

Rapidly Progressive Dementia

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REVIEW ARTICLE



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ABSTRACT

PURPOSE OF REVIEW: This article presents a practical approach to the evaluation of patients with rapidly progressive dementia.

RECENT FINDINGS: The approach presented in this article builds upon the standard dementia evaluation, leveraging widely available tests and emergent specific markers of disease to narrow the differential diagnosis and determine the cause(s) of rapid progressive decline. The discovery of treatment-responsive causes of rapidly progressive dementia underscores the need to determine the cause early in the symptomatic course when treatments are most likely to halt or reverse cognitive decline.

SUMMARY: A pragmatic and organized approach to patients with rapidly progressive dementia is essential to mitigate diagnostic and therapeutic challenges and optimize patient outcomes.

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INTRODUCTION

Cognitive impairment in patients with rapidly progressive dementia (RPD) develops faster than expected for a known dementia syndrome. Although the definition of *rapid* varies in practice, it is generally accepted that the interval from first symptom to dementia onset is measured in weeks or months, with the majority of patients with RPD progressing from independence to complete (or near-complete) dependence within 1 to 2 years. Patients meeting these criteria are rare, accounting for 3% to 4% of dementia cases in clinical practice.¹⁻³ Yet, despite their rarity, patients who are rapidly declining present a disproportionately great clinical challenge owing to the breadth of potential causes, the plethora of available tests to consider, and the need to complete the assessment with an urgency that matches the rate of decline. The importance of timely evaluation is further exemplified by increasing recognition of eminently treatable autoimmune or inflammatory causes of RPD.^{2,4-6}

The practical approach to RPD builds upon the standard dementia evaluation, as discussed throughout this *Continuum* issue, with modifications intended to optimize the speed of evaluation and improve early recognition of patients with potentially reversible causes of RPD. A timely assessment begins with timely referrals and triage of appropriate patients. Although most patients with RPD can be efficiently evaluated in the outpatient setting, a timely assessment may require patients to be added onto busy clinic schedules. Selected patients may benefit from referral to a specialty center with dedicated resources and clinic

teams equipped to rapidly evaluate patients. Patients with especially rapid rates of decline, psychoses, refractory seizures, prominent encephalopathy, or other medical complications may require inpatient admission. Regardless of the care setting, it is important to eliminate barriers at each stage of the assessment, recognizing that in RPD, as in stroke, time is brain.

Thinking pragmatically, the assessing clinician is encouraged to ask five key questions when facing a patient with suspected RPD:

- 1 Does my patient have RPD?
- 2 What causes of RPD are most likely in my patient?
- 3 Do common tests suggest a common cause of RPD?
- 4 What additional tests may clarify the cause of RPD?
- 5 Does my patient have a treatable cause of RPD?

In answering these questions, the clinician is encouraged to draw upon common clinical skills and accessible diagnostic tests to narrow the differential diagnosis and prioritize next steps in the evaluation. Early detection of potentially treatment-responsive forms of RPD is emphasized throughout the approach, with the goal of facilitating early treatment and optimizing long-term outcomes in affected patients.

DOES MY PATIENT HAVE RAPIDLY PROGRESSIVE DEMENTIA?

In contrast to Supreme Court Justice Potter Stewart's infamous statement, "I know it when I see it,"⁷ recognizing RPD requires a rigorous and consistent approach. As with typically progressive dementia, a detailed clinical history incorporating a reliable collateral source is paramount. An ideal informant should exhibit knowledge of the patient's preexisting cognitive baseline and ongoing interaction with the patient, including sufficient exposure to detect change in performance over time and define the impact of cognitive decline on function, necessary criteria for the diagnosis of dementia.⁸ Assuming these criteria are met, the next step is to discern the age at symptomatic onset and the rate of decline. This task is not trivial. As the onset of most neurodegenerative dementias is insidious, patients and caregivers are likely to misinterpret or discount early symptoms, leading them to underestimate the time course of symptomatic decline. Additionally, the lack of a reliable reference standard challenges efforts to qualify patients with faster-than-expected rates of decline. These challenges contribute to the observation that one of the most common "causes" of RPD is an incomplete history.

Reliable diagnostic criteria are needed to promote accurate diagnosis of RPD in practice and reproducibility in research. Criteria incorporating measures of function are preferred over those emphasizing performance on cognitive/neuropsychological testing, acknowledging the potential for bedside measures of cognitive function to overstate impairment in patients with visuo-perceptual or language impairment and in patients with prominent encephalopathy. The Clinical Dementia Rating (CDR) is one such measure, providing a composite score that reflects the degree of impairment in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care),⁹ with high interrater reliability, validity, and reproducibility when administered by experienced clinicians.^{10,11} Using the

CDR, patients with RPD may be reliably characterized as those who progress from cognitive normality (CDR 0) to moderate (CDR 2) or severe (CDR 3) impairment within a 2-year period, a rate of progression that greatly exceeds that reported in patients with typical neurodegenerative dementing disorders.¹² CDR box scores can be summed across domains, and the CDR sum of boxes can be used to track longitudinal dementia progression, permitting rates of decline to be standardized and compared across centers, disorders, and studies.

WHAT CAUSES OF RAPIDLY PROGRESSIVE DEMENTIA ARE MOST LIKELY IN MY PATIENT?

The causes of RPD span the spectrum of neurologic diseases. The breadth of possibilities mandates a comprehensive yet strategic approach to the evaluation that systematically considers the possible causes of neurologic dysfunction while prioritizing common causes of RPD. Mnemonic tools (eg, VITAMINS) may be useful for this purpose (TABLE 13-1).

The understanding of common causes of RPD has been largely informed by cohort studies and autopsy series from specialized centers with expertise in surveillance and diagnoses of prion diseases.¹³⁻¹⁵ It is not surprising, therefore, that Creutzfeldt-Jakob disease (CJD) rises to the top of the list of common causes, with prevalence approaching 60%.¹⁶ CJD is a uniformly fatal spongiform encephalopathy caused by the formation and transmission of malformed prion proteins throughout central nervous system (CNS) tissues. Most cases are sporadic (85% to 95%), with an average age at symptomatic onset in the seventh decade, a symptomatic course of 1 to 2 years, and no obvious triggering event, exposure, or contributing factors (CASE 13-1). The diagnostic definition of definite sporadic CJD has remained constant across time, requiring the detection of abnormal protease-resistant prion protein by neuropathologic, immunocytochemical, or biochemical techniques in a patient with a progressive neuropsychiatric syndrome.²⁰ By contrast, the diagnostic criteria for probable sporadic CJD has evolved in step with advances in imaging techniques and disease-specific biomarkers.²¹⁻²⁵ Revised criteria emphasize detection of core clinical features (rapidly progressive cognitive impairment with two or more of the following features: myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal signs, or akinetic mutism), with supportive evidence from EEG (generalized periodic sharp or sharp-wave complexes), brain MRI (restricted diffusion in the caudate, or caudate-putamen, or caudate-putamen-thalamus, or at least two of temporal, parietal, and occipital cortical regions), or “positive” real-time quaking-induced conversion (RT-QuIC) assay for misfolded prion protein in the CSF (TABLE 13-2). The diagnosis may also be established in patients with a progressive neuropsychiatric syndrome and positive RT-QuIC in the CSF or other tissues.^{24,26}

Familial/inherited causes attributable to mutations in the *PRNP* gene encoding the prion protein account for 5% to 15% of cases, whereas variant and iatrogenic causes account for a small minority.²⁷

Although the contributions of CJD to RPD should not be understated, several patient populations were underrepresented in these series. These include younger patients in whom autoimmune and inflammatory brain diseases may be more common,²⁸ patients assessed outside of prion disease surveillance centers,^{2,29,30} and individuals assessed in primarily outpatient settings where rare presentations of common age-related neurodegenerative diseases account for a

KEY POINTS

- Although the definition of *rapid* varies in practice, it is generally accepted that in rapidly progressive dementia (RPD), the interval from first symptom to dementia onset is measured in weeks or months.
- Patients who are rapidly declining present a disproportionately great clinical challenge.
- The practical approach to RPD builds upon the standard dementia evaluation, with modifications intended to optimize the speed of evaluation and improve early recognition of patients with potentially reversible causes of RPD.
- In RPD, as in stroke, time is brain.
- As the onset of most neurodegenerative dementias is insidious, patients and caregivers are likely to misinterpret or discount early symptoms.
- The breadth of possible causes of RPD mandates a comprehensive yet strategic approach to the evaluation that systematically considers the possible causes of neurologic dysfunction while prioritizing common causes of RPD.
- Common causes of RPD differ markedly in populations with limited access to health care and varied exposures.
- In RPD, as in all areas of neurology, the past medical history focuses the differential diagnosis.

TABLE 13-1

Causes of Rapidly Progressive Dementia Organized by Etiology Using the Mnemonic VITAMINS

Vascular

- ◆ Ischemic or hemorrhagic infarction (single strategic lesion or multifocal)
- ◆ Subdural hematoma
- ◆ Cerebral venous thrombosis
- ◆ Central nervous system vasculitis (primary or systemic)
- ◆ Cerebral amyloid angiopathy
 - ◇ With related inflammation
 - ◇ Noninflammatory
- ◆ Posterior reversible encephalopathy syndrome (PRES)
- ◆ Retinocochleocerebral vasculopathy (Susac syndrome)
- ◆ Hereditary
 - ◇ Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
 - ◇ Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome

Infectious

- ◆ Bacterial or viral encephalitis/meningitis
- ◆ Fungal encephalitis/meningitis
- ◆ Subacute sclerosing panencephalitis (SSPE)
- ◆ Human immunodeficiency virus (HIV)-associated neurologic decline (HAND)

Toxic-metabolic

- ◆ Electrolyte disturbances
- ◆ Hepatic encephalopathy
- ◆ Renal failure
- ◆ Thyroid/parathyroid dysfunction
- ◆ Nutritional/vitamin deficiencies
 - ◇ Vitamin B₁ (thiamine)
 - ◇ Vitamin B₁₂ (cyanocobalamin)
 - ◇ Vitamin B₃ (niacin)
 - ◇ Folate
- ◆ Hereditary
 - ◇ Wilson disease
 - ◇ Porphyria
- ◆ Environmental
 - ◇ Heavy metals (eg, lead, mercury, arsenic)
 - ◇ Other (eg, toluene)

Autoimmune/inflammatory

- ◆ Autoimmune encephalitis
 - ◇ With antibodies against neuronal cell-surface antigens (eg, N-methyl-D-aspartate [NMDA] receptor, leucine-rich glioma inactivated protein 1 [LGI1]/contactin-associated protein-like 2 [CASPR2])

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- ◇ With antibodies against intraneuronal/cytoplasmic antigens (eg, Hu, Ri, Yo)
- ◇ Seronegative
- ◆ Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)
- ◆ Multiple sclerosis (including atypical variants: eg, tumefactive multiple sclerosis)
- ◆ Anti-myelin oligodendrocyte glycoprotein (MOG) syndrome
- ◆ Acute demyelinating encephalomyelitis (ADEM)
- ◆ Systemic inflammatory disease (central nervous system [CNS] lupus, Sjögren syndrome, Behçet disease)
- ◆ Granulomatous disease (eg, sarcoidosis)
- ◆ Cerebral amyloid angiopathy with related inflammation
- ◆ Medication-induced (eg, checkpoint inhibitors)

Metastases/neoplastic

- ◆ Metastases to the CNS (commonly lung, breast, renal, thyroid, melanoma)
- ◆ Primary CNS tumors (glioma, oligodendroglioma, gliomatosis cerebri)
- ◆ Lymphoma (primary, systemic, intravascular)
- ◆ Leptomeningeal carcinomatosis or lymphomatosis
- ◆ Paraneoplastic encephalitis

Iatrogenic

- ◆ Medication overuse/polypharmacy
- ◆ Medication toxicity
 - ◇ Over-the-counter medications (eg, bismuth, anticholinergic medications)
 - ◇ Prescription medications (eg, benzodiazepines, narcotics, neuroleptics, phenytoin, valproic acid, lithium)
- ◆ Indirect medication effect (eg, immune activation with checkpoint inhibitors, immunocompromise with immunosuppressants, leukoencephalopathy with intrathecal methotrexate)
- ◆ Traumatic brain injury
- ◆ Extrapontine myelinolysis
- ◆ Radiation-induced leukoencephalopathy
- ◆ Substance abuse

Neurodegenerative

- ◆ Prion disease
- ◆ Alzheimer disease
- ◆ Frontotemporal lobar degeneration
- ◆ Lewy body disease
- ◆ Huntington disease

Systemic/seizures/structural

- ◆ Nonconvulsive status epilepticus
- ◆ Hypoxia/hypercarbia
- ◆ Hydrocephalus (normal or high pressure)

substantially greater proportion of RPD.^{1,31} These series also primarily catalog the North American and European experience with RPD. Common causes of RPD differ markedly in populations with limited access to health care and varied exposures. Indeed, experience in India implicates infectious complications as the most common cause of RPD, with leading diagnoses including subacute sclerosing panencephalitis (a chronic complication of measles infection in younger individuals), neurosyphilis (due to infection with *Treponema pallidum*), and progressive multifocal leukoencephalopathy (due to JC virus infection or reactivation in immunocompromised individuals).³² Together these points emphasize the need to weigh various patient-specific risk factors when defining the likely causes of RPD.

Age and Sex

The age of the patient greatly influences the causes of RPD. Younger patients are more likely to present with autoimmune or inflammatory diseases, inherited

CASE 13-1

A 65-year-old woman with medically managed hypertension and hypothyroidism presented to the emergency department with a 6-week history of progressive left-sided clumsiness, slow halting speech, and confusion/disorientation.

On examination, she was disoriented and amnesic, with left-sided pyramidal-pattern weakness, hyperreflexia, and increased tone. Her gait was broad-based and unstable. Screening serum studies were normal. Neuroimaging confirmed diffusion restriction within the cortical ribbon and deep nuclei (FIGURES 13-1A and 13-1B). Routine EEG demonstrated right greater than left mild generalized slowing. CSF was acellular, with normal protein and glucose. Based on these initial test results, Creutzfeldt-Jakob disease (CJD) was presumed to be the most likely cause of her rapidly progressive dementia (RPD). Specific tests were ordered in blood and CSF before her discharge home with hospice care. Disease-associated autoantibodies were not detected. CSF 14-3-3 protein was positive, total tau was markedly elevated (12,433 pg/mL; normal <250 pg/mL), and real-time quaking induced conversion (RT-QuIC) assay detected the presence of proteinaceous infectious materials (ie, prions).

The patient died within 1 month. Brain autopsy confirmed spongiform changes (FIGURE 13-1C). Granular deposits were detected using a monoclonal antibody to the prion protein. Mutations within the prion protein gene were not detected. The final diagnosis was definite sporadic CJD (MM1 subtype).

leukoencephalopathies, inborn errors of metabolism, or other metabolic or storage deficiencies.²⁸ Older patients, on the other hand, are more likely to present with neurodegenerative diseases, including Alzheimer disease (AD), Lewy body disease, frontotemporal lobar degeneration, and vascular disease.^{1,14,30,31} Variant CJD represents an exception to age-based stratification, with a median age at symptomatic onset of 29 years and a presentation characterized by prominent psychiatric and sensory symptoms attributable to remote exposure to prion-contaminated beef.²⁷ Although surveillance for variant CJD continues, reported cases are predominantly linked to the consumption of cattle products contaminated with the agent of bovine spongiform encephalopathy in the United Kingdom in the 1990s.³³ Rare cases have been reported since 2000, including one attributed to occupational exposure in a laboratory technician.³⁴

Sex-specific differences in RPD are not generally recognized; however, systemic and brain-specific autoimmune diseases are known to be more common in females of childbearing age, warranting specific consideration.³⁵ Leucine-rich

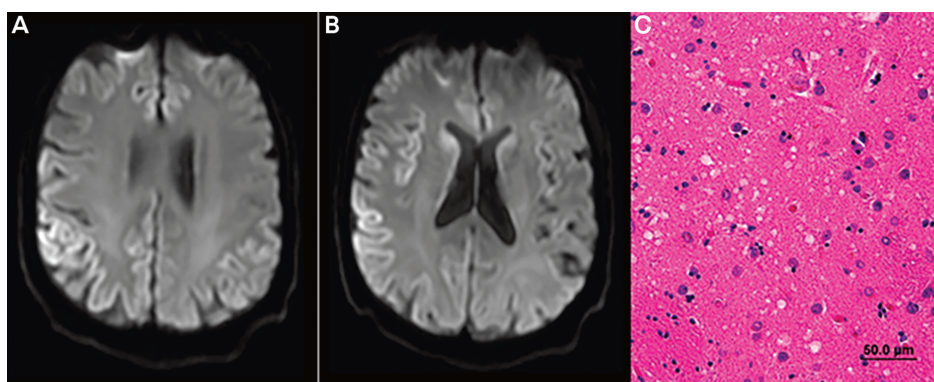


FIGURE 13-1
Imaging and histopathology of the patient in **CASE 13-1**. Axial diffusion-weighted MRI slices show restricted diffusion within the cortical ribbon (**A**) and caudate heads (**B**). Hematoxylin and eosin (H&E)-stained section (**C**) shows spongiform changes.

Sporadic CJD is a common cause of RPD. Patients typically present in the seventh decade of life with rapid progressive symptoms and signs localized to cortical structures, cerebellum, or deep nuclei. Clinical evolution is dictated by the direct spread of prion proteins to adjacent brain areas. Thalamic involvement leads to decreased consciousness, inanition, and death within months of symptomatic onset. This case exemplifies the utility of brain MRI in the diagnostic evaluation of RPD and the role/importance of additional biomarkers (specific tests). Marked elevations of CSF total tau (>1150 pg/mL) together with a positive RT-QuIC assay for prions establishes the antemortem diagnosis with a high degree (>98%) of clinical certainty.^{17,18} Brain autopsy is still recommended to confirm the diagnosis (definite CJD), etiology (ie, sporadic, familial, iatrogenic), and molecular subtype.

Case details were included within Day GS, et al, Neurology.¹⁹

COMMENT

glioma inactivated protein 1 (LGI1) antibody-mediated RPD represents a unique exception, being more common in older men (median age at symptomatic onset, 63 to 65 years).^{36,37} Hyponatremia and stereotyped faciobrachial dystonic seizures are common early in the symptomatic course, often predating cognitive impairment.^{36,38,39} Detection of these findings may prove useful when attempting to distinguish these patients from those with primary neurodegenerative or psychiatric disease.⁴⁰

Risk Factors

In RPD, as in all areas of neurology, the past medical history focuses the differential diagnosis. The presence of multiple vascular risk factors (eg, hypertension, dyslipidemia, diabetes, past stroke, atrial fibrillation, or coronary artery disease) should prompt consideration of RPD due to vascular cognitive impairment, particularly when cognitive decline is temporally related to imaging-confirmed infarction. Active renal, hepatic, or thyroid disease should lead the clinician to consider metabolic derangement as the cause of RPD. A history of cancer necessitates consideration of possible recurrence, spread, or paraneoplastic phenomenon. A history of malnutrition or malabsorption should raise the prospect of Wernicke-Korsakoff syndrome, prompting immediate treatment with high-dose parenteral thiamine (vitamin B₁).

TABLE 13-2

Amended Protocol for Clinical Diagnosis Indicating Probable Sporadic Creutzfeldt-Jakob Disease^a

Probable sporadic Creutzfeldt-Jakob disease

I plus two of II and typical EEG

OR

I plus two of II and typical MRI neuroimaging

OR

I plus two of II and positive CSF 14-3-3

OR

I or one of II and positive CSF RT-QuIC

Possible sporadic Creutzfeldt-Jakob disease

I plus two of II and duration <2 years and exclusion of other causes in complete diagnostic workup

Clinical symptoms and signs

I Progressive cognitive impairment

II Additional symptoms and signs

A Myoclonus

B Visual or cerebellar signs

C Pyramidal or extrapyramidal signs

D Akinetic mutism

CSF = cerebrospinal fluid; EEG = electroencephalography; MRI = magnetic resonance imaging; RT-QuIC = real-time quaking-induced conversion assay.

^a Modified with permission from Hermann P, et al, *Neurology*.²⁴ © 2018 American Academy of Neurology.

Medications may directly accelerate cognitive decline in susceptible individuals (eg, anticholinergics, benzodiazepines, narcotics) or indirectly lead to RPD by predisposing patients to opportunistic infections or primary or secondary CNS malignancy (eg, immunosuppressants⁴¹), autoimmune disease (eg, checkpoint inhibitors⁴²), or leukoencephalopathy (eg, methotrexate¹³). Recreational or occupational exposure to illicit substances, heavy metals, or other toxins may similarly impair cognition or predispose to infection, cerebrovascular events, or myelosuppression. Past or present high-risk behaviors, including sexual practices, may predispose to sexually transmitted infections (eg, human immunodeficiency virus [HIV], neurosyphilis), warranting specific consideration and expanded testing in at-risk patients.⁴³ Beyond these conventional risk factors, a history of exotic travel or insect or animal bites and vaccination history (or lack thereof) may also inform the differential diagnosis.

The implications of family history in deciphering causes of RPD are readily apparent. Autosomal dominant causes of prion disease, AD, frontotemporal lobar degeneration (including *C9orf72* hexanucleotide repeat expansions presenting with frontotemporal lobar degeneration with or without motor neuron disease), and other inherited metabolic or storage disorders are well recognized within families. Accordingly, genetic counseling and testing should be considered in patients with a family history of similar conditions, syndromes that affect multiple relatives across multiple generations, or unexplained untimely death in first-degree relatives. Earlier than expected age at symptomatic onset; marked cerebral atrophy in a patient with rapid decline (ie, atrophy out of proportion to the duration of dementia); or other unexplained leukoencephalopathy, calcifications, or iron deposition may provide additional clues to a heritable cause. Genetic testing may also be considered in patients with unexplained RPD, acknowledging that families may be estranged, genetic causes may go unrecognized, or family members may die before the onset of neurologic symptoms. Autosomal recessive disorders may be particularly difficult to decipher, especially in small families, warranting expanded genetic analyses in the patient and other family members if the cause of RPD remains unknown. Consultation with an experienced geneticist is recommended when considering a genetic cause of RPD given the plethora of pathogenic variants associated with RPD, ever-expanding diagnostic panels and techniques for analyses of nuclear and mitochondrial DNA, and the potential implications of a “positive” test for the patient and family members.⁴⁴

Symptomatic Onset and Progression

The time course over which symptoms emerge, patterns of decline, and rates of progression may further inform the causes of RPD. The abrupt onset of symptoms and signs (evolving over minutes, hours, or days) may suggest a vascular or infectious cause, whereas impairment due to autoimmune encephalitis or inflammatory causes typically evolves over weeks to months. Neurodegenerative diseases, including prion diseases, may emerge over months or even a year, although hyperacute presentations are recognized.^{4,31,45} Although most causes of RPD demonstrate a steady rate of progression, stepwise decline may suggest a vascular etiology, whereas prominent fluctuations may point to an autoimmune or endocrine/metabolic cause of RPD or Lewy body disease.^{4,31,46} Apart from CJD, diseases that progress the fastest tend to be associated with the highest potential for treatment responsiveness and potential reversibility

KEY POINTS

- Medications may directly accelerate cognitive decline in susceptible individuals or indirectly lead to RPD.
- Genetic counseling and testing should be considered in patients with a family history of similar conditions, syndromes that affect multiple relatives across multiple generations, or unexplained untimely death in first-degree relatives.
- The time course over which symptoms emerge, patterns of decline, and rates of progression may inform the causes of RPD.
- A comprehensive and ordered neurologic examination is critical to determine whether cognitive deficits are attributable to a focal, multifocal, or systemic process.
- In RPD, the neurologic examination represents a single measure of a dynamic and rapidly evolving process.
- It is especially important to differentiate faciobrachial dystonic seizures from the myoclonic movements commonly observed in patients with Creutzfeldt-Jakob disease (CJD), given the similarities in age at symptomatic onset and implications of this finding on treatment.
- High-yield core tests include screening serum studies and urinalysis, structural neuroimaging, CSF analyses, and EEG. Specific tests are more varied in accessibility, cost, and application and should be reserved for selected patients when justified by the clinical scenario.

(FIGURE 13-2). This relationship exemplifies the need for an especially rapid evaluation in patients who decline the fastest.

Examination Findings

A systematic approach to the examination begins upon walking into the examination room. Obvious cachexia may point toward a nutritional, metabolic, or (para)neoplastic cause of RPD, whereas fever, meningismus, and rigors suggest an infectious cause (requiring prompt consideration of empiric treatment with antivirals and antibiotics). Prominent psychosis is often seen in patients with toxic and metabolic derangement, autoimmune causes, or Lewy body disease.^{46,47} More subtle behavioral disturbances (eg, disinhibition, apathy) may point to a structural (primary/secondary CNS malignancy) or neurodegenerative cause. The general physical examination may further focus the differential diagnosis, supporting or refuting a metabolic (eg, asterixis in the patient with renal or hepatic insufficiency, other stigmata of chronic liver disease in the patient with hepatic encephalopathy, myxedema in the patient with thyroid insufficiency), autoimmune/inflammatory (eg, joint and skin changes in the patient with systemic lupus erythematosus), infectious (eg, septic emboli in the patient with bacterial endocarditis), or (para)neoplastic cause of RPD (eg, peripheral lymphadenopathy or organomegaly in a patient with lymphoma; unilateral Horner syndrome in a patient with a Pancoast lung tumor).

Much emphasis is placed on the neurologic examination in RPD and for good reason. A comprehensive and ordered neurologic examination is critical to determine whether cognitive deficits are attributable to a focal, multifocal, or systemic process. Particular attention should be directed toward eliciting upper motor neuron signs (spasticity, pyramidal distribution of weakness, hyperreflexia, and extensor plantar responses), lower motor neuron signs (fasciculations, muscle atrophy, and motor weakness), and extrapyramidal features (eg, tremor, rigidity, bradykinesia/akinesia, postural instability), recognizing the association between these signs and specific causes of RPD (TABLE 13-3). In RPD, the neurologic examination represents a single measure of a dynamic and rapidly evolving process. Focal or lateralized findings may generalize as the disease progresses, whereas patients who are hypertonic/hyperkinetic may become hypotonic and bradykinetic as neuronal cell bodies are lost. For this reason, the neurologic examination should be repeated at each visit.

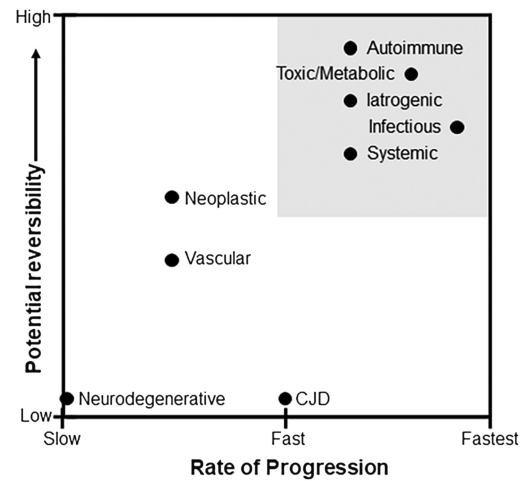


FIGURE 13-2 Common causes of rapidly progressive dementia stratified by rate of progression and potential reversibility. Causes in the top right quadrant (shaded area) typically associate with the most rapidly progressive presentations and the greatest potential for response to appropriate treatments; practical approaches to rapidly progressive dementia should prioritize their detection.

CJD = Creutzfeldt-Jakob disease.
 Reprinted with permission from Day GS, Tang-Wai DF, Neurodegener Dis Manag.¹⁶ © 2014 Future Medicine Ltd.

Given its relative frequency, it is important to recognize the findings that may suggest a diagnosis of sporadic CJD. Although diagnostic criteria tend to emphasize myoclonus and akinetic mutism,^{23,25} these traits generally appear late in the disease course. By contrast, cerebellar signs (midline or appendicular ataxia), motor or sensory signs, and cortical-localizing signs (eg, aphasia, apraxia, cortical visual loss) may be detected in isolation or in combination at first presentation.^{1,48}

Examination findings that point to a potentially treatment-responsive cause of RPD bear special consideration. Involuntary chewing movements (orofacial dyskinesias) and limb dyskinesias are detected in a substantial proportion of patients with anti-*N*-methyl-*D*-aspartate (NMDA) receptor encephalitis,⁴⁹ whereas brief, repetitive, stereotyped dystonic movements of the face, arm, and (sometimes) leg (faciobrachial [with or without crural] dystonic seizures) are highly suggestive of LGI1 antibody encephalitis.³⁸ It is especially important to differentiate faciobrachial dystonic seizures from the myoclonic movements commonly observed in patients with CJD, given the similarities in age at symptomatic onset and implications of this finding on treatment responsiveness and long-term outcome (**CASE 13-2**).

DO COMMON TESTS SUGGEST A COMMON CAUSE OF RAPIDLY PROGRESSIVE DEMENTIA?

The myriad of available diagnostic tests presents a practical dilemma when evaluating the patient with RPD. Is it better to order all tests at once, at great inconvenience and even greater cost to the patient? Or is a stepwise approach to testing preferred, accepting potential diagnostic delays associated with the staged return of results? Although both approaches have merits, general consensus favors a hybrid approach that prioritizes the early application of widely available core tests in all patients, followed by specific tests ordered in specific patients.^{1-3,13,16,29} In this context, high-yield core tests include screening serum studies and urinalysis, structural neuroimaging (prioritizing MRI), CSF analyses (unless prevented by a definite or relative contraindication), and EEG. Specific tests are more varied in accessibility, cost, and application and should be reserved for selected patients when justified by the clinical scenario (**TABLE 13-4**).

Serum Screening Tests and Urinalysis

The diagnostic evaluation begins with serum screening and urinalysis to exclude obvious metabolic causes (eg, hepatic or renal encephalopathy), infection, intoxication, or other derangement. This is particularly important in patients with multiple medical comorbidities or preexisting (mild) cognitive impairment, who may be especially susceptible to metabolic perturbations, systemic effects of focal infections, or adverse consequences of medications or toxic exposures. Older patients represent a particularly high-risk group, noting the association between advancing age, active health issues, cognitive impairment, and polypharmacy.⁵¹

Neuroimaging

Structural neuroimaging should be completed early in the evaluation. Brain MRI is preferred over CT, providing superior visualization of cortical and subcortical structures, deep nuclei, and posterior fossa and brainstem structures and greater sensitivity for detection of demyelinating, neoplastic, or infectious lesions. Sensitivity may be further increased through administration of IV contrast.

KEY POINTS

- The sensitivity and specificity of MRI for the diagnosis of CJD may exceed 90% in cohorts with suspected CJD, with good interrater reliability when interpreted by experienced neuroradiologists.
- Cortical ribboning may be seen in patients with CJD and in patients with other causes of RPD, including subacute sclerosing panencephalitis, autoimmune encephalitis, herpes simplex encephalitis, high-grade glioma (or other malignancies), seizures, and hypoglycemia and other causes of metabolic derangement.
- Lumbar puncture can be safely and efficiently performed at the bedside even in patients who are severely impaired and should be completed in all patients with RPD following reasonable exclusion of space-occupying lesions and bleeding diatheses.
- Abnormalities on routine measures may point toward a common cause of RPD, focusing further evaluations for etiologies such as CJD; neurodegenerative diseases; or autoimmune, inflammatory, or infectious causes.
- Unexpected findings on routine tests may provide an important early clue to an alternative etiology, prompting further evaluation for less common causes of RPD.

CT images are preferred when an urgent need exists to exclude a mass lesion, hemorrhage, or infarct or when MRI is unavailable, impractical to obtain, relatively contraindicated (eg, patient with claustrophobia, agitation, inability to lie flat), or absolutely contraindicated (eg, patient with an incompatible implanted device).

Although neuroimaging findings are often considered nonspecific, certain findings point toward a specific cause of RPD, informing next steps in the diagnostic evaluation (FIGURE 13-4). Cortical ribboning is worthy of specific mention because of its close association with CJD⁵² and emphasis within updated CJD diagnostic criteria.²³⁻²⁵ In this context, cortical ribboning refers to gray matter hyperintensities that are best seen within the cortical ribbon (on diffusion-weighted imaging more than on T2/fluid-attenuated inversion recovery [FLAIR] images, often with corresponding restricted diffusion on the apparent diffusion coefficient map). Similar findings may be seen in the deep

TABLE 13-3 Common Findings on Physical Examination in Patients With Rapidly Progressive Dementia Organized by Etiology Using the Mnemonic VITAMINS

Rapidly progressive dementia etiology	General abnormalities on examination	Neurologic abnormalities on examination							
		Focal cranial nerves	Upper motor neuron signs ^a	Lower motor neuron signs ^b	Extrapyramidal ^c	Myoclonus	Sensory	Ataxia	
Vascular	Stigmata of systemic vasculitis	+	++	-	-	+	+	+	+
Infectious	Fever, vital sign changes, meningismus, rigors, lymphadenopathy, other organ dysfunction	++	++	+	-	+	+	-	-
Toxic-metabolic	Cachexia/weight loss, prominent psychosis, stigmata of liver disease, myxedema, asterixis, other organ dysfunction	+	-	-	+	++	+	++	++
Autoimmune/inflammatory	Stereotyped movements (eg, faciobrachial dystonic seizures), joint inflammation, skin rash/ulceration, other organ dysfunction	-	++	+	-	++	+	+	+

CONTINUED ON PAGE 913

nuclei. In general, cortical signal changes should be present in more than one area, not including areas vulnerable to artifactual signal change (eg, the anterior cingulate cortex), and should not enhance or show mass effect.⁵³ The severity and extent of cortical ribboning tends to parallel clinical signs, predicting CJD subtype⁵⁴ and reflecting pathologic changes associated with prion disease.⁵⁵ The sensitivity and specificity of MRI for the diagnosis of CJD may exceed 90% in cohorts with suspected CJD, with good interrater reliability when interpreted by experienced neuroradiologists.⁵⁶ Although compelling for CJD, cortical ribboning may also be seen in patients with other causes of RPD, including subacute sclerosing panencephalitis,⁵⁷ autoimmune encephalitis,⁴⁷ herpes simplex encephalitis,⁵⁸ high-grade glioma (or other malignancies), seizures,⁵⁹ and hypoglycemia and other causes of metabolic derangement.⁶⁰ Other findings worthy of note include T2 hyperintensities within the temporal lobes that may or may not enhance, implicating limbic (autoimmune) encephalitis.⁴⁷ Other findings

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Rapidly progressive dementia etiology	General abnormalities on examination	Neurologic abnormalities on examination						
		Focal cranial nerves	Upper motor neuron signs ^a	Lower motor neuron signs ^b	Extrapyramidal ^c	Myoclonus	Sensory	Ataxia
Metastases/neoplastic	Cachexia/weight loss, lymphadenopathy, other organ dysfunction	+	++	+	-	-	+	+
Iatrogenic	Other organ dysfunction	-	+	-	+	-	-	+
Neurodegenerative	Cachexia/weight loss	-	+	-	+	+	+	+
Systemic/seizures/structural	Stereotypical gait changes (hydrocephalus), involuntary movements, unexplained alterations in consciousness	-	+	-	-	-	-	-

++ = common; + = possible; - = uncommon.

^a Examples of upper motor neuron signs include pyramidal-pattern weakness, hyperreflexia, and upgoing toe.

^b Examples of lower motor neuron signs include distal and proximal weakness and hyporeflexia.

^c Examples of extrapyramidal findings include tremor, rigidity, akinesia/bradykinesia and postural instability; cortical sensory signs include graphesthesia, astereognosis, and extinction/neglect.

may suggest specific autoimmune causes of RPD, including T1 hyperintensities within the basal ganglia reported in association with LGI1 autoantibodies.⁶¹

Additional neuroimaging should be pursued in selected patients, including angiography or venography in patients with suspected vasculitis. Imaging of additional body structures (chest, abdomen, pelvis) should be considered in patients with suspected malignant, paraneoplastic, or granulomatous causes of RPD. Although CT is often the modality of choice for chest, abdomen, and pelvis surveillance, fludeoxyglucose positron emission tomography (FDG-PET) may improve detection of subcentimeter lesions that might otherwise be missed or misinterpreted on structural imaging. Ultrasound may be required to evaluate for germ cell tumors, including ovarian or mediastinal teratomas, and testicular masses associated with autoimmune/paraneoplastic causes of RPD in younger patients.

CSF Analyses

Lumbar punctures can be safely and efficiently performed at the bedside even in severely impaired patients and should be completed in all patients with RPD

CASE 13-2

A 76-year-old woman presented from hospice care for a second opinion following a diagnosis of Creutzfeldt-Jakob disease. Her cognitive decline began 8 months earlier, typified by prominent memory deficits, psychosis (delusions and visual hallucinations), and compulsive behaviors necessitating full-time nursing care. Her family reported persistent “myoclonus” of the right hand with time-locked grimacing of the face. Initially, these events occurred several times per day; however, over the past several months, they had been occurring hundreds of times per day.

On examination, she was oriented only to person. She had no focal deficits. Counting backward provoked a stereotyped dystonic spasm of the left face, arm, and foot (faciobrachial-crural dystonic seizure, [VIDEO 13-1](#)).

The patient was admitted to the hospital. No structural lesion was identified on brain imaging. Prolonged video-EEG demonstrated mild to moderate slowing, with several stereotyped motor events ([FIGURE 13-3A](#)). A diagnostic lumbar puncture was performed and showed 3 white blood cells/mm³ and elevated protein (109 mg/dL). Blood and CSF were sent for specific disease-associated autoantibodies, and high-dose methylprednisolone started for presumed autoimmune dementia. Leucine-rich glioma inactivated protein 1 (LGI1) autoantibodies were detected in serum and CSF using indirect immunofluorescent and cell-based assays ([FIGURE 13-3B](#)), establishing the diagnosis of rapidly progressive dementia (RPD) due to LGI1 antibody encephalitis. Plasma exchange was administered (5 treatments over 10 days), with improvement in her mental status. Pulse steroids were continued once weekly for 8 weeks, with a gradual taper. The patient continued to improve over the ensuing 8 months, eventually returning to independent living.

following reasonable exclusion of space-occupying lesions and bleeding diatheses. Standard CSF tests should include cell count and differential, with measurement of protein and glucose levels (referencing serum glucose levels). Results of these routine measures generally return within hours, enabling rapid integration within the diagnostic plan. Measures of albumin, immunoglobulins, and oligoclonal bands in paired CSF and serum samples may further inform blood-brain barrier permeability and CSF-specific antibody syntheses (unique CSF oligoclonal bands). These measures may inform the differential diagnosis, although they frequently take more than 72 hours to process. Abnormalities on routine measures may point toward a common cause of RPD, focusing further evaluations for etiologies such as CJD; neurodegenerative diseases; or autoimmune, inflammatory, or infectious causes (TABLE 13-5). Tests for infectious agents and malignant or monoclonal cell populations (cytology and flow cytometry) should be added for patients with systemic features, including fevers and weight loss; patients at higher risk of malignancy (eg, past history of malignancy, smokers); and patients with confirmed or suspected immunodeficiency.

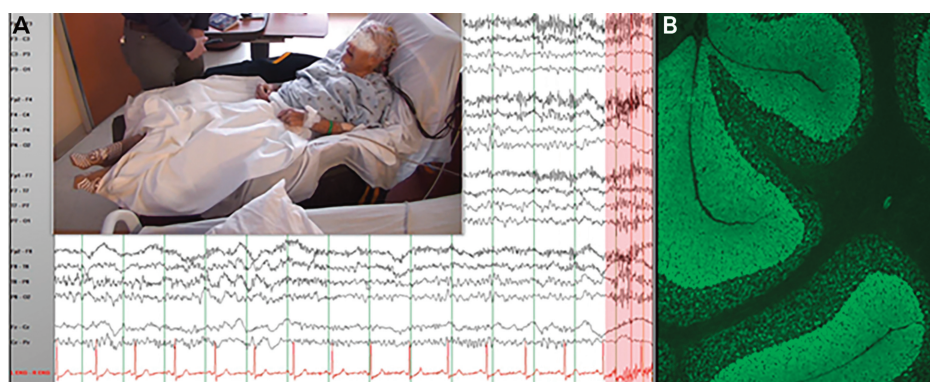


FIGURE 13-3 Still image of the patient in **CASE 13-2** experiencing a left faciobrachial-crural seizure (A), with continuous EEG monitoring. Typical EEG findings (frontal infraslow activity⁵⁰) are obscured by motor artifact associated with the seizure (shaded red area). B, Results of indirect immunofluorescent assay of murine cerebellum section showing prominent synaptic staining within the molecular layer in a pattern typical of leucine-rich glioma inactivated protein 1 (LGI1) antibody encephalitis (subsequently confirmed with cell-based assay [not shown]).

Inaccurate descriptions of abnormal movements in patients with RPD may contribute to incorrect diagnoses and management. The detection of faciobrachial (with or without crural) seizures in this patient raised the prospect of LGI1 antibody encephalitis as the cause of RPD. Antibody tests in serum and CSF established the diagnosis of definite LGI1 antibody-mediated encephalitis, a treatment-responsive cause of RPD. This case exemplifies the importance of accurately describing and classifying abnormal movements and the critical importance of recognizing stereotyped movements that may suggest a potentially treatment-responsive cause of RPD.

COMMENT

TABLE 13-4

Common and Specific Tests to Consider in Patients With Rapidly Progressive Dementia^{a,b}

Modality	Common tests	Specific tests	Additional research tests
Blood/serum	Complete blood cell count, basic metabolic panel (including calcium, magnesium, and phosphorus), hepatic enzymes and tests of function, coagulation profile, thyroid function tests, vitamin B ₁₂ level, testing for syphilis and human immunodeficiency virus (HIV), rheumatologic screen (erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody), immunoglobulin index/oligoclonal banding ^c	Additional rheumatologic tests (extractable nuclear antigen antibodies, cytoplasmic/perinuclear antineutrophil cytoplasmic antibody, double-stranded DNA, rheumatoid factor, C3, C4), vitamin B ₁ level (whole blood), ^d medication levels, toxicology screen, blood smear, hypercoagulability testing, infectious screen (eg, Lyme antibody, West Nile virus antibody, <i>Tropheryma whipplei</i>), enterovirus testing, autoimmune encephalitis panel, ^e antithyroglobulin and antithyroperoxidase antibodies, aquaporin-4 or anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, cancer-associated antibodies (eg, CA-125, CEA, PSA), heavy metal screen, copper and ceruloplasmin	Next-generation metagenomic sequencing for occult infection, murine tissue-based immunofluorescence assay screening for antibody binding to neural tissue, screening for novel or recently reported disease-associated antibodies, nonspecific biomarkers (eg, neurofilament light chain)
Urine	Urinalysis, toxicology screen	Culture and sensitivity, urine protein electrophoresis, urinary copper, heavy metal screen (24 hours)	
Neuroimaging	Brain MRI (including T1-weighted, T2-weighted, fluid-attenuated inversion recovery [FLAIR], diffusion-weighted imaging, apparent diffusion coefficient, hemosiderin sequences), CT head with contrast (if brain MRI not possible)	Brain MRI with contrast, MR/CT angiography/venography, conventional angiography, fludeoxyglucose positron emission tomography (FDG-PET), amyloid/tau PET	Magnetic resonance spectroscopy, functional MRI (fMRI), neuroinflammatory PET biomarkers

CONTINUED ON PAGE 917

Modality	Common tests	Specific tests	Additional research tests
CSF	Cell count and differential, protein, glucose, immunoglobulin index/ oligoclonal banding ^c	Real-time quaking-induced conversion (RT-QulC) assay for prions, 14-3-3 protein Western blot, total tau enzyme-linked immunosorbent assay (ELISA), viral polymerase chain reaction (PCR) (eg, HSV, VZV, EBV), bacterial culture and sensitivity, fungal culture, cryptococcal antigen, <i>Mycobacterium</i> testing, Venereal Disease Research Laboratory (VDRL), <i>T. whipplei</i> PCR, JC virus antibody and PCR, autoimmune encephalitis panel, ^c cytology and flow cytometry, angiotensin-converting enzyme (for sarcoidosis), Alzheimer disease biomarkers (amyloid-β40, amyloid-β42, total tau, phosphorylated tau), high-volume lumbar puncture with video before and after (for normal pressure hydrocephalus)	Next-generation metagenomic sequencing for occult infection, murine tissue-based immunofluorescence assay screening for antibody binding to neural tissue, screening for novel or recently reported disease-associated antibodies, nonspecific biomarkers (eg, neurofilament light chain), RT-QulC assay for other disease-specific proteins (eg, α-synuclein)
EEG	Routine EEG	Ambulatory EEG, continuous EEG	Quantitative EEG
Other imaging		Body imaging (CT chest, abdomen, pelvis), ultrasound (ovaries, testes), body FDG-PET, mammogram	
Other tests		Endoscopy with biopsy, nerve conduction studies/EMG, polysomnography, ophthalmologic examination or vitreous sampling, fluorescein angiogram, audiometry, genetic testing for known disease-associated mutations, muscle/nerve biopsy, brain/meningeal biopsy, biopsy of other site(s)	Autonomic testing (eg, tilt-table testing, quantitative sudomotor axon reflex test [QSART]), whole-exome sequencing exploratory genetic testing, next-generation metagenomic sequencing of biopsy tissue

CA-125 = cancer antigen 125; CEA = carcinoembryonic antigen; CSF = cerebrospinal fluid; CT = computed tomography; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; EEG = electroencephalogram; EMG = electromyography; HSV = herpes simplex virus; MR = magnetic resonance; MRI = magnetic resonance imaging; PSA = prostate specific antigen; VZV = varicella-zoster virus.

^a Data from Geschwind MD³ and Day GS, Tang-Wai DF.¹⁶

^b Common tests should be ordered for all patients with rapidly progressive dementia. Specific tests should be ordered to confirm or refute specific diagnoses, as supported by history, physical examination, and results of common tests. Additional research tests may be considered in selected patients but may not be widely accessible or standardized/approved for clinical use.

^c Test in blood and CSF (paired sample preferred).

^d If checking vitamin B₁ level, be sure to start high-dose parenteral thiamine for treatment of possible vitamin B₁ deficiency (ie, Wernicke-Korsakoff syndrome).

KEY POINTS

- The ease of use, wide availability, relatively low cost, and excellent safety profile of EEG justify its inclusion as a core or common test in patients with RPD.
- The EEG represents a temporal measure of an evolving process. EEG findings may be subtle early in the symptomatic course, with typical findings associated with specific causes of RPD emerging as the disease progresses.
- Good biomarkers provide objective measures of biological or pathogenic processes that may be applied to stratify disease risk or prognosis, inform clinical diagnosis, and monitor response to interventions. A clear need exists to develop and apply disease-specific biomarkers when assessing for and managing patients with RPD.
- The development of a real-time quaking induced conversion (RT-QuIC) assay capable of detecting minute amounts of abnormal prion proteins within CSF has transformed the diagnostic approach to CJD. A positive RT-QuIC leaves little doubt as to the underlying cause of RPD.
- Although total tau is not a specific biomarker, elevations above approximately 1150 pg/mL are reported in more than 90% of patients with probable or definite CJD.

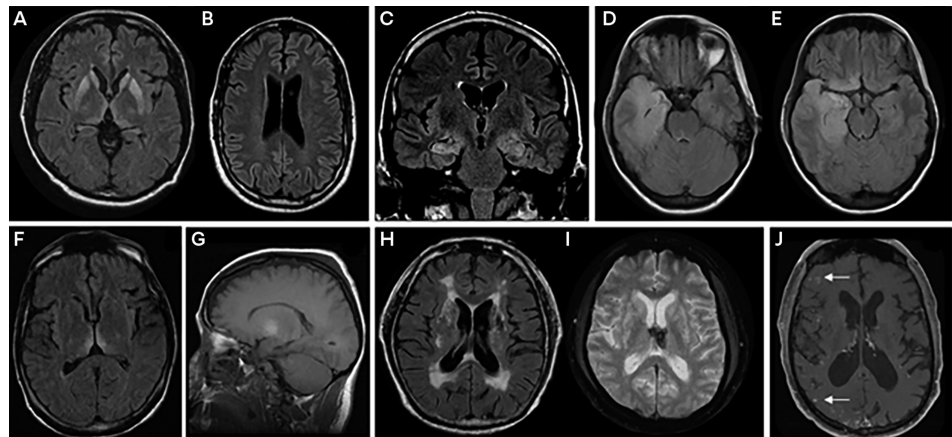


FIGURE 13-4 Neuroimaging findings associated with specific causes of rapidly progressive dementia. Creutzfeldt-Jakob disease: Axial fluid-attenuated inversion recovery (FLAIR) images show striatal thalamus (A) and cortical (B) hyperintensities. Autoimmune/inflammatory encephalitis: Coronal FLAIR image (C) shows bilateral limbic/hippocampal hyperintensities. Infectious encephalitis: Axial noncontrast FLAIR images (D, E) show right anteromedial temporal lobe hyperintensities in a patient with herpes simplex encephalitis. Metabolic/nutritional deficiency: Axial FLAIR image (F) shows dorsomedial thalamic hyperintensities in a patient with Wernicke-Korsakoff syndrome due to thiamine (vitamin B₁) deficiency; sagittal noncontrast T1-weighted image (G) shows basal ganglia hyperintensity indicating metabolic encephalopathy in a patient with hepatic dysfunction. Vascular disease: Axial FLAIR image (H) shows strokes and diffuse ischemic white matter changes; axial gradient recalled echo (GRE) image (I) shows bilateral anterior and dorsomedial thalamic hemorrhage causing acute-onset amnesia; axial postcontrast T1-weighted image (J) shows enhancement of vessels in the right hemisphere (arrows), suggesting central nervous system vasculitis. Reprinted with permission from Day GS, Tang-Wai DF, Neurodegener Dis Manag.¹⁶ © 2014 Future Medicine Ltd.

Unexpected findings on routine tests may also provide an important early clue to an alternative etiology, prompting further evaluation for less common causes of RPD (CASE 13-3). CSF pleocytosis (generally, >5 white blood cells/mm³) is a particularly important finding providing direct evidence of CNS inflammation (lymphocytic predominance) or infection (neutrophilic or lymphocytic predominance), two potentially treatable causes of RPD. The lack of objective evidence of inflammation in a patient with a presumed autoimmune/inflammatory cause of RPD should raise suspicion about such causes. However, “normal CSF” may be reported in as many as 14% of patients with autoimmune encephalitis (low cell count, normal protein, and absent oligoclonal bands).⁶² Noninflammatory CSF may be even more common in individuals older than 60 years of age.^{40,62} Although less common, pleocytosis may also occur in patients with other noninflammatory/infectious causes of RPD. In such cases, the lack of objective improvement following appropriate treatment should prompt reconsideration of the diagnosis and further evaluation (CASE 13-4).

EEG

Although it is true that EEG findings are generally nonspecific, the ease of use, wide availability, relatively low cost, and excellent safety profile of EEG justify its inclusion as a core or common test in patients with RPD. EEG is also one of the few tests that can be used to assess patients over a protracted period. Continuous monitoring may be particularly valuable when assessing patients with fluctuating

symptoms, including intermittent/transient alterations of consciousness, or when an epileptic etiology of impairment is suspected.

Diffuse slowing (<8 Hz) on EEG is so common in RPD that a normal posterior dominant rhythm should call into question a possible functional or nonorganic cause of impairment in a patient with RPD. Additional findings may point to a specific cause of impairment, warranting particular attention (FIGURE 13-7). Detection of extreme delta phenomena (with or without delta brush) may point toward an underlying autoimmune-mediated cause of impairment associated with antibodies against NMDA receptors;⁶³ frontal lobe infraslow activity⁵⁰ and an electrodecremental pattern preceding faciobrachial (with or without crural) dystonic movements may point toward antibodies against LGI1 antigens, whereas a musicogenic seizure may point toward antibodies against glutamic acid decarboxylase 65 (GAD-65) antigens.⁶⁴ Diagnostic and prognostic applications of EEG continue to be explored in patients with autoimmune encephalitis, with the potential that EEG findings may parallel disease severity, identify treatment-responsive patients, and associate with long-term outcomes.

Like the physical examination, the EEG represents a temporal measure of an evolving process. EEG findings may be subtle early in the symptomatic course, with typical findings associated with specific causes of RPD emerging as the

Results of Routine CSF Tests and Diagnostic Associations

TABLE 13-5

Etiology	Routine CSF tests			
	Nucleated cells	Protein	Glucose	Oligoclonal bands/ IgG index
Vascular				
Ischemic	↔	↑	↔	↔
Hemorrhagic	↑	↑	↔	↔
Vasculitis	↑↑	↑	↔	↔
Infectious				
Bacterial	↑↑↑	↑↑	↓↓	↑/↔
Viral	↑↑	↑↑	↔	↑/↔
Fungal	↑↑	↑	↓↓	↑/↔
Toxic-metabolic	↔	↑/↔	↔	↔
Autoimmune/inflammatory	↑↑	↑/↔	↔/↓	↑/↔
Metastases/neoplastic	↑/↔	↑/↔	↔	↔
Iatrogenic	↔	↔	↔	↔
Neurodegenerative	↔	↑/↔	↔	↔
Systemic/seizures/structural	↔	↑/↔	↔	↔

↑ = increased; ↑↑ = greatly increased; ↑↑↑ = markedly increased; ↔ = equivocal/unchanged; ↓ = decreased; ↓↓ = greatly decreased; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

disease progresses (eg, 1-Hz periodic complexes in CJD). Accordingly, the absence of these findings should not dissuade further testing for common causes of RPD in at-risk patients. Repeat testing may be required to support the diagnosis, determine the cause of deterioration or new fluctuations, and assess response to treatment.

WHAT ADDITIONAL TESTS MAY CLARIFY THE CAUSE OF RAPIDLY PROGRESSIVE DEMENTIA?

Good biomarkers provide objective measures of biological or pathogenic processes that may be applied to stratify disease risk or prognosis, inform clinical diagnosis, and monitor response to interventions. Established and emerging disease-specific biomarkers should be requested to rule in or rule out specific diagnoses in patients once the differential diagnosis has been sufficiently narrowed using common tests. A clear need exists to develop and apply disease-specific

CASE 13-3

A 65-year-old man with a history of psoriatic arthritis and family history of late-onset Alzheimer disease presented from hospice care for a second opinion concerning the cause of RPD. Ten months earlier, he had developed a low-grade fever with no cause detected despite extensive investigations. He had continued to experience intermittent fevers associated with a rapid decline in mental status, declining gait, and urinary incontinence over the ensuing 3 months. He also developed second-degree heart block requiring pacemaker placement (MRI compatible). Testing at that time established normal MRI of the brain and spine without contrast enhancement. CSF studies were notable for hypoglycorrhachia (glucose of 26 mg/dL) and positive 14-3-3 protein. He continued to decline, becoming unable to speak, walk, or feed himself within 6 months of symptom onset, leading to a diagnosis of probable Creutzfeldt-Jakob disease.

Upon presentation to a tertiary care center for further assessment, he was akinetic with responses limited to yes or no. He was cachectic and afebrile. Common tests were repeated. Serum studies were normal. No lesions were apparent on repeat MRI of the brain and spine with contrast. Repeat CSF studies redemonstrated low glucose (31 mg/dL). Body imaging was requested to screen for occult infections, granulomatous disease, or disease-associated neoplasms, disclosing several enlarged mediastinal lymph nodes and thyroid nodules. Fludeoxyglucose positron emission tomography (FDG-PET) demonstrated broadly distributed hypermetabolism within the cardiac myocardium, mediastinal and thyroid nodules, and spinal canal (most pronounced along the sacrum) (FIGURE 13-5). Core needle biopsy of the thyroid confirmed granulomatous inflammation, establishing the diagnosis of sarcoidosis. High-dose methylprednisolone was started, leading to marked improvement in his mental status within 1 week. Infliximab was added, and he was discharged to inpatient rehabilitation. Serial follow-up confirmed ongoing improvement in neurologic function over the following year.

biomarkers when assessing for and managing RPD, with the goal of leveraging test results to support the diagnosis and inform treatment and counseling recommendations.

Biomarkers of Creutzfeldt-Jakob Disease

Biomarker development over the past 3 decades has greatly advanced the antemortem diagnosis of CJD. In particular, the development of an RT-QuIC assay capable of detecting minute amounts of abnormal prion proteins within CSF has transformed the diagnostic approach to CJD, with sensitivity of second-generation assays exceeding 90% and near-perfect specificity in cohorts with suspected CJD.^{17,65,66} These findings justify the integration of RT-QuIC within updated CJD diagnostic criteria²⁴⁻²⁶ and support testing in any patient in whom prion disease is suspected. Second-generation RT-QuIC assays for human prion disease are performed in the United States on CSF samples submitted to the

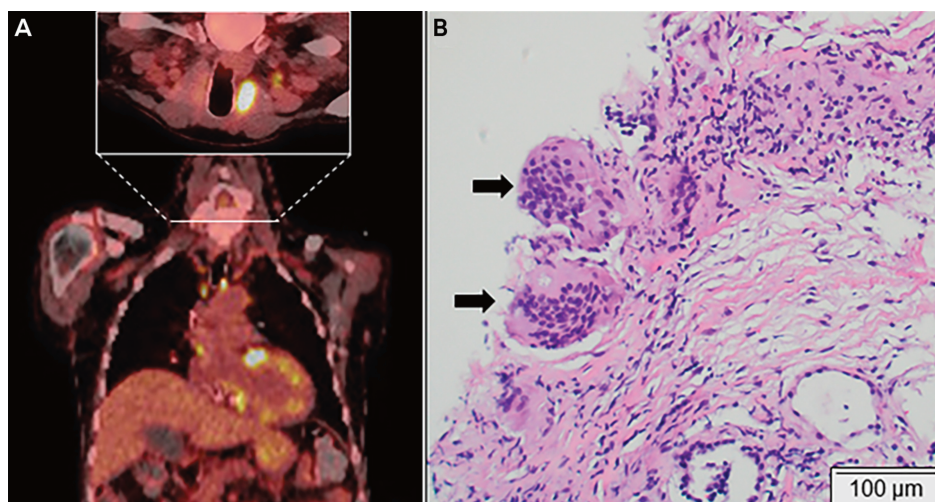


FIGURE 13-5 Imaging of the patient in **CASE 13-3**. **A**, Fludeoxyglucose positron emission tomography (FDG-PET) imaging shows increased metabolism within mediastinal, thyroid (*inset*), and myocardial tissues. **B**, Hematoxylin and eosin (H&E)-stained needle core biopsy of the thyroid shows non-necrotizing granulomatous inflammation with giant cells (*arrows*).

Unexpected findings on routine/common CSF tests should prompt evaluation for other causes of rapidly progressive dementia (RPD). Hypoglycorrhachia is a particularly rare finding in RPD, associated with a relatively limited differential diagnosis, including infectious, infiltrative (eg, granulomatous), and neoplastic causes. The history of fever of unknown origin and heart block provide additional clues to the ultimate cause of RPD in this patient, whereas the positive 14-3-3 protein in a patient with biopsy-proven sarcoidosis exemplifies the nonspecific nature of this marker of neuronal damage/loss.

COMMENT

National Prion Disease Pathology Surveillance Center at Case Western Reserve University in Cleveland, Ohio.

A positive RT-QuIC leaves little doubt as to the underlying cause of RPD; only one of 450 RT-QuIC–positive patients who underwent autopsy at the National Prion Disease Pathology Surveillance Center had a non-CJD diagnosis (Alzheimer disease and vascular cause of dementia).¹⁷ However, a negative test may still raise important questions. In the largest series conducted to date, younger age and male sex were associated with false-negative reporting, as were analyses on “noncolorless” CSF samples. Greater odds of false-negative reporting were also noted in patients with fatal familial insomnia (inherited and sporadic), Gerstmann-Straussler-Scheinker syndrome, variably protease-sensitive proteinopathy, and the VV1 and MM2 subtypes of sporadic CJD.¹⁷ These findings suggest that patient-, sample-, and disease-specific factors may affect assay performance. Careful interpretation of results is required when faced with negative RT-QuIC results, particularly when other diagnostic tests (eg, MRI and other CSF biomarkers) implicate CJD (CASE 13-5).

CASE 13-4

A 47-year-old woman with celiac disease and migraines presented with a 2-month history of diffuse holocephalic headaches associated with progressive confusion, personality changes, and memory loss. MRI of her brain showed diffuse temporal lobe T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity, with left greater than right sulcal effacement and additional T2/FLAIR signal spanning the splenium of the corpus callosum (FIGURE 13-6A). An urgent EEG showed bilateral temporoparietal sharp waves with a right-sided predominance. Diagnostic lumbar puncture confirmed pleocytosis (19 white blood cells/mm³, lymphocytic predominant) with normal protein and glucose. Acyclovir, broad-spectrum antibiotics, and IV steroids were promptly provided for presumed encephalitis, and the patient was admitted to the neurology service for further management. Her mental status improved slightly following the initiation of steroids, and she became alert to person, place, and year. Her speech was slow but fluent. No focal deficits were noted on examination. Infectious studies returned negative, and antimicrobial agents were discontinued. A diagnosis of autoimmune encephalitis was considered. Blood and CSF was sent for autoantibody testing, and empiric high-dose methylprednisolone was started together with plasma exchange.

No improvement was noted in the patient’s condition. Imaging was repeated 10 days later and demonstrated persistent T2/FLAIR mesial temporal hyperintensity with increasingly expansile appearance of the left temporal lobe and callosal lesions (FIGURE 13-6B). Stereotactic biopsy of the left callosal lesion was pursued given the lack of interval response. Histopathologic analyses confirmed diffuse astrocytic glioma with molecular features suggestive of glioblastoma (World Health Organization Grade IV). The patient was transferred to the neurosurgical service for further treatment.

The value of RT-QuIC is amplified when interpreted together with other available biomarkers of neuronal injury. Although total tau is not a specific biomarker—elevated levels are recorded in patients with neuronal injury or degeneration from multiple causes—elevations above approximately 1150 pg/mL are reported in more than 90% of patients with probable or definite CJD.^{17,18} CSF 14-3-3 protein may add incremental value in the RPD, although the nonspecific nature of this marker and inferior sensitivity relative to neuroimaging (T2/FLAIR and diffusion-weighted imaging changes in the cortical ribbon and deep nuclei) and other CSF biomarkers (ie, RT-QuIC and total tau) have reduced enthusiasm for its use in the diagnosis of CJD.¹⁸ The application of blood-based biomarkers that may inform CJD diagnosis and disease course continue to be explored, including nonspecific markers of neuroaxonal injury (eg, neurofilament light chain and total tau).⁶⁷⁻⁶⁹

Although false-negative results are possible with any test for CJD, true negative results are more likely. Unexpected negative results therefore warrant prompt reconsideration of the differential diagnosis and expansion of

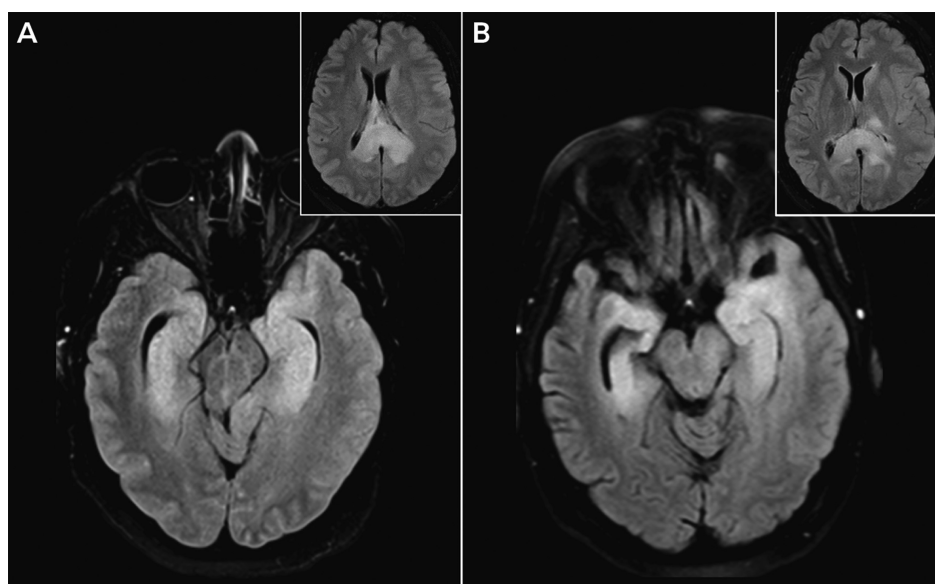


FIGURE 13-6 Imaging of the patient in **CASE 13-4**. Axial fluid-attenuated inversion recovery (FLAIR) images show bilateral temporal lobe and corpus callosal lesions (*insets*) at presentation (**A**) and 10 days later following empiric immunosuppressant treatment (**B**).

This patient with expansile bitemporal lesions and CSF pleocytosis was appropriately treated for infectious and autoimmune/inflammatory causes of rapidly progressive dementia. The lack of objective improvement following empiric treatment appropriately prompted reconsideration of the diagnosis and further testing, including brain biopsy. In retrospect, the callosal lesion provided an important clue to the ultimate etiology, recognizing the association between midline-crossing splenial lesions and glioblastoma, lymphoma, and progressive multifocal leukoencephalopathy.

COMMENT

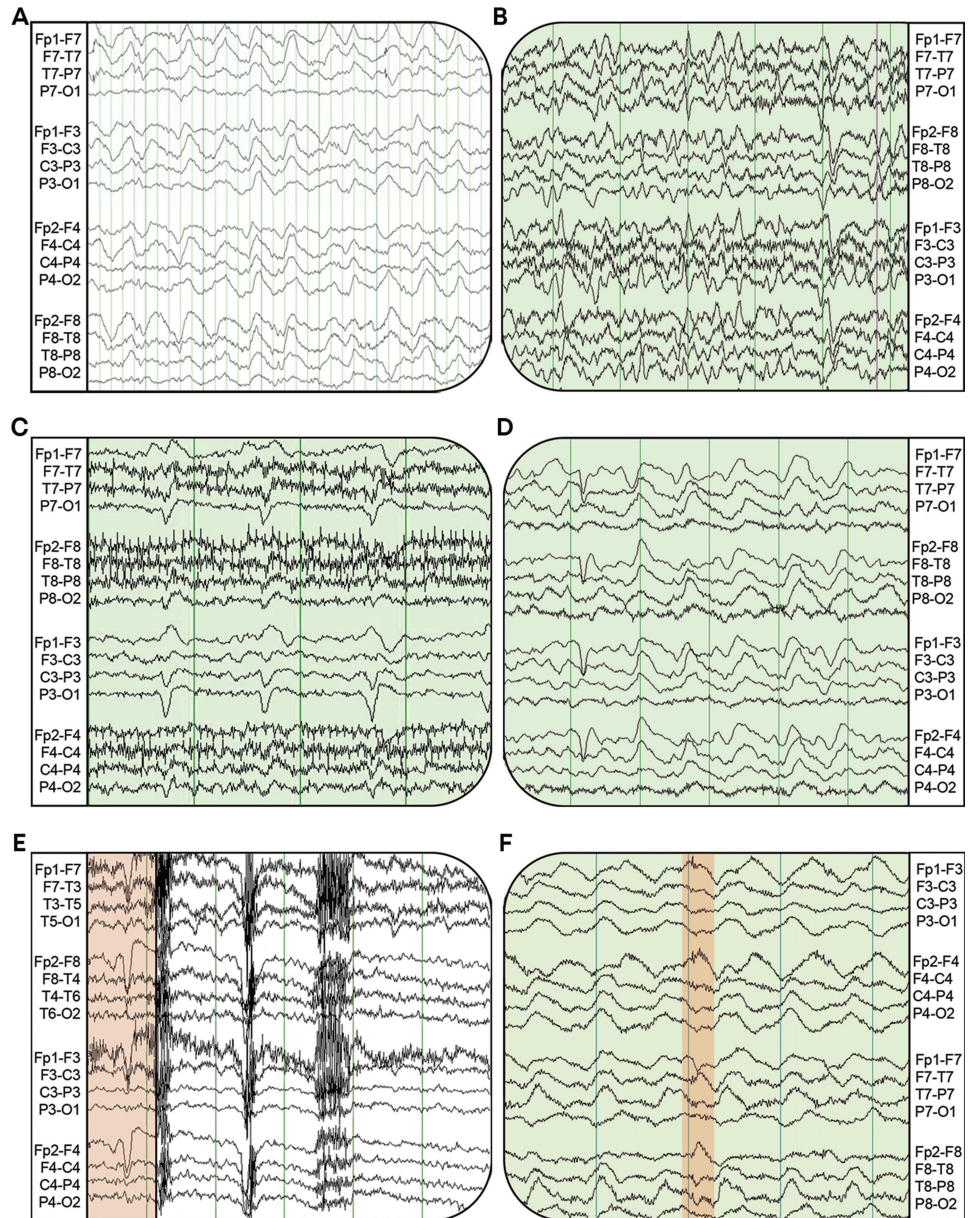


FIGURE 13-7

Common EEG findings in patients with rapidly progressive dementia (RPD). **A**, Generalized diffuse slowing in a patient with RPD due to Alzheimer disease. **B**, Triphasic waves in a patient with RPD associated with metabolic encephalopathy. **C**, Lateralized (left) periodic discharges in a patient with RPD associated with a left occipital glioma and frequent complex partial seizures. **D**, Frontal intermittent rhythmic delta activity in a patient with hydrocephalus associated with cryptococcal meningitis. **E**, Frontal infraslow activity (*light brown shaded area*) preceding a faciobrachial dystonic seizure in a patient with RPD associated with leucine-rich glioma inactivated protein 1 (LGI1) autoantibodies. **F**, Extreme delta brush in a patient with autoimmune RPD associated with *N*-methyl-D-aspartate (NMDA) receptor autoantibodies, *light brown shaded area* highlighting segment with beta rhythm superimposed on the crests of delta waves. All images displayed in traditional 10-20 placement; distance between green vertical bars = 1 second.

the clinical evaluation. The importance of this point is supported by findings from autopsy series that consistently report non-prion disease diagnoses in more than 30% of the brains of patients with suspected CJD submitted to prion disease surveillance centers. Autoimmune encephalitis accounts for a substantial proportion of these cases, establishing the potential for treatable forms of RPD to masquerade as CJD.^{5,6} These findings emphasize the need to interpret test results together with findings from clinical history, examination, common tests, and other disease-specific measures. Stated more simply, good tests are important when evaluating patients with RPD, but good clinical acumen is critical.

Biomarkers of Neurodegenerative Diseases

AD is the most common cause of dementia, accounting for between 60% and 80% of all cases of typically progressive dementia and for the majority of RPD caused by typical neurodegenerative diseases.^{1,6,14,31} Cerebral deposition of amyloid- β (A β) plaques occurs relatively early in AD, with in vivo detection of A β plaques strongly associated with the presence of AD neuropathologic change at death.⁷⁰ Several PET tracers of A β are now approved for clinical use, permitting in vivo visualization of AD pathology. However, the high frequency of AD neuropathology with increasing age⁷¹⁻⁷³ and potential coassociation between amyloid plaques and prion pathology limits diagnostic application in older patients with RPD.⁷⁴ In contrast, the accrual of tau neuropathology is closely linked to the emergence of symptoms, syndromic presentation, and progression of AD dementia, raising the possibility that tau PET may be used to identify patients with rapidly progressive AD.

Early studies have identified the performance characteristics and relative specificity of tau PET markers of AD-associated neurofibrillary tangles and other tau neuropathology.⁷⁵ These studies inform the patterns of deposition, expected rates of accrual, and patterns of longitudinal spread in patients with AD.⁷⁶⁻⁷⁸ Tau PET measures have also been evaluated in study participants with Lewy body disease,⁷⁹ progressive supranuclear palsy,⁸⁰ and corticobasal syndrome,⁸¹ establishing patterns of tracer retention that differentiate patients with these neurodegenerative diseases. CJD is associated with profound elevations in soluble tau, without cerebral tau deposition on autopsy⁸² or substantial tau PET tracer retention.¹⁹ Whether clinically approved tau PET tracers can be practically applied to differentiate between patients with RPD caused by various neurodegenerative diseases remains to be determined.

Beyond neuroimaging, biofluid biomarkers of specific neurodegenerative disease continue to be developed. Measures of CSF A β (A β ₄₂ and A β ₄₀), total tau, and phosphorylated tau at position 181 (p-tau₁₈₁) (AD biomarkers) are now available through commercial laboratories. Plasma markers of A β have recently been developed,^{83,84} with selected measures approved for clinical use in the United States and measures of phosphorylated tau expected soon.⁸⁵

The ability to simultaneously measure multiple analytes—including common and specific tests—presents a substantial advantage for biofluid biomarkers, with the potential to use aggregate data to improve diagnoses and inform the pathologic processes that contribute to rates of progression in patients with RPD. To this end, CSF biomarker ratios have been shown to differentiate patients with RPD due to CJD from patients with RPD due to AD, with greater total tau to phosphorylated tau ratios identifying patients with CJD (and ratios increasing

KEY POINTS

- CSF 14-3-3 protein may add incremental value in the assessment of RPD, although the nonspecific nature of this marker and inferior sensitivity have reduced enthusiasm for its use in the diagnosis of CJD.
- Unexpected negative test results in patients with RPD warrant prompt reconsideration of the differential diagnosis and expansion of the clinical evaluation.
- Alzheimer disease is the most common cause of dementia, accounting for between 60% and 80% of all cases of typically progressive dementia and for the majority of RPD caused by typical neurodegenerative diseases.
- The ability to simultaneously measure multiple analytes presents a substantial advantage for biofluid biomarkers, with the potential to use aggregate data to improve diagnoses and inform the pathologic processes that contribute to rates of progression in patients with RPD.
- Although antibodies may be associated with specific clinical syndromes, atypical presentations are the rule, not the exception, in RPD.
- Antibody testing should be performed simultaneously in serum and CSF, recognizing the superior sensitivity of antibody measures tested in specific biofluids using commercial platforms.

throughout the disease course)⁸⁶ and higher A β ₄₂/A β ₄₀ ratios identifying patients with rapidly progressive AD.⁸⁷

Biomarkers of Autoimmune/Inflammatory Causes of Rapidly Progressive Dementia

Although many autoimmune/inflammatory diseases present with recognizable clinical syndromes (eg, progressive psychiatric and neurologic impairment associated with NMDA receptor autoantibodies, paraneoplastic limbic encephalitis associated with Hu antibodies),⁶¹ clinical symptoms and signs may easily be mistaken for CJD (CASE 13-2)^{5,6,88} or common neurodegenerative diseases, contributing to delays in diagnosis and treatment. These findings emphasize the need for biomarkers that identify patients with autoimmune/inflammatory causes of RPD.

CASE 13-5

A 49-year-old woman presented with a 12-month history of increasing anxiety and forgetfulness. She had forgotten how to operate her phone or turn on her car. Her verbal output decreased 6 months into her symptomatic course, and she progressed to muteness. She had developed diffuse myoclonic jerks, exacerbated by startle. A diagnosis of Creutzfeldt-Jakob disease (CJD) was considered, and appropriate testing was ordered at an outside hospital. Brain MRI was reported as normal. EEG showed generalized slowing (mixed delta/theta range), more pronounced on the left. Routine CSF analyses were normal, with negative 14-3-3 protein (measured via a regional laboratory). A course of empiric steroids and IV immunoglobulin (IVIg) were provided, without improvement. No lesions were observed on body imaging. The patient continued to decline, warranting transfer to an academic hospital for reassessment.

On assessment, the patient was nonverbal and bedbound with dystonic posturing of her upper extremities. Diagnostic testing was repeated, with MRI of her brain demonstrating increased T2/fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging signal within the left-sided cortical ribbon, most pronounced in frontal, parietal, and temporal areas (FIGURE 13-8). CSF was acellular with normal protein and glucose. No disease-associated autoantibodies were detected in blood or CSF. CSF was sent to a national prion disease reference center: 14-3-3 protein was positive, total tau was markedly elevated (>4000 pg/mL), and a second-generation real-time quaking-induced conversion (RT-QuIC) assay for abnormal human prion protein was negative.

The patient was diagnosed with CJD. She was placed on hospice care and died 3 months later. A brain-only autopsy was performed and demonstrated neuronal loss, gliosis, and spongiform changes diffusely within the cortical ribbon. Granular deposits were detected using a monoclonal antibody to the prion protein. Mutations within the prion protein gene were not detected. The final diagnosis was definite sporadic CJD (V_{V1} subtype).

Antibodies against neural-specific antigens represent obvious biomarkers of autoimmune/inflammatory causes of RPD. Patients at higher risk include younger patients and those with acute or subacute declines in cognitive function. The early emergence of neuropsychiatric features, seizures, or movement disorders may provide clues in addition to objective measures of inflammation on MRI and in CSF (common tests). Antibody testing should also be considered in individuals with stereotyped syndromes, including faciobrachial dystonic seizures and hyponatremia (associated with LGI1 autoantibodies) and prominent sleep dysfunction, bulbar symptoms, and gait dysfunction (associated with immunoglobulin-like cell adhesion molecule 5 [IgLON5] antibodies).⁴⁰ Although antibodies may be associated with specific clinical syndromes, atypical presentations are the rule, not the exception, in RPD. For this reason, it is prudent to measure panels or groups of antibodies, providing broader diagnostic

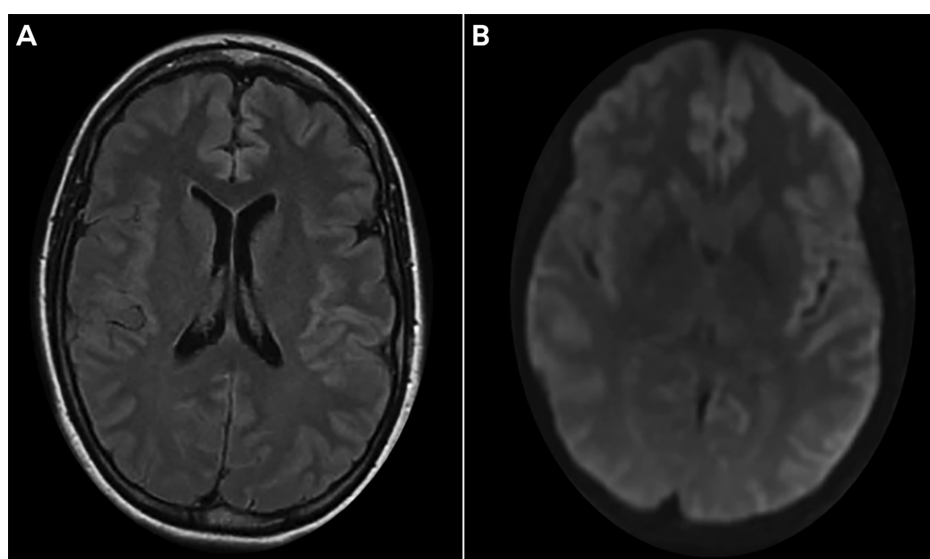


FIGURE 13-8 Imaging of the patient in **CASE 13-5**. Axial fluid-attenuated inversion recovery (FLAIR) (A) and diffusion-weighted image (B) show increased signal within the cortical ribbon, most prominent in left frontal, parietal, and temporal areas.

Sensitive and specific RT-QuIC assays for prions have greatly improved the antemortem diagnosis of CJD, justifying their integration within revised CJD diagnostic criteria. However, as this case exemplifies, good tests are not perfect tests. This reality emphasizes the need to interpret specific test results together with clinical findings and the results of other investigations and the importance of neuropathology in validating clinical acumen, assessing test performance, and establishing the definitive cause of rapidly progressive dementia.

COMMENT

coverage guided by the clinical scenario. When possible, antibody testing should be performed simultaneously in serum and CSF, recognizing the superior sensitivity of antibody measures tested in specific biofluids using commercial platforms (eg, NMDA receptor autoantibodies in CSF^{89,90} and LGI1 autoantibodies in serum³⁷).

Rapid evolution in antibody discovery requires the ordering clinician to maintain a reasonable knowledge of clinically relevant autoantibodies, available tests, and their limitations. The corollary of this is the need to recognize antibodies with unclear or less specific associations with autoimmune/inflammatory brain disease to avoid premature diagnostic closure and unnecessary diagnostic testing (eg, malignancy screening) and treatments.^{91,92} This list includes isolated blood-based antibodies against the ganglionic nicotinic acetylcholine receptor, voltage-gated calcium channel (P/Q-type), and voltage-gated potassium channel complex (without LGI1 or contactin-associated proteinlike 2 [CASPR2] autoantibodies).^{91,93} Low-titer antibodies against GAD-65 and antithyroperoxidase and thyroglobulin antibodies are frequently detected in patients without definite neurologic disease and healthy individuals, warranting further scrutiny.⁹⁴⁻⁹⁶

Cerebral amyloid angiopathy with related inflammation deserves special mention as a disease arising from an autoimmune/inflammatory response against vascular amyloid deposits. Patients with cerebral amyloid angiopathy with related inflammation typically present with RPD, with symptoms arising over weeks to months and focal signs localizing to affected brain regions. Advances in neuroimaging allow the diagnosis to be made with a high degree of certainty in most patients (revealing asymmetric white matter lesions associated with microscopic or macroscopic hemorrhages),⁹⁷ with further support from CSF biomarkers confirming low A β 40 and A β 42 and elevations in phosphorylated tau.⁹⁸ Biopsy may still be required to establish the diagnosis in patients with inconsistent or atypical imaging findings.⁹⁹ Clinical and biomarker features associated with favorable responses to treatment and long-term prognoses continue to be recognized.^{98,100}

Other Tests to Consider

Additional tests may be indicated in selected patients. Tissue cultures, IgG/IgM antibody measures, and polymerase chain reaction (PCR) tests for specific pathogens should be ordered when an infectious agent is suspected. Next-generation metagenomic sequencing is a promising new technology for the identification of novel infectious pathogens in the research setting with emerging clinical applications.¹⁰¹ Nerve conduction studies and EMG may be used to look for peripheral nerve involvement, which may broaden or narrow the differential diagnosis.

Direct tissue evaluation may be necessary when common and specific tests have failed to reveal a definitive etiologic diagnosis. The diagnostic yield of brain biopsy varies but may be as high as 65% in well-evaluated populations with RPD.¹⁰² Brain biopsy may be especially important when neoplastic (eg, CNS lymphoma) or autoimmune/inflammatory (eg, small vessel vasculitis, encephalitis of unclear origin) causes of RPD remain in the differential diagnosis given the importance of a tissue-based diagnosis in optimizing treatment selection and duration of administration.^{103,104} Risks associated with biopsy are well recognized, including hemorrhage, stroke, and infection. These risks must

be balanced against the likelihood of a benefit associated with a definitive diagnosis and specific treatment plan. A thorough evaluation should be completed before pursuing brain biopsy. This may include assessment of peripheral body tissues looking for lower-risk biopsy targets, including peripheral lymphadenopathy or granulomatous disease identified on body imaging. Blind muscle or skin biopsy may be considered in neuroinvasive or proliferative diseases with potential systemic involvement (eg, intravascular lymphoma, neurosarcoidosis).¹⁰⁵

DOES MY PATIENT HAVE A TREATABLE CAUSE OF RAPIDLY PROGRESSIVE DEMENTIA?

The discovery of immune-mediated causes of RPD underscores the need to improve the diagnosis of RPD early in the symptomatic course when treatments are most likely to halt or reverse declines in cognition. Accordingly, treatment-responsive causes of RPD should be considered at each step of the diagnostic evaluation. Enhancement on neuroimaging or focal T2 hyperintensities may point toward an autoimmune/inflammatory condition (eg, limbic encephalitis), CNS infection, granulomatous disease, cerebral amyloid angiopathy with related inflammation, a nutritional/metabolic deficit (eg, Wernicke-Korsakoff syndrome), or other potentially treatable cause of RPD. Imaging studies should be closely followed by direct CSF measures, including common and specific tests for inflammation and testing for disease-associated autoantibodies.

Empiric treatment should be promptly considered when infection or acute nutritional deficiencies are suspected. Antivirals (eg, acyclovir) or antibiotics (or both) should be provided to any patient suspected of having a CNS infection. Likewise, high doses of parenteral thiamine (vitamin B₁) should be administered to any patient with potential nutritional deficiency and RPD. Thiamine repletion is especially critical in patients with extraocular movement abnormalities (including gaze-evoked nystagmus) and ataxia, given the high likelihood of Wernicke-Korsakoff syndrome. The low cost of thiamine and low potential for meaningful side effects argues for a low threshold for thiamine repletion in at-risk patients. When deciding on the optimal dose of thiamine, the mantra “some is good, more is better” applies.¹⁰⁶ Doses of parenteral thiamine above 200 mg provided 2 to 3 times a day for 5 days are likely sufficient to correct the brain thiamine deficiency and prevent further damage.

Immunotherapies should be provided to patients with possible autoimmune encephalitis once blood and CSF has been collected for autoantibody testing. The emphasis on early treatment acknowledges the relationship between shorter time to treatment and better long-term outcomes in this population.^{37,47,107-109} Patient-specific needs and practical concerns (ie, mode of delivery, venous access, cost) will influence the therapeutic choice. A short-course of high-dose IV steroids is the most common empiric therapy but may not be appropriate in patients with difficult-to-manage blood sugars or prominent psychosis. IV immunoglobulin (IVIg) is another common first-line therapy, although the comparatively high cost, questionable efficacy in the initial management of LGI1 antibody encephalitis,^{110,111} and prothrombotic risks present reasons for pause.

Although it is important to consider the need for empiric therapy early in the disease course, the benefits of early treatment must be balanced against the potential diagnostic costs. Granulomatous disease and hematologic malignancies

KEY POINTS

- Rapid evolution in antibody discovery requires the ordering clinician to maintain a reasonable knowledge of clinically relevant autoantibodies, available tests, and their limitations.
- Direct tissue evaluation may be necessary when common and specific tests have failed to reveal a definitive etiologic diagnosis in a patient with RPD.
- The diagnostic yield of brain biopsy varies but may be as high as 65% in well-evaluated populations with RPD.
- The discovery of immune-mediated causes of RPD underscores the need to improve the diagnosis of RPD early in the symptomatic course when treatments are most likely to halt or reverse declines in cognition. Accordingly, treatment-responsive causes of RPD should be considered at each step of the diagnostic evaluation.
- Empiric treatment should be promptly considered when infection or acute nutritional deficiencies are suspected.
- Thiamine repletion is especially critical in patients with extraocular movement abnormalities (including gaze-evoked nystagmus) and ataxia, who may be at the highest risk of Wernicke-Korsakoff syndrome.
- Immunotherapies should be provided to patients with possible autoimmune encephalitis once blood and CSF has been collected for autoantibody testing.

may respond to empiric steroids, albeit temporarily, with a high likelihood of relapse without escalation of treatment. High-dose methylprednisolone may also impede postsurgical healing in patients who require invasive diagnostic or therapeutic procedures. For these reasons, empiric treatment may need to be deferred pending completion of necessary tests and procedures.

Comorbid diseases are common in patients with RPD, including cerebrovascular disease, mood disorders, and occult or frank sleep dysfunction (eg, sleep-disordered breathing or nocturnal movements). Evaluation for and treatment of potential secondary modifiers of dementia may promote brain health and improve quality of life for patients and caregivers, although these comorbid conditions have not been shown to alter the time to severe dementia or death in older patients with RPD.¹

NEXT STEPS IN RAPIDLY PROGRESSIVE DEMENTIA

The cases of reversible dementia featured in this article emphasize the need for sensitive and specific markers of treatment-responsive RPD. On this front, the rise of CSF and blood-based biomarkers shows promise. Preliminary findings suggest that patients with antibody-mediated impairment may exhibit low-normal CSF markers of neuronal injury (visinin-like protein 1 [VILIP-1] and total tau) and synaptic proteins (synaptosomal-associated protein of 25 kDa [SNAP-25], neurogranin).¹¹² Biomarker differences may reflect disease-specific differences in pathophysiology, with decreases in synaptic proteins in patients with treatment-responsive autoimmune/inflammatory diseases resulting from antibody-mediated internalization of cell-surface receptors,^{113,114} a pattern opposite to that observed in patients with neurodegenerative disease.¹¹⁵ These biomarkers (or biomarker panels) may eventually be applied to improve recognition of patients with potentially reversible RPD early in the disease course. Recent advances in PET tracers also provide promise, with the potential to leverage emerging PET markers of neuroinflammation to identify patients with inflammatory contributions to RPD.¹¹⁶

Longitudinal studies applying standardized definitions of RPD and systematic protocols are needed to clarify the optimal approach to diagnosis and management in RPD. Ideally, these studies will include provisions for serial biofluid and neuroimaging biomarkers. Serial measures are required to inform the relationship between biomarkers and specific causes of RPD and to decode the mechanistic contributors to RPD, necessary prerequisites to the development and implementation of disease-specific treatments.

CONCLUSION

A pragmatic and organized approach to the evaluation of patients with RPD is needed to support efficient and accurate diagnosis. Widely accessible blood and urine tests, neuroimaging, CSF analyses, and EEG should be obtained in all patients and the results used to direct further diagnostic evaluation. Specific tests should be requested in selected patients to confirm or refute specific diagnoses. A surprising proportion of RPD cases are potentially treatable, with long-term outcomes dependent on the timely administration of appropriate therapy. This realization emphasizes the need to consider reversible causes early in the diagnostic assessment and to empirically treat patients when appropriate.

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VIDEO LEGEND

VIDEO 13-1

Faciobrachial-crural seizure in a patient with leucine-rich glioma inactivated protein 1 (LGI1) antibody encephalitis. Video shows a 76-year-old woman with LGI1 antibody encephalitis. The patient is engaging in a cognitive task (counting backward). Speech arrest occurs at 30 seconds, with associated involuntary, synchronous dystonic contracture of the left face, arm, and distal lower limb consistent with a faciobrachial-crural dystonic seizure.

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KEY POINTS

- Evaluation for and treatment of potential secondary modifiers of dementia may promote brain health and improve quality of life for patients and caregivers.
- Longitudinal studies applying standardized definitions of RPD and systematic protocols are needed to clarify the optimal approach to diagnosis and management of RPD.

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