Causes of rapidly progressive dementia (RPD) are distinguished by the evolution of symptoms and signs over a number of days, weeks or months. The causes of RPD are diverse, spanning the spectrum of primary and secondary neurological diseases.

The focus of history taking, examination and cognitive assessment is to elicit specific features supportive of an etiologic diagnosis. Clinical assessment should be used to focus investigations and treatments.

Attention must be directed to identifying potentially reversible causes of RPD. Patients with fluctuating disease and symptoms of limbic encephalitis (acute-onset memory loss, behavioral changes and seizures) may be particularly responsive to treatments.

Low-risk, accessible tools with high diagnostic yield – serum screening tests, cerebrospinal fluid analysis, MRI of the brain and EEG – should be completed in all patients. Expanded/extended testing should be requested to target specific diagnoses once the initial assessment is completed.

Invasive testing should be reserved for refractory cases. A brain biopsy may be required to make the diagnosis. The decision to proceed with invasive testing should weigh the potential benefits against the potential periprocedural risks.

A trial of immune-modulating treatments is recommended in patients without a specific etiologic diagnosis, once infection has been excluded.

A marked response following treatment with immune-mediating medications may be seen in antibody-mediated brain diseases and steroid-responsive encephalopathy, and should trigger specific investigations for associated autoantibodies.

A practical approach to RPD can be applied to narrow the differential diagnosis by prioritizing clinical assessment and the use of widely accessible investigations.

The goal of assessment remains to rapidly identify and intervene in patients with potentially reversible causes of RPD.
SUMMARY Making a diagnosis of rapidly progressive dementia requires practical adaptation of the skills used to assess patients with chronic causes of cognitive impairment. An expedited assessment, commensurate with the accelerated pace of the disease, is required to identify the cause of symptoms amidst a myriad of possibilities. Features upon history, physical examination and cognitive assessment that support specific diagnoses are reviewed, and a stratified approach to testing is presented. The use of readily-accessible investigations is prioritized, acknowledging the implications and applications of novel diagnostic tests. The coordinated use of clinical and laboratory measures are promoted as a means of facilitating rapid evaluation, with the ultimate goal of identifying patients with potentially reversible causes of rapidly progressive dementia.

The loss of function in patients with rapidly progressive dementia (RPD) is defined as evolving hyperacutely (over days or weeks), subacutely (over months or 1–2 years) or more rapidly than expected with a known dementia syndrome [1]. Compared with the more common chronic neurodegenerative causes of dementia, the decline in patients with RPD is readily recognized by family members and caregivers as a dramatic departure from baseline. For this reason, recognizing a patient with RPD is relatively easy, often obviating a formal review and debate of diagnostic criteria for dementia/neurocognitive disorders [2]. However, discerning the underlying cause of rapidly progressive symptoms and signs presents a decidedly greater challenge. The potential causes of RPD are extensive (Box 1), emphasizing the need for a standardized approach to evaluation, with the goal of determining cause (or at least etiologic category) and guiding interventions.

The standard approach to the clinical assessment of patients with chronic dementia also applies to the patient with RPD [3–5]. A thorough history and examination is of paramount importance to establish the baseline health status, the circumstances surrounding symptom onset, and the order and rate of progression of symptoms. Unique to the evaluation of the patient with RPD is the need to complete the assessment at a speed that matches the pace of the disease. Accordingly, clinical assessment and investigations should be prioritized in an effort to readily identify potentially treatable causes of RPD. This is best accomplished within the framework of a stratified diagnostic strategy that can be applied broadly by physicians operating in a wide variety of clinical settings.

RPD & the differential diagnosis
Although no population-based studies estimating the incidence or prevalence of RPD have been published, case series exploring the diagnosis in patients with RPD attest to the diversity of pathogenic mechanisms. A definitive cause of RPD was identified in 95.4% (644 out of 675) of patients included in the five largest case series (Figure 1) [6–10]. Of these, spongiform encephalopathy attributed to Creutzfeldt–Jakob disease (CJD) represented the most common diagnosis, accounting for 58.5% (377 out of 644) of cases. Cumulatively, neurodegenerative diseases, such as Alzheimer’s disease, represented the second most common cause of RPD (22.5%; 145 out of 644) [6–10]. Remarkably, 18.8% (121 out of 644) of cases were attributed to potentially treatable conditions [6–10], emphasizing the critical importance of a thorough and complete diagnostic evaluation in patients with RPD. Importantly, potentially treatable causes of RPD in these series included a number of disorders best characterized as acute encephalopathies (i.e., B12 deficiency, Wernicke’s encephalopathy and toxic/metabolic encephalopathies), but not patients diagnosed with delirium. From a practical perspective it remains important to entertain the diagnosis of delirium in all patients presenting with acute changes in mental status, disturbance in attention, disorganized thinking and an altered level of consciousness [2], recognizing the high mortality and morbidity associated with diagnosis [11], and the high potential for reversibility.

Developing a rapid approach to the patient with RPD
The systematic approach to RPD does not require the assessing clinician to develop an entirely new skill set, but rather to concentrate their skills on eliciting specific aspects of the patient history and physical examination (Table 1), and on completing the cognitive assessment. This information, in turn, must be used to further refine investigations and treatments with the goal of discerning the cause of RPD among a myriad of possibilities.
Refining the history taking
The history should begin by clarifying the baseline health and cognitive status of the patient. The remainder of questions should be posed to document relevant risk factors, especially cerebrovascular risk factors or exposures that may contribute to the presentation (including past medical history, medications, social habits, nutritional status and family history), determine pre-eminent and associated symptoms affecting general health and the integrity of the nervous system, and establish the presence of cognitive and/or behavioral impairment that significantly affects the patient's activities of daily living. Care must be taken to clearly delineate presenting symptoms and signs, and to determine disease progression, as this information is critical to establish the diagnosis of RPD, and to evaluate the potential relationship between disease onset and relevant exposures [12]. Owing to the high degree of cognitive impairment anticipated in patients with RPD, the patient history must be corroborated with a family member or caregiver. Additional aspects to consider early in the history include the need to differentiate RPD from acute changes superimposed on more chronic cognitive impairment, the implications of age, gender, course and rate of disease progression on the differential diagnosis, and the possibility that symptoms may represent limbic encephalitis.

Is it really a RPD?
In studies of chronic dementia, caregivers may underestimate the duration of illness due to a tendency to equate major incidents with the onset of disease (e.g., loss of employment, getting lost, social lapses and first seizure) [13]. Prior related symptoms are commonly attributed to 'normal aging,' or are overlooked. Thus, to construct a true timeline, questions should specifically inquire about changes in cognition or behavior. Once the diagnosis of RPD is confirmed, information at each stage of the patient history should be used to refine the differential diagnosis, beginning with the age of the patient.

Age of the patient
Autoimmune/inflammatory [9,14,15], infectious [16], paraneoplastic [1], and genetic/metabolic/mitochondrial diseases abound during the first five decades of life, and account for many cases of RPD in younger patients (<50 years of age) [8,9]. Conversely, the percentage of patients

Box 1. Primary and secondary causes of rapidly progressive dementia, divided by etiology.

**Neurodegenerative**
- Alzheimer's disease
- Corticobasal degeneration
- Dementia with Lewy bodies
- Familial spastic paraparesis
- Frontotemporal lobar degeneration
- Motor neuron disease
- Progressive supranuclear palsy
- Prion disease (i.e., Creutzfeldt-Jakob)
- Progressive subcortical gliosis

**Autoimmune/inflammatory**
- Acute disseminated encephalomyelitis
- Antibody-mediated encephalomyelitis
- Anti-GAD65 autoimmunity
- Behçet's disease
- Celiac sprue
- Limbic encephalitis
- Multiple sclerosis
- Neuropsychiatric lupus
- Sarcoidosis
- Sjögren's syndrome
- Steroid-responsive encephalopathy

**Vascular**
- CADASIL
- Cerebral amyloid angiopathy
- CNS vasculitis
- MELAS
- Strategic infarction
- Subdural hematoma
- Vascular dementia

**Metabolic**
- Cerebrotendinous xanthomatosis
- Extrapontine myelinolysis
- Liver failure
- MELAS
- NBIA
- Neuronal ceroid lipofuscinosis
- Nutritional deficiency (i.e., vitamin B1, B3 or B12, or folate)
- Porphyria
- Renal failure

For further reviews of potential causes see [1,16,86,87]. Secondary causes of rapidly progressive dementia.

†Includes primary and secondary (infectious, neoplastic, connective tissue disease and drug-induced) causes of vasculitis.

‡Viral causes include H1N1, herpes simplex virus, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, West Nile virus, Epstein–Barr virus and human herpes virus-6. Bacterial causes include spirochetel, Bartonella, Mycoplasma, Tropheryma, Mycobacterial and Rickettsial agents. Fungal causes include Coccidioides, Aspergillus, Histoplasma, Cryptococcus and Blastomyces. Parasitic causes include toxoplasmosis, trypanosomiasis, granulomatous amoebic and neurocysticercosis. CADASIL: Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MELAS: Mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms; NBIA: Neurodegeneration with brain iron accumulation disorders; PRES: Posterior-reversible encephalopathy syndrome.
Box 1. Primary and secondary causes of rapidly progressive dementia, divided by etiology (cont.).

<table>
<thead>
<tr>
<th>Metabolic' (cont.)</th>
<th>Toxic'</th>
<th>Infectious'†,§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid/parathyroid dysfunction</td>
<td>Bismuth</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Heavy metal (lead, arsenic and mercury)</td>
<td>Fungal</td>
</tr>
<tr>
<td>Manganese</td>
<td>Medication-induced</td>
<td>Parasites</td>
</tr>
<tr>
<td>Radiation-induced leukoencephalopathy</td>
<td>PRES</td>
<td>Viral</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Brain metastases</td>
<td>Other</td>
</tr>
<tr>
<td>Paraneoplastic limbic encephalitis</td>
<td>Lymphomatoid granulomatosis</td>
<td>Bipolar affective disorder</td>
</tr>
<tr>
<td>Primary CNS neoplasms</td>
<td>Paraneoplastic limbic encephalitis</td>
<td>Hypoxic-ischemic encephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal pressure hydrocephalus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other psychiatric illnesses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

For further reviews of potential causes see [1,16,86,87].
†Secondary causes of rapidly progressive dementia. Includes primary and secondary (infectious, neoplastic, connective tissue disease and drug-induced) causes of vasculitis.
§Viral causes include HIV, herpes simplex virus, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, West Nile virus, Epstein–Barr virus and human herpes virus-6. Bacterial causes include spirochetal, Bartonella, Mycoplasma, Tropheryma, Mycobacterial and Rickettsial agents. Fungal causes include Coccidioides, Aspergillus, Histoplasma, Cryptococcus and Blastomyces. Parasitic causes include toxoplasmosis, trypanosomiasis, granulomatous amoebic and neurocysticercosis.
CADASIL: Cerebral autosomal-dominant arteriopathy with subacute infarcts and leukoencephalopathy; Toxoplasmosis, trypanosomiasis, granulomatous amoebic and neurocysticercosis.
MELAS: Mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms; NBIA: Neurodegeneration with brain iron accumulation disorders; PRES: Posterior-reversible encephalopathy syndrome.

Gender differences
Gender differences do not appear to associate with specific etiologic diagnoses of RPD [6-10]; however, younger patients with more frequent autoimmune causes of RPD may have been under-represented in the largest case series. Female gender is a well-established risk factor for autoimmune disease, especially during child-bearing years [20]. Female predominance is also reported in most paraneoplastic syndromes [21], anti-NMDA receptor encephalitis (81.1%) [22] and steroid-responsive autoimmune encephalopathy (SRE; 85%) [23]. Male predominance is reported with encephalopathy associated with autonctosomes against voltage-gated potassium channel (VGKC) subunits (68.8%) [24], emphasizing the need to consider the diagnosis in men with RPD – particularly those presenting with hyponatremia and seizures [25].

Course & rate of disease progression
Stratification based upon the rate of progression (developing over days to weeks versus months to years) and the course of RPD (fluctuating versus relentlessly progressive) may be used to differentiate etiologic causes of RPD. Characteristically, CJD and secondary causes of RPD exhibit the most aggressive rates of progression, with symptoms evolving over weeks to months [8]; although hyperacute presentations are described. Unique to CJD, death usually occurs within 12 months of presentation [7].

Gender differences do not appear to associate with specific etiologic diagnoses of RPD [6-10]; however, younger patients with more frequent autoimmune causes of RPD may have been under-represented in the largest case series. Female gender is a well-established risk factor for autoimmune disease, especially during child-bearing years [20]. Female predominance is also reported in most paraneoplastic syndromes [21], anti-NMDA receptor encephalitis (81.1%) [22] and steroid-responsive autoimmune encephalopathy (SRE; 85%) [23]. Male predominance is reported with encephalopathy associated with autonctosomes against voltage-gated potassium channel (VGKC) subunits (68.8%) [24], emphasizing the need to consider the diagnosis in men with RPD – particularly those presenting with hyponatremia and seizures [25].

Are rapidly progressive symptoms due to limbic encephalitis?
Limbic encephalitis is a condition characterized by rapid-onset short-term memory loss, behavioral changes and seizures [28]. Misdiagnosis is common, with many patients initially diagnosed with primary psychiatric disease [21,29]. The condition
is first suggested on history, and further supported by investigations demonstrating medial temporal lobe T2-weighted hyperintensities on MRI and inflammation within cerebrospinal fluid (CSF).

Although limbic encephalitis was originally considered to be a paraneoplastic disease associated with a poor outcome, nonparaneoplastic and potentially treatable causes are increasingly described [28,30]. Of the nonparaneoplastic syndromes, encephalopathy associated with antibodies against CNS NMDA receptors and VGKC subunits are particularly worthy of consideration, as dramatic improvements in cognition and levels of functioning may be seen in both syndromes following administration of antibody-depleting immunotherapies [22,31]. Although these diseases are more common in younger patients, patients at the extremes of age have been reported (anti-NMDA receptor encephalitis: 8 months to 84 years of age [15,32]; VGKC: 2–88 years of age [25]). Specific autoantibody testing is justified; therefore, in all patients with RPD with associated psychiatric or behavioral disturbances, and movement disorders, seizures or autonomic instability.

Additional questions

It is important to screen for additional symptoms that may associate with specific causes of RPD. Profound weight loss (not due to forgetting meal preparation, as is typically seen in neurodegenerative disorders such as Alzheimer’s disease), may herald a neoplastic or paraneoplastic cause of RPD [33]. Recurrent fevers may suggest systemic infections, autoimmune/connective tissue disease or hematologic malignancy. Marked weight loss associated with chronic diarrhea is described with Tropheryma whipplei infection causing Whipple’s disease [34]. When the onset of encephalitis is associated with intense diarrhea, a novel disorder mediated by autoantibodies against DPP6 should also be considered [35]. A history of immunosuppression (secondary to active disease or medication use) broadens the spectrum of etiologies to include opportunistic malignancies and infectious agents in the differential diagnosis. RPD is rarely described in association with Lyme’s disease [36], neurocysticercosis [37], tuberculosis [38] and familial prion diseases.

Finally, a thorough medication review is of great importance, as iatrogenic ‘toxic’ exposures represent a frequent cause of hospitalization in North America, with an elevated risk in elderly individuals [39]. The risk of toxic/metabolic disturbances causing RPD may be even higher in patients with pre-existing cognitive impairment, raising suspicion in patients with a prior history of mild cognitive impairment or chronic dementia. Patients with DLB may be particularly susceptible, with prolonged or even irreversible cognitive decline described following minor surgery [7] or exposure to antipsychotic medications [40].

Refining the physical examination

The focus of the physical examination is to identify and document signs that corroborate the patient history, support an etiological diagnosis and focus investigations. The CNS is the primary site of compromise in RPD but other areas
of the body can be involved. Early differentiation between encephalopathies affecting the brain, spinal cord and/or peripheral nervous system is of particular importance in directing neuroimaging and narrowing the differential diagnosis. Taking a ‘head-to-toe’ approach, the following physical findings should be considered together with the patient history to narrow the differential diagnosis.

### Vital signs
Cachexia is a common finding in neoplastic or paraneoplastic disease [33] and an independent risk factor for nutritional deficiencies associated with RPD (i.e., Wernicke’s encephalopathy) [41]. Fever and meningismus may suggest a diagnosis of meningitis/encephalitis. Vital signs should be documented with the patient in recumbent and standing positions to look for evidence of orthostatic hypotension compatible with autonomic failure described in neurodegenerative (i.e., DLB) [42], paraneoplastic [43] and antibody-mediated diseases [43,44] with cognitive impairment.

### Neurological examination
A complete neurological examination is essential. Particular attention should be directed towards identifying upper motor signs (spasticity, pyramidal distribution of weakness, relative hyperreflexia, and extensor or asymmetrical plantar responses) and lower motor signs (fasciculations, muscle atrophy and motor weakness), in an effort to detect patterns associated with specific diseases.

Encephalomyelitis with or without cranial neuropsychies is commonly seen with infectious/parainfectious (e.g., West Nile virus, poliomylitis and tic-borne encephalitis) and inflammatory/autoimmune disease processes (e.g., acute disseminated encephalomyelitis, paraneoplastic diseases and chronic lymphocytic inflammation

### General physical examination
Lymphadenopathy and/or splenomegaly may point towards a hematologic/lymphogenous or chronic infectious cause of RPD. Abnormalities on cardiac or carotid auscultation may support a vascular and/or embolic etiology (i.e., endocarditis). Dilated ophthalmologic assessment should be performed in all patients with RPD examining for papilledema, vascular beading (suggestive of vasculitis) or lymphomatous/infectious aggregates. Finally, all patients should undergo careful dermatologic inspection for rashes or eruptions suggestive of inflammatory or infectious disease, or lacerations, track marks or insect/animal bites that may suggest an extrinsic cause of RPD.

### Table 1. Findings on history and physical examination supportive of an etiologic diagnosis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>CJD</th>
<th>Neurodegenerative</th>
<th>Autoimmune/inflammatory</th>
<th>Vascular</th>
<th>Metabolic</th>
<th>Toxic</th>
<th>Neoplastic/paraneoplastic</th>
<th>Infectious</th>
</tr>
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<tbody>
<tr>
<td>History</td>
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<td>Age (years):</td>
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<tr>
<td>Young (&lt;50)</td>
<td>vCJD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Old (≥50)</td>
<td>sCJD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Onset:</td>
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<tr>
<td>Acute†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Subacute‡</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Relapsing–remitting</td>
<td>X (DLB)</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Symptoms of limbic encephalitis</td>
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<tr>
<td>Systemic signs</td>
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<tr>
<td>Neurological examination</td>
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<tr>
<td>Upper motor neuron signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X (SSPE)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Asterix</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

†Acute onset occurs over days to weeks.
‡Subacute onset occurs over months to years.
CJD: Creutzfeldt–Jakob disease; sCJD: Sporadic Creutzfeldt–Jakob disease; SSPE: Subacute sclerosing panencephalitis; vCJD: Variant Creutzfeldt–Jakob disease; X: Expected findings.
with pontine perivascular enhancement responsive to steroids), presenting with clinical signs compatible with inflammation of the brain and spinal cord. In a patient with a low likelihood of an infectious or autoimmune cause, the presence of both upper and lower motor neuron signs may suggest a diagnosis of frontotemporal lobar degeneration (FTLD) with motor neuron disease (MND) [7], and may predict a shorter survival time (2.3 years) [45], compared with patients with more typical FTLD (7–8 years) [46,47].

Movement disorders are commonly reported in patients with neurodegenerative [7,48,49] and secondary causes of RPD [50,51]. Stereotyped hyperkinetic movements are reported in association with CNS Whipple’s disease (oculomasticatory myorhythmia) [34]; in patients with anti-NMDA receptor encephalitis (orofacial dyskinesias, among others, in 55% of patients) [52–54]; and anti-LGI1 limbic encephalitis (faciobrachial dystonic seizures) [55,56]. The recognition of atypical hypokinetic movements in patients with RPD is of equal diagnostic/prognostic significance: catatonia may suggest a diagnosis of anti-NMDA receptor encephalitis in younger patients [52], while the coassociation of FTLD-MND and parkinsonism may herald an especially rapid decline [49]. Cerebellar ataxia affecting gait and/or limbs, parkinsonism, oposclonus myoclonus, chorea and tremor are most often seen in patients with paraneoplastic disorders, although prion disorders must also be considered.

It is important to note that the physical examination of the patient with RPD represents a single measure of a dynamic process. Findings (or lack thereof) must, therefore, be interpreted in light of the stage and severity of disease. Many causes of RPD associated with focal or lateralized findings early in the disease process may generalize as the disease progresses. Similarly, processes associated with prominent hypertonia or hyperkinetic movements owing to cortical hyperexcitability, may progress to hypotonia or bradykinesia as neuronal cell bodies are lost. Whenever possible, records should be obtained from prior assessments to document early signs in severely affected patients, and to determine the progression of the disease.

Cognitive testing
Cognitive assessment is an extension of the physical examination of the patient with impaired mentation, and is best applied early in the course of illness before progression of the pathology renders the patient ‘untestable’. A number of tools are available to quantify impairment and identify the cognitive domains affected in the mild-to-moderately impaired patient with RPD (Table 2). Although no measures have been evaluated in RPD, defining cognitive dysfunction may assist with localizing the deficit and clarifying the diagnosis.

Investigating RPD
The number of tests that can be ordered for the patient with RPD is expansive, with high costs, associated risks to the patient and potential to unnecessarily delay diagnosis. We support a three-tier testing strategy that allows for a stratified approach to investigations and prioritizes identification of potentially reversible causes of RPD (Figure 3). The first tier — core tests — includes low-risk, accessible tools, with a...
high diagnostic yield and minimal turn-around times, and should be completed in all patients with RPD. The availability of expanded and extended tests varies between centers; accordingly, these tests should be requested on a per patient basis as resources allow.

Serum and CSF studies are the backbone of core tests providing rapid surveillance of organ function (Table 3). Diagnostic lumbar puncture should be completed once a space-occupying lesion and bleeding diathesis has been excluded. Routine CSF analysis should be completed in all cases, including screening for infectious agents. When practical, 3–5 ml of CSF should be stored to facilitate expanded/extended testing in the future, as warranted by changes in clinical condition. A toxicology screen (urine and serum) is an important part of the assessment, and should be performed in all patients to exclude iatrogenic causes of cognitive impairment.

HIV infection should be excluded in all patients, due to the association with RPD owing to viral proliferation and/or opportunistic infections [57]. Similarly, testing for Treponema pallidum causing neurosyphilis should be completed, acknowledging the recent resurgence in patients with and without HIV [58,59].

MRI of the brain with and without gadolinium is indispensable in the evaluation of patients with RPD, and is critical to screen for structural (neoplastic, infectious and hemorrhagic), demyelinating/inflammatory, vascular, neurodegenerative or metabolic causes (Figure 4) [6,7,60,61]. Whenever possible, imaging should be completed under protocols providing sagittal views of the corpus callosum and juxtacortical structures (commonly involved in demyelinating disease), and coronal views of medial temporal lobes (commonly involved in limbic encephalitis and neurodegenerative diseases). In the presence of renal failure (i.e., estimated glomerular filtration rate is <30 ml/min/1.73 m²), noncontrast MRI should be obtained to prevent nephrogenic systemic fibrosis [62].

Combined with the patient history and physical assessment, an EEG can be used to support diagnosis and estimate prognosis of patients with acute encephalopathy [63], as some EEG patterns are associated with specific causes of RPD (Table 4). Whenever possible, EEG should be obtained in states of wakefulness, drowsiness and sleep.

Expanded and/or extended testing may be warranted following core investigations. Unlike

Table 2. Cognitive domains and available screening tests.

<table>
<thead>
<tr>
<th>Tools</th>
<th>Executive function</th>
<th>Memory</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization</td>
<td>Frontal</td>
<td>Temporal</td>
<td>Lobes in the brain</td>
</tr>
<tr>
<td>Praxis</td>
<td>Modified Trails</td>
<td>Clock draw</td>
<td>Reading, writing, naming, comprehension, repetition, semantic fluency</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>Calculations (digit span)</td>
<td>Clock drawing</td>
<td>Reading, writing, naming, comprehension, repetition, semantic fluency</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Cube copy, intersecting pentagons</td>
<td>Clock drawing</td>
<td>Reading, writing, naming, comprehension, repetition, semantic fluency</td>
</tr>
<tr>
<td>Facial recognition</td>
<td>Right temporal</td>
<td>Clock drawing</td>
<td>Reading, writing, naming, comprehension, repetition, semantic fluency</td>
</tr>
</tbody>
</table>

Table 3. Diagnostic surveillance table for organ function.

<table>
<thead>
<tr>
<th>Tools</th>
<th>Tools</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Serum</td>
<td>CSF</td>
</tr>
<tr>
<td>Study</td>
<td>Study</td>
<td>Study</td>
</tr>
<tr>
<td>Analysis</td>
<td>Analysis</td>
<td>Study</td>
</tr>
<tr>
<td>Core tests</td>
<td>Core tests</td>
<td>Core tests</td>
</tr>
<tr>
<td>Rapid surveillance</td>
<td>Rapid surveillance</td>
<td>Rapid surveillance</td>
</tr>
<tr>
<td>Organ function</td>
<td>Organ function</td>
<td>Organ function</td>
</tr>
<tr>
<td>Table</td>
<td>Table</td>
<td>Table</td>
</tr>
</tbody>
</table>

Table 4. Summary of causes of RPD.

<table>
<thead>
<tr>
<th>Causes of RPD</th>
<th>Causes of RPD</th>
<th>Causes of RPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral proliferation</td>
<td>Opportunistic infections</td>
<td>Infections</td>
</tr>
<tr>
<td>Neurodegenerative</td>
<td>Metabolic</td>
<td>Other</td>
</tr>
</tbody>
</table>

core tests, however, the clinician is advised to select from groups of tests as directed by the differential diagnosis. If no alternate involved organ is identified (i.e., outside of the CNS), brain biopsy remains the invasive procedure of choice for establishing a diagnosis. Historically, the diagnostic sensitivity of biopsy has approached 57–65% in patients with dementing conditions, impacting treatment in 11–44% of cases [64,65]. With the advent of autoantibody testing and wider application of CSF biomarkers, the sensitivity has been reported as high as 73.7% (14 out of 19 cases), altering treatment in 21.1% (four out of 19 cases) [66]. This improvement may reflect the improved selection of patients with primarily neurodegenerative pathology, including prion diseases. Beyond altering treatment, a positive biopsy may prove useful when providing counseling concerning the probability of recovery and the risk of relapse. In rare cases, this information may even have direct implications for surviving family members (e.g., FTLD-MND [67,68] and familial prion diseases) [19]. These observations exemplify the value of brain biopsy in the declining patient in whom expanded/extended investigations have failed to confirm a diagnosis. In all cases, this value must be weighed against the risks associated with the procedure, including hemorrhage, stroke and infection.

Extended testing can be readily completed within most tertiary health centers or in partnership with commercial diagnostic laboratories. Novel clinical syndromes are being

---

**Figure 3. Stratified approach to diagnostic testing in rapidly progressive dementia.**

Investigations listed under ‘extended testing’ may be classified as ‘expanded testing’ (i.e., SPECT) and considered earlier in the diagnostic algorithm depending on local experience and the availability of resources.

Table 3. Results of core serological and cerebrospinal fluid tests supportive of an etiologic diagnosis.

<table>
<thead>
<tr>
<th>Testing modality</th>
<th>CJD</th>
<th>Neurodegenerative</th>
<th>Autoimmune/ inflammatory</th>
<th>Vascular</th>
<th>Metabolic</th>
<th>Toxic</th>
<th>Neoplastic/paraneoplastic</th>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC: Hb, WBC, MCV, smear</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes: Na⁺, Ca²⁺, Mg²⁺</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function: AST, ALT, alkaline phosphatase, GGT, bilirubin, ammonia, albumin</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X (e.g., alkaline phosphatase with bony invasion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid: TSH, T3, T4, anti-TPO, anti-TG</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X (e.g., lithium, amiodarone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatological screen: ESR, CRP, ANA, ENA, RF, ANCA, SPEP</td>
<td></td>
<td></td>
<td>X (vasculitis)</td>
<td>X (vasculitis)</td>
<td></td>
<td></td>
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<tr>
<td>Vitamin B12</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious: syphilis, Lyme disease, HIV serology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other: Anti-NMDA-receptor Ab, anti-VGKC subunit Ab</td>
<td></td>
<td>Anti-coaguability panel</td>
<td></td>
<td>Marks for mitochondrial dysfunction (i.e., lactate and pyruvate)</td>
<td></td>
<td></td>
<td>Cancer-specific biomarkers (i.e., CA-125, CEA, PSA); paraneoplastic panel (anti-Hu, Ri, Yo, Ma-1/2, CV2 [CRMP5], GAD65, amphiphysin)</td>
<td>PCR for specific agents, WNV serology if exposures prevalent</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell count and differential</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>(vasculitis)</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Protein</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Glucose</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>IgG index</td>
<td>+</td>
<td></td>
<td>Low (bacterial/fungal)</td>
<td>+</td>
<td>(paraneoplastic)</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Oligoclonal banding</td>
<td>+</td>
<td></td>
<td></td>
<td>+ (paraneoplastic)</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Cytology</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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</tbody>
</table>

*Measurement requires use of plastic (polypropylene) tubes to avoid absorbance of β-amyloid into the tube walls
+: High; ++: Very high; Ab: Antibody; ANA: Antinuclear antigen; ANCA: Antineutrophil cytoplasmic antibodies; CBC: Complete blood count; CJD: Creutzfeldt-Jakob disease; ENA: Extraneuronal antigen; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; MCV: Mean cell volume; P-tau: Phosphorylated tau; RF: Rheumatoid factor; SPEP: Serum protein electrophoresis; T3: Triiodothyronine; T4: Thyroxine; T-tau: Total tau; TG: Thyroglobulin antibody; TPO: Thyroid peroxidase antibody; VGKC: Voltage gated potassium channel; WBC: White blood cell; WNV: West Nile virus; X: Abnormality expected.
### Table 3. Results of core serological and cerebrospinal fluid tests supportive of an etiologic diagnosis (cont.).

<table>
<thead>
<tr>
<th>Testing modality</th>
<th>CJD</th>
<th>Neurodegenerative</th>
<th>Autoimmune/ inflammatory</th>
<th>Vascular</th>
<th>Metabolic</th>
<th>Toxic</th>
<th>Neoplastic/paraneoplastic</th>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal fluid (cont.)</td>
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<td></td>
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<tr>
<td>Gram stain, bacterial/viral/fungal testing</td>
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<td></td>
<td></td>
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<tr>
<td>Other</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-3-3 (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-tau (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSE (+)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100b (+)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (+)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>PCR for specific agents</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

1. Measurement requires use of plastic (polypropylene) tubes to avoid absorbance of β-amyloid into the tube walls.

2. +: High; ++: Very high; Ab: Antibody; ANA: Antinuclear antigen; ANCA: Antineutrophil cytoplasmic antibodies; CBC: Complete blood count; CJD: Creutzfeldt–Jakob disease; ENA: Extranuclear antigen; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; MCV: Mean cell volume; P-tau: Phosphorylated tau; RF: Rheumatoid factor; SPEP: Serum protein electrophoresis; T3: Triiodothyronine; T4: Thyroxine; T-tau: Total tau; TG: Thyroglobulin antibody; TPO: Thyroid peroxidase antibody; VGKC: Voltage gated potassium channel; WBC: White blood cell; WNV: West Nile virus; X: Abnormality expected.

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**Diagnosing CJD**

Prion diseases remain an important and prevalent cause of RPD in published case series [6–10]. This pathologically distinct class of disease arises from the intrinsic (sporadic CJD or familial/genetic CJD) or extrinsic (variant CJD or iatrogenic CJD) transformation of the normal cellular PrP<sub>c</sub> into a disease-causing conformation (PrP<sub>Sc</sub>; for review see [70]). The unregulated propagation of this stable protease-resistant monomer throughout interconnected neuronal networks ultimately culminates in extensive neuronal loss, gliosis, and vacuolation, and explains the rapid accrual of cognitive dysfunction [70,71].

Updated criteria for the diagnosis of sporadic CJD have been proposed [72]. While the diagnosis of ‘definite CJD’ continues to require identification of PrP<sub>Sc</sub> with immunohistochemistry [72], the diagnosis of ‘probable CJD’ has been modified to integrate a compatible clinical history with supportive core/expanded testing, including fluid-attenuated inversion recovery hyperintensities and/or restricted diffusion within cortical, striatal and thalamic areas on MRI [73,74], and CSF studies confirming elevated 14-3-3 protein and tau [75,76]. The modified criterion appears to have adequate diagnostic sensitivity and specificity in patients with RPD [77,78]. Additional brain-derived proteins have been suggested as sensitive CSF biomarkers in CJD (i.e., NSE and S100b), and may be combined with other tests to improve diagnostic sensitivity and specificity. EEG findings, including periodic complexes [80], may further support the diagnosis.

Recently described methods for the detection of PrP<sub>Sc</sub> in CSF (real-time quaking-induced conversion measurement of PrP<sub>Sc</sub>) may allow definitive CJD to be diagnosed through non-invasive techniques [81]. This test remains to be validated, however, in clinical practice.

Finally, the value of autoantibody testing was recently evaluated in a series including patients described on an ongoing basis – with [82–84] and without [69] associated autoantibodies. Referral to a tertiary care center should be considered if extended testing is not available at a patient’s center or if specific immunosuppressive therapies are required for patients with suspected tumor-or antibody-mediated limbic encephalitis.
with clinically suspected CJD. Autoantibodies against neuronal surface antigens were detected within the CSF of 1.7% (six out of 346) of cases [82], emphasizing the importance of expanded/extended testing in patients without histopathologically confirmed CJD. Autoantibodies were not detected in any case of definite CJD [82].

**Empiric treatment of RPD**

Empiric treatment should be provided to all patients in whom the diagnosis is unclear following completion of core testing. Secondary causes of RPD remain the most likely to respond to appropriate therapies; thus, a treatment trial may be viewed as a diagnostic test [8]. A low threshold should be maintained for administration of intravenous acyclovir – particularly in patients presenting with seizures and pyrexia, suggestive of viral encephalitis. Additionally, all patients with a possible history of malnutrition should receive urgent treatment with high doses of intravenous thiamine [41]. Rapid resolution of encephalopathy following correction of thiamine deficiency in the brain is compatible with the diagnosis of Wernicke’s encephalopathy. In the majority of RPD cases, nonspecific treatments can be administered concurrently with expanded/extended investigations to further narrow the differential diagnosis and improve the selection of therapeutics.

Remarkable responses to immunosuppressive therapies have been described in patients with autoantibody-mediated diseases affecting the CNS [22,29,31]. This finding justifies the early use of nonspecific immune-modulating therapies in patients with suspected limbic encephalitis (e.g., pulse corticosteroids, intravenous immunoglobulin and plasmapheresis), in whom infection has been excluded. A treatment response should increase suspicion of encephalopathy associated with autoantibodies against neuronal surface antigens (e.g., NMDA receptors or VGKC subunits), differentiating these syndromes from paraneoplastic diseases associated with onconeural/intracellular...
autoantibodies [21,29], which tend not to respond to immune modulation.

**Conclusion**

The causes of RPD are vast, with symptoms and signs attributable to a variety of diseases capable of disrupting cerebral function. A practical approach to RPD prioritizes the early identification of patients with potentially reversible causes, and, when appropriate, early administration of disease-modifying therapies. Clues from the patient’s history, physical examination and cognitive assessment can be used together with core investigations to narrow the differential diagnosis, and focus expanded/extended tests in an effort to minimize risk to the patient and maximize the likelihood of establishing a rapid diagnosis in the rapidly declining patient with RPD.

**Future perspective**

Resting state functional MRI measures, recently applied to the differentiation of subtypes of neurodegenerative diseases [83], may be readily applied to the characterization and evaluation of cerebral dysfunction in patients with RPD, offering the potential of an ancillary test to corroborate and quantify cognitive impairment in this population. This tool has already been used to evaluate patients with limbic encephalitis, correlating memory impairment with hippocampal disconnection, and executive dysfunction with disruptions in subcortical activity in patients with anti-NMDA receptor encephalitis [84]. Equally exciting is the steady characterization of new autoantibodies in patients with encephalopathy [29], offering specific diagnoses for conditions formerly labeled as ‘chronic encephalitis’ [9] or ‘encephalitis of unknown etiology’ [85], and offering hope for the expanded application of immune-modulating therapies in RPD. Together, these biomarkers promise to contribute to the clinical evaluation of RPD, equipping the astute clinician with additional noninvasive tools to assist in discerning a diagnosis and rapidly identifying patients with potentially reversible RPD. Even in causes of RPD with no known cure, such as CJD, the application of sensitive and specific noninvasive biomarkers (i.e., CSF real-time quaking-induced conversion measurement of PrPSc [81]) may facilitate accurate diagnosis earlier in the course of illness. Early diagnosis may provide an opportunity for therapeutic intervention as more agents that alter disease pathogenesis become available.

**Financial & competing interests disclosure**

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No writing assistance was utilized in the production of this manuscript.
of interest


17. Comprehensive review of the diagnosis and treatment of infectious causes of RPD.


31. Reviews autoimmune disorders of the CNS that are associated with autoantibodies against neuronal surface antigens. An approach for the recognition of patients with probable autoantibody-mediated disease is discussed along with criteria for diagnosis.


A practical approach to the diagnosis & management of rapidly progressive dementia

REVIEW

42 Kaufmann H, Biaggioni I. Autonomic failure of print).
58 Del Campo CM. Wernicke encephalitis? Tonic seizures: a diagnostic clue of anti-LGI1 receptor encephalitis. Pathogenic effects of anti-NMDA receptor antibodies are reported, with applications for disease diagnosis and management.
61 Geschwind MD. Rapidly progressive dementia: prion diseases and other rapid dementias. Continuum (Minneap. Minn.) 16(2 Dementia), 31–56 (2010).
Summarizes laboratory, neuroimaging and neurophysiologic findings in patients with Creutzfeldt–Jakob disease and applies these within an updated diagnostic criterion.


These findings advance the pathophysiological understanding of autoantibody-mediated encephalopathy.


**Website**

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