

# Clinical and Pathological Examples of Alzheimer's Disease, Dementia With Lewy Bodies, and Frontotemporal Dementia

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**THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA** includes Alzheimer's disease (AD) (most common), dementia with Lewy bodies (DLB), vascular dementia, **frontal-temporal dementia (FTD)**, Parkinson's disease, normal pressure hydrocephalus, and others. Post-mortem examination of patients with dementia reveals that mixed pathology is very common. Though much progress has been made in developing new diagnostic biomarkers, making a dementia diagnosis still requires a careful history from the patient and a knowledgeable informant. Determining the primary and secondary symptoms and the temporal course of the cognitive and functional decline are the keys to differential diagnosis. Has the onset of cognitive decline and progression been abrupt and step-wise, as seen with multi-infarct dementia, or insidious and gradual, consistent with AD? Knowing the patient's educational and occupational history can be helpful in estimating their level of cognitive reserve. Treatment of dementia is based on targeting the principal symptom, which may be memory loss, depression, Parkinsonism, or eliminating medications with deleterious side-effects.

AD is currently recognized as a progressive neurodegenerative disorder with preclinical, mild cognitive impairment, and dementia stages. There is increasing evidence supporting a AD pathological cascade with regional oligomeric and fibrillar amyloid extracellular deposits beginning ten to 20 years before the onset of cognitive symptoms, followed by accumulation of intracellular hyperphosphorylated tau protein, and later cortical and hippocampal atrophy on MRI.<sup>1</sup> Amyloid PET imaging and spinal fluid markers of amyloid and tau can detect the changes in amyloid burden during the prodromal period, providing an opportunity for detection and intervention before the full pathological and clinical expression of the illness.<sup>2</sup>

## CLINICAL PHENOTYPES OF COMMON DEMENTIA SYNDROMES

### Alzheimer's disease

Gradual onset and progression of episodic memory impairment is usually the cardinal feature of AD. The most common symptoms are misplacing items frequently, trouble keeping track of details, becoming repetitive, difficulty multi-tasking, and managing complex tasks such as balancing a checkbook, preparing a holiday meal, or navigating while driving. MRI may show diffuse cortical and hippocampal atrophy, and ventricular enlargement. Treatment with a cholinergic inhibitor tends to stabilize memory function during the first year of treatment and may make subsequent decline more gradual. However, the disease progresses despite treatment and disease-modifying treatments are needed.

The National Institute of Aging and an International Working Group have proposed new research diagnostic criteria for AD which include guidelines for the diagnosis of the mild cognitive impairment and preclinical stages of AD.<sup>3,6</sup>

### Case example of MCI due to AD

A 66 year-old woman with a family history of dementia was evaluated for

trouble misplacing items, being repetitive, and trouble recalling names. She was still managing her full-time job and driving without difficulty. Her Mini-Mental State Exam score was 28 and her **Montreal Cognitive Impairment Assessment (MOCA)** was 23.<sup>7</sup> Her MRI scan was normal. Apolipoprotein epsilon E genotype was 3,4. Detailed neuropsychological testing demonstrated an isolated impairment in episodic memory. The clinical diagnosis of mild cognitive impairment due to AD was supported by an elevated tau/amyloid ratio in CSF and elevated retention on amyloid PET scans consistent with AD. She was treated with a cholinesterase inhibitor and is participating in a clinical trial of an amyloid-lowering agent to try and slow the progression of AD.

Amyloid PET imaging can be used as a screening tool to detect the build up of cerebral amyloid in the preclinical stage of AD.

### Case example of Preclinical AD

A 77 year-old man with no cognitive complaints responded to an ad for an Alzheimer's study because his mother had dementia at age 80. His MMSE was 29 with 3/3 recall. MRI showed "mild

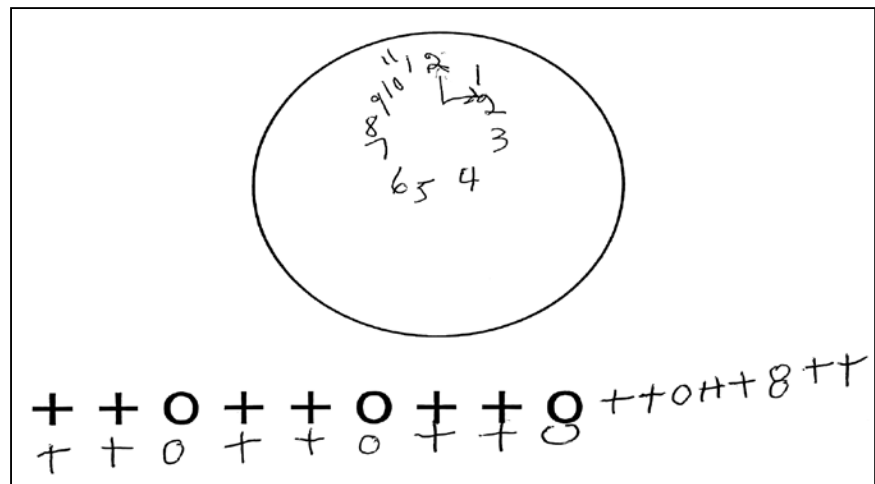


Figure 1. Clock drawing and copying of alternating sequences in the case of DLB. Clock drawing demonstrates evidence of visuospatial and executive impairment with central placement of numbers with mild micrographia. Copying of alternating sequences reveals executive impairment in continuing the sequence after the stimulus.

cortical atrophy, appropriate for age". His clinical dementia rating scale was 0. His amyloid PET score met the research criteria for preclinical Alzheimer's disease. He would be eligible to participate in a future clinical trial of an amyloid-lowering agent to delay the onset of cognitive symptoms.<sup>8</sup>

### **CLINICAL PHENOTYPE OF DEMENTIA WITH LEWY BODIES**

The presenting symptoms of DLB vary widely and include amnesia, Parkinsonism, **REM behavior disorder (RBD)**, depression, hallucinations, delirium, and syncope. RBD is characterized by active sleep with thrashing, talking, or acting out of dreams. Patients may be injured crashing into furniture and dreams frequently have a violent quality. RBD is caused by onset of REM without atonia and may herald the presence of a Parkinsonian disorder greater than five years before the onset of cognitive or motor symptoms. RBD usually responds to a low dose benzodiazepine such as clonazepam given at bedtime.

### **Case example of DLB**

A 70 year-old man began crashing into the walls at night during violent dreams two to three nights per week. He had no cognitive or neurological impairment. A sleep study revealed RBD which was successfully treated with low dose clonazepam. Six years later he developed mild cognitive symptoms and very mild Parkinsonian signs and seven years later he began seeing well-formed animals. MMSE was 26 and clock drawing showed central placement of the numbers with mild micrographia (see below). MOCA score was 18. A diagnosis of DLB was made. Treatment with a cholinesterase inhibitor stabilized memory symptoms and decreased the frequency and intensity of visual hallucinations for 12 months. After the first year his cognitive, behavioral, and motor symptoms progressed gradually despite treatment.

The diagnosis of probable DLB requires dementia plus 2/3 of the following, Parkinsonism, well-formed visual hallucinations, and fluctuating alertness. Executive and visuospatial deficits are often prominent in DLB and the MOCA is a more sensitive measure of cognitive impairment than the MMSE.

It is important to identify the target symptom, cognitive, behavioral, motor, or active sleep, when treating DLB. There is a prominent cholinergic deficit in patients with DLB and these patients often respond well to treatment with cholinesterase inhibitors. Patients with DLB may be sensitive to side-effects of CNS medications, especially to neuroleptics. Low doses of CNS medications should be used with careful monitoring for side-effects.

The pathological diagnosis of DLB requires the presence of cortical cytoplasmic inclusions (Lewy bodies) composed of alpha synuclein protein. Post-mortem examination in patients with DLB frequently demonstrates mixed pathology with amyloid plaques in addition to cortical Lewy bodies.

### **CLINICAL PHENOTYPE OF FRONTAL TEMPORAL DEMENTIA**

There are three common subtypes of FTD, **behavioral variant (bvFTD)**, formerly Pick's disease, **progressive non-fluent aphasia (PNFA)**, and semantic dementia. The clinical and pathological spectrum of **frontal temporal dementia (FTD)** has recently been broadened due to discovery of new dominant mutations and now includes Parkinsonian conditions such as corticobasal degeneration and progressive supranuclear palsy as well as amyotrophic lateral sclerosis.

Patients with FTD are usually younger than patients with AD. Patients with behavioral variant FTD present with early decline in social conduct, emotional blunting, apathy, and compulsive behavior with relatively preserved episodic memory. Speech in PNFA is non-fluent and is characterized by at least one of the following, agrammatism, phonemic paraphasias, and anomia.<sup>9</sup> The cardinal feature of semantic dementia is failure to understand what common words mean.

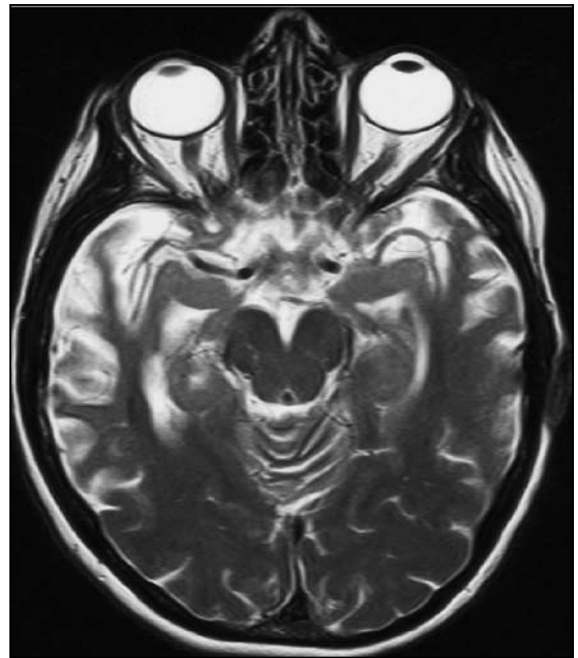


Figure 2 Axial T-2 non-contrast MRI in the case of FTD. The MRI shows significant anterior temporal lobe atrophy greatest on the right in the case of bvFTD.

### **Pathology and genetics of FTD spectrum disorders**

Behavioral variant FTD is usually associated with cytoplasmic protein accumulations of tau (Pick bodies) or TDP-43. The tau pathology seen in bvFTD may be caused by a mutation in the tau gene on chromosome 17 or occur sporadically.<sup>10</sup> TDP-43 inclusions may be due to a mutation in the progranulin gene, located next to the tau gene on chromosome 17, be associated with a hexanucleotide repeat due to a mutation on chromosome 9p21, or are sporadic.<sup>11-13</sup> Semantic dementia is associated with asymmetric degeneration of the dominant temporal lobe and is primarily associated with TDP-43 inclusions that are usually sporadic. In general, two-thirds of cases of progressive aphasia are due to FTD and one-third to AD pathology. PSP and CBD are almost always associated with tau pathology. FTD-ALS is associated with ubiquitin positive TDP-43, tau negative, inclusions and may be associated a mutation on chromosome 9p21.<sup>12,13</sup>

### **Case example of bvFTD**

A 55 year-old woman presented with gradual onset and progression of difficulty finding words and a change in behavior over one year. She was still working full-time as a business executive and driving

without difficulty. She was more anxious and impatient and had decreased regard for the feelings of others. Her MMSE was 25 with 3/3 on delayed recall. She had mild word finding difficulty and a normal sensorimotor exam. Her MRI revealed prominent temporal and frontal lobe atrophy. Her mother had a progressive dementia beginning in her late fifties with a similar pattern of asymmetric atrophy on MRI. Her mother's autopsy demonstrated FTD, tau + Pick type. Genetic testing revealed a mutation in the tau gene on chromosome 17. Our patient experienced a steady decline in behavior and language over six years and now requires full-time care. Trials of cholinesterase inhibitors, memantine, and a number of medications to control behavioral symptoms were ineffective. No medications are currently approved to treat FTD but future trials are likely to target the primary pathology such as tau or progranulin.

## SUMMARY

Dementia syndromes usually consist of distinct clinical and pathological phenotypes. A careful history is required to document the onset and progression of symptoms to generate the differential diagnosis. New biomarker tests can provide evidence to increase diagnostic certainty. Disease-specific interventions, based on advances in genetic and molecular biomarkers, are likely to have the greatest impact when given in preclinical and early symptomatic phases.

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