementia?

Work-up:





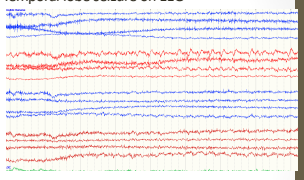
- Blood:
  - TSH, ammonia, B12, ANA/dsDNA
  - TPO/TG Ab's
  - Paraneoplastic panel (serum)
- MRI
- EEG
- Lumbar Puncture
  - Protein/cells/glucose
  - VDRL, ACE, +/- lyme
  - Malignant cell screen
  - Tau/Amyloid panel
  - Paraneoplastic panel (Mayo encephalitis or dementia panel)

Mead S, Rudge P (April 2017). "CJD mimics and chameleons". *Practical Neurology*.

Case 2:

- EEG: frequent temporal lobe seizures
- Autoimmune antibody panel +LGI1
  - *Malignancy w/u normal*
- IV methylprednisolone x 5 days – dramatic improvement; followed by steroid burst once weekly over 8 weeks
- Back to work full time, seizures well controlled, mood & visual sx gone

Temporal lobe seizure on EEG



Serum paraneoplastic panel
Sept 2018:

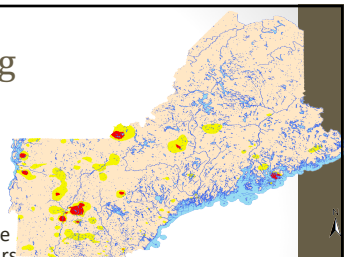
Result Name	Result	Unit	Reference Value
Neuronal (V-G) K+ Channel Ab, S	0.49	nmol/L	≤0.02
LGI1-IgG CBA, S	Positive		Negative
GAD65 Ab Assay, S	0.14	nmol/L	≤ 0.02

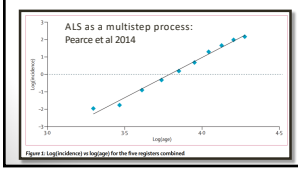
When to refer to Neurologist

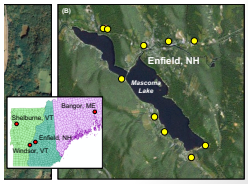
- Establish diagnosis; rule out treatable causes
  - ***→Rapidly progressive dementia,***
  - ***→cognitive decline in <65 yrs old***
- Guide testing
- Discuss prognosis
- Symptom management can be done by psychiatry, neurology, geriatrics, or palliative care

Genetic Testing

- GENE ≠ DISEASE
- Neurodegenerative disorders are complex interaction of **genes + environment**.
- ALS: "clusters" exist due to environmental factors (6-hit hypothesis)





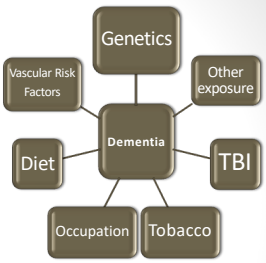


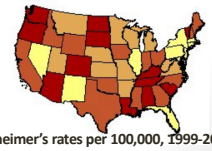
Genetic Testing

- Early onset AD:
  - Amyloid precursor protein
  - Presenilin 1 & 2

  →Consider genetic testing
- Late onset AD
  - APOE e4 ↑risk; currently tested by **23andMe**
  - More likely polygenetic + environmental factors

  →Genetic testing NOT recommended!





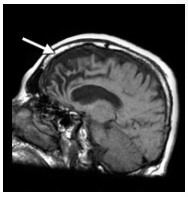
Alzheimer's rates per 100,000, 1999-2014.
Source: CDC Wonder

Rx Treatment of Alzheimer's

- AChE Inhibitors: donepazil, rivastigmine
  - → Mild to moderate AD (not MCI)
  - → May help Lewy Body Dementia
  - → AE: GI, sleep, rarely heart block
  - → B12/Folate can increase effectiveness
- NMDA antagonist: Namenda (memantine)
  - → Moderate to severe AD
  - → AE: GI, sleep, rarely heart block
- Antidepressants
  - Help irritability, agitation, anxiety, depression.
  - Low dose!!
- Hallucinations, delusions, agitation
  - Trazodone 25mg QHS
  - Quetiapine 25-50mg (black box warning)

Rx Treatment of FTD

- **AVOID AChE-Inhibitors**



- SSRIs/SNRIs
  - → Can help with disinhibition, perseverative behavior, hyperorality
  - → Citalopram, sertraline, trazadone
- Antipsychotics
  - → Quetiapine, risperidone (dissolvable)

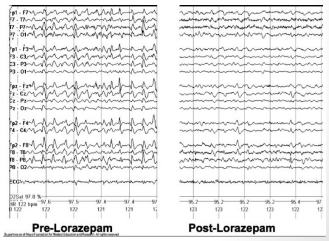
Treatment of Lewy Body Dementias

- AChE-Inhibitors
  - → If nausea: try patch
- Memantine less evidence
- REM sleep behavior disorder:
  - → Melatonin 1-6 mg QHS
  - → Clonazepam 0.25mg QHS
- SSRIs/SNRIs
  - → Can help with apathy, depression
  - → Sertraline, venlafaxine, buproprion are more activating
- Hallucinations/Psychosis
  - → Nuplazid (pimavanserin) FDA approved, fewer side effects
  - → Quetiapine 12.5-25 mg doses
  - → *Treat only if bothersome!*

- PT, SLP/swallow eval

Seizures

- ↑ risk in Alzheimer's & vascular dementia pts
- Often underdiagnosed (non-convulsive)
- DLB: unresponsive episodes often NOT seizures
- Triggers: infx/UTI
- Treatment:
  - Keppra 250-200 BID
  - Lamictal 100-150BID
  - Avoid older AEDs



Global Deterioration Scale

- Subjective and objective description of patient function
- Follows predictable pattern
- Can help us to best treat patients now and educate families for the future

Stage	Deficits in cognition and function	Usual care setting
1	**Subjectively and objectively normal**	Independent
2	Subjective complaints of mild memory loss. Objectively normal on testing. No functional deficit	Independent
3	**Mild Cognitive Impairment (MCI)** Earliest clear-cut deficits. Functionally normal but co-workers may be aware of declining work performance. Objective deficits on testing. Denial may appear.	Independent
4	**Early dementia** Clear-cut deficits on careful clinical interview. Difficulty performing complex tasks, e.g. handling finances, travelling. Denial is common. Withdrawal from challenging situations.	Might live independently – perhaps with assistance from family or caregivers.
5	**Moderate dementia** Can no longer survive without some assistance. Unable to recall major relevant aspects of their current lives, e.g. an address or telephone number of many years, names of grandchildren, etc. Some disorientation to date, day of week, season, or to place. They require no assistance with toileting, eating, or dressing but may need help choosing appropriate clothing.	At home with live-in family member. In seniors' residence with home support. Possibly in facility care, especially if behavioural problems or comorbid physical disabilities.
6	**Moderately severe dementia** May occasionally forget name of spouse. Largely unaware of recent experiences and events in their lives. Will require assistance with basic ADLs. May be incontinent of urine. Behavioural and psychological symptoms of dementia (BPSD) are common, e.g. delusions, repetitive behaviours, agitation.	Most often in Complex Care facility.
7	**Severe dementia** Verbal abilities will be lost over the course of this stage. Incontinent. Needs assistance with feeding. Lose ability to walk.	Complex Care

Capacity vs Competency

Capacity	Competency
• Ability to make a particular decision at a specific time or in a specific situation. • Determined by a clinician. No gold standard test. • A universal concept. • The law assumes that all adults have capacity unless there is contrary evidence.	• Legal capacity. • Determined by a judge in court. Restricted by rules of legal system. • A threshold for a patient to retain decision-making power in a particular activity or set of activities.

Capacity

4 abilities characterize capacity:

- Understanding (what is…..?)
- Appreciation (applying facts to one's own situation)
- Reasoning (ability to compare options)
- Expressing a choice. Should be consistent/stable over time.

Any clinician can determine capacity.

- Depends on cognition but is NOT the same as cognition.
  - i.e. capacity in FTD vs AD is
  - Cannot be determined by MMSE/MOCA or other test
- Clinicians must help supply optimal conditions for functioning of the individual
  - Take into account fluctuations in cognition (day-to-day, sundowning, fatigue/drowsiness)
  - Treatment of reversible conditions can improve capacity (infections, delirium, medication side effects).
- Clinicians must strike a balance between respecting patient's autonomy and acting in their best interest.

Driving

Risks for unsafe driving:

Level A
- Clinical Dementia Rating scale

Level B
- Caregiver's rating of a person's driving ability as marginal or unsafe

Level C
- History of traffic citations
- History of crashes
- Reduced driving mileage
- Self-reported situational avoidance
- Mini-Mental State Examination scores of 24 or less
- Aggressive or impulsive personality characteristics

Driving: AAN Guidelines

CLINICAL DEMENTIA RATING: 0 to 2

Categories	Impairment 0	0.5	1	2
Memory (major category)	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness, partial recollection of events, "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost
Secondary categories				
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place
Judgment and problem solving	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulties in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired
Community affairs	Independent function at usual level in job, shopping, and volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home; appears well enough to be taken to function outside a family home
Home and hobbies	Life at home, hobbies, and intellectual interests are well-maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment in function at home, more difficult chores abandoned, more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained
Personal care	Fully capable of self-care	Fully capable of self-care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects

Relatively low risk → Relatively high risk

Risk Management
- Encourage family support for alternate transportation.
- Strongly consider voluntary surrender of driving privileges.
- Consider DMV referral or professional driving evaluation, based on state guidelines.

Intervention pursuant to state guidelines

Source: American Academy of Neurology, www.aan.com

Driving

American Academy of Neurology (AAN) handout – aan.com

AAN Summary of Evidence-based Guideline for PATIENTS and THEIR FAMILIES

DRIVING WITH DEMENTIA: UNDERSTANDING THE SAFETY RISKS

This fact sheet may help you understand the safety risks of driving with dementia.

Neurologists from the American Academy of Neurology are doctors who identify and treat diseases of the brain and nervous system. The following evidence-based information* is provided by experts who carefully reviewed all available scientific studies on the safety risks of driving with dementia.

If you have dementia and still drive, consider the risks carefully. Keep in mind that unsafe driving can stem from poor thinking ability. Nearly all people with dementia must eventually give up driving. Preparing now will make the transition easier.

What is dementia?

Dementia is a brain disorder. It leads to loss of brain function. Dementia affects functions such as memory, language, and thinking ability. Judgment and behavior also are affected. Dementia usually occurs in people over age 60. The disease risk increases with age.

Most types of dementia are degenerative. This means the problem gets worse over time. The problem usually cannot be reversed. The most common type of dementia is Alzheimer's disease. Another type, Lewy body disease, also

or lower). Weak evidence shows that the MMSE may help identify people with dementia at risk for unsafe driving. However, it is not clear what score clearly defines the risk.

Neuropsychological tests also are available. These look at specific aspects of thinking ability. They examine how thinking ability affects behavior. They also provide scores for brain functions. These tests may help to show if a person has dementia, and may help detect the disease severity. However, there is not enough evidence to show if they help identify unsafe driving risk due to dementia.

How to treat MCI & slow dementia progression

SPOILER – THERE IS NO MAGIC PILL OR SUPPLEMENT!!

- Wean medications that might affect cognition
  - Benzos, muscle relaxants, pain meds, anticholinergics
  - Constantly review med list for things no longer needed.
- DO NOT prescribe Donepezil/Memantine – no benefit, not FDA approved
- Sleep – screen for OSA
- Treat HTN, HLD, diabetes
- Treat depression
- Stress reduction
- Physical exercise
- Cognitive exercise

Preventing/Slowing Dementia

- **Supplements:**
  - B vitamins – if elevated homocysteine levels
  - Folic acid – enhances therapeutic effect of ACE-I
  - Long chain omega-3 fatty acids (DHA, EPA)
  - Weaker evidence: ginko biloba, phosphatidylserine
- **Diet**
  - Long chain omega-3 fatty acids (DHA, EPA)
  - Flavenoids, found in berries and dark cocoa
  - Cacao powder (NOT cocoa!) - antioxidant
  - Coffee (caffeinated)
  - Certain diets: Mediterranean diet, MIND diet
  - Calorie restriction: >2100 calories per day = 2X risk for dementia
  - Intermittent fasting

MIND diet

Mediterranean Diet and the Dietary Approaches to Stop Hypertension (DASH) diets

Seniors who followed the MIND diet ↓↓ risk of developing Alzheimer's by ~53%

When followed but not followed rigorously, the MIND diet ↓↓ Alzheimer's by ~35%.

- BEANS
- BERRIES
- FISH
- GREEN LEAFY VEGETABLES
- NUTS
- POULTRY
- OLIVE OIL
- OTHER VEGETABLES
- WHOLE GRAINS
- WINE

- BUTTER AND STICK MARGARINE
- CHEESE
- FAST OR FRIED FOODS
- PASTRIES AND SWEETS
- RED MEATS

Questions?