Subtle cognitive decline in a patient with depression and anxiety

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After several months of subtle cognitive decline, Mr. M, age 53, has a panic attack and presents to the ED. He has a history of major depressive disorder and anxiety. What is the correct diagnosis?

CASE Anxious and confused

Mr. M, age 53, a surgeon, presents to the emergency department (ED) following a panic attack and concerns from his staff that he appears confused. Specifically, staff members report that in the past 4 months, Mr. M was observed having problems completing some postoperative tasks related to chart documentation. Mr. M has a history of major depressive disorder (MDD), hypertension, hyperlipidemia, and type 2 diabetes.

HISTORY A long-standing diagnosis of depression

Mr. M reports that 30 years ago, he received care from a psychiatrist to address symptoms of MDD. He says that around the time he arrived at the ED, he had noticed subtle but gradual changes in his cognition, which led him to skip words and often struggle to find the correct words. These episodes left him confused. Mr. M started getting anxious about these cognitive issues because they disrupted his work and forced him to reduce his duties. He does not have any known family history of mental illness, is single, and lives alone.

EVALUATION After stroke is ruled out, a psychiatric workup

In the ED, a comprehensive exam rules out an acute cerebrovascular event. A neurologic evaluation notes some delay in processing information and observes Mr. M having difficulty following simple commands. Laboratory investigations, including a comprehensive metabolic panel, are unremarkable. An MRI of Mr. M's brain, with and without contrast, notes no acute findings. He is discharged from the ED with a diagnosis of MDD.

Before he presented to the ED, Mr. M's medication regimen included duloxetine 60 mg/d, buspirone 10 mg 3 times a day, and aripiprazole 5 mg/d for MDD and anxiety. After the ED visit, Mr. M's physician refers him to an outpatient psychiatrist for management of worsening depression and panic attacks. During the psychiatrist's evaluation, Mr. M reports a decreased interest in activities, decreased motivation, being easily fatigued, and having poor sleep. He denies having a depressed mood, difficulty concentrating, or having

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problems with his appetite. He also denies suicidal thoughts, both past and present.

Mr. M describes his mood as anxious, primarily surrounding his recent cognitive changes. He does not have a substance use disorder, psychotic illness, mania or hypomania, posttraumatic stress disorder, or obsessive-compulsive disorder. He reports adherence to his psychiatric medications. A mental status exam reveals Mr. M to be anxious. His attention is not well sustained, and he has difficulty describing details of his cognitive struggles, providing vague descriptions such as "skipping thought" and "skipping words." Mr. M's affect is congruent to his mood with some restriction and the psychiatrist notes that he is experiencing thought latency, poverty of content of thoughts, word-finding difficulties, and circumlocution. Mr. M denies any perceptual abnormalities, and there is no evidence of delusions.

What is the next logical step?

a) Increase duloxetine and follow up in 1 month
b) Initiate an alternate antidepressant and follow up in 1 month
c) Refer Mr. M for psychotherapy
d) Obtain collateral information to rule out a medical problem

Clinical Point

Cognitive decline can be subtle, gradual, and easily missed, which makes it important to obtain as much collateral information as possible

The authors' observations

Mr. M's symptoms are significant for subacute cognitive decline that is subtle but gradual and can be easily missed, especially in the beginning. Though his ED evaluation—including brain imaging—ruled out acute or focal neurologic findings and his primary psychiatric presentation was anxiety, Mr. M's medical history and mental status exam were suggestive of cognitive deficits.

Collateral information was obtained from his work colleagues, which confirmed both cognitive problems and comorbid anxiety. Additionally, given Mr. M's high cognitive baseline as a surgeon, the new-onset cognitive changes over 4 months warranted further cognitive and neurologic evaluation. There are many causes of cognitive impairment (vascular, cancer, infection, autoimmune, medications, substances or toxins, neurodegenerative, psychiatric, vitamin deficiencies), all of which need to be considered in a patient with a nonspecific presentation such as Mr. M's. The psychiatrist confirmed Mr. M's current medication regimen, and discussed tapering aripiprazole while continuing duloxetine and buspirone.

EVALUATION A closer look at cognitive deficits

Mr. M scores 12/30 on the Montreal Cognitive Assessment (MoCA), indicating moderate cognitive impairment (***Table 1***, ***page 43***). The psychiatrist refers Mr. M to Neurology. During his neurologic evaluation, Mr. M continues to report feeling anxious that "something is wrong" and skips his words. The neurologist confirms Mr. M's symptoms may have started 2 to 3 months before he presented to the ED. Mr. M reports unusual eating habits, including yogurt and cookies for breakfast, Mexican food for lunch, and more cookies for dinner. He denies having a fever, gaining or losing weight, rashes, headaches, neck stiffness, tingling or weakness or stiffness of limbs, vertigo, visual changes, photophobia, unsteady gait, bowel or bladder incontinence, or tremors.

When the neurologist repeats the MoCA, Mr. M again scores 12. The neurologist notes that Mr. M answers questions a little slowly and pauses for thoughts when unable to find an answer. Mr. M has difficulty following some simple commands, such as "touch a finger to your nose." Other in-office neurologic physical exams (cranial nerves, involuntary movements or tremors, sensation, muscle strength, reflexes, cerebellar signs) are unremarkable except for mildly decreased vibration sense of his toes. The neurologist concludes that Mr. M's presentation is sug-

Table 1

Mr. M's Montreal Cognitive Assessment score

1. Alternating trail making: 1 point	0/1 point
2. Visuoconstructional skills (cube): 1 point	0/1 point
3. Visuoconstructional skills (clock): 3 points	1/3 points • Unable to connect number to letter • Unable to copy cube • 1 point for contour; unable to place appropriate numbers or hands
4. Naming (animals): 3 points	3/3 points
5. Memory (registration)	No points awarded
6. Attention: 6 points	1/6 points • Able to repeat forward digits; unable to repeat reverse digits • >2 errors for tapping hand • Unable to do serial 7
7. Sentence repetition: 2 points	0/2 points
8. Verbal fluency (words with letter F): 1 point	0/1 point
9. Abstraction: 2 points	0/2 points
10. Delayed recall: 5 points	1/5 points • No cue: red • Category cue: church • Multiple choice cue: face, velvet, daisy
11. Orientation: 6 points	6/6 points
Total	12/30 points (Normal: ≥26/30)

gestive of subacute to chronic bradyphrenia and orders additional evaluation, including neuropsychological testing.

What is the most likely diagnosis for Mr. M?

a) Neurologic decline due to vitamin B12 deficiency
b) Primary progressive aphasia (PPA) secondary to neurodegenerative disorder
c) Adverse effect of aripiprazole secondary to poor cytochrome P450 2D6 metabolism
d) Conversion disorder

The authors' observations

Physical and neurologic exams were not suggestive of any obvious causes of cognitive decline. Both the mental status exam and 2 serial MoCAs suggested deficits in executive function, language, and memory. Each of the differential diagnoses considered was ruled out with workup or exams (***Table 2, page 44***), which led to a most likely diagnosis of neurodegenerative disorder with PPA. Neuropsychological testing confirmed the diagnosis of nonfluent PPA.

Primary progressive aphasia

PPA is an uncommon, heterogeneous group of disorders stemming from focal degeneration of language-governing centers of the brain.[1,2] The estimated prevalence of PPA is 3 in 100,000 cases.[2,3] There are 4 major variants of PPA (***Table 3***,[4] ***page 45***), and each presents with distinct language, cognitive, neuroanatomical, and neuropathological characteristics.[4] PPA is usually diagnosed in late middle life; however, diagnosis is often delayed due to the relative obscurity of the disorder.[4] In Mr. M's case, it took approximately 4 months

Clinical Point

PPA is an uncommon group of disorders stemming from focal degeneration of language-governing centers of the brain

Table 2

The diagnostic workup for Mr. M

Differential diagnosis	Pertinent workup	Result
Delirium	Level of consciousness was normal (awake, alert)	Ruled out
Degenerative	• Presented subjective and objective findings (chronic timeline, difficulty with speech and multiple cognitive domains) • Brain MRI (***Figure***, ***page 47***) showed cerebral volume loss in frontotemporal region • CSF study results confirmed neurodegenerative etiology (14-3-3, elevated total tau)	Diagnosis favored Alzheimer disease based on CSF biomarker
Psychiatric	Psychiatric evaluation	Ruled out (Note: mood disorder or anxiety can present secondary to dementia)
Vascular	MR angiogram of brain, brain MRI, and carotid Doppler all nonindicative of vascular disease process	Ruled out
Obstructive	Brain imaging did not show any hydrocephalus or obstructive pattern	Ruled out
Traumatic	• No pertinent history of trauma • Brain imaging negative for traumatic process	Ruled out
Neoplastic	No pertinent history, no constitutional signs, no masses found in brain imaging	Ruled out
Infections	• HIV, syphilis, Lyme workup all negative • CSF study indicated nonprion disease • Brain imaging did not show abscesses or signs of infections	Ruled out
Demyelinating	• Neurologic physical exam unremarkable • Brain MRI negative for white matter lesions	Ruled out
Autoimmune	Autoimmune workup (blood, CSF) was negative	Ruled out
Drugs/toxins/ medications	• Urine drug screen was negative and no history of substance abuse • Not on usual suspect medications and aripiprazole serum level was subtherapeutic • Heavy metal study was negative	Ruled out
Metabolic/endocrine/ vitamin deficiency	• Normal electrolytes on basic metabolic panel • Normal TSH and free T4 • Normal B1, B12	Ruled out

HIV: human immunodeficiency virus; TSH: thyroid-stimulating hormone

Clinical Point

PPA can be mistaken for a primary psychiatric disorder such as depression or anxiety

of evaluations by various specialists before a diagnosis was confirmed.

The initial phase of PPA can present as a diagnostic challenge because patients can have difficulty articulating their cognitive and language deficits. PPA can be commonly mistaken for a primary psychiatric disorder such as MDD or anxiety, which can further delay an accurate diagnosis and treatment. Special attention to the mental status exam, close observation of the patient's language, and assessment of cognitive abilities using standardized screenings such as the MoCA or Mini-Mental State Examination can be helpful in clarifying the diagnosis. It is also important to rule out developmental

Table 3

Major variants of primary progressive aphasia

Nonfluent/agrammatic (PPA-G) speech • Abnormal message production, including grammar, structure • Effortful speech, word-finding hesitations • Impaired comprehension (but single word preserved) • Impaired repetition Cognitive/behavioral • Dysexecutive, orofacial > limb apraxia Associated neurologic • Parkinsonism, PSP, CBS, some MND Affected neuroanatomy • Lei anterior perisylvian, subcortical Pathology • FTLD with tauopathy most common • FTLD-TDP (TDP-43 inclusions)	**Logopenic (PPA-L) speech** • Word retrieval impairment causing fluency problem and anomia • Circumlocutions and phonemic paraphasia • Grammar and comprehension preserved • Repetition preserved Cognitive/behavioral • Reduced digit span, limb apraxia, acalculia, visuospatial agnosia Associated neurologic • Myoclonus Affected neuroanatomy • Lei perisylvian, early TPJ Pathology • Usually Alzheimer disease • Rarely FTLD
Mixed (PPA-M) speech • Impaired word comprehension, grammar Cognitive/behavioral • Can be variable, from dysexecutive to apraxia to none Associated neurologic • Variable, from parkinsonism, PSP, CBS, MND, to none Affected neuroanatomy • Usually inferior frontal gyrus, anterior temporal lateral Pathology • Variable and uncertain due to too few cases examined in autopsy	**Semantic (PPA-S) speech** • Single word comprehension and object naming are impaired • Grammar and repetition are preserved • Speech is vague and may contain semantic paraphasia and circumlocution Cognitive/behavioral • Prosopagnosia, visual agnosia, other agnosia • Disinhibition, lack of empathy, obsessions Associated neurologic • Usually none Affected neuroanatomy • Lei > right anterior temporal lateral Pathology • Usually FTLD-43 (type C); Pick's disease

CBS: corticobasal syndrome; FTLD: frontotemporal lobar degeneration; MND: motor neuron disease; PPA: primary progressive aphasia, PSP: progressive supranuclear palsy; TPJ: temporal parietal junction

Source: Reference 4

problems (eg, dyslexia) and hearing difficulties, particularly in older patients.[4]

TREATMENT Adjusting the medication regimen

The neurologist completes additional examinations to rule out causes of rare neurodegenerative disorders, including CSF autoimmune disorders, Creutzfeldt-Jakob disease, and Alzheimer disease (AD) (***Table 4***, ***page 46***). Mr. M continues to follow up with his outpatient psychiatrist and his medication regimen is adjusted. Aripiprazole and buspirone are discontinued, and duloxetine is titrated to 60 mg twice a day. During follow-up visits, Mr. M discusses his understanding of his neurologic condition. His concerns shift to his illness and prognosis. During these visits, he continues to deny suicidality.

What is the most appropriate psychiatric management for Mr. M?

a) Psychoeducation
b) Discharge Mr. M because his anxiety is based on a neurologic condition

continued

Clinical Point

A mental status exam, close observation of language, and assessment of cognitive abilities can help clarify a diagnosis of PPA

Table 4

Mr. M's neurodegenerative workup results

Condition	Results		Comments
Autoimmune, CSF	No informative autoantibodies detected		Rules out autoimmune disease
Creutzfeldt-Jakob disease	CSF RT-QUIC	Negative	Rules out Creutzfeldt-Jakob disease
	T-tau	598 pg/mL (ref 0 to 1,149 pg/mL)	Indirect markers of neurodegenerative disease
	14-3-3 gamma	5,139 AU/mL (ref <30 to 1,999 AU/mL)	
Alzheimer disease	A-beta 42	334.6 pg/mL	Not consistent with Alzheimer disease: P-tau <54 pg/mL and ATI >1.2 Borderline: P-tau 54 to 68 pg/mL and/or ATI 0.8 to 1.2 Alzheimer disease: P-tau >68 pg/mL and ATI <0.8
	T-tau	559.7 pg/mL	
	P-tau	71 pg/mL	
	ATI	0.37	

ATI: A-beta 42/T-tau index; CSF RT-QUIC: cerebrospinal fluid real-time quaking-induced conversion; P-tau: phosphorylated tau; ref: reference range; T-tau: total tau

Clinical Point

Early identification and accurate diagnosis of PPA is critical to avoid unnecessary exposure to medications

c) Refer to Psychotherapy
d) Collaborate with Neurology and family
e) Ongoing medication management for anxiety
f) A, C, D, and E

The authors' observations

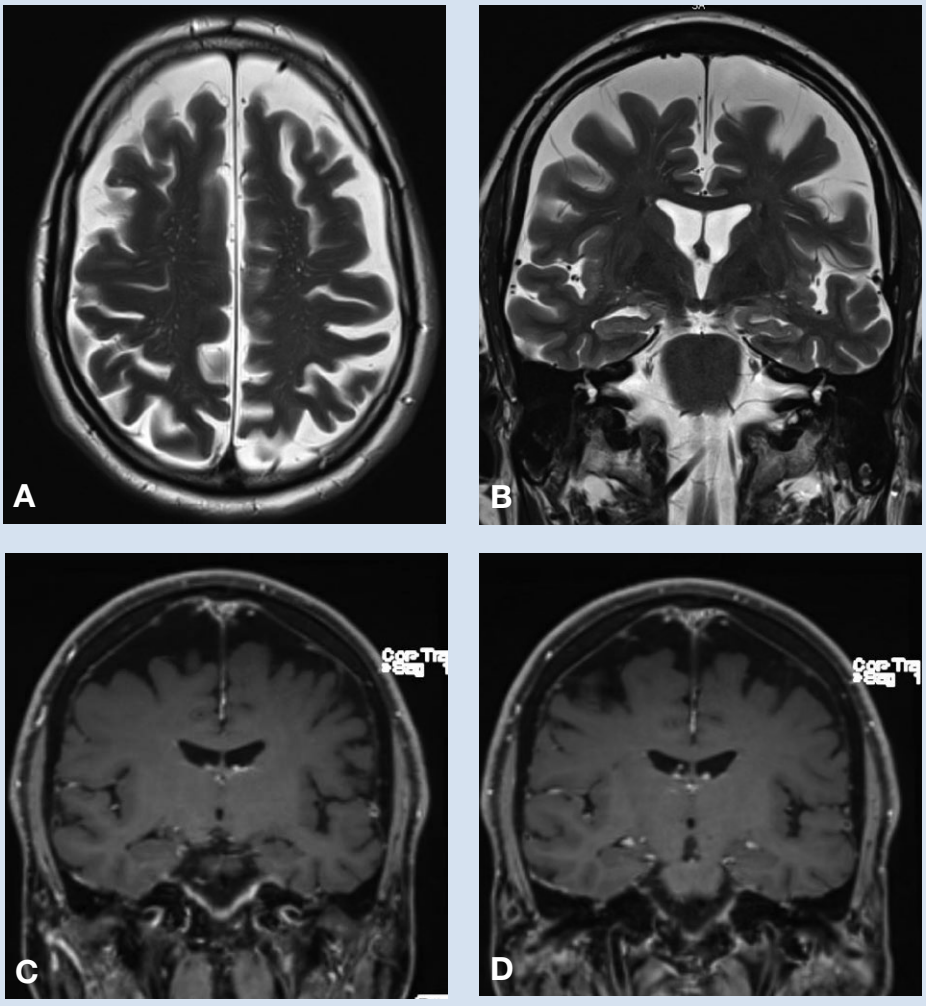
Mr. M's neurodegenerative workup identified an intriguing diagnostic challenge. A repeat brain MRI (***Figure, page 47***) showed atrophy patterns suggestive of frontotemporal lobar degeneration (FTLD). On the other hand, his CSF ATI (A-beta 42/T-tau index, a value used to aid in the diagnosis of AD) was <1, suggesting early-onset AD.[5,6] Although significant advances have been made to distinguish AD and FTLD following an autopsy, there are still no reliable or definitive biomarkers to distinguish AD from FTLD (particularly in the early stages of FTLD). This can often leave the confirmatory diagnosis as a question.[7]

A PPA diagnosis (and other dementias) can have a significant impact on the patient and their family due to the uncertain nature of the progression of the disease and quality-of-life issues related to language and other cognitive deficits. Early identification and accurate diagnosis of PPA and its etiology (ie, AD vs FTLD) is important to avoid unnecessary exposure to medications or the use of polypharmacy to treat an inaccurate diagnosis of a primary psychiatric illness. For example, Mr. M was being treated with 3 psychiatric medications (aripiprazole, buspirone, and duloxetine) for depression and anxiety prior to the diagnosis of PPA.

Nonpharmacologic interventions can play an important role in the management of patients with PPA. These include educating the patient and their family about the diagnosis and discussions about future planning, including appropriate social support, employment, and finances.[4] Pharmacologic interventions may be limited, as there are currently no disease-modifying treatments for PPA or FTLD. For patients with nonfluent PPA or AD, cholinesterase inhibitors such as donepezil or *N*-methyl-D-aspartate receptor antagonists such as memantine may be utilized, though benefits can be

Figure

Mr. M's brain MRI with contrast



Diffuse cerebral volume loss is disproportionately greater in the frontal and anterior lobes without associated disproportionate hippocampal volume loss. A: Series 9, #25, Axial T2. B: Series 15, #22, Coronal T2. C: Series 20, #101, Coronal T1. D: Series 20, #104, Coronal T1.

limited.[4] Recent research has explored the role of transcranial magnetic stimulation and suggest short-term benefits, as have case reports of behavioral interventions targeting language.[8]

Psychiatrists should continue to treat patients with PPA for comorbid anxiety or depression, with appropriate medications and/or supportive therapy to guide the patient through the process of grief. Assessing for suicide risk is also important in patients diagnosed with dementia. A retrospective cohort study of patients age ≥60 with a diagnosis of dementia suggested that the majority of suicides occurred in those with a new dementia diagnosis.[9] End-of-life decisions such as advanced directives should be made when the patient still

Clinical Point

Pharmacologic options are limited because there are no disease-modifying treatments for PPA or FTLD

Related Resources

- Primary progressive aphasia. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/8541/primary-progressive-aphasia
- Moller MD, Parmenter BA, Lane DW. Neuropsychological testing: A useful but underutilized resource. Current Psychiatry. 2019;18(11):40-46,51.

Drug Brand Names

Aripiprazole • Abilify	Duloxetine • Cymbalta
Donepezil • Aricept	Memantine • Namenda

Clinical Point

Patients with a new dementia diagnosis should be assessed for suicide risk

has legal capacity, ideally as soon as possible after diagnosis.[10]

OUTCOME Remaining engaged in treatment

Mr. M continues to follow-up with the Neurology team. He has also been regularly seeing his psychiatric team for medication management and supportive therapy, and his psychiatric medications have been optimized to reduce polypharmacy. During his sessions, Mr. M discusses his grief and plans for the future. Despite his anxiety about the uncertainty of his prognosis, Mr. M continues to report that he is doing reasonably well and remains engaged in treatment.

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Bottom Line

Patients with primary progressive aphasia and rare neurodegenerative disorders may present to an outpatient or emergency setting with symptoms of anxiety and confusion. They are frequently misdiagnosed with a primary psychiatric disorder due to the nature of cognitive and language deficits, particularly in the early stages of the disease. Paying close attention to language and conducting cognitive screening are critical in identifying the true cause of a patient's symptoms.