REVIEW ARTICLE

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Reversible Dementias

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ABSTRACT

PURPOSE OF REVIEW: This article describes the clinical features that suggest a reversible cause of dementia.

RECENT FINDINGS: Substantial variability exists in the presenting features and clinical course of patients with common neurodegenerative causes of dementia, but the response to available therapies and eventual outcomes are often poor. This realization has influenced the evaluation of patients with dementia, with diagnostic approaches emphasizing routine screening for a short list of potentially modifiable disorders that may exacerbate dementia symptoms or severity but rarely influence long-term outcomes. Although a standard approach to the assessment of dementia is appropriate in the vast majority of cases, neurologists involved in the assessment of patients with dementia must recognize those rare patients with reversible causes of dementia, coordinate additional investigations when required, and ensure expedited access to treatments that may reverse decline and optimize long-term outcomes.

SUMMARY: The potential to improve the outcome of patients with reversible dementias exemplifies the need to recognize these patients in clinical practice. Dedicated efforts to screen for symptoms and signs associated with reversible causes of dementia may improve management and outcomes of these rare patients when encountered in busy clinical practices.

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INTRODUCTION

The vast majority of dementia cases encountered in North American clinics are attributable to neurodegenerative diseases, including Alzheimer disease (AD), Lewy body disease, frontotemporal lobar degeneration, and cerebrovascular disease. Although the clinical presentation and longitudinal course of these disorders varies, the long-term prognosis is uniform: cognitive deficits, disability, and functional impairment gradually progress, leading to death. Accordingly, the standard diagnostic assessment focuses on screening for common, potentially modifiable comorbidities and disorders that may worsen or cause cognitive impairment (ie, depression, vitamin B_{12} deficiency, and hypothyroidism), and rare structural causes that may necessitate alternative treatment (eg, subdural hematomas, primary or secondary brain tumors).[1] Although this standard approach to assessment is appropriate in the majority of cases, neurologists involved in the diagnosis and management of patients with dementia must recognize the symptoms and signs that suggest a reversible cause of dementia, coordinate additional investigations when required, and ensure expedited access to treatments that may reverse decline and optimize long-term outcomes.

Although truly reversible causes of dementia account for a small proportion of cases in outpatient clinics,[2,3] the potential to dramatically improve the outcome of even a small number of patients justifies the development of diagnostic strategies that promote detection of these rare patients. Even when diagnosis and treatment do not result in complete resolution of symptoms, the potential to modify disease progression and improve quality of life for patients and family members warrants screening for reversible causes of dementia. But how can these patients be identified?

FINDING THE NEEDLE IN THE HAYSTACK

For the busy clinician managing a full clinic schedule, the challenge of identifying the rare patient with a reversible dementia may bring to mind any number of tired analogies connoting futility. Clearly, strategies are needed to promote recognition of patients with potentially treatable causes of dementia. In the clinic, this can be accomplished by implementing a universal approach to dementia assessment that relies upon standard testing[1] and active monitoring for atypical features on history, examination, and investigations that may point to a reversible cause of dementia. Atypical features that may indicate a reversible cause of dementia include the following:

- Rapid unexplained decline in function
- Younger than expected age at symptom onset
- Prominent fluctuations
- Acute or chronic high-risk exposures
- A history of high-risk behaviors (past or present)
- Unexplained or unanticipated findings on the neurologic examination
- Performance on neurocognitive testing that is incongruent with the clinical history

These "red flags" that suggest a reversible dementia are illustrated here through a review of selected cases featuring patients with well-characterized causes of reversible dementia. These representative cases were selected to familiarize the reader with the clinical features and test results that point to a reversible cause of dementia.[3–5]

Red Flag 1: Rapid Unexplained Decline

Potentially reversible causes of rapidly progressive dementia are well recognized in retrospective case series,[6–9] with the prevalence of specific causes varying with patient (eg, age, risk factors[7,10]) and clinic-specific factors (eg, level of care, academic affiliations[11,12]). Accordingly, patients with rapidly progressive dementia warrant an expedited assessment, with the goal of rapidly identifying and remedying reversible causes of and contributors to dementia. Core testing should be obtained in all patients with rapidly progressive dementia, including screening serum studies, neuroimaging (favoring MRI), routine CSF analyses, and EEG. Findings on history and examination and the results of initial testing may justify further testing,[8] or repeat testing, as illustrated in **CASE 11-1**.

Red Flag 2: Younger Than Expected Age at Symptom Onset

Younger than expected age at symptom onset is a well-recognized marker of secondary causes of dementia,[6–8,15] warranting careful evaluation and screening

KEY POINTS

- Neurologists involved in the diagnosis and management of patients with dementia should recognize the symptoms and signs that suggest a reversible cause of dementia.
- Truly reversible causes of dementia account for a small proportion of cases in outpatient clinics.
- Patients with rapidly progressive dementia warrant an expedited assessment, with the goal of rapidly identifying and remedying reversible causes of and contributors to dementia.
- Younger than expected age at symptomatic onset is a well-recognized marker of secondary causes of dementia, warranting careful evaluation and screening for reversible causes.

CASE 11-1

A 57-year-old woman presented to an outpatient tertiary care clinic for the evaluation of rapid cognitive decline developing over 9 months. She was a retired engineer. Her history was notable for long-standing daily stabbing headaches, which were initially intermittent and refractory to a trial of indomethacin. Titration of topiramate coincided with the emergence of cognitive symptoms, including mild forgetfulness and disorientation to date, and increasing fatigue, which persisted despite stopping the medication. Six months before assessment, the patient reported increasing imbalance. A subsequent fall resulted in a right arm fracture, complicated by a pneumothorax, which necessitated hospital admission and surgical management. Serum studies on admission were normal, including thyroid stimulating hormone (TSH), vitamin B_{12} level, and rapid plasma regain (RPR) testing. Brain MRI and EEG were performed to evaluate contributors to cognitive decline; they were considered "normal." Diagnostic lumbar puncture was bland (2 white blood cells/mm^3, protein 32 mg/dL, glucose 67 mg/dL, negative oligoclonal bands, negative infectious studies, negative autoimmune encephalitis panel, and negative cytology).

The patient's headaches and cognitive status improved over the course of her hospital admission, with the patient returning to 80% to 90% of her baseline functioning. However, shortly following discharge, her cognition rapidly declined, resulting in an inability to manage instrumental activities of daily living (ie, bill paying and medication management). The emergence of new dysphagia, with decreasing oral intake, prompted percutaneous enterogastric tube placement. A diagnosis of rapidly progressive dementia of unclear cause was provided, and the patient was encouraged to seek a second opinion concerning the cause.

At the time of her second opinion in a tertiary care memory clinic (3 months following discharge from the hospital), the patient and her husband reported that she had progressive short-term memory loss, fatigue, imbalance, dysphagia, and increasing urinary incontinence requiring a suprapubic catheter. She had no history of trauma, recent international travel, infectious exposures, hallucinations/psychoses, or depressive symptoms.

Performance on the Short Test of Mental Status[13] demonstrated marked impairment in delayed verbal recall (0/4 items) and orientation (3/8 items). On examination, the patient was drowsy and even fell asleep during the evaluation. She had mild hypokinetic dysarthria, with reduced voluntary elevation of the palate and an absent gag reflex. She had no focal signs on motor examination; however, toes were upgoing bilaterally. Reflexes and sensation were intact. She had marked truncal ataxia, impairing independent ambulation.

Given the apparent progression of neurologic deficits, diagnostic brain MRI was repeated (FIGURE 11-1), demonstrating "brain sag," with loss of the suprasellar, quadrigeminal, and prepontine cisterns, flattening of the pons, and slight inferior displacement of the cerebellar tonsils consistent with intracranial hypotension without associated pachymeningeal enhancement. The cause of her rapidly progressive dementia was attributed to an occult CSF leak.[14]

The patient underwent an empiric fluoroscopically guided two-level low thoracic and high lumbar interlaminar epidural blood patch, with immediate resolution of her headaches. One month later, she reported being "100% back to normal."

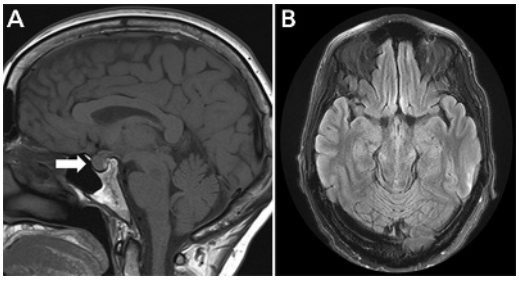

FIGURE 11-1
Imaging of the patient in CASE 11-1 with rapidly progressive cognitive decline and daily headaches. Sagittal noncontrast T1-weighted (*A*) and axial fluid-attenuated inversion recovery (FLAIR) (*B*) MRIs demonstrate "brain sag," with loss of the suprasellar, quadrigeminal, and prepontine cisterns, flattening of the pons, and slight inferior displacement of the cerebellar tonsils consistent with intracranial hypotension. The pituitary gland is prominent, with a convex superior border (*arrow*). Postcontrast T1-weighted images (*not shown*) did not reveal pachymeningeal enhancement.

COMMENT

The patient in this case meets accepted definitions of rapidly progressive dementia,[12,15] with cognitive impairment evolving over months. In retrospect, the clinical history included several clues that pointed to a reversible dementia, including the rapid unexplained progression of symptoms and the apparent resolution of symptoms during her hospitalization (during which she was immobilized and supine, improving her CSF leak). Although initial testing failed to establish the diagnosis, continued decline justified the need for repeat testing, which led to the correct diagnosis and treatment. Diffuse pachymeningeal enhancement is commonly reported in association with spontaneous intracranial hypotension. However, as this case illustrates, the finding is not required for the diagnosis. In a cross-sectional study enrolling 99 patients with spontaneous hypotension, pachymeningeal enhancement was detected in 83% of cases.[16] In the absence of such findings, the clinical diagnosis may be supported by detection of radiologic features of "brain sagging" (downward sloping of the third ventricular floor, observed in 61%), venous distension (convex inferior border of the dominant transverse venous sinus at its midportion, observed in 75%), or myelographic evidence of a CSF leak (in 55% of cases).

for reversible causes (even more so when younger age at symptomatic onset occurs together with rapidly progressive deficits). Although more likely in younger women (particularly women of childbearing age), autoimmune encephalitis is recognized in patients of all ages and both sexes.[17,18] In addition to "core testing," as noted earlier, the high potential for reversibility justifies testing the CSF and blood for autoantibodies known to associate with autoimmune encephalitis. Autoantibody testing should be considered in all patients meeting criteria for possible autoimmune encephalitis (eg, subacute onset of memory deficits, mental status change, or psychiatric symptoms, with at least one of the following: new focal central nervous system findings, unexplained seizures, CSF pleocytosis, or MRI features suggestive of encephalitis).[18] Testing should likewise be considered in patients 60 years of age or older with characteristic central nervous system syndromes (including unexplained faciobrachial dystonic seizures; gait instability, brainstem dysfunction, and sleep disorder; or subacute confusion, memory loss, and behavioral change), even if neuroimaging and CSF findings do not suggest an underlying autoimmune disease.[19] In the United States, testing is available via several commercial laboratories.

As patients age, detection of reversible causes of dementia may be challenged by the rising prevalence of more typical neurodegenerative dementing illnesses, including primary progressive aphasia[20] and Creutzfeldt-Jakob disease (CJD) (**CASE 11-2**).[21] In such situations, the astute clinician is advised to weigh all available evidence in pursuit of the most accurate and appropriate diagnosis. When diagnostic uncertainty persists, additional disease-specific biomarkers may help to clarify the diagnosis (eg, CJD-specific biomarkers[22–25]). In a similar fashion, empiric treatment of autoimmune encephalitis may be considered when appropriate, with close monitoring for a sustained objective response. Many causes of autoimmune encephalitis are treatment responsive, with long-term outcomes largely dependent upon early recognition and timely provision of appropriate immunosuppressant treatments.[18,26–28]

Red Flag 3: Prominent Fluctuations

Prominent fluctuations can be seen in dementia with Lewy bodies but can also be a manifestation of reversible dementias, as illustrated in **CASE 11-1** and **CASE 11-2**. Beyond the reversible dementias highlighted in these cases, toxic-metabolic disturbances,[30] medications,[31] untreated sleep disorders (including obstructive sleep apnea),[32] and psychiatric illnesses may all present with prominent fluctuations in cognition.

Rarer reversible causes of dementia may also warrant consideration when supported by history and examination, including transient epileptic amnesia. Transient epileptic amnesia is associated with acute and transient memory disruptions lasting minutes (typically less than an hour) that are often accompanied by fluctuations in attention and amnesia.[33] Although the symptomatic expression may lead to an initial diagnosis of transient global amnesia, the frequency of attacks (recurrent attacks occurring a median of 12 times per year) and brief duration (median duration 30 to 60 minutes) commonly distinguish patients with transient epileptic amnesia.[34,35] Also unique to transient epileptic amnesia, patients may experience unusual forms of interictal memory impairment, including accelerated loss of newly acquired memories over days to weeks despite normal retention at standard (ie, about

30-minute) intervals (sometimes called *accelerated long-term forgetting*),[36] and autobiographical amnesia.[37] The most important indicators to the epileptic origin of acute memory impairment are the frequency of occurrence and the short duration of the attacks.[38] Transitory sleep states remain a high-risk period for seizures[39]; accordingly, a history of rhythmic nocturnal movements (not suggestive of dream enactment behaviors) or tongue biting, particularly following sleep onset or waking, should prompt consideration of an epileptic etiology. EEG may be helpful in establishing the diagnosis of transient epileptic amnesia, with epileptiform abnormalities or nonspecific focal slow waves detected in many affected patients.[35] However, a normal EEG does not exclude the diagnosis. In such cases, prolonged EEG may increase the diagnostic yield (**CASE 11-3**), particularly when sufficient sleep-wake periods are captured. Episodes of transient epileptic amnesia (ie, seizures) usually respond promptly to treatment with drugs used for the treatment of focal epilepsies, although interictal impairment may persist.[33,35,38]

Red Flag 4: High-risk Exposures

Careful screening for high-risk medications (including over-the-counter medications[31]), drugs, and toxins is imperative when making a new diagnosis of dementia. Narcotic, benzodiazepine, and anticholinergic medications are common precipitants of cognitive decline. Patients with other active health issues may be particularly susceptible to the cognition-impairing effects of medications. Anticholinergic medications may be especially problematic in patients with AD-associated degeneration of acetylcholine-producing basal forebrain cells (**CASE 11-4**).[41] Anticholinergic medications may even contribute to the progression of neurodegenerative pathology, raising concerns about their continued use in at-risk patient populations.[42]

Excessive alcohol consumption represents another prevalent high-risk exposure, with an established relationship with malnutrition in general and thiamine (ie, vitamin B_1) deficiency in particular, leading to Wernicke encephalopathy. Accordingly, patients with an active or recent history of alcohol abuse should be considered at risk for the acute and chronic sequelae of excessive consumption. Thiamine is an essential vitamin critical to glucose metabolism and, by extension, brain function. Without thiamine, glucose is metabolized through less efficient anaerobic pathways, leading to acidosis of periventricular structures (ie, thalami, mammillary bodies, ocular motor nuclei, cerebellar vermis) and to the cardinal manifestations of Wernicke encephalopathy: altered mental status (eg, confusion, encephalopathy), ocular abnormalities (eg, nystagmus, ophthalmoplegia), and cerebellar dysfunction (eg, gait disturbance, ataxia).[43–46] If promptly recognized, the life-threatening effects of thiamine deficiency may be counteracted by administration of high doses of parenteral thiamine (**CASE 11-5**).[47,48] It is especially critical that thiamine be provided before refeeding or parenteral administration of glucose-containing substances, as carbohydrate loading may increase thiamine utilization, provoking or exacerbating clinical manifestations of Wernicke encephalopathy.[49] If overlooked, the consequences of thiamine deficiency may become irreversible, leading to death or severe cognitive impairment (ie, Korsakoff syndrome).[43,50] The high potential for response to appropriate treatment, high cost of delayed diagnosis, and low risk of complications associated with parenteral thiamine supplementation justify expedited treatment in all patients with

KEY POINTS

- Autoantibody testing should be considered in all patients meeting criteria for possible autoimmune encephalitis and in patients 60 years of age or older with characteristic central nervous system syndromes, even if neuroimaging and CSF findings do not suggest an underlying autoimmune disease.
- Toxic-metabolic disturbances, medications, untreated sleep disorders (including obstructive sleep apnea), and psychiatric illnesses may all present with prominent fluctuations in cognition.
- Transient epileptic amnesia is associated with acute and transient memory disruptions lasting minutes (typically less than an hour) that are often accompanied by fluctuations in attention.
- Anticholinergic medications may be especially problematic in patients with Alzheimer disease–associated degeneration of acetylcholine-producing basal forebrain cells.
- If promptly recognized, the life-threatening effects of thiamine deficiency may be counteracted by administration of high doses of parenteral thiamine.
- The high potential for response to appropriate treatment, high cost of delayed diagnosis, and low risk of complications associated with parenteral thiamine supplementation justify expedited treatment in all patients with possible nutritional deficiency and features consistent with Wernicke encephalopathy.

CASE 11-2

A 48-year-old woman with a history of degenerative disk disease causing chronic back pain and remote menometrorrhagia (managed with hysterectomy and bilateral salpingo-oophorectomy), presented with gradual-onset progressive word-finding difficulty. Despite her symptoms, she continued to maintain function at home, including bill paying, home maintenance, and cooking. Two months after symptom onset, she reported "not feeling well," with unexplained "anxiety and worry" and new frontal headaches. Her husband noted increasing paraphasic errors, with intermittent confusion of word meaning and object use. Three months after the first symptoms appeared, her level of consciousness began to fluctuate, with periods of profound disorientation. One morning, her husband found her unable to speak, necessitating emergent assessment and admission to her local hospital under her primary care physician. At that time, extensive serologic testing was normal. Brain MRI demonstrated normal parenchyma, with extracranial findings suggestive of sinusitis. Routine CSF studies confirmed a lymphocytic pleocytosis (20 nucleated cells/mm^3), without evidence of viral or bacterial infection. Her primary care physician diagnosed the patient with chronic sinusitis, despite the absence of typical symptoms or signs attributable to sinusitis. Subsequently she was discharged home on oral antibiotics and a prednisone taper (40 mg/d, tapering over several weeks).

Two weeks following discharge, she had resumed many of her activities. Her headaches, anxiety, and mood symptoms had improved. The word-finding difficulties persisted but were less bothersome. Unfortunately, 3 months later (6 months from symptom onset), she experienced new-onset dysarthria and right-hand clumsiness. She began to forget to take her medications and pay the bills. She lost the ability to write checks, appearing as though she had forgotten how to hold a pen.

She presented to the emergency department of an academic hospital and was promptly admitted to the neurology service. Comprehension was intact at the time of admission, with impaired fluency and mild dysarthria. Her speech was agrammatic, with frequent phonemic paraphasias, and repetition was impaired. Cranial nerves were normal. Mild pyramidal pattern weakness was evident in the right upper extremity, with slowing of rapid alternating movements and pronator drift. Primary sensation was normal; however, she was unable to identify a ring when placed in her right hand (astereognosis). There was mild ideomotor apraxia in her right hand. She had no ataxia, gait imbalance, or involuntary movements. Bedside cognitive testing confirmed deficits in short-term memory (4/10 recall of a 10-word list after 5-minute delay), verbal fluency (impaired animal naming), and performance on speeded tasks (eg, unable to complete Trail Making Test Part B in the 180 seconds allotted).

Diagnostic tests were repeated, including brain MRI, and revealed increased T2 signal within the cortical ribbon of the left hemisphere, with associated diffusion restriction in a pattern suggestive of possible sporadic Creutzfeldt-Jakob disease (CJD) (FIGURE 11-2).[29] CSF studies again showed evidence of inflammation, with 35 nucleated cells/mm^3 (87% lymphocytes) and 10 CSF-specific oligoclonal bands. Testing for disease-associated autoantibodies was performed in blood and CSF (autoimmune encephalitis panel). IgG autoantibodies against central *N*-methyl-D-aspartate (NMDA) receptors were identified in the CSF (titer of 1:32), establishing the diagnosis of NMDA receptor encephalitis. No tumor was identified on whole-body fludeoxyglucose positron emission tomography (FDG-PET).

Pulse methylprednisolone (250 mg IV 4 times a day for 5 days) and IV immunoglobulin (IVIg; 2 g/kg divided over 5 days) were administered, with an excellent response. The patient was discharged home following completion of her treatment.

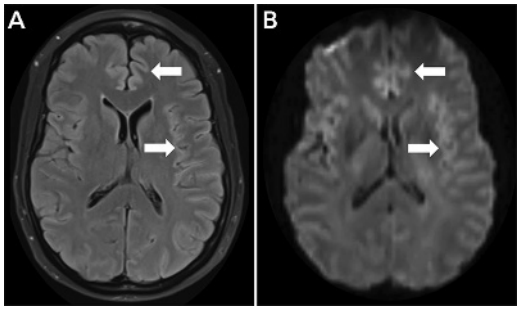

FIGURE 11-2
Imaging of the patient in CASE 11-2 with progressive aphasia and increasing confusion. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows increased signal throughout the cortical ribbon of the left frontal and parietal areas (*arrows*) associated with mild cortical edema. *B*, Axial diffusion-weighted MRI shows diffusion restriction corresponding to the areas of increased FLAIR signal (*arrows*).

COMMENT

This patient presented with progressive expressive aphasia and right-sided apraxia and astereognosis, implicating left-sided cortical dysfunction. The brain MRI demonstrated corresponding T2-hyperintense changes within the cortical ribbon, concerning for sporadic CJD. While primary progressive aphasia and CJD may manifest in the fifth decade of life, other etiologies, including autoimmune encephalitis, are more common in this age group and better explain the overall presentation and findings (including CSF leukocytosis) in this case. Ultimately, detection of CSF NMDA receptor IgG autoantibodies confirmed the clinical diagnosis of NMDA receptor encephalitis and ensured timely provision of appropriate immunomodulatory treatments. Two months later, she had resumed all her normal daily activities, with residual symptoms of mild difficulties with verbal articulation. Five months later, she was cognitively normal, with improved performance on cognitive testing.

possible nutritional deficiency and features consistent with Wernicke encephalopathy.[47,48]

Red Flag 5: High-risk Behaviors (Past and Present)

Before 2001, testing for neurosyphilis was routinely recommended in patients with a new diagnosis of dementia, recognizing the potential for latent infection to manifest with reversible cognitive impairment.[51] The recommendation not to routinely screen for syphilis in more recent guidelines acknowledges the

CASE 11-3

A 59-year-old man with hypertension and coronary artery disease presented with a 2-year history of intermittent forgetfulness and inattentiveness, culminating in lapses in bill paying, occasional way-finding difficulty, and job loss. The patient's wife affirmed the inconsistent nature of symptoms, with no identified triggers or exacerbating/alleviating factors. The patient had no symptoms of excessive daytime sleepiness, changes in personality, or low mood. Medications were limited to an antiplatelet drug, a statin, and an antihypertensive agent.

Neurologic examination and performance on bedside cognitive testing (Mini-Mental State Examination [MMSE][40] score of 30) were normal. Serum vitamin B_{12} and thyroid function tests were normal. Brain MRI confirmed mild global atrophy, with associated periventricular T2 hyperintensity and a chronic infarct within the right corona radiata (FIGURE 11-3A).

One year later, he reported progression of forgetfulness with increasing geographic disorientation, word-finding difficulty, and difficulty operating devices and appliances (eg, dialing the phone, programming the microwave). His wife described two distinct episodes associated with confusion (blank staring, decreased responsiveness) and incoherent speech that lasted 5 minutes without associated motor abnormalities. Neurologic examination was again normal. Performance on the MMSE declined (28/30) but remained within the normal range. Given the progression of deficits, he was diagnosed with very mild dementia and started on donepezil. A routine EEG was normal.

His cognitive symptoms continued over successive years, with short-term memory loss, word-finding difficulty, and way-finding difficulty beginning to interfere with activities of daily living. His wife described him as an unsafe driver who frequently missed red lights and stop signs. Driving cessation was recommended following an at-fault accident. Seven years following initial symptom onset (at age 65), he returned to clinic for the assessment of recurrent "spells," characterized by abrupt-onset memory loss and confusion, now lasting 20 to 30 minutes each and occurring several times per week. His wife also reported he had severe nightmares, with rhythmic movements while sleeping and tongue biting. Neurologic examination was again normal, with comparable performance on the MMSE (27/30). Brain MRI was unchanged. Prolonged video-EEG

decreasing prevalence of this disease in patients without traditional risk factors.[1] Syphilis testing should still be considered in patients with dementia from endemic regions within and beyond the United States[52] and in those with a past or present history of high-risk behaviors, including individuals with multiple sexual partners, men who have sex with men, IV drug users, and persons with other sexually transmitted infections. Even a remote history of high-risk behaviors may place a patient at risk and justify further evaluation (CASE 11-6).

demonstrated occasional epileptiform potentials over the right temporal leads (FIGURE 11-3B).

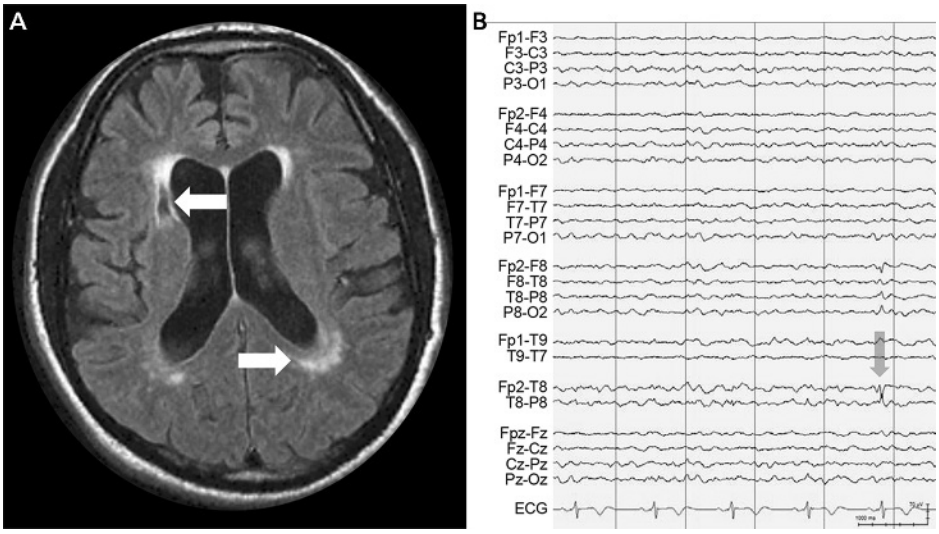

FIGURE 11-3

Imaging of the patient in CASE 11-3 with intermittent memory problems. *A,* Axial fluid-attenuated inversion recovery (FLAIR) MRI demonstrates mild diffuse volume loss with increased periventricular hyperintense signal (*bottom arrow*) and a well-demarcated area of established infarction (*top arrow*), consistent with small vessel ischemic disease. *B,* Spike-and-wave discharges were captured during a routine awake EEG (bipolar montage; 70-Hz high-frequency filter, 1.6-Hz low-frequency filter), with phase reversal over the right temporal leads (*arrow*), suggestive of a focal epileptiform discharge. Bar graph (*lower right*) indicates recording amplitude and time scales.

COMMENT

The detection of prominent fluctuations in symptoms and performance on cognitive tests in this case raise the possibility of a potentially reversible cause of dementia. Although initial EEG did not show epileptiform potentials, extended monitoring confirmed intermittent epileptiform discharges, supporting the diagnosis of transient epileptic amnesia and enabling effective treatment. Levetiracetam was titrated to 1000 mg orally 2 times a day, with complete resolution of spells and improvement in cognition.

An immunocompromised state, whether inherited or acquired, represents an additional high-risk "exposure," increasing the chances of reactivation of latent infection in previously exposed patients. Accordingly, testing for neurosyphilis (along with other opportunistic infections) should be performed in any patient with dementia with a new or established diagnosis of human immunodeficiency virus (HIV) and in individuals on chronic immunosuppressant therapies. Neuroimaging findings consistent with cerebral gummas and CSF profiles showing unexplained mononuclear pleocytosis,

CASE 11-4

A 71-year-old woman returned to clinic for follow-up of logopenic variant primary progressive aphasia. Five years earlier, she had presented with gradually progressive difficulties with verbal expression, necessitating retirement from her position as an administrative assistant. One year ago, she had reported very mild short-term memory deficits. She scored 27/30 on the Mini-Mental State Examination (MMSE),[40] with 3/3 delayed verbal recall. An amyloid positron emission tomography (PET) scan (completed as part of a study protocol) demonstrated diffuse cortical tracer retention, supporting a diagnosis of Alzheimer disease as the cause of her dementia. She was maintained on donepezil (10 mg orally every morning) and escitalopram (5 mg orally every morning) for low mood, with appropriate management of comorbid vascular risk factors. In the 6 months preceding her reassessment, the patient's husband reported a precipitous decline in her verbal output, with worsening memory deficits and gait instability leading to multiple falls.

Neurologic examination revealed mild length-dependent sensory loss in the lower extremities and a broad-based unsteady gait, without focal deficits. She scored 23/30 on the MMSE with 1/3 delayed verbal recall, impaired repetition, and difficulty spelling the word *world* backward. A comprehensive review of medications uncovered prescriptions for amitriptyline (for neuropathic pain) and oxybutynin (for urge incontinence), both initiated within the past 6 months. Both anticholinergic medications were stopped. Gabapentin was prescribed for the management of mild neuropathic pain, and the patient was referred to urology for intravesicular botulinum toxin injections to manage urge incontinence.

COMMENT

The patient in this case had biomarker (amyloid PET) evidence supportive of cerebral amyloidosis and a corresponding clinical diagnosis of logopenic variant primary progressive aphasia due to Alzheimer disease. Despite the diagnosis of an irreversible neurodegenerative dementia, additional changes in clinical status warranted assessment for potential reversible contributors to cognitive decline, including anticholinergic medications. One month following cessation of the offending medications, the patient's gait, postural stability, performance on cognitive testing (MMSE score of 27/30, with 3/3 on delayed verbal recall), and overall quality of life had substantially improved.

elevated protein, and elevated oligoclonal bands should prompt consideration of neurosyphilis.[54,55] Further screening for other sexually transmitted or opportunistic infections (eg, HIV, cryptococcal meningitis, and JC virus) should also be considered in any patient with an active or past history of neurosyphilis.

Red Flag 6: Unexplained/Unanticipated Findings on the Neurologic Examination

The insidious onset and slow progression of short-term memory deficits in an older patient most commonly connote a diagnosis of symptomatic AD.[56] However, the neurologic examination should be largely normal in patients with amnestic AD, owing to early sparing of homotopic (motor/sensory) cortices by AD neuropathologic change.[57] By extension, therefore, the discovery of abnormal neurologic findings—whether subtle or pronounced—warrants consideration of atypical causes of dementia, including reversible causes.

The detection of progressive memory loss, gait apraxia, and urinary incontinence may be associated with a diagnosis of normal pressure hydrocephalus (NPH), justifying further evaluation. It is important to note, however, that the detection of the triad of features is neither required nor sufficient to establish the diagnosis of NPH; NPH may occur in patients with one or two features of the triad, or findings associated with NPH may arise secondary to any condition leading to stretching/damage of the frontal periventricular white matter fibers (regardless of intraventricular pressure). Accordingly, detection of features of the triad warrants screening for secondary causes of NPH (eg, history of subarachnoid hemorrhage, traumatic brain injury, or meningitis) in addition to high-pressure hydrocephalus (eg, ventricular outflow obstruction, ventricular entrapment) and other relevant etiologies (eg, dorsal midbrain or thalamic lesions, strategic infarctions, moderate to severe periventricular leukoencephalopathy owing to small vessel ischemia). For more information, refer to the article "Normal Pressure Hydrocephalus" by Neill R. Graff-Radford, MBBCH, FRCP, FAAN, and David T. Jones, MD,[58] in this issue of *Continuum*. Other abnormalities that would necessitate an urgent evaluation include localizing signs implicating an underlying focal lesion, whether vascular, neoplastic, demyelinating/inflammatory, or other (eg, subdural hematoma).

Red Flag 7: Incongruent Cognitive Testing

Performance on cognitive testing that is substantially better or worse than expected from the clinical history should trigger investigations for reversible causes of dementia. Initial screening should focus on detection of conditions known to compromise encoding and recall of learned information, resulting in inconsistent or widely fluctuating performance on tasks or subjective symptoms. Special attention should be paid to screening for mood disorders, sleep dysfunction, medication use (including medications reviewed in the section Red Flag 4: High-risk Exposures), and sensory impairment (especially hearing loss), owing to the high prevalence of each of these disorders, their potential to interfere or disrupt sustained attention, and their potential treatment responsiveness.

KEY POINTS

- Syphilis testing should be considered in patients with dementia from endemic regions within and beyond the United States and in those with a past or present history of high-risk behaviors.
- A thorough history, including screening for past or present high-risk behaviors, is imperative when investigating patients with unusual presentations of cognitive impairment.
- The discovery of abnormal neurologic findings—whether subtle or pronounced—warrants consideration of atypical causes of dementia, including reversible causes.
- Detection of features of the triad of progressive memory loss, gait apraxia, and urinary incontinence warrants screening for causes of normal pressure hydrocephalus and high-pressure hydrocephalus.
- Performance on cognitive testing that is substantially better or worse than expected from the clinical history should trigger investigations for reversible causes of dementia.
- Sleep dysfunction, attributable to obstructive sleep apnea or other causes, is increasingly identified as a contributor to cognitive impairment.

Sleep dysfunction, attributable to obstructive sleep apnea or other causes, is increasingly identified as a contributor to cognitive impairment. Recent studies even suggest that sleep disruption may affect amyloid homeostasis, with implications for the development of AD.[59,60] These associations emphasize the importance of routinely evaluating patients with cognitive symptoms for comorbid sleep pathology. Particular attention should be paid to patients with physical attributes that place them at the highest risk of clinically significant obstructive sleep pathology, including increased neck circumference (>40 cm), body mass index greater than 35 kg/m^2,

CASE 11-5

A 47-year-old woman presented to the emergency department with new seizures and altered mental status. Her past medical history was notable for excessive daily alcohol consumption and poor nutritional status, with an 18-kg (40-lb) weight loss over the preceding year. Her family affirmed a 3-month history of increasing forgetfulness, resulting in missed appointments and an inability to manage bill paying. The week before her presentation, she had enrolled in a medically supervised alcohol cessation program, initiated chlordiazepoxide and disulfiram, and abruptly stopped consuming alcohol. On the day of admission, she was involved in a minor motor vehicle accident. Immediately following the accident, she had a witnessed loss of consciousness, with convulsions. Emergency medical services were called, and she was transferred to the hospital.

On arrival, the patient was alert and oriented, and her general physical examination was normal. Her speech was pressured and tangential. Neurologic examination showed bilateral end-gaze nystagmus, with hypometric saccades in all directions. Motor bulk, tone, and power were normal. Reflexes were normal, and toes were downgoing. Ataxia was noted on finger-to-nose and heel-to-shin testing. Gait was broad-based and unsteady. Bedside cognitive testing confirmed impaired orientation (oriented to person only), attention (eg, unable to complete Trail Making Test Part A in the 180 seconds allotted), and short-term recall (2/10 recall of a 10-word list after 5-minute delay). Clock drawing was markedly impaired (FIGURE 11-4A). Standard hematologic and electrolyte measures were in the normal range, with the exception of low-normal serum sodium (134 mmol/L; normal >135 mmol/L). Blood alcohol level was undetectable. A noncontrast brain CT demonstrated diffuse atrophy (involving the cerebellum) without acute findings. CSF was acellular, with normal protein and glucose levels.

The patient was admitted to the neurology service with a presumptive diagnosis of Wernicke encephalopathy and alcohol withdrawal seizures. High-dose thiamine (500 mg IV 3 times a day) was started in the emergency department and continued on admission. Brain MRI was completed the following day (FIGURE 11-4B) and showed increased signal within the medial thalami bilaterally, consistent with the clinical diagnosis of Wernicke encephalopathy.

retrognathia, and an "apple-shaped" body habitus (a marker of central obesity).[61–63] In these patients, it may be reasonable to consider referral for sleep consultation and polysomnography (or other formal measures of sleep function), particularly with a history of witnessed snoring or apneas (CASE 11-7) or symptoms of excessive daytime sleepiness, recognizing that the clinical manifestations of obstructive sleep apnea are all too often underreported.[68]

Behavioral variant frontotemporal dementia (bvFTD) represents an important irreversible cause of incongruent findings on history and test

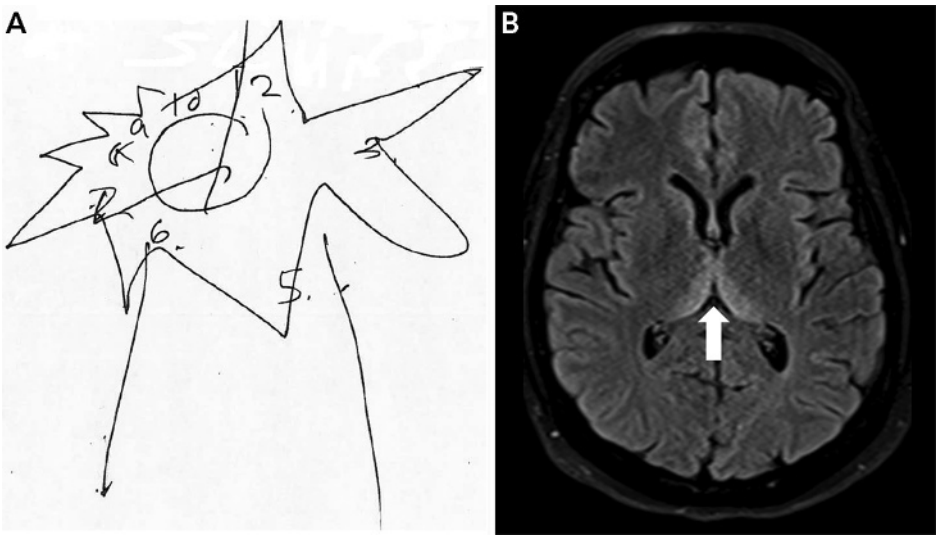

FIGURE 11-4
Clock drawing and brain MRI of the patient in CASE 11-5 presenting with seizure and abrupt decline in mental status. *A,* Patient rendering of a clock indicating the time "20 past 8." *B,* Fluid-attenuated inversion recovery (FLAIR) MRI shows increased signal within the bilateral medial thalami (*arrow*), supporting the clinical diagnosis of Wernicke encephalopathy due to vitamin B_1 deficiency.

COMMENT

Wernicke encephalopathy is a medical emergency warranting prompt treatment with high doses of parenteral thiamine while investigating for other causes of impairment. Following appropriate thiamine repletion, neurologic symptoms and signs improved in this patient. She also had no seizure recurrence and was discharged to home with recommendations to continue counseling for alcohol cessation. One month later, cognition had markedly improved.

performance that is worthy of special mention. Disparity in reported symptoms and objective performance on cognitive testing is common in patients with bvFTD, owing to the early loss of social judgment, empathy, and respect of social norms, with relative preservation of memory and visuospatial function. Reasonably sensitive and specific diagnostic criteria for bvFTD are available to assist with diagnosis in the outpatient environment and should be applied to relevant patients.[69]

CONCLUSION

The standard dementia assessment emphasizes routine screening for common medical comorbidities or less common structural causes that may necessitate further evaluation or management; it is meant to be applied to routine

CASE 11-6

A 54-year-old businessman with essential hypertension and psoriatic arthritis managed with infliximab developed new holocephalic headaches while vacationing in the Caribbean. Shortly after returning to the United States, he presented to the emergency department of his local hospital with sudden-onset alexia and aphasia. Stroke protocol head CT was normal, and his deficits improved before initiation of acute stroke therapies. The patient was admitted for further evaluation and management. Brain MRI, completed the next day, demonstrated nonspecific T2 hyperintensity in the left frontal parafalcine gyrus, without restricted diffusion (consistent with chronic sequelae of small vessel disease). Erythrocyte sedimentation rate was elevated at 73 mm/h, although serum markers of connective tissue disease were normal. Subsequent diagnostic lumbar puncture revealed increased opening pressure (33 cm H_2O), with 104 nucleated cells/mm^3 (69% lymphocytes, 31% monocytes). CSF protein was elevated (91 mg/dL); CSF glucose was normal. Four CSF-specific oligoclonal bands were detected, with an elevated IgG synthesis rate. Bacterial, fungal, and mycoplasma cultures; Herpesviridae polymerase chain reaction (PCR); and testing for West Nile virus and human immunodeficiency virus (HIV) antibodies were negative. Histiocytes and polyclonal atypical lymphocytes (T-cell predominant) were identified on CSF cytology. The patient was diagnosed with aseptic meningitis, infliximab was stopped, and he was discharged home.

Mild word-finding difficulty persisted over months, with interval development of short-term memory impairment, which interfered with his ability to run his business. He also reported drenching night sweats, associated with a 6.8-kg (15-lb) weight loss. Subsequently, he was referred to a tertiary care center for further evaluation. Neurologic examination at the time of assessment was normal, except for impaired verbal fluency with rare phonemic paraphasic errors. Global cognitive function was assessed using the Montreal

patients with probable neurodegenerative dementing illnesses. Reversible dementias are rare in clinical practice, with causes that span the gamut of neurologic disease. As a result, the clinician must prioritize detection of rare reversible causes of dementia while efficiently evaluating and treating patients with more typical (neurodegenerative) causes of dementia. The detection of red flags on history, examination, or investigations should trigger additional investigations, as appropriate. Neuroimaging (favoring MRI) is critically important in many cases, with additional consideration of EEG, CSF analyses, and other measures when atypical features necessitate further investigation. The continued development of disease-specific biomarkers may improve detection of rare patients with potentially reversible dementias. However, no checklist or diagnostic protocol is expected to outperform the neurologist who remains committed to identifying and treating patients with reversible dementia.

Cognitive Assessment (MoCA), with points lost for impaired fluency, repetition, and delayed recall (3/5). His final score of 22/30 was consistent with cognitive impairment.[53]

Relevant investigations were repeated, including brain MRI (which was unchanged) and a diagnostic lumbar puncture. CSF demonstrated persistent leukocytosis (29 nucleated cells/mm^3) and elevated protein (89 mg/dL), CSF-specific oligoclonal bands (13), and elevated IgG synthesis rate. Venereal Disease Research Laboratory (VDRL) testing, not performed on his initial evaluation, was reactive (titer of 1:8); serum rapid plasmin reagin (RPR; titer of 1:1024) and treponemal antibodies were similarly reactive.

The patient was diagnosed with neurosyphilis. Urgent treatment with IV penicillin G (4 million units every 4 hours) for 14 days was provided, followed by IM penicillin G (2.4 million units in one dose). The patient affirmed his commitment to his wife but did acknowledge having another partner over a decade ago. He denied other potential exposures.

COMMENT

A thorough history, including screening for past or present high-risk behaviors, is imperative when investigating patients with unusual presentations of cognitive impairment. As this case illustrates, dementia may emerge as a late complication of *Treponema pallidum* infection, with the potential to respond to appropriate treatment with penicillin. Four weeks following treatment, this patient's word-finding difficulties had completely resolved. His family reported that he was "brighter" and more engaged. His follow-up plans included repeat CSF analyses and VDRL testing 6 months following initial treatment.

CASE 11-7

A 56-year-old man with a paternal history of early-onset Alzheimer disease dementia (age at onset 55 years) was referred for evaluation of short-term memory deficits. His past medical history was notable for depression (managed with a selective serotonin reuptake inhibitor [SSRI]), type 2 diabetes mellitus, dyslipidemia, hypertension, and obesity. The patient endorsed difficulty recalling his schedule, resulting in several missed appointments over the past 6 months. He also acknowledged several missed bill payments over the preceding year and frequent forgetfulness of work-related passwords. Despite these difficulties, he continued to work full time and to meet his employer's expectations. Review of systems was notable for symptoms of low mood and poor sleep, ongoing for 2 years, which were associated with mild headaches on awakening and excessive daytime sleepiness. His wife described frequent snoring and nocturnal apneas.

His performance on cognitive testing suggested moderate severity impairment in all domains (episodic memory, language, processing speed), with a score of 20/30 on the Mini-Mental State Examination (MMSE); the remainder of his neurologic examination was normal. On further screening, he indicated a positive response to 6/8 questions on an abbreviated version of the Geriatric Depression Scale,[64] consistent with active depression, and 18/22 questions on the Epworth Sleepiness Scale,[65] indicating abnormally increased sleepiness. The dose of his SSRI was increased, and he was referred for an outpatient sleep assessment, including polysomnography.

Overnight polysomnography with standard respiratory monitoring confirmed an apnea-hypopnea index of 61 per hour of sleep, associated with desaturations to an SaO_2 of 83% and 5.8 respiratory effort–related arousals per hour of sleep, meeting criteria for severe obstructive sleep apnea.[66,67] Continuous positive airway pressure of 12 cm H_2O effectively eliminated apneas, with the appearance of consolidated sleep and an apnea-hypopnea index of 0.

COMMENT

This patient's cognitive symptoms completely resolved with sustained use of nocturnal continuous positive airway pressure, exemplifying the importance of screening for and treating sleep pathology in at-risk patients with cognitive symptoms. Six months later, he reported overall improvement in sleep quality and mood symptoms, with complete resolution of cognitive symptoms.

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