Clinical Reasoning: A 56-year-old man with cognitive impairment and difficulty tying his necktie

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SECTION 1

A 56-year-old previously healthy man presented with cognitive complaints. He described forgetting recent conversations and leaving tasks unfinished. He reported no problems with long-term memory, no personality changes, and he continued to perform all activities of daily living (ADLs) independently. His initial neurologic examination was normal, including a perfect score on the Mini-Mental State Examination (MMSE). Over the

next 2 years, he developed difficulty reading his analog watch, managing finances, and making simple calculations while shopping. He also reported difficulty tying his necktie.

Questions for consideration:

1. What is the differential diagnosis for the patient's cognitive decline?
2. What features on examination could help narrow the differential diagnosis?

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SECTION 2

Cognitive decline more than expected for age with preserved independent ADLs suggests mild cognitive impairment, which progresses to dementia at an annual rate of 5%–15%.¹ In addition to Alzheimer disease (AD), the differential diagnosis for our patient's subsequent cognitive decline includes vascular dementia, dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD). Potentially reversible etiologies such as metabolic (vitamin B₁₂ deficiency), endocrine (hypothyroidism), toxic syndromes (medication effects), structural lesions (primary or metastatic brain tumor), and psychiatric conditions (depression) must be excluded as well. The patient's B₁₂ and thyroid-stimulating hormone levels were normal. His complaints of difficulty tying his necktie could be due to deficits in strength, coordination, sensation, or higher-level action sequencing, requiring further characterization.

On neurologic examination, the patient scored 26/30 on the MMSE (figure, A). Formal neuropsychiatric testing confirmed deficits in multiple cognitive

domains including memory, executive function, attention, and visuospatial skills with relative preservation of language. Strength, sensation, and reflexes were normal, without tremor or ataxia. He had increased tone, cogwheeling, and slowed finger tapping in the left arm, but normal right arm tone and movements. When attempting to pantomime use of a saw with his left hand, his hand moved in a circular motion. When asked to mimic waving goodbye with his left hand, he simply held his hand parallel to the table. Right-handed gestures were normal. Similarly, he had interval progression of his motor symptoms and now had masked facies, decreased blink rate, and decreased arm swing on the left when walking, though there was no retropulsion.

Questions for consideration:

1. How do the patient's examination findings thus far contribute to determining the differential diagnosis?
2. Which additional features on history and examination could help narrow the differential diagnosis?

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Figure Representative studies

(A) The patient was asked to copy the overlapping pentagons, demonstrating marked difficulty with visuospatial constructions. (B) Axial fluid-attenuated inversion recovery MRI shows right greater than left parietal and frontal atrophy, out of proportion to age. (C) FDG-PET shows right greater than left hypometabolism in the basal ganglia, temporal lobes, and parietal lobes.

SECTION 3

The patient's examination demonstrates asymmetric parkinsonism, but no resting tremor or shuffling gait. The patient's difficulty with motor tasks in the setting of preserved strength, sensation, and coordination suggests apraxia. His inability to pantomime to verbal command and difficulty imitating gestures are consistent with ideomotor apraxia. Difficulty tying his necktie was possibly due to both difficulty sequencing the component actions (ideational apraxia) and diminished dexterity (limb-kinetic apraxia).

The differential diagnosis for parkinsonism with cognitive decline includes idiopathic Parkinson disease (PD) with PD-associated dementia, DLB, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA). Parkinsonism typically precedes dementia in PD-associated dementia, while dementia may precede parkinsonism in DLB.

On further history, the patient denied anosmia, constipation, abnormal nighttime behaviors, visual hallucinations, urinary incontinence, erectile dysfunction, orthostatic hypotension, and falls. The patient's wife described a situation during which the patient's left hand involuntarily mimicked his wife's movements as she was paying a toll; the patient recalled that during this event his arm was not under volitional control. On further examination, the patient had intact extraocular movements, with no limitation in vertical gaze. He had intermittent dystonic posturing of his left hand, most notable while walking, myoclonus of the left arm, and extinction to double simultaneous stimulation on the left side.

Question for consideration:

1. How do these additional history and examination findings narrow the differential diagnosis?

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SECTION 4

This combination of asymmetric parkinsonism and cortical sensory deficits is characteristic of corticobasal syndrome (CBS). Although this patient has prominent asymmetric parkinsonism on examination, he lacks other features of synucleinopathies, such as anosmia, constipation, and REM sleep disorder. The presence of early cognitive features is atypical for PD, and there were no hallucinations or fluctuations to suggest DLB. He had no symptoms of autonomic or cerebellar dysfunction to suggest MSA, and no early features of PSP such as postural instability or falls. The characteristic vertical gaze impairment of PSP is usually a late finding, so its absence does not exclude this diagnosis.

CBS is characterized by asymmetric parkinsonism and cortical deficits. Diagnostic criteria differentiate between probable and possible CBS. Probable CBS requires the asymmetric presentation of at least 2 of

the following features: limb rigidity or akinesia, dystonia, or myoclonus; and least 2 of the following: orobuccal or limb apraxia, cortical sensory deficit, or alien limb phenomenon. Possible CBS is suggested by the symmetric presentation of probable CBS features, but requires only one feature from each category.² Our patient met criteria for probable CBS with asymmetric rigidity, dystonia, myoclonus, apraxia, cortical sensory deficits, and the alien limb phenomenon. CBS describes a clinical syndrome, while CBD is a pathologic diagnosis. CBS may be caused pathologically by CBD, AD, PSP, or FTLT. Our patient underwent MRI and FDG PET, shown in the figure.

Question for consideration:

1. What neuroimaging findings are demonstrated and do they support the clinical diagnosis of CBS?

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SECTION 5

MRI demonstrated global atrophy disproportionately affecting the right parietal lobe including the postcentral gyrus (figure, B). PET revealed decreased tracer uptake in the right basal ganglia and bilateral parietal lobes, right more than left

(figure, C). Focal asymmetric parietal and basal ganglia atrophy³ and hypometabolism⁴ are consistent with CBS.

Question for consideration:

1. How is CBS treated?

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SECTION 6

Although there is no disease-modifying treatment for CBS, many symptoms can be controlled pharmacologically.⁵ Levodopa may be used for parkinsonism but is often unsuccessful.⁵ Dystonia may respond to botulinum toxin injection; myoclonus can be treated with benzodiazepines or levetiracetam.

Cognitive symptoms may respond to acetylcholinesterase inhibitors and NMDA receptor antagonists, particularly if the underlying cause is AD pathology, but may worsen behavioral symptoms in patients with underlying FTLT pathology.⁵ Nonpharmacologic interventions include physical and speech therapy, and patients should be routinely assessed for the development of dysphagia.⁵

Our patient was treated with levodopa, with minimal effect on his parkinsonism. His intermittent dystonia and myoclonus did not interfere with his daily functioning and therefore did not require specific intervention. Physical therapy and speech therapy allowed him to ambulate with assistance and tolerate a regular diet. His cognitive symptoms progressed clinically to dementia, requiring assistance on most of his ADLs, although he continues to live at home with aid from his family.

DISCUSSION CBS can be caused pathologically by multiple entities. When characteristic tau-positive lesions are found on autopsy, the condition is referred to as CBD. In autopsy series, CBD, AD, and PSP all account for about 25% of cases. The remainder is composed of pathology consistent with FTLT or PD.⁶

Although CBD, PSP, and AD are all tauopathies, they differ in the specific tau isoform involved (4R in CBD and PSP vs 4R and 3R in AD), as well as gross and microscopic findings at autopsy.⁷ In CBD, histology demonstrates ballooned cortical neurons, tau-positive astrocytic plaques, and tau-positive thread-like lesions in the neuropil of gray and white matter throughout the cortex and basal ganglia. The characteristic lesion of PSP, the tufted astrocyte, is found in a similar distribution, though typically with less cortical involvement than in CBD. Additionally, prominent midbrain atrophy differentiates PSP from CBD.⁷ The hallmark of AD pathology is amyloid-containing senile plaques and involvement of the hippocampi. Many cases of CBS have mixed underlying pathology.

Clinical criteria have been proposed to distinguish patients with CBD from other pathologic causes of CBS.² Probable sporadic CBD requires probable CBS beginning at or after age 50 years, excluding patients with positive family histories or suspected tau-related genetic mutations. Possible CBD is characterized by insidious onset and gradual progression of possible CBS over at least 1 year. The accuracy of these criteria ranges from 47% to 68%.⁸ Our patient

meets criteria for probable CBD as the underlying etiology based on age and no family history of similar disorders.

As specific therapies for AD and other tau-associated diseases emerge, antemortem clinical and radiologic predictors of underlying pathology in patients with CBS are essential. Early memory loss and early visuospatial deficits, both present in our patient, may predict underlying AD pathology.^{9,10} Quantitative MRI using voxel-based morphometry can identify relatively focal patterns of atrophy in specific areas of the posterior frontal lobes in CBD compared to more widespread atrophy when AD is the underlying etiology of CBS.¹¹ When consistent with AD, Pittsburgh compound B–PET imaging and CSF biomarker profiles can serve as additional exclusion criteria for possible and probable CBD.² Continued advances in biomarkers offer the possibility for earlier differentiation of underlying pathologic subtypes of CBS, and potentially earlier trials of disease-modifying agents.

AUTHOR CONTRIBUTIONS

Jessica M. Baker: drafted and revised the manuscript, designed the study, and analyzed and interpreted data. Joel Salinas: drafted and revised the manuscript, designed the study, and analyzed and interpreted data. Aaron L. Berkowitz: drafted and revised the manuscript, designed the study, and analyzed and interpreted data.

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