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# Diagnosis and treatment of rapidly progressive dementias

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## Summary

Rapidly progressive dementias are conditions that typically cause dementia over weeks or months. They are a particular challenge to neurologists as the differential diagnosis often is different from the more typical, slowly progressive dementias. Early and accurate diagnosis is essential, as many of the etiologies are treatable. The information in this review is in part based on experience through our rapidly progressive dementia program at the University of California San Francisco, Memory and Aging Center. As treatment of a rapidly progressive dementia is entirely dependent on the diagnosis, we present a comprehensive, structured, but pragmatic approach to diagnosis, including key clinical, laboratory, and radiologic features. For the 2 most common causes of rapid dementia, treatment algorithms for the autoimmune encephalopathies and symptomatic management for the neurodegenerative causes are discussed.



**A**lthough no formal definition exists for what constitutes a rapidly progressive dementia (RPD), generally we use the term when dementia occurs in less than 1–2 years from illness onset, but more commonly over weeks to months.<sup>1</sup> Because these conditions are relatively uncommon, the appropriate diagnostic workup and treatments often are unfamiliar to many neurologists. Accurate, thorough, and prompt diagnosis is important as many RPDs are treatable, and even curable. In this article, we present a practical, systematic approach for RPD diagnosis as well as treatment algorithms for the management of immunotherapy-responsive and other dementias.

## Etiology of RPDs

The breakdown of etiologies of RPDs varies among dementia centers. At our center (University of California, San Francisco, Memory and Aging Center), the diagnostic breakdown of RPDs

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has been 62% prion disease (all forms), 15% other neurodegenerative diseases, 8% autoimmune, 4% infectious, and 2% each psychiatric, cancer, toxic-metabolic, and vascular causes; 4% were of undetermined etiology, often leukoencephalopathies.<sup>2</sup> Of all RPDs referred to our dementia program, 17% had potentially treatable etiologies (50% autoimmune, 13% each infectious, psychiatric, and cancer, and 10% toxic-metabolic). Our center has a bias toward prion disease as this is a focus of our clinical research program.<sup>3</sup> A major dementia referral center in Greece found the most common cause was dementia (27%) due to reversible causes (toxic/metabolic, infectious, autoimmune, vasculitis, and hydrocephalus included in this group) followed by Alzheimer disease (AD, 18%), frontotemporal dementia (16%), Creutzfeldt-Jakob disease (CJD) (13%), and various other neurodegenerative diseases (13%).<sup>4</sup> At the US National Prion Disease Pathology Surveillance Center, of the 1,106 patients autopsied, 68% were diagnosed with prion diseases, 17% with neurodegenerative conditions, 3% vascular, 2% each immune-mediated and neoplasms, 1% each infection and toxic-metabolic, and 4% undetermined (insufficient tissue). Potentially treatable causes, including immune-mediated disorders, neoplasms, infectious diseases, and toxic/metabolic encephalopathies, were found in 6.4% of all cases.<sup>5</sup>

### Diagnostic approach

**Clinical assessment** Making the correct diagnosis of an RPD is often difficult, but is the key to appropriate treatment. RPD diagnosis usually requires a systematic and thorough approach. A detailed medical history, including emphasis on elucidating first symptoms, documenting all prescribed and nonprescribed medications and any relevant family history, is imperative. Examination should establish if any other neurologic features are present and determine whether other organ systems are involved, so physical and neurologic examination must be thorough. Cognitive assessment can be done with a brief test, such as the Montreal Cognitive assessment (MoCA; [www.mocatest.org](http://www.mocatest.org)), but a more detailed assessment might further refine the localization of cognitive deficits (particularly for neurodegenerative conditions). Use of the mnemonic VITAMINS (table 1) is a useful way to review potential etiologies for RPDs: vascular, infectious, toxic-metabolic, autoimmune, metastases/neoplasm, iatrogenic/inborn error of metabolism, neurodegenerative, or systemic/seizures.

**Laboratory tests** As many RPDs have overlapping clinical features, ancillary testing is necessary. Although it is important to be pragmatic and avoid unnecessary costs and testing-associated morbidity, the diagnostic workup should be comprehensive and cover the most frequent causes of RPD, with special attention to potentially treatable conditions.

Figure 1 shows 2 levels of laboratory testing: a first level of tests that should be ordered or at least considered in most RPDs, and a second level, which includes tests to consider in selected cases. For the first level, always remember the mantras that “common things are common” and “don’t forget the basics!”—metabolic disturbances are a frequent cause of acute/subacute encephalopathy in older patients (delirium). The second level of tests depends on the results from the first level. In the vast majority of cases, combining clinical findings, the serologic dementia screen, CSF, and neuroimaging will help narrow down the differential diagnoses and determine additional types of tests to be ordered.

Screening for serum (in some cases, also CSF) antibodies causing autoimmune and paraneoplastic encephalopathies<sup>6</sup> is important as many of these conditions are treatable and even reversible. Knowing the specific antibodies might help to better define the syndrome or identify the underlying cancer,<sup>7</sup> as well as indicate likelihood of response to treatment.<sup>8,9</sup> Probably the most common antibodies associated with autoimmune (paraneoplastic or non-paraneoplastic) encephalopathy are the intraneuronal antibodies anti-Hu (most frequently associated with small-cell lung carcinoma [SCLC]), anti-Ma2 (testicular germ-cell tumors), anti-CV2/CRMP5 (SCLC, thymoma, and others) and the neuronal surface antibodies AMPA receptor (AMPA) antibody, VGKC-complex (LG11 and Caspr2) antibodies, and GABA<sub>B</sub> receptor (GABA<sub>B</sub>R) antibody.<sup>6</sup>

Supplemental Data

[neurology.org/cp](http://neurology.org/cp)

**Table 1** Some causes of rapidly progressive dementia, organized by VITAMINS mnemonic<sup>a</sup>

Disease	Onset	Demographics <sup>b</sup>	Clinical features	MRI	CSF	Other tests	Treatment
<b>Vascular</b>							
<b>Multi-infarct VaD</b>	A/S	>50 years, risk factors for vascular disease	Stepwise cognitive decline, with localizing motor, visual, or sensory signs	Multiple regions of T2/FLAIR hyper in vascular territories	Nondiagnostic	—	Secondary prophylaxis, treatment of risk factors, AChI
<b>Strategic infarct dementia</b>	A	>50 years, risk factors for vascular disease	Sudden onset of cognitive impairment, memory loss	Hippocampal, thalamic, angular gyrus, PCA/ACA territory infarct(s)	Nondiagnostic		Secondary prophylaxis, treatment of risk factors, IV high-dose corticosteroids
<b>Inflammatory CAA<sup>e1</sup></b>	S	>40 years, M = F	Subacute cognitive decline, headache, seizures	Microbleeds on T2, <sup>c</sup> large/confluent hyper T2 lesions (hypo on T1)	—	Homozygous APOE ε4 genotype; biopsy for confirmation	
<b>Primary CNS angiitis</b>	A	Peak ~50 years, M > F <sup>e2</sup>	Cognitive decline, multifocal neurologic symptoms	Multiple grey or white matter T2-hyper	Might show pleocytosis or elevated protein	CNS angiogram or brain and meningeal biopsy	IV high-dose corticosteroids; immunosuppression
<b>Cerebral venous sinus thrombosis</b>	A/S	Adults, F > M, pregnancy, hypercoagulable states	Cognitive decline, AMS/confusion, focal neurologic signs, headache	Venous clot; T2-hyper in adjacent GM and WM; possible restricted diffusion or hemorrhage	Normal	MRV, hypercoagulable tests	Anticoagulation
<b>Infectious</b>							
<b>Neurosyphilis</b>	S	Consider risk factors	Cognitive decline, psychosis, depression, pupillary abnormalities	Nonspecific atrophy, may be normal	CSF VDRL	Serum RPR	Crystalline IV penicillin G for 10–14 days <sup>e3</sup>
<b>Whipple disease</b>	S	Adults; rare in older adults	Dementia, psychiatric symptoms, movement disorder, ophthalmoplegia, myoclonus, GI disturbance	Normal vs FLAIR hyper in MTL, midbrain, diencephalon (± CE)	<i>Tropheryma whippelii</i> PCR	Jejunal biopsy (PAS + staining or PCR)	Ceftriaxone 2 g/d x 2 weeks → co-trimoxazole (≥1 year) <sup>e4</sup>
<b>Lyme disease</b>	S	Any age; prevalence variable in different regions	Dementia, cranial neuropathy, meningitis, psychosis, polyradiculopathy; neurologic manifestations are late	Normal in most cases	Lymphocytic pleocytosis; intrathecal production of Abs	Serology	Ceftriaxone 2 g/d x 14 days <sup>e5</sup>

Continued

Table 1 Continued

Disease	Onset	Demographics <sup>b</sup>	Clinical features	MRI	CSF	Other tests	Treatment
<b>HIV dementia</b>	A/S	Seroconversion, older HIV-positive adults, low CD4	Psychomotor slowing, executive dysfunction, depression, movement disorders	Cortical atrophy; nonspecific white matter changes	Increased protein, mild pleocytosis	HIV serology; serum and CSF viral loads	CNS penetrating HAART
<b>Herpetic meningoencephalitis</b>	A	Any age	Altered level of consciousness, focal deficits, seizures, behavioral changes; fever	Medial temporal lobe hyper on FLAIR, asymmetric; later hemorrhagic necrosis <sup>e6</sup>	Lymphocytic pleocytosis, ↑RBC, HSV-1 PCR+	EEG: focal abnormalities, PLEDs	IV acyclovir for 14–21 days (start early if suspected) <sup>e6</sup>
<b>Toxic-metabolic</b>							
<b>Wernicke syndrome</b>	A	Risk factors: alcoholism, malnutrition	Cognitive impairment, eye movement abnormalities, ataxia	T2 hyper in medial thalamus and mammillary bodies <sup>e7</sup>	Nondiagnostic	—	Thiamine
<b>Extrapontine myelinolysis</b>	A	Rapid correction of electrolyte disturbance (e.g., hyponatremia)	May take few days to develop symptoms; encephalopathy, movement disorders, para/quadripareisis	Hyper T2 lesions (CE) in pons, cerebellum, basal ganglia, thalamus; may take days to appear <sup>e8</sup>	Nondiagnostic	—	Symptomatic
<b>Vitamin B12 deficiency</b>	S	Older adults, pernicious anemia, veganism, fad diets	Cognitive impairment (infrequent, but treatable), sensory ataxia, paresthesias	Nondiagnostic	Nondiagnostic	↓Vitamin B12, ↑MMA, ↑homocysteine	Vitamin B12
<b>Acquired hepatocerebral degeneration</b>	S	Cirrhosis (portosystemic shunting)	Apathy, inattention, parkinsonism, cranial dyskinesia	Pallidal T1 hyper, T2 normal <sup>e9</sup>	Nondiagnostic	—	Treatment of liver disease, but might be irreversible; liver transplant
<b>Acute intermittent porphyria<sup>e10,e11</sup></b>	A/S	20s–30s; F > M	Abdominal pain, autonomic dysfunction, behavioral changes, altered consciousness	Normal	Nondiagnostic	Elevated PBG/ALA in urine	Carbohydrates, intravenous haem arginate; avoid certain medications and metabolic disturbances
<b>Autoimmune</b>							
<b>NMDAR encephalopathy<sup>e12</sup></b>	A/S	Median 19 years, F > M	Flu-like prodrome, prominent psychiatric features (psychosis), hyperkinesias, autonomic instability	Normal in 45%. T2 hyper in cerebral/cerebellar cortex with meningeal CE	Lymphocytic pleocytosis, OCB frequent	Screening for tumor (mostly ovarian teratoma)	See figure 2A; relapse in 25%

Continued

**Table 1** Continued

Disease	Onset	Demographics <sup>b</sup>	Clinical features	MRI	CSF	Other tests	Treatment
<b>Encephalopathy with VGKC antibodies<sup>c</sup> (LG11 antigen)<sup>e12</sup></b>	S	Median 60 years	Limbic encephalitis, hyponatremia, seizures, myoclonus, ataxia, unilateral brachial-facial spasms	MTL hyper on FLAIR in 85%; might be normal	Normal/↑ protein, OCB infrequent	<20% with tumors (SCLC, thymoma) EEG slowing	See figure 2A; infrequent relapse
<b>Limbic encephalitis (paraneoplastic)<sup>e13</sup></b>	S	Any age (depends on antibody)	Neuropsychiatric symptoms (anxiety, hallucinations), seizures, cognitive decline, headache, tremor, subacute onset, fluctuating course	MTL hyper on T2/FLAIR; might be normal	Lymphocytic pleocytosis, ↑/normal protein ±OCB	Most frequent Abs: anti-CV2/CRMP5, Hu, Ma2 (10% seronegative) EEG slowing	See figure 2A
<b>Acute demyelinating encephalomyelitis</b>	A	More frequent in children	Flu-like prodrome, post vaccination/viral infection; encephalopathy with multifocal neurologic signs	Multifocal T2/FLAIR hyper, sometimes with CE <sup>e14</sup>	Mild pleocytosis, protein <100 mg/dL	—	IV corticosteroids (or PE, immunoglobulin)
<b>Metastasis/neoplasia</b>							
<b>Primary CNS lymphoma</b>	S	Most 50–70 years	Neuropsychiatric symptoms, focal neurologic deficits, seizures	Focal hypo or hyper T2 lesions with CE; seldom DWI hyper <sup>e15</sup>	Lymphocytic pleocytosis; flow cytometry for lymphoma cells	High LDH, ESR; biopsy	Specific lymphoma treatment
<b>Gliomatosis cerebri</b>	S	Older adults	AMS, dementia, seizures, headache, focal deficits	T2/FLAIR hyper in 2+ lobes; ± mass effect; ± CE <sup>e16</sup>	—	Brain biopsy	Radiation ± chemotherapy
<b>Iatrogenic/inborn errors of metabolism</b>							
<b>Medications</b>	A/S	Older adults	Attention to temporal relationship between initiating drug use and cognitive symptoms	Nondiagnostic	Nondiagnostic	Nondiagnostic	Discontinuation
<b>Neurodegenerative</b>							
<b>CJD<sup>e17</sup></b>	S	Mostly 50–70 years; M = F	Subacute cognitive decline with behavioral, pyramidal, extrapyramidal, cerebellar, myoclonus, or visual symptoms	Cortical or subcortical hyper on DWI	↑↑Total-tau, ↑14-3-3, and ↑NSE	EEG: slowing; PSWCs	See figure 2B

Continued

**Table 1** Continued

Disease	Onset	Demographics <sup>b</sup>	Clinical features	MRI	CSF	Other tests	Treatment
<b>Alzheimer disease</b>	S	>60 years	Early short-term memory impairment	Hippocampal atrophy, later spreading to temporal, parietal, and frontal regions	↓Aβ <sub>42</sub> , ↑phospho-tau, ↑total tau	PET with amyloid ligand	See figure 2B
<b>LBD</b>	S	>50 years	Cognitive dysfunction, parkinsonism, visual hallucinations, behavioral changes, fluctuations	Normal or non-specific atrophy	Nondiagnostic	FDG-PET: occipital hypo	See figure 2B
<b>bvFTD</b>	S	40–70 years	Behavioral changes (apathy, disinhibition, loss of empathy/sympathy, repetitive behaviors), executive dysfunction	Frontal or temporal atrophy	Nondiagnostic	FDG-PET: frontal/temporal hypo	See figure 2B
<b>CBS</b>	S	50–70	Cognitive dysfunction, asymmetric motor abnormalities, or aphasia	Asymmetric atrophy, parietal or frontal	In AD etiology, ↓Aβ <sub>42</sub> , ↑phospho-tau, ↑total tau	—	Depends on etiology, AD vs primary tauopathy
<b>Systemic/seizures</b>							
<b>Hypertensive encephalopathy</b>	A	Uncontrolled hypertension, eclampsia, chemotherapy	Headaches, confusion, visual changes, seizures, coma	FLAIR hyper in occipitoparietal WM	Nondiagnostic	—	Treatment of hypertension
<b>Seizures/NCSE</b>	A	Older adults	Cognitive dysfunction, fluctuations in alertness	DWI hyper in cortical or subcortical GM <sup>e18</sup>	Might have mild pleocytosis	EEG	AEDs

<sup>a</sup>This list is not meant to be comprehensive, but to focus on the most frequent causes or potentially treatable causes. Listed are the most typical abnormalities seen in ancillary testing, which might not be present in all cases. References e1-e18 are available at [www.neurology.org/cp](http://www.neurology.org/cp).

<sup>b</sup>Most frequent ages, sex, or risk factors.

<sup>c</sup>VGKC complex encephalopathy is due to leucine-rich glioma inactivated 1 (LGI1) antibodies.

Abbreviations: A = acute (days/weeks); ACA = anterior cerebral artery; AChI = acetylcholinesterase inhibitors; AED = antiepileptic drug; ALA = delta-aminolevulinic acid; AMS = altered mental status; bvFTD = behavioral variant of frontotemporal dementia; CAA = cerebral amyloid angiopathy; CBS = corticobasal syndrome; CE = contrast enhancement; CJD = Creutzfeldt-Jakob disease; ESR = erythrocyte sedimentation rate; GM = gray matter; Hyper = hyperintensities/hypermetsabolism; Hypo = hypointensities/hypometabolism; LBD = Lewy body dementia; LDH = lactate dehydrogenase; MMA = methylmalonic acid; MRV = magnetic resonance venography; NCSE = non-convulsive status epilepticus; OCB = oligoclonal bands; PBG = porphobilinogen; PCA = posterior cerebral artery; PE = plasma exchange; RBC = red blood cells; S = subacute (weeks/months); SCLC = small-cell lung carcinoma; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin/norepinephrine reuptake inhibitor; WM = white matter.



**Figure 1 Suggested diagnostic tests for initial rapidly progressive dementia evaluation**

Blood tests	CSF	Imaging	Urine/Other
<b>Basic panel of tests</b>			
<ul style="list-style-type: none"> <li>- Complete blood count</li> <li>- Basic metabolic panel (+Ca,P,Mg)</li> <li>- Liver function tests (including ammonia)</li> <li>- Renal function tests</li> <li>- Thyroid function tests</li> <li>- Anti-TG and Anti-TP antibodies</li> <li>- Vitamin B12/MMA/homocysteine</li> <li>- Rheumatologic screen (ANA, ESR, CRP, RF, ANCA, SSA, SSB)</li> <li>- Rapid plasma reagin (RPR)</li> <li>- HIV serology</li> <li>- Paraneoplastic/autoimmune antibodies</li> </ul>	<ul style="list-style-type: none"> <li>- Cell count and differential</li> <li>- Protein</li> <li>- Glucose</li> <li>- IgG index</li> <li>- Oligoclonal bands</li> <li>- VDRL</li> <li>- 14-3-3/NSE/total tau</li> </ul>	<ul style="list-style-type: none"> <li>- Brain MRI (including FLAIR, DWI and ADC sequences), at least one scan with and without contrast</li> </ul>	<ul style="list-style-type: none"> <li>- Urine analysis (and culture if indicated)</li> <li>- EEG</li> </ul>
<b>Tests to consider in selected cases</b>			
<ul style="list-style-type: none"> <li>- Lyme disease (in endemic areas)</li> <li>- Cancer screen</li> <li>- Blood smear</li> <li>- Coagulation profile</li> <li>- Hypercoagulability testing</li> <li>- Copper and ceruloplasmin</li> <li>- Additional rheumatologic tests (complement, dsDNA, anti-Sm, anti-RNP, anticardiolipin, anti-SCL 70, Anti-Jo, anti-centromere antibodies)</li> </ul>	<ul style="list-style-type: none"> <li>- Bacterial, fungal, acid-fast bacilli stains and cultures</li> <li>- Cytology</li> <li>- Flow cytometry</li> <li>- Whipple PCR</li> <li>- Cryptococcal antigen</li> <li>- Viral PCRs and cultures</li> </ul>	<ul style="list-style-type: none"> <li>- Cancer screen (CT chest, abdomen, and pelvis with and without contrast; mammogram; body PET scan)</li> <li>- MR angiography or brain angiogram</li> <li>- MR spectroscopy</li> <li>- Carotid ultrasound</li> <li>- Echocardiogram</li> </ul>	<ul style="list-style-type: none"> <li>- Heavy metal screen (24h urine)</li> <li>- Copper (24h urine)</li> <li>- Porphobilinogen (PBG)/delta-aminolevulinic acid (ALA) in urine (24h)</li> <li>- EMG/nerve conduction study</li> <li>- Brain biopsy</li> </ul>

ANA = antinuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; anti-TG = anti-thyroglobulin; anti-TP = anti-thyroperoxidase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NSE = neuron-specific enolase; RF = rheumatoid factor. Modified from Geschwind et al.<sup>2</sup>

The clinical presentation of AEs varies greatly and includes cognitive decline and psychiatric changes developing over days, weeks, or months. Seizures, myoclonus, extrapyramidal symptoms, ataxia, or signs of hypothalamic or autonomic dysfunction can also be observed.<sup>10,11</sup> The term limbic encephalitis (LE) is often used to describe a classic phenotype of AE characterized by subacute onset of behavioral changes, memory problems, and seizures. But frequently the disease is multifocal and other parts of the CNS are affected (such as hypothalamus or brainstem), characterizing an autoimmune encephalomyelitis.<sup>10,12</sup>

Clinical features and demographics might give clues as to the antibody causing an AE. Encephalopathy due to VGKC complex antibodies (caused by LGI-1 receptor antibodies)<sup>13</sup> can cause RPD that resembles CJD, though hyponatremia due to SIADH might be a clue as it is not typical of CJD, but is found in about 60% of cases with VGKC complex antibody encephalopathy.<sup>14</sup> AMPAR antibody encephalitis is more frequent in middle-aged women<sup>15</sup>; in a male under 50, anti-Ma2 antibodies (usually associated with testicular tumors) and testicular ultrasound should be considered.<sup>11,16,17</sup> AMPAR antibody encephalitis is associated with SCLC, breast or thymus tumors, and GABA<sub>B</sub>R antibody encephalitis is associated with LE and frequent seizures.<sup>6</sup> Several excellent reviews on these antibody-mediated encephalopathies have recently been published.<sup>11,17-19</sup>

Encephalopathy associated with NMDA receptor (NMDAR) antibodies has a distinct clinical presentation (table 1).<sup>11,18</sup> It occurs more frequently in children or young adults, but has been reported up to the eighth decade of life. Psychiatric symptoms are prominent at onset; hyperkinetic movements such as dystonia, orofacial dyskinesias or chorea, seizures and signs of autonomic instability, and ultimately pulmonary distress necessitating intubation are later clinical features.<sup>20</sup>



*The clinical presentation of autoimmune encephalopathies (AEs) varies greatly and includes cognitive decline and psychiatric changes developing over days, weeks, or months.*

A reasonable basic screen for autoimmune and paraneoplastic encephalopathies in the context of RPDs might include anti-Hu, anti-Ma2, anti-CV2, VGKC complex (LG11 and anti-CASPR2 if available) antibodies, anti-amphiphysin, GAD65, and NMDAR antibodies. Although less common, in the appropriate clinical context, consider AMPAR and GABA<sub>B</sub>R antibodies. We recommend sending complete panels of antibodies when feasible, as many patients have more than one antibody, and some antibodies identify the syndrome, others the neoplasm. In seronegative cases in which one has a high degree of suspicion for an AE, or NMDAR encephalopathy is possible, CSF testing should complement serum testing, particularly when treatment with IV immunoglobulin (IVIg) or plasma exchange has already been given, as antibody levels in the CSF might remain elevated.<sup>20,21</sup>

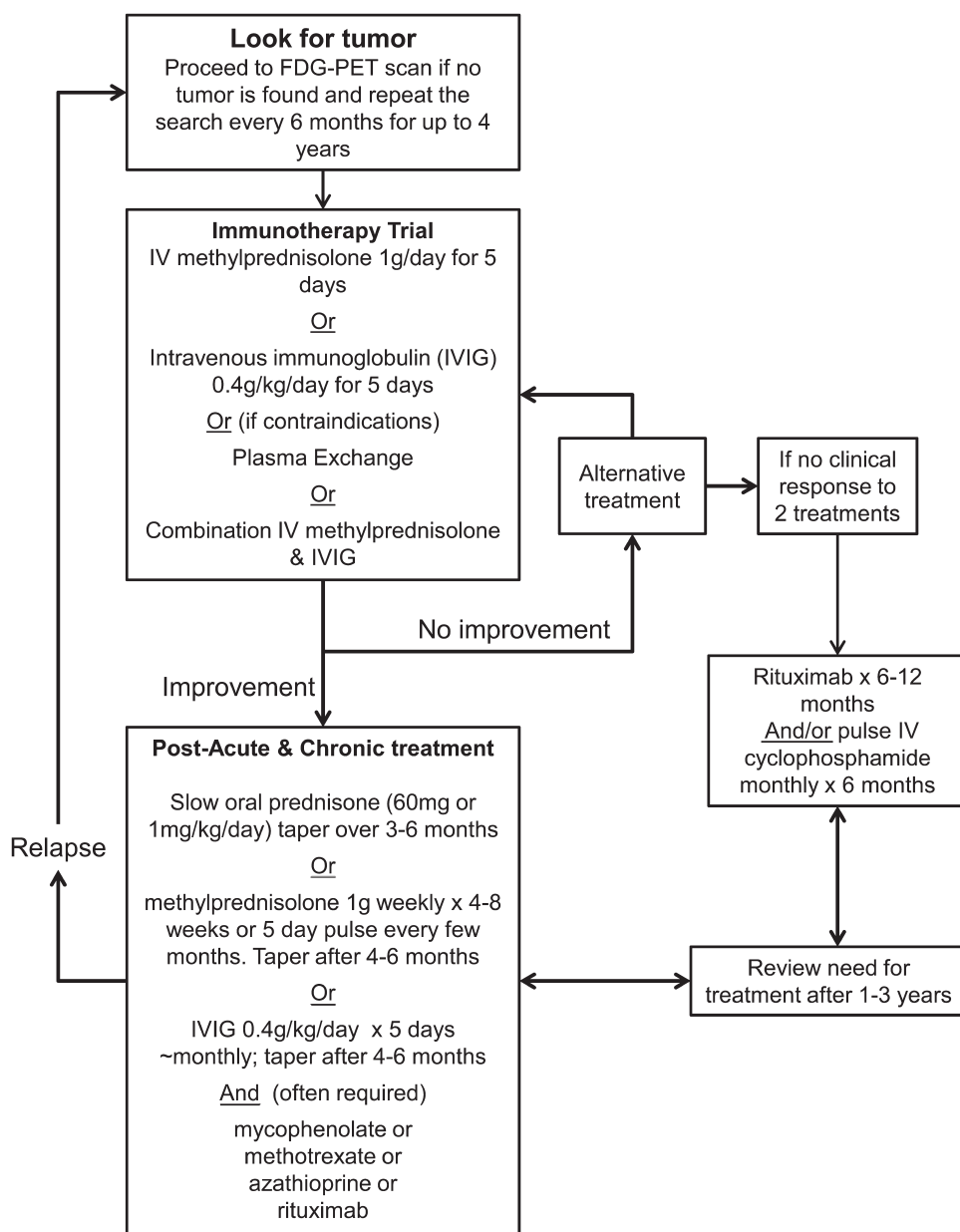
When autoimmune encephalitis is considered, it is critical to screen for tumors (figure 1). Paraneoplastic encephalopathies can precede identification of the associated neoplasia by as many as 3 years (though most often less than 1 year), and so if the initial screening is negative, regular cancer screening is required (figure 2).<sup>6,11</sup> The chance of finding a tumor, however, is variable and depends on the antibody: for example, whereas a causative tumor is found in more than 95% of patients with encephalitis associated with anti-Hu or anti-Ma2, it is found in less than 20% of patients with LG11 receptor antibodies.<sup>11,18</sup> AMPAR antibodies are associated with finding a tumor in 70% of cases, but with GAD65 antibodies, which are infrequently associated with encephalopathy, a tumor is found in only 8% of cases.<sup>11</sup>

Autoimmune encephalopathies also occur with systemic autoimmune diseases (often associated with vasculitis).<sup>22</sup> Serologic screening for rheumatologic disorders is also recommended for RPD evaluation, although often serology will be normal and brain biopsy might be indicated<sup>23</sup> (figure 1; table 1).

**CSF** A lumbar puncture should be performed in almost all patients with RPD. It may be particularly helpful with infectious, autoimmune, and neoplastic disorders (figure 1). Lymphocytic pleocytosis, elevated protein level, high immunoglobulin G index, or oligoclonal bands are often present in AEs,<sup>6</sup> particularly those of paraneoplastic etiology,<sup>24</sup> although they are not specific and might occur in patients with CJD, neuroinfections generating a strong immune response (e.g., subacute sclerosing panencephalitis), or neoplasias. In CJD, basic CSF analysis is typically normal, but in our cohort 50% of cases show mildly increased protein levels (usually 50–100 mg/dL).<sup>25</sup> Mild pleocytosis or oligoclonal bands sometimes occur in prion disease.<sup>26</sup> Markers for evidence of rapid neuronal injury, such as 14-3-3 protein, neuron-specific enolase (NSE), and total tau might be helpful to confirm the rapid course, rapid neuronal injury, and might be helpful in the rare cases of sCJD in which the DWI MRI is nondiagnostic. Testing for A $\beta$ <sub>42</sub>, phospho-tau, and total-tau might be helpful when AD is in the differential.<sup>27</sup>

**Neuroimaging** A brain MRI in patients with RPD should include T1 with and without contrast, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI)

**Figure 2** Proposed non-evidence-based treatment algorithm for autoimmune paraneoplastic and non-paraneoplastic encephalopathies



Adapted from Mckeon et al.<sup>19</sup>

and apparent diffusion coefficient (ADC) map, and hemosiderin (e.g., gradient echo or susceptibility) sequences (table 1). Space-occupying lesions (such as most tumors or certain infections, such as toxoplasmosis) should prompt a directed investigation (sometimes requiring biopsy). Certain tumors, such as lymphomas and gliomatosis/lymphomatosis cerebri, however, might not present as space-occupying lesions. In sCJD, DWI abnormalities are characterized by cortical (i.e., cortical ribboning) or deep nuclei hyperintensities, usually with concomitant hypointensities on ADC map.<sup>28,29</sup> Hyperintensities are typically more prominent on DWI than FLAIR. If abnormalities are brighter on FLAIR than DWI or there is isolated limbic involvement, this suggests against CJD and should prompt investigations into other etiologies (e.g., autoimmune, toxic-metabolic).<sup>28</sup>

*In cases in which the diagnosis is clear, such as when an explanatory neural-specific autoantibody is identified, then a more aggressive approach to immunosuppression might be appropriate.*

**EEG** EEG is necessary to rule out seizures as the cause of RPD. EEG might also reveal a pattern typical of CJD with periodic sharp wave complexes (PSWCs; seen in about 2/3 of sCJD cases<sup>30</sup>) or the periodic pattern seen in SSPE. PSWCs, however, might also be seen in hepatic encephalopathy, HE, end-stage AD and DLB, and possibly other conditions.<sup>25,31</sup>

**Brain biopsy** Brain biopsy is sometimes necessary when the less invasive workup is nondiagnostic. At our center, we found that brain biopsy was diagnostic in 65% of patients with RPD (excluding nonlymphomatous tumors or patients with HIV), and the results led to initiation of therapy in 44%.<sup>23</sup> In our CJD cohort, 14% of brain biopsies were false negative. Brain biopsies in dementia (not necessarily RPD) generally have had diagnostic yields of 20%–57%, finding treatable causes in about 10% of cases.<sup>23,32</sup> Schott et al.<sup>33</sup> provide a pragmatic guide for physicians when brain biopsy in dementia is being considered.

## Treatment

**Autoimmune and paraneoplastic encephalopathies** *When to give a trial of immunotherapy?* If an autoimmune encephalopathy is suspected, then a trial of immunotherapy is recommended (figure 2). Certain clinical clues might suggest an autoimmune disorder: a fluctuating clinical course; the detection of a neural-specific paraneoplastic or non-paraneoplastic antibody; other serum markers of autoimmunity such as thyroid antibodies; and detection of inflammatory markers in the CSF.<sup>34</sup> The diagnosis of an autoimmune dementia, however, essentially hinges on whether an objective clinical improvement can be demonstrated with immunotherapy.<sup>19</sup> Usually the improvement in cognition in responders is striking.<sup>17</sup> In responsive patients, the shorter the delay to treatment, often the better the clinical outcome.<sup>19</sup>

Overall, encephalopathies associated with neuronal surface antigens have better response to treatment than those associated with intraneuronal antibodies. Among the intraneuronal antibodies, LE with anti-Ma2, VGKC-associated, anti-CV2, and AMPAR antibodies, for example, often have excellent response to treatment.<sup>6</sup> In a recent observational study, the following clinical and laboratory findings predicted a good response to treatment: subacute onset, fluctuating course, headache, tremor, CSF pleocytosis, or protein >100 mg/dL.<sup>17</sup>

*When not to give a trial of immunotherapy?* Immunosuppression should probably be avoided if infections that might be exacerbated by immunosuppression are high on the differential. If lymphoma is in the differential, steroids should be avoided, as they will cause necrosis of the tumor cells, likely rendering future biopsies nondiagnostic and delaying appropriate treatment.<sup>1</sup> It is also important to realize that some conditions that are not necessarily primarily immune-mediated sometimes respond well, albeit sometimes only temporarily, to immunosuppression or related treatments. In fact, IVIg has shown some benefit in AD in phase 2 clinical trials and is in phase 3 trials currently ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

*How to give steroids* As the steroid trial is sometimes also a diagnostic test as well as a treatment, it is important to give a sufficiently high dose so that a clinical response is clear. Unfortunately, there are no data as to the minimum sufficient steroid dose for treatment of immune-mediated

**Figure 3** Proposed management algorithm for more common neurodegenerative causes of RPD

bvFTD	LBD	AD	CJD	
Trial selective serotonin reuptake inhibitor (SSRI) or Serotonin and norepinephrine reuptake inhibitor (SNRI)	Optimize <b>cognitive function</b> with acetylcholinesterase inhibitor	Optimize cognitive function: acetylcholinesterase inhibitor and/or memantine		
	<b>REM sleep disorder:</b> Trial of clonazepam or melatonin (if fails, consider quetiapine)	SSRIs for behavioral symptoms		
	<b>Depression:</b> Trial of SSRI or SNRI			
	Symptomatic management of <b>dysautonomia and parkinsonism*</b>			
<b>Depression:</b> SSRI	<b>Psychosis:</b> citalopram, escitalopram, quetiapine or other less-parkinsonian atypical antipsychotic	<b>Myoclonus:</b> Only treat with clonazepam or leviteracetam if affecting quality of life. If not helpful consider valproic acid	<b>Cognitive function:</b> Consider acetylcholinesterase inhibitor or memantine, although unclear if helpful. If available (in Europe) consider flurpiritine.	<b>Disease modifying treatment:</b> Consider oral doxycycline and/or quinacrine or intraventricular pentosan polysulphate (PPS) - but no convincing human data to support any of their use.

AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CJD = Creutzfeldt-Jakob disease; LBD = Lewy body dementia; RPD = rapidly progressive dementia. Quinacrine failed to show benefit in a clinical trial.<sup>38</sup> LBD management adapted from: Boeve BF (2005), Clinical, diagnostic, genetic and management issues in dementia with Lewy bodies, Clin Sci 109(4), 343-354.<sup>39</sup>

dementias; we usually give 1 g of IV methylprednisolone per day for 5 days or equivalent. It is imperative to document baseline measures of clinical features, EEG, neuropsychology, and imaging so that changes can be objectively measured.<sup>17</sup>

**Alternative first-line immunotherapy** Patients who cannot tolerate steroids or in whom they might be contraindicated should be given a course of IVIg or plasma exchange (PLEX). IVIg or PLEX might also be indicated when corticosteroids initially are effective, but repeat trials fail to show benefit or corticosteroids fail initially, but there is strong suspicion of an autoimmune etiology. PLEX sometimes is reserved for the critical care setting<sup>19</sup> and has a higher adverse event rate; it should be used with caution in patients with anti-NMDA encephalitis with autonomic involvement.<sup>35</sup>

**Combined therapy** In cases in which the diagnosis is clear, such as when an explanatory neural-specific autoantibody is identified, then a more aggressive approach to immunosuppression might be appropriate.<sup>35</sup> Some experts recommend early treatment using a combination of corticosteroids and IVIg followed by a course of concurrent rituximab and cyclophosphamide if there is no clinical improvement after 1 cycle.<sup>35</sup> We tend to use single treatments initially, so that it is clear which agent is effective. It does not make sense to use plasma exchange shortly after IVIg as the potential therapeutic benefit of IVIg would be removed. Clinical response might take days to weeks.

**Maintenance therapy** In patients with a positive response to the trial of immunotherapy, relapse rate is high and longer term treatment (figure 2) is usually required to maintain remission.<sup>17,19</sup> Appropriate osteoporosis and *Pneumocystis jiroveci* pneumonia prophylaxis should be considered in all patients,<sup>19</sup> as well as screening for latent tuberculosis. For clinicians not comfortable administering immunosuppressive therapy, advice can be sought from a neuroimmunologist or rheumatologist.<sup>12</sup>

**Toxic-metabolic** Treatment of toxic-metabolic etiologies varies depending on the specific disorder. Some disorders, such as thiamine deficiency, are easier and cheaper to treat empirically rather than to test for thiamine levels. When treating a patient with suspected Wernicke encephalopathy, remember never to give glucose alone without thiamine, as this might

**Table 2** Ten diagnostic pearls for rapidly progressive dementia

1. Do not forget the basics: common things are common
2. Verify time course: often symptoms began earlier than records state
3. Be thorough: try using a mnemonic: VITAMINS
4. Diagnose infections and tumors early for potential treatment
5. CJD is the great mimicker: it can look like anything (and vice versa)
6. Do not rely on CSF 14-3-3 for CJD diagnosis: interpret CSF biomarkers with caution
7. Brain MRI with appropriate sequences: contrast, coronal/axial FLAIR, DWI, ADC
8. Read your own MRIs: most CJD cases will have DWI-positive cortex "cortical ribboning" that has been missed
9. If diagnosis not clear, get body imaging w/contrast (or consider PET)
10. Consider autoimmune etiologies: CSF IgG Index and OCBs; serum ± CSF for antibody testing

Abbreviations: ADC = apparent diffusion coefficient; CJD = Creutzfeldt-Jakob disease; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; IgG = immunoglobulin G; OCB = oligoclonal band; PET = positron emission tomography. Adapted from Geschwind, Creutzfeldt-Jakob disease and related disorders, session 1KP.008, 63rd AAN meeting, 2011.

exacerbate the underlying condition. When considering B12 deficiency, measuring homocysteine and methylmalonic acid, as well as B12, might reveal early signs of a B12 deficiency.<sup>2</sup> As some patients do not absorb oral B12, retesting levels after initiating treatment is required. If levels are not sufficiently high, IM treatment is appropriate.

**Infectious** Treatment of infectious RPD essentially involves detection of the infection and appropriate treatment in consultation with infectious disease specialists. If viral encephalitis is suspected, antivirals should be commenced immediately before awaiting results of investigation; viral PCR on CSF might remain positive even after treatment has been commenced.<sup>36</sup> We routinely screen for HIV, syphilis, and Lyme disease, as they are treatable if diagnosed early.<sup>1,25</sup> Opportunistic fungal infections such as aspergillosis and cryptococcus might present as RPD and the opportunity to diagnose and treat should not be missed. Although rare, CNS Whipple disease is probably underdiagnosed as it might not present with gastrointestinal symptoms and classic facial movements; we recently were involved with an RPD case mistaken for CJD and then DLB, but only diagnosed with Whipple at autopsy. As Whipple is treatable with antibiotics, we recommend a low threshold for considering this infection.

**Neurodegenerative** CJD is uniformly fatal and more than 85% of patients with CJD die within 1 year of onset.<sup>37</sup> Despite active efforts with drug development and clinical trials, currently there is no curative or disease-modifying treatment for CJD or other neurodegenerative causes for RPD. Some symptomatic treatment options for CJD, AD, behavioral variant frontotemporal dementia, and Lewy body dementia are shown in figure 3.

## CONCLUSIONS

RPDs can be a diagnostic challenge to neurologists because they are infrequent in clinical practice and the spectrum of differential diagnoses is broad. The use of a systematic approach to diagnosis (VITAMINS) is helpful to cover the main diagnostic etiologies. Treatment success depends on accurate and early diagnosis and searching for potentially treatable causes is one of the mainstays of the diagnostic workup. Even when the RPD etiology is not treatable per se, there are still options of symptomatic treatments aiming at a better quality of life for patients. Ten diagnostic pearls for RPD are provided in table 2.

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