Section Editor
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Clinical Reasoning: A 75-year-old man with 3 years of visual difficulties

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SECTION 1

A 75-year-old man with hypertension and hyperlipidemia presented with 3 years of progressive visual difficulties. Ophthalmologic evaluation revealed cataracts, but his vision was unchanged following cataract surgery. The patient described difficulty reaching for objects accurately and distinguishing objects from their background (for example, identifying his cat sitting on his couch). On one occasion, he intended to sit on a chair, but inadvertently sat on an adjacent table. He had sustained several car accidents. He had no difficulty reading or recognizing faces.

The patient's initial examination was reported to suggest mild impairment in attention (inability to spell "world" backward) and difficulty performing simple

calculations, but normal memory, speech, and language. Visual acuity and fields were normal. He was unable to interpret Ishihara color plates, but could distinguish individual colors accurately. He had difficulty drawing a clock and copying intersecting pentagons. Ocular ductions were normal, but he could not voluntarily initiate horizontal saccades to a target. On finger-nose testing, he could not accurately reach the target; after happening upon the examiner's palm, he traced up to the finger. Strength, sensation, reflexes, and gait were described as normal.

Question for consideration:

1. What is the localization and differential diagnosis of his deficits?

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SECTION 2

The patient has deficits of visuospatial processing including ocular apraxia (inability to initiate saccades), optic ataxia (impaired visually guided movements as demonstrated by his performance on finger–nose testing), and simultanagnosia (impaired processing of simultaneous stimuli, as demonstrated by impaired performance on the Ishihara color plates in spite of preserved color discrimination). These findings suggest Balint syndrome, often caused by bilateral parieto-occipital pathology. Etiologies of Balint syndrome include middle cerebral artery–posterior cerebral artery borderzone infarction, posterior reversible encephalopathy syndrome, malignancy involving the occipital lobes, and neurodegenerative disease.

In this patient, symptom evolution over several years suggests a neurodegenerative process such as posterior cortical atrophy (PCA). PCA is characterized by visual processing deficits and parieto-occipital cortical atrophy,

most commonly due to neurofibrillary tangles and senile plaques (Alzheimer-type pathology), although Lewy body and tau pathology occur less frequently.

Additional history revealed that the patient kicked and shouted during sleep, his handwriting had become smaller, his movements had slowed, his voice had become softer, and his sense of smell had diminished. The patient had not complained of any of these symptoms, describing them only after specific inquiry. He reported no hallucinations, abnormal fluctuations in wakefulness or mood, orthostasis, or incontinence. On examination, he had mildly decreased facial expression, subtle cogwheeling at the wrists bilaterally with reinforcement, and a slightly slow gait with normal arm swing and turning. No tremor was observed.

Question for consideration:

1. How do the additional findings guide the differential diagnosis?

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SECTION 3

Micrographia, bradykinesia, hypophonia, hypomimia, and cogwheeling are stigmata of parkinsonism. The history of violently acting out vivid dreams suggests REM sleep behavior disorder (RBD). RBD is associated with greater than 50% risk of developing neurodegenerative disease (most commonly synucleinopathy) at 15 years after onset, over 80% risk at 20 years, and over 90% risk at 25 years.¹ These features, along with the patient's cognitive impairment, suggested dementia with Lewy bodies (DLB).

Although definitive diagnosis of DLB requires pathologic confirmation, a probable diagnosis can be made antemortem if the patient has the central feature of dementia with 2 core features (fluctuating cognition, visual hallucinations, parkinsonism) or one core feature with one suggestive feature (RBD, neuroleptic sensitivity, low dopamine transporter uptake in the basal ganglia on PET or SPECT).² Our patient met criteria for probable DLB with cognitive deficits impairing function, one core feature (parkinsonism), and one suggestive feature (RBD).

Whereas the core features of visual hallucinations and parkinsonism are specific for DLB in patients with dementia (99% and 82% specificity, respectively), they are often absent (22% and 26% sensitivity, respectively).³

Although RBD is considered only a suggestive feature of DLB, it increases the odds of autopsy-confirmed diagnosis of DLB sixfold compared to each of the core features of DLB, which only increase these odds twofold.⁴ Visuospatial impairment in a patient with dementia, not considered a core or suggestive feature of DLB, may have higher sensitivity (74%) for identifying DLB than either of the core features of hallucinations or parkinsonism, although its specificity is poor (55%), since visual processing deficits may accompany DLB, PCA, and Alzheimer disease (AD).³

Although visual processing deficits can be present in both PCA and DLB, hallucinations are less common in PCA. In one study of patients diagnosed with PCA, all patients who had hallucinations eventually developed RBD or parkinsonism, ultimately meeting diagnostic criteria for probable DLB; no patients with PCA without hallucinations met criteria for DLB.⁵ The authors suggest that if patients diagnosed with PCA develop hallucinations, a diagnosis of DLB should be strongly considered.⁵ Our patient reported no hallucinations.

Question for consideration:

1. What further evaluation can help to distinguish between etiologies of the patient's cognitive deficits?

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(A) Axial T1-weighted MRI demonstrates symmetrical cortical atrophy. (B) SPECT scan demonstrates occipital and parietal hypoperfusion. (C) Pathologic specimen of the midbrain demonstrates bilateral degeneration of the substantia nigra. (D, E) Hematoxylin & eosin (D) and α -synuclein (E) stains demonstrate Lewy bodies in the substantia nigra (D) and amygdala (E).

SECTION 4

Structural neuroimaging can aid in the diagnosis of neurodegenerative diseases by demonstrating patterns of atrophy suggestive of particular diseases: medial temporal and temporoparietal atrophy in AD, frontotemporal atrophy in frontotemporal dementia, and occipitoparietal atrophy in PCA. Neuroimaging studies may also reveal non-neurodegenerative causes of dementia such as vascular disease, normal-pressure hydrocephalus, or structural lesions (e.g., malignancy).

Nuclear imaging modalities (e.g., PET and SPECT) may be helpful early in a dementing illness before structural changes are evident on MRI. Hypoperfusion and hypometabolism in temporoparietal regions without involvement of occipital or primary sensorimotor regions are highly predictive of AD, whereas occipital and temporoparietal hypoperfusion suggest DLB. At present, amyloid imaging and functional MRI are primarily research tools, but hold promise for the diagnosis of dementia, especially in early or pre-symptomatic stages.

In our patient, MRI demonstrated subtle, symmetrical, diffuse cortical atrophy, without structural lesions, ventriculomegaly, or significant stigmata of vascular disease (figure, A). SPECT showed hypoperfusion of occipital, parietal, and temporal cortices, supporting the diagnosis of DLB (figure, B).

Question for consideration:

1. How should the patient's symptoms be treated?

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SECTION 5

Cholinesterase inhibitors such as donepezil and rivastigmine and the NMDA receptor antagonist memantine have been shown to improve cognition and behavior in patients with DLB.

Our patient was treated with rivastigmine with no clear benefit. Over the following year, he experienced several freezing episodes and could no longer ambulate independently. A trial of carbidopa/levodopa (half of a 25/100 mg tablet 3 times daily) was initiated, but led to visual hallucinations and was discontinued. His hallucinations resolved, but over subsequent months he became increasingly disoriented and anxious, and his mobility continued to decline. He and his family decided to transition to hospice care. He died 2 years after presentation.

Brain autopsy revealed degeneration of the substantia nigra (figure, C), moderate to numerous Lewy bodies in the substantia nigra, locus ceruleus, raphe, basal forebrain, amygdala, and transentorhinal cortex (figure, D and E), and sparse Lewy bodies and Lewy neurites in frontal and temporal neocortices. There was limited Alzheimer pathology (Braak stage 1) in the hippocampi and entorhinal cortices. Moderate arteriosclerosis of the intracranial vasculature was noted, but with no evidence of cerebral infarction. These findings confirmed the diagnosis of DLB.

DISCUSSION DLB is the second leading cause of degenerative dementia after AD, accounting for 15% of dementia cases. While the core features of hallucinations, fluctuations, and parkinsonism are easily recognized, prominent visuospatial processing deficits may precede these. Impairment on clinical tests of visuospatial processing (e.g., clock drawing, copying tasks) can aid in distinguishing DLB from AD when core features of DLB are absent.^{3,6} In addition to considering a diagnosis of PCA in patients with subacute decline in visual cognition, it is important to search for clinical features of DLB that the patient may not initially report, such as hallucinations, parkinsonism, and RBD.

Neuroimaging can aid in the distinction between neurodegenerative causes of visual processing deficits: posterior-predominant cortical atrophy occurs in PCA, whereas occipital hypoperfusion without disproportionate occipital atrophy is supportive of DLB. Occipital hypoperfusion in DLB likely relates to decreased cholinergic input from the basal forebrain and brainstem, and treatment with cholinesterase inhibitors has been shown to improve occipital perfusion,⁷ suggesting an important role for the cholinergic system in the pathophysiology of the disease. In spite of occipital hypoperfusion in DLB, there is typically no occipital atrophy⁸ and autopsy studies

show a minimal burden of Lewy bodies in the occipital lobes.⁹

Although occipital hypoperfusion may explain visual processing deficits in DLB, the origin of visual hallucinations remains incompletely understood. Visual hallucinations in patients with DLB correlate with an increased burden of Lewy bodies in the parahippocampal and inferior temporal regions, independent of the severity of dementia.¹⁰ Disrupted input from the hypoperfused occipital lobes to the diseased medial temporal lobes may lead to hallucinations in DLB through a “release” of imagery from medial temporal regions.¹⁰

The study of visual phenomena in DLB—both visual processing deficits and hallucinations—holds promise for developing a deeper understanding of clinical–pathophysiologic correlations in this disease. In order to develop effective therapeutic strategies for neurodegenerative conditions such as PCA and DLB, it is critical to improve the early, accurate identification of these clinically overlapping yet pathologically distinct disorders.

AUTHOR CONTRIBUTIONS

Dr. Berkowitz conceived of the manuscript, drafted the initial manuscript, revised the manuscript, and created the figure. Dr. Rose prepared the pathologic specimens and revised the manuscript. Dr. Daffner was responsible for the care of the patient, including diagnosis and treatment, and revised the manuscript. Dr. Prasad drafted the initial manuscript, revised the manuscript, and created the figure.

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REFERENCES

1. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol* 2013;12:443–453.
2. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies third report of the DLB consortium. *Neurology* 2005;65:1863.
3. Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Jody Corey-Bloom J. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain* 2006;129:729–735.
4. Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnosis of dementia with Lewy bodies. *Neurology* 2011;77:875–882.
5. Josephs KA, Whitwell JL, Boeve BF, et al. Visual hallucinations in posterior cortical atrophy. *Arch Neurol* 2006;63:1427–1432.
6. Gnanalingham KK, Byrne EJ, Thornton A. Clock-face drawing to differentiate Lewy body and Alzheimer type dementia syndromes. *Lancet* 1996;347:696–697.

7. Mori T, Ikeda M, Fukuhara R, Nestor PJ, Tanabe H. Correlation of visual hallucinations with occipital rCBF by donepezil in DLB. *Neurology* 2006;66:935–937.
8. Middelkoop HA, van der Flier WM, Burton EJ, et al. Dementia with Lewy bodies and AD are not associated with occipital lobe atrophy on MRI. *Neurology* 2001;57:2117–2120.
9. Yamamoto R, Iseki E, Murayama N, et al. Investigation of Lewy pathology in the visual pathway of brains of dementia with Lewy bodies. *J Neuro Sci* 2006;246:95–101.
10. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease related to Lewy bodies in the temporal lobe. *Brain* 2002;125:291–403.

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