DIFFERENTIAL DIAGNOSIS OF DEMENTIA

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"My mom has dementia, not Alzheimer's." This statement may reflect a lack of understanding that dementia is not one specific disease, but encompasses a wide range of symptoms associated with cognitive impairment severe enough to affect a person's ability to independently perform everyday activities. Alzheimer's disease accounts for the majority of all dementia cases. Accurate diagnosis may be complicated by other causes of dementia that have symptoms and pathologies similar to Alzheimer's disease. Knowing the key clinical symptoms and pathology of different causes of dementia can help in the accurate diagnosis of patients, so they will receive the care, treatment and support services appropriate for their condition and maintain the highest possible quality of life. Other common types of dementia encountered include vascular dementia (VaD), dementia with Lewy bodies (DLB), Parkinson dementia (PD), frontotemporal dementia (FTD), and mixed dementia (two or more etiologies, most commonly AD and VaD). Creutzfeldt-Jakob disease, Huntington's, Wernicke-Korsakoff syndrome and normal pressure hydrocephalus are just a few of the dementias that appear less frequently.

It is important to rule out common health issues that can cause dementia-like symptoms such as depression, untreated sleep apnea, delirium, side effects of medications, thyroid problems, certain vitamin deficiencies, metabolic toxicity (including alcohol) and tumor lesions. These conditions often may be reversed with treatment.

Physicians define dementia based on the criteria given in the Diagnostic and Statistical Manual of Mental Disorders (DSM). To meet the DSM-5 diagnostic criteria for major neurocognitive disorder (NCD), an individual must have evidence of significant cognitive decline in memory or another cognitive ability, such as language or learning, that interferes with independence in everyday activities. For example, an individual may need assistance with complex activities such as paying bills or managing medications. In mild cognitive impairment (MCI), an individual has evidence of modest cognitive decline, but the impairment may not interfere with performing complex activities. For example, a person may be increasingly reliant on memory aids, reminder notes or electronic devices, but can still pay bills and manage their medications. MCI can develop for multiple reasons, and individuals living with MCI may go on to develop dementia; others will not. For neurodegenerative diseases, MCI can be an early stage of the disease continuum including for Alzheimer's if biomarkers confirm the hallmark changes in the brain. Although there are commonalities among the dementias (or NCDs), examining the course, clinical features and related biomarkers of a patient's cognitive impairment can help differentiate between the various common subtypes (Table 1). This helps determine the care, treatment and support services appropriate for the specific disease underlying the dementia.

Table 1. Differentiating between common forms of dementia

	Alzheimer's Dementia (AD)	VascularDementia (VaD)	Dementia with Lewy Body (DLB)	Parkinson's Disease Dementia (PDD)	Frontotemporal Dementia (FTD)
Course	Insidious onset and gradual progression [1]	Based on location and extent of cerebrovascular event (CVE) [1,4] Can be stepwise decline [2,4]	Insidious onset with gradual progression [1]	Insidious onset with gradual progression [1]	Insidious onset with gradual progression [1]
Presentation	Memory loss and impaired learning early in the disease [1] Visuospatial and language deficits present in moderate to severe stages [1]	Temporal relationship between CVE and onset of cognitive impairment [1] Subcortical ischemic vascular disease: dysexecutive function [4]	Fluctuating cognition and functional impairment with parkinsonism, REM sleep disorder, visual hallucinations [4] Cognitive symptoms start shortly before or concurrently with motor symptoms [1,4] Resting tremor less frequent [4]	Cognitive decline is usually later, >1 year after motor symptoms [1,2,4] Cognitive features: bradyphrenia, inattention, executive dysfunction, visuospatial dysfunction [4] Movement features: bradykinesia, rigidity, resting tremor	Behavioral variant (bvFTD): behavioral disinhibition, apathy, loss of sympathy or empathy, perseverative stereotyped speech, compulsive/ritualistic behavior, hyperorality, dietary changes [4] Language variant (PPA): loss of word memory, including speech production, word finding, comprehension, grammar [1] May present with both types [1]

	Alzheimer's Dementia (AD)	VascularDementia (VaD)	Dementia with Lewy Body (DLB)	Parkinson's Disease Dementia (PDD)	Frontotemporal Dementia (FTD)
Associated Features	Behavioral and psychological symptoms are common: – Early: depression, apathy [2] – Moderate to severe: impaired communication, confusion, poor judgement, behavioral changes [2] – Late: gait disturbance, dysphagia [2]	May have history of transient ischemic attack/ stroke [1,4] Personality and mood changes [1] May exhibit parkinsonian features with bradykinesia, gait disturbance, rigidity [4] Slow, gradual progression due to small vessel disease [1,4]	Nearly 50% have severe neuroleptic sensitivity Falls, syncope, autonomic dysfunction are common [1] May have history of delirium during illness or surgery [1]	Apathy, anxiety, depression, hallucinations, delusions, personality changes, rapid eye movement sleep disorder and excessive daytime sleepiness [1]	Extrapyramidal symptoms may be present in later stages [1] Overlaps with AD[4] and other neurological conditions, such as progressive supranuclear palsy, corticobasal degeneration and motor neuron disease [1] Majority present between ages 56-65 [2]
Most Common Risk Factors	Age and genetics (APOE-e4, family history and Down's syndrome), physical activity, smoking, education, staying socially and mentally active, blood pressure, diet, traumatic brain injury [3]	Hypertension, dyslipidemia, diabetes, smoking, atrial fibrillation and cerebral amyloid angiopathy [4]	Genetic risk identified but no family history in most cases [1,2]	Clinical predictors of dementia: age, male sex, greater motor symptoms, hallucinations, REM sleep disorder and vascular risk factors (hypertension, smoking, etc.) [4]	Up to 40% are familial [2,4] Occurs in patients with motor neuron disease [2] Brief cognitive assessments often normal [2]
Diagnostic Imaging	Hippocampal and temporoparietal atrophy on MRI/CT [1] Hypometablism in parietal, temporal and frontal lobes on FDG-PET [4] Several amyloid and tau PET tracers have been FDA approved, but clinical availability is limited [4]	Focal infarcts, confluent white matter changes, generalized atrophy on MRI/CT [4] Multifocal hypometabolism (in areas of injury) on FDG-PET [4]	Diffuse atrophy, white matter changes in temporal lobes (medial structures preserved) on MRI/CT [4] Hypometabolism posteriorly on FDG-PET [4] Abnormal dopamine transporter scan (DaT)	May have structurally normal MRI/CT [4] Hypometabolism posteriorly on FDG-PET [4] Abnormal dopamine transporter scan (DaT)	Atrophy in frontal and/or temporal lobes on MRI/CT[4] Atrophy may be symmetric or focal asymmetric [4] Hypometabolism in frontal and/or temporal lobes on FDG-PET [4]
Fluid Biomarkers to Assist in Diagnosis	CSF amyloid beta (Lumipulse G B-Amyloid ratio is only FDA approved assay) [5]	None	None	None	None
Other	Often coexists with VaD [1]	Only 12% have pure VaD [4] Often coexists with AD and/or DLB [1] Depression is often present [2]	Often coexists with AD and/or VaD [1]	Distinguish from medication-induced parkinsonism, which may occur when dopamine-blocking drugs are prescribed for behavioral symptoms [1] Often coexists with AD and/or VaD [1]	May be mistaken for depression, bipolar or schizophrenia [1]

There are laboratory-developed blood tests currently on the market that can be ordered by clinicians to aid in the diagnosis of memory complaints. These tests do not have FDA approval yet. At this time, it is recommended that blood tests only be used by specialty care doctors who are seeing patients with memory complaints. They are not recommended for individuals who do not have any cognitive or memory symptoms.

1. American Psychiatric Association, American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5, 5th ed. Washington, D.C: American Psychiatric Association; 2013.

2. Budson AE, Solomon PR. Memory Loss: A Practical Guide for Clinicians. [Philadelphia]: Elsevier Saunders; 2011.

3. Alzheimer's Association. 2022 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2022; 18.

4. American Academy of Neurology: Continuum (Minneap Minn) 2022; 28 (3, Dementia)

5. FDA News Release. FDA Permits Marketing for New Test to Improve Diagnosis of Alzheimer's Disease; 2022 via FDA.gov.