

Alzheimer's disease and non-Alzheimer's dementias

Brendan Kelley, MD
Associate Professor – Clinical
Department of Neurology
The Ohio State University Wexner Medical Center

Dementia

- A descriptive term, not a disease
- Practical definition:
- Cognitive and/or behavioral changes severe enough to impair daily functioning
- Represents a change from previous level of function

Irreversible versus Reversible

- Dementia does not imply an etiology
- Many potential causes of cognitive impairment
 - Stroke
 - Traumatic brain injury
 - Neurodegenerative diseases
 - Brain tumor
 - Toxic/Metabolic encephalopathy (medical causes)
 - Delirium
 - Depression/Psychiatric disorders

Alzheimer's disease

Alzheimer's Disease

- A disease
- NOT Normal aging
- Represents a change from previous level of function
- Clinical
- Pathological
- Prognosis

Alzheimer's Disease Statistics

- Approximately 5 million Americans afflicted
- Estimates suggest this will rise to 14 million by 2030
- Incidence and prevalence double each 5 years after age 60
- 30-50% (or more) of those over age 85

Scope of Alzheimer's

- | | |
|---|--|
| <ul style="list-style-type: none">• National<ul style="list-style-type: none">– 5M people with AD– 11 Million caregivers– 12.5 Billion hrs unpaid care– \$144 Billion (\$11.50/hr)• By 2050 >\$2 Trillion/yr | <ul style="list-style-type: none">• Ohio<ul style="list-style-type: none">• 230,000 people with AD• 435,000 caregivers• 495 Million hrs unpaid care• \$5.7 Billion (\$11.50/hr) |
|---|--|

2012 Alzheimer's Disease Facts and Figures – Alz Assoc

Alzheimer's Disease

- Prodrromal symptoms – Mild Cognitive Impairment
 - Repeating oneself
 - Increased difficulties misplacing objects
 - Becoming lost/disoriented in familiar locations
 - New difficulties handling finances, managing medications, following recipes, etc.
 - Increasing reliance upon spouse and family to manage tasks previously handled independently

Alzheimer's Disease

- Early dementia
 - Personality changes (withdraw, loss of “zest”)
 - Memory difficulties
 - Difficulties finding words
 - More easily lost/disoriented
 - Impaired financial judgments
 - More difficulties with organizing thoughts, logic

Alzheimer's Disease

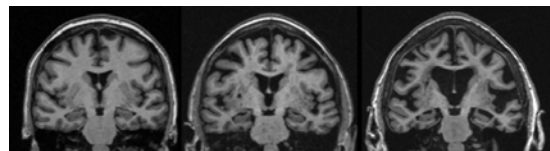
- Moderate dementia
 - Diminished self-care
 - Sleep disturbances (napping, day-night reversals)
 - Difficulty recognizing people
 - More reliant on reminders for basic activities
 - Delusional thinking
 - Behavior changes

Alzheimer's Disease

- Late dementia
 - Increasing/complete assistance for basic activities
 - May refuse to eat or others efforts at basic care
 - May not recognize close family
 - Language output may be gibberish
 - Weight loss
 - Increased sleep
 - Diminished mobility
 - Seizure more common
 - Medical complications

Alzheimer's Disease - Diagnosis

- Diagnosis only “definite” at autopsy
- Probable AD
 - Clinical features
 - MRI/CT
 - Brain PET scan
 - Neuropsychological testing
 - Laboratory studies
 - Spinal fluid



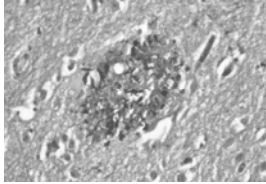
Normal

MCI

AD

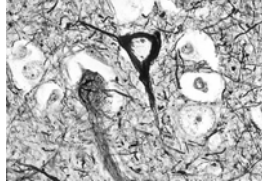
Alzheimer's Disease - Pathology

Amyloid plaques



β -Amyloid

Neurofibrillary tangles



Tau

Greenfield's Neuropathology, 8th ed. / edited by Seth Love, David N. Louis, David W. Ellison

Alzheimer's Disease - Prognosis

- Survival – median 10.3 years, can range from 2-20 years
- Generally, decline is slower in early dementia
- Pace of deterioration increases during moderate stage
- Late stage dementia – medical complications

Non-Alzheimer's dementia

Non-Alzheimer's Dementias

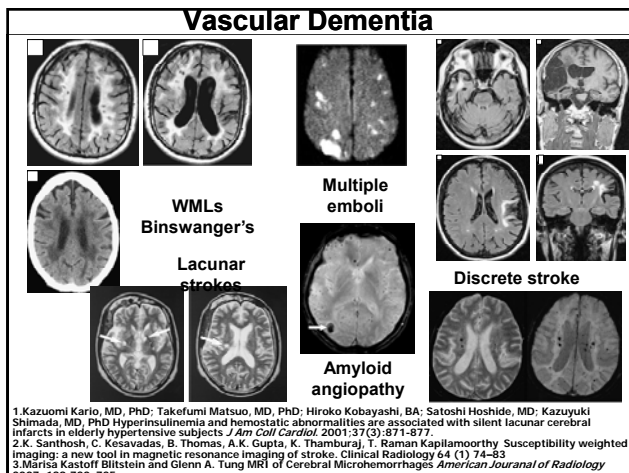
- Although AD is most common, other diseases do occur
- The second most common cause – Vascular Dementia
- The second most common degenerative cause – Lewy body disease
- Other diseases – FTD, CBS, PSP, PD+D
- Rare diseases – CJD, others

Vascular Dementia

- Numerous sets of clinical and research criteria exist for VaD
- None have been widely adopted; these criteria differ among themselves, are not interchangeable, and lack sensitivity
- Most revolve around 3 core concepts:
 - Recognition of dementia
 - Recognition of cerebrovascular disease
 - Probable association between the two

Vascular Dementia (VaD)

- Abrupt or stepwise deterioration
- Psychomotor slowing > memory difficulty
- Retrieval versus encoding memory deficit
- Worse sentence complexity
- Focal neurologic abnormalities
- Parkinsonism on exam
- More common apathy, depression, delusions



VaD Treatment

- Cholinesterase inhibitors
- Address modifiable stroke risk factors
- Anti-platelet medications
- Assess for depression

VaD Outcomes

	VaD	AD
5 Year Mortality	63.6%	31.8%
Nursing Home Rate	31.8%	20.6%

Lewy Body Disease (LBD)

- Core (≥ 2 ; probable, 1; possible)
 - Fluctuating cognition
 - Recurrent visual hallucinations
 - Parkinsonism
- Suggestive (probable 1 core + ≥ 1 ; possible 0 core + ≥ 1)
 - RBD
 - Severe neuroleptic sensitivity
 - SPECT or PET shows low DAT activity

LBD Symptoms

- Cognitive
- Parkinsonism
- Hallucinations
- Sleep – RBD
- Autonomic

LBD Treatments

- Cognitive – cholinesterase inhibitors (AChE-I)
- Parkinsonism – Levodopa (avoid agonists)
- Hallucinations – AChE-I, Quetiapine, Clozapine
- Sleep – melatonin, clonazepam
- Autonomic – fludrocortisone, midodrine, mestinon

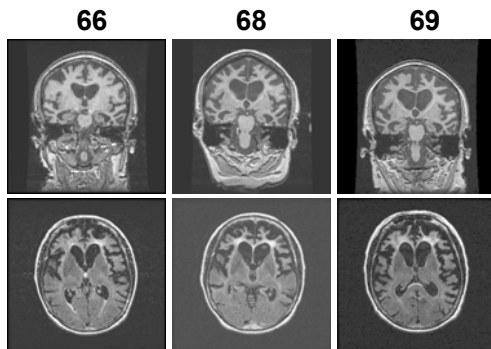
Frontotemporal dementia Clinical overview

- Gradual, progressive decline in behavior and/or language
- Younger age (mid-50s to 60s), but can be seen as early as 20 and as late as 80
- Represents 10-20% of younger dementia cases
- Estimated 50,000-60,000 Americans
- Equal incidence Men:Women
- As the disease progresses, it becomes increasingly difficult for people to plan or organize activities, behave appropriately in social or work settings, interact with others, to care for oneself, and communication deficits develop - leading to increasing dependency.

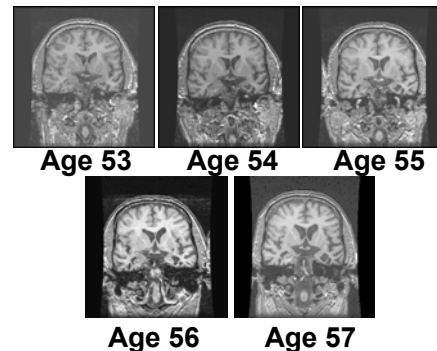
Frontotemporal dementia Clinical features

- Behavioral variant FTD (bvFTD)
 - Disturbance of social and personal behavior
 - Hyperoral, hypersexual,
 - Changes in feeding patterns
 - Executive function, attention
 - Anxiety, obsessive-compulsive behaviors
- Language function
 - Semantic dementia (SD)
 - Progressive nonfluent aphasia (PNFA)
 - Logopenic aphasia (LPA)

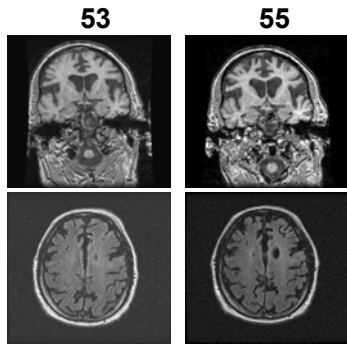
Frontotemporal dementia MRI features (bvFTD)



Frontotemporal dementia MRI features (SD)



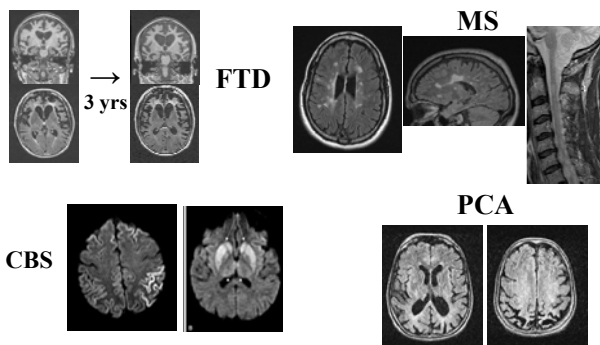
**Frontotemporal dementia
MRI features (PNFA →behavioral)**



**Frontotemporal dementia
Pathological findings**

- Frontal and temporal atrophy with neuronal loss and gliosis
- Microscopic heterogeneity
 - FTD-Tau (40% of cases)
 - FTD-TDP43 (perhaps 30-40%)

Other Non-AD dementias



**Dementia Differential
Diagnosis and Treatment**

Anahita Adeli, MD
 Assistant Professor – Clinical
 Department of Neurology
 The Ohio State University Wexner Medical Center

Management and Treatment of Patients with Dementia

- 1) Basic needs and wellbeing**
- 2) Safety**
- 3) Pharmacologic therapies**

Management and Treatment of Patients with Dementia

- 1) Basic needs and wellbeing**
- 2) Safety**
- 3) Pharmacologic therapies**

Basic Needs & Wellbeing

- **Regular meals**
- **Good nutrition**
- **Adequate fluid consumption**
- **Socialization and stimulation**
- **Recognize and manage pain**
- **Minimizing medications with anticholinergic properties**
- **Early recognition and treatment of delirium**

Basic Needs & Wellbeing

- **Evaluation of weight loss**
 - **Calorie count**
 - **Decreased sense of smell and taste**
 - **Aberrant motor behaviors**
 - **Depression or psychosis**
 - **Oral pathology**
 - **Dysphagia**
 - **Feeding apraxia**
 - **Medication side effect**
 - **GI ailment or medical cause**

Management and Treatment of Patients with Dementia

- 1) Basic needs and wellbeing**
- 2) Safety**
- 3) Pharmacologic therapies**

Safety

- Referral to outpatient or home OT/PT can be considered when:
 - Unsteady gait or dizziness
 - Frequent falls
 - Inappropriate use of the walker or cane
 - Unsteadiness in shower
 - Decline in vision or visual perceptual abilities resulting in impairment of ADLs
 - Difficulty with transfers
 - Weakness or deconditioning

Safety

- Home safety evaluation by an occupational therapist
 - Minimizes danger and maximizes independence
 - Consider in all patients who are living independently or with a spouse who is elderly
 - Evaluate flooring, house layout, trip hazards, bathing safety and stair-climbing ability
 - Make recommendations that can be implemented to reduce safety risks

Safety: Wandering

- Minimize wandering
 - GPS monitoring device (e.g. pager, wristwatch)
 - Door alarm or bell
 - Place locks out of sight
 - For wandering that occurs in the middle of night, use a bed alarm and restrict fluid intake a couple hours prior to bedtime to minimize awakenings
 - Provide 24 hour supervision

Safety

- **Disconnect stove and oven**
- **Remove weapons from the home**
- **Program the telephone with frequently use phone numbers and emergency medical contacts**
- **Emergency alert system**
- **Limit the maximum hot water temperature**
- **Block phone solicitors**

Safety: Driving

- **The following symptoms can interfere with safe driving:**
 - **Poor vision**
 - **Memory loss**
 - **Difficulty judging distances and spaces**
 - **Easy distractibility**
 - **Inability to predict upcoming traffic problems**
 - **Difficulty or slowed decision-making and problem solving**
 - **Slowed reaction time**

Safety: Driving

- **A diagnosis of Alzheimer's disease or another type of dementia is never by itself a sufficient reason to revoke one's driving privilege**
- **Discussions should take place**
 - **Early in the disease**
 - **Involve the patient and caregiver**

Safety: Driving

- **Caregivers should regularly observe the patient's driving**
 - **Difficulty navigating to familiar places**
 - **Inappropriate lane changing**
 - **Confusing the brake and gas pedals**
 - **Failing to observe traffic signals**
 - **Making slow or poor decisions**
 - **Hitting the curb while driving**
 - **Driving at an inappropriate speed (often too slow)**
 - **Becoming angry or confused while driving**

Safety: Driving

- The following are associated with an increased risk of unsafe driving:
 - The Clinical Dementia Rating scale (Level A)
 - A caregiver's rating of a patient's driving ability as marginal or unsafe (Level B)
 - A history of traffic citations (Level C)
 - A history of crashes (Level C)
 - Reduced driving mileage (Level C)
 - Self-reported situational avoidance (Level C)
 - MMSE scores of 24 (Level C)
 - Aggressive or impulsive personality characteristics (Level C)

AAN Practice Parameter update: Evaluation and management of driving risk in dementia, 2010

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, deflect 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

*Impairment is the decline from the subject's usual level of functioning. Clinical Dementia Rating (CDR) = Memory score unless 3 or more of the secondary categories score above or below the Memory score, in which case the CDR = the majority of the secondary categories. For complete instructions, see Morris.⁴¹

AAN Practice Parameter update: Evaluation and management of driving risk in dementia, 2010

Safety: Driving

- Early in the disease, while driving is continued, the following limitations can be considered:
 - Locally
 - Daytime hours
 - Not in inclement weather

Safety: Driving

- If appropriate limits cannot be agreed upon by the patient, caregiver, and health care provider, a referral for an on-the-road driving evaluation, often conducted by an occupational therapist, can be informative in determining if a patient is safe to continue driving

Safety: Medication Assistance

- **Factors contributing to medication non-adherence in dementia:**
 - Depression
 - Complex dosing schedule
 - Behavioral problems
 - Denial
 - Memory problems and executive dysfunction

Safety: Medication Assistance

- **To maintain independence in patients with mild dementia, a variety of options exists**
 - Weekly pill organizer filled by the patient or caregiver
 - Automatic pill dispenser with alarm
 - Visiting nurse or hired help dispensing the proper amount of medicine
- **Observe the patient's ability to use these devices appropriately**

Long-term care facility or arranging for 24/7 supervision should be considered when:

- Cannot recognize a dangerous situation
- Cannot use the telephone for getting help
- Unhappiness alone at home
- Wandering
- Increasing confusion
- Reliable medication administration can not be guaranteed despite using a medication organizer
- Behavioral symptoms are a regular occurrence
- Gait disorder resulting in falls
- Attempting potentially unsafe activities that are off limits when unsupervised

Options for increased level of supervision

- Scheduled outings with friends and family
- Home delivered meals
- Homemaker/companion services
- Adult day programs
- Home health aide
- Memory care assisted living facility
- Skilled nursing facility (+/- secured unit)

Management and Treatment of Patients with Dementia

- 1) Basic needs and wellbeing
- 2) Safety
- 3) Pharmacologic therapies

Pharmacologic Therapies

- While treatments are available that can ameliorate some symptoms, there is no FDA approved disease-modifying therapy for any of the neurodegenerative dementias
- The current FDA approved treatments are not expected to improve cognition, but rather delay decline for a period of time (average of 6 to 12 months)

Pharmacologic Therapies

- Goal of treatment is to temporary stabilize or slow symptomatic progression
 - prolong independence
 - delay institutionalization
 - maintain quality of life
 - minimize caregiver burden
- Actual clinical improvement may not be seen
- Demonstrated efficacy: cognition, global function, ADLs, behavior

Pharmacologic Therapies

- Acetylcholine (ACh) is a neurotransmitter important for learning, memory, and attention
- In Alzheimer's disease, there is severe loss of basal forebrain cholinergic neurons with subsequent loss of cholinergic neurotransmission in the cerebral cortex
- Cholinergic deficiency has been implicated in the cognitive and behavioral manifestations of Alzheimer's disease

Pharmacologic Therapies

- The cholinesterase inhibitors block the action of the acetylcholinesterase (AChE) from breaking down Ach thereby increasing the amount of Ach that remains in the synaptic cleft

Pharmacologic Therapies

- Glutamate is the primary excitatory amino acid in the CNS and activates N-methyl-d-aspartate (NMDA) class of glutamate receptors
- Excessive activation of NMDA receptors results in excitotoxicity and is thought to lead to neuronal cell death and contribute to the pathogenesis of Alzheimer's disease
- Memantine is an antagonist of NMDA receptors

Medication	Mechanism of Action	Available Doses	FDA Approved Indications- Dementia Severity	FDA Approved Indications- Dementia Subtype
Donepezil Oral	AChE inhibitor	5 mg, 10 mg, 23 mg daily	mild, moderate, and severe	Alzheimer's disease
Rivastigmine Oral	AChE inhibitor, BChE inhibitor	1.5 mg, 3 mg, 4.5 mg, 6 mg BID	mild, moderate	Alzheimer's disease, Parkinson's disease
Rivastigmine Transdermal	AChE inhibitor, BChE inhibitor	4.6 mg/24 hour, 9.6 mg/24 hr, 13.3 mg/24 hr	mild, moderate, severe	Alzheimer's disease, Parkinson's disease

Medication	Mechanism of Action	Available Doses	FDA Approved Indications- Dementia Severity	FDA Approved Indications- Dementia Subtype
Galantamine Oral	AChE inhibitor, modulates nicotinic ACh Rs to increase ACh	Immediate release: 4 mg, 8mg, 12mg BID Extended release: 8 mg, 16 mg, 24 mg daily	mild, moderate	Alzheimer's disease
Memantine Oral	NMDA R antagonist + dopamine antagonist	Immediate release: 5 mg, 10 mg BID Extended release: 7 mg, 14 mg, 21 mg, 28 mg daily	moderate, severe	Alzheimer's disease

Cholinesterase Inhibitors: Side Effects

- Nausea
- Vomiting
- Decrease in appetite
- Weight loss
- Diarrhea
- Dizziness
- Sleep disturbances
- Muscle cramps

Start LOW, Go SLOW

Cholinesterase Inhibitors

- No clear difference in efficacy despite the slight variations in the mode of action
- If one is not tolerated, try switching to a different one
- Considerations:
 - Administration schedule
 - Cost to patient
 - Formulation

Memantine: Side Effects

- Dizziness
- Headache
- Changes in behaviors
- Fatigue

Pharmacologic Therapies: Practical Points

- Donepezil HCl 23 mg daily is an FDA approved medication for the treatment of moderate to severe AD
 - based on a small improvement in score on a neuropsychological test
 - no significant difference in functional outcome when compared with the 10 mg dose
 - GI side effects side effects are significantly greater and the cost substantially greater, therefore, this medication is not frequently prescribed

Pharmacologic Therapies: Practical Points

- Rivastigmine
 - Oral formulation tends to have most GI adverse effects, especially nausea and emesis
 - Only cholinesterase inhibitor available as a transdermal patch
 - Patch is waterproof→ No changes required to bathing routine
 - Patch tends to be better tolerated with fewer systemic adverse effects, however, dermatitis can lead to drug discontinuation

Greenspoon et al, *CNS Drugs* 2011

Pharmacologic Therapies: Practical Points

- If the patient is not suffering any adverse effects, these medications are typically continued to avoid risking clinical deterioration by discontinuing the medication
- Small studies and case reports suggest that discontinuation of cholinesterase inhibitors may result in worsening behavioral symptoms (e.g. agitation) and abrupt worsening of cognition

Conclusions

- The care of the patient with dementia involves working with caregivers to optimize a patient's general health and well being
- Safety should be regularly evaluated during the course of the disease
- Currently, there are no disease modifying therapies for any of the neurodegenerative dementias
- Symptomatic therapies, e.g. AChE inhibitors and memantine, are available and delay decline for a period of time