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Rapidly Progressive Dementia

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As a major prion disease referral center in the United States, the authors are referred several rapidly progressive dementia (RPD) cases every week, most of which are referred with a potential diagnosis of Creutzfeldt-Jakob disease (CJD). The number of referrals increased dramatically with the identification of quinacrine as a potential therapy for CJD and commencement of the first United States CJD treatment trail in May 2005 [1,2]. The authors recognized the need for a broader diagnostic approach to RPD after observing that 15% to 20% of these referrals were the result of other nonprion conditions, many of which were treatable. Physicians, and even neurologists, generally are not trained formally in the assessment of RPDs. This review hopes to provide a more thorough appreciation of the myriad etiologies for RPDS and to offer a possible diagnostic decision tree or algorithm, based largely on the experience of the authors' center.

Most dementias develop slowly, allowing an unhurried outpatient evaluation. Algorithms for the assessment of these patients have been developed and refined, and most neurologists are well acquainted with these approaches. A careful history usually detects dementia secondary to medications or depression, and routine laboratory assessments help to eliminate metabolic conditions that can cause dementia, including anemia, electrolyte imbalance, liver or kidney failure, thyroid disease, and vitamin B_{12} deficiency. The majority of slowly progressive dementias are secondary to Alzheimer's disease (AD), although there is an increasing recognition of non-AD dementias, including frontotemporal dementia (FTD) (see article by Josephs elsewhere in this issue), subcortical ischemia vascular disease (see article by Chui elsewhere in this issue), dementia with Lewy bodies

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(DLB) (see article by Boeve elsewhere in this issue), and other parkinsonian dementias, such as cortical basal degeneration (CBD) and progressive supranuclear palsy (see elsewhere in this issue) [3]. With the possible exceptions of DLB and CBD, however, the disorders that commonly lead to slowly progressive adult dementia, such as AD and FTD, rarely present as RPDs [4–6]. Patients who have a RPD often require consideration of a different set of disorders.

The primary aim of this article is to instruct clinicians in an approach to the differential diagnosis of RPD that will broaden their scope of inquiry and, particularly, identify RPDs that are treatable and potentially reversible. This article is organized around the following categories: neurodegenerative, autoimmune, toxic and metabolic, infectious, neoplastic, and vascular, emphasizing the RPDs most difficult to diagnose or least likely be recognized. As many types of conditions can cause RPD and they can progress quickly, it is important to have an organized, systematic approach to diagnosis. The mnemonic, VITAMINS, often is useful for summarizing some of the major categories of etiologies for RPDs (Box 1). Box 2 lists many etiologies of RPD (many of which are not discussed in this review). When considering patients who have a RPD, it may be helpful to use the information in Boxes 1 and 2 to ensure a complete differential is considered. RPDs that present with space-occupying brain lesions easily identified by CT or MRI scan are not discussed in this article. Figs. 1 and 2 provide an outline for the diagnostic approach that the authors use in evaluating patients who have RPD. Fig. 1 shows the overall approach, whereas Fig. 2 details an expanded evaluation when standard testing is inconclusive.

Over the past 5 years, the authors' dementia center has been referred approximately 825 RPD cases, many with a presumptive diagnosis of CJD. After reviewing records and in many cases evaluating the patients, determined the diagnostic breakdown of this group was determined as 54% prion disease (37% probable or definite sporadic, 15% genetic, and 2% acquired), 28% undetermined (because of insufficient records, although most met

Box 1. VITAMINS mnemonic for categories of conditions causing rapidly progressive dementias

*V*ascular
*I*nfectious
*T*oxic-metabolic
*A*utoimmune
*M*etastases/neoplasm
*I*atrogenic
*N*eurodegenerative
*S*ystemic

Box 2. Differential diagnosis of rapidly progressive dementias

Neurodegenerative
CJD (sporadic, iatrogenic, familial)
AD
DLB
FTD
CBD
Progressive supranuclear palsy (PSP)

Infectious
Viral encephalitis, including herpes simplex virus
HIV dementia
Progressive multifocal leukoencephalopathy
Subacute sclerosing panencephalitis (young adults)
Fungal infections (immunosuppression [eg, central nervous system (CNS) aspergillosis])
Syphilis
Parasites
Lyme disease (rarely encephalopathy)
Balamuthia
Whipple's disease

Toxic/metabolic
Vitamin B_{12} (cyanocobalamin) deficiency
Vitamin B_1 (thiamine) deficiency
Niacin deficiency
Folate deficiency (dementia rare)
Uremia
Wilson's disease
Portosystemic encephalopathy
Acquired hepatocerebral degeneration
Porphyria
Bismuth toxicity
Lithium toxicity
Mercury toxicity
Arsenic toxicity
Electrolyte abnormalities

Autoimmune
Hashimoto's encephalopathy (HE)
Paraneoplastic (autoimmune) limbic encephalopathy (PLE)
Nonparaneoplastic autoimmune (eg, anti–voltage-gated potassium channel [VGKC] antibodies mediated)
Lupus cerebritis

Other CNS vasculitides
Sarcoid

Endocrine abnormalities
Thyroid disturbances
Parathyroid abnormalities
Adrenal diseases

Neoplasm related
Nonautoimmune paraneoplastic conditions
Metastases to CNS
Primary CNS lymphoma (PCNSL)
Intravascular lymphoma
Lymphomatoid granulomatosis
Gliomatosis cerebri

criteria for possible CJD; see article by Eggenberger elsewhere in this issue), and, importantly, 18% who had other nonprion conditions, many of which were treatable. The diagnostic breakdown of these nonprion RPDs was 26% neurodegenerative, 15% autoimmune, 11% infectious, 11% psychiatric, and 9% miscellaneous other, whereas 28% still were undetermined, often

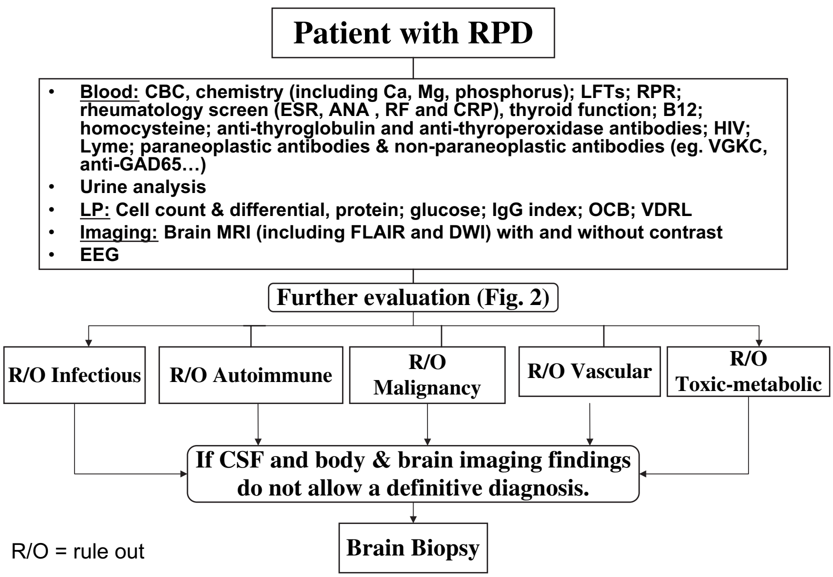

Fig. 1. RPD evaluation. AFB, acid-fast bacillus; Ca, calcium; CBC complete blood count; LDH, lactate dehydrogenase; LFT, liver function tests; LP, lumbar puncture; OCB, oligoclonal bands; Mg, magnesium.

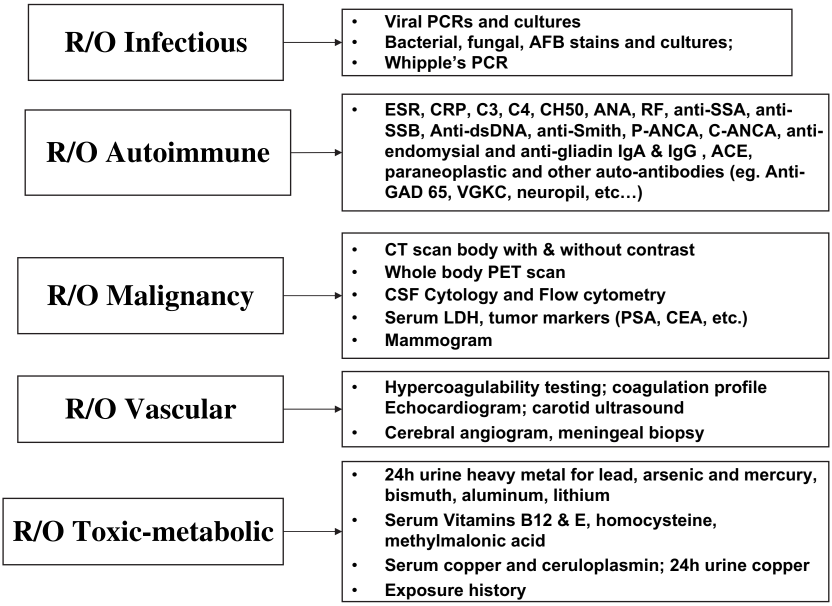

Fig. 2. Further RPD evaluation. AFB, acid-fast bacillus; CBC complete blood count; LDH, lactate dehydrogenase; LFT, liver function tests; LP, lumbar puncture; OCB, oligoclonal bands; Mg, magnesium.

leukoencephalopathies or encephalopathies of unknown etiology (M. Geschwind, MD, PhD, unpublished data, 2007). Because the authors' efforts in improving diagnosis of RPDs was prompted by the necessity to differentiate prion diseases from other causes of RPD, following is a brief discussion of some of the salient issues in diagnosis of the prototypical RPD, prion disease (discussed in detail in article by Eggenberger elsewhere in this issue).

Degenerative dementias as rapidly progressive dementias

Prion diseases

When considering a RPD in particular patients who have prominent motor or cerebellar dysfunction, CJD should be high on the differential. Some key features to consider with prion disease, based on the authors' experiences, are discussed in this article.

The most commonly used clinical criteria for probable sporadic CJD s(sCJD) [7,8] do not allow early diagnosis of CJD and use ancillary tests (electroencephalogram [EEG] and cerebrospinal fluid [CSF] protein 14-3-3) that many consider to have poor sensitivity or specificity and not useful in clinical practice [9–11]. A major problem with these criteria is that they include signs or symptoms, such as akinetic mutism and the characteristic

EEG, that often do not occur until late stages of the illness. These criteria also do not include features that often are early signs of the illness, such as behavioral changes or aphasia [12]. The authors identified the first symptom in 114 subjects who had sCJD referred to the center and found the most common were cognitive (39% of patients), followed by cerebellar (21%), behavioral (20%), constitutional (20%), sensory (11%), motor (9%), and visual (7%). Three of these categories—behavioral, constitutional, and sensory symptoms (headache, malaise, vertigo, and so forth)—are not included in current diagnostic criteria. Furthermore, the authors have found that ancillary tests in World Health Organization criteria that are required for a probable sCJD diagnosis, EEG or 14-3-3, are neither sensitive nor specific. In a recent evaluation of a RPD cohort (150 sCJD and 47 nonprion RPD subjects), the authors found the 14-3-3 to have a sensitivity of 48% and a specificity of 66%. The EEG had a sensitivity of less than 45% by the time patients had an EEG at the authors' institution, which generally was not their first EEG. This increased to approximately 50% when patients then were followed prospectively during their entire disease course (M. Geschwind, MD, PhD, unpublished data, 2007) [13]. In the authors' cohort, the preliminary data suggest that two other surrogate biomarkers for sCJD, total tau and neuron-specific enolase, have somewhat higher sensitivity and specificity for CJD than 14-3-3 or EEG. The authors believe these CSF biomarkers merely are signs of rapid neuronal injury, are not specific for prion disease, and, therefore, are of questionable diagnostic usefulness. A prion-specific test is needed [14–16].

Typically chronic degenerative dementias

AD rarely is rapid, but unusual presentations can be mistaken for CJD [4]. Several cases of AD are reported in conjunction with angiopathy (cerebral amyloid angiopathy) presenting as adult-onset RPD [17–19]. Other nonprion neurodegenerative diseases that also can present, albeit rarely, in a more fulminant fashion, include DLB, FTD (in particular the subtype with motor neuron disease), CBD, and PSP. Patients who have AD typically survive a median of 11.7 (SD ±0.6) years, patients who have FTD 11 years (SD ±0.9), patients who have PSP/CBD 11.8 years (SD ±0.6) [20], and patients who have PSP alone 5.6 years [21] from first symptom. More rapid onset or progression can occur [20,22–25]. In a large German study, of 413 autopsied suspected cases of CJD, 7% had AD and 3% had DLB. Myoclonus and extrapyramidal signs occurred in more than 70% of patients who had DLB and more than 50% of the patients who had AD [4]. Similarly, in a French pathologic study of 465 patients who had suspected CJD, the two most frequent non-CJD pathologic diagnoses were AD and DLB [26].

Parkinsonian dementias, such as DLB and FTD-spectrum disorders, including PSP, CBD, and FTD, are discussed in articles elsewhere in this issue and, thus, are mentioned only briefly in this article. DLB is a progressive dementia often associated with fluctuations in cognitive function, persistent well-formed visual hallucinations, or parkinsonism (see the article by Boeve elsewhere in this issue) [27]. Duration of DLB often is shorter than for many other neurodegenerative dementias; one study suggests 3-year survival [28], although rapid decline with death in 1 year can occur. Periodic sharp waves may be seen on EEG, leading to confusion with CJD [26,29]. In several large cohort studies, DLB was the second most common condition mistaken for CJD [4,26]. FTD rarely is rapidly progressive, although it typically has a faster course than AD. Patients typically present with a frontal syndrome, including behavioral, personality, and cognitive changes occurring over years, followed by dementia (see article by Josephs elsewhere in this issue). Fifteen percent or more of patients who have FTD develop amyotrophic lateral sclerosis and these patients typically die within 1.4 years from the time of diagnosis [30–33]. Corticobasal degeneration (CBD) is a clinically and pathologically heterogeneous atypical parkinsonian dementia often confused clinically with AD, PSP, or FTD (see article by Boeve elsewhere in this issue) [34–38]. Many features of CBD, including myoclonus; alien limb; and visual, sensory, and motor deficits, overlap with features of CJD. The converse also is true; CJD sometimes can present as a rapid cortical basal syndrome [39] or with a protracted course over 2 to 3 years with features indistinguishable from CBD; however, the fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) MRI abnormalities seen in CJD are not found in CBD [40]. As in CJD, patients who have PSP develop dementia, akinetic-rigid parkinsonism (symmetric bradykinesia and axial rigidity), postural instability, and swallowing and speech problems and often progress to a hypokinetic, mute state [41–46]. Abnormalities of eye movements, particularly slowed velocity of saccades progressing to supranuclear gaze palsy, are part of the PSP syndrome (see article by Boeve elsewhere in this issue). CJD mimicking PSP has been reported [47].

Neurofilament inclusion body disease (NIBD) is a recently described pathologic condition that can present clinically as FTD or CBD. The four index cases were all more rapid than typical degenerative dementias, with duration of only 2 to 4 years. Brain MRI and pathology showed frontal, temporal, and caudate atrophy. A distinguishing feature of NIBD is the presence of intracytopasmic neuronal inclusions that stain strongly with antibodies to neurofilament proteins and ubiquitin, but not tau or α-synuclein [48]. One case of NIBD also presented as an early-onset rapidly progressive FTD with features of primary lateral sclerosis [49].

Fahr's disease is a neurodegenerative disease of unknown cause with basal ganglia calcification that typically presents with a movement and neuropsychiatric disorder. Although usually very slowly progressive, a 50-year-old patient was reported with a rapidly progressive frontal behavioral and cognitive presentation of Fahr's disease (idiopathic basal ganglia calcification) resulting in dementia within 6 months. Patients who have Fahr's disease have extensive basal ganglia calcification, a finding that is not present in CJD [50]. Rarely, genetic neurodegenerative diseases also may present as a RPD. A case recently was reported of a man who had the fragile X premutation who presented in his mid-60s with a rapid course of tremor, gait ataxia, parkinsonism, and cognitive deficits [51].

Autoimmune encephalopathies (paraneoplastic and nonparaneoplastic)

Over the past few years, there has been a growing awareness and identification of autoimmune causes of encephalopathy or RPDs. Initially, most of these autoimmune conditions were believed to be paraneoplastic—due to antibodies or other components of the immune system, against the cancer, cross-reacting with antigens of the nervous system. In many of these conditions, however, no cancers have been identified, despite repeated comprehensive searches for a tumor. This section dise cusses paraneoplastic and nonparaneoplastic autoimmune encephalopathies.

Paraneoplastic neurologic disorders (PNDs) often present as a rapidly progressive limbic encephalopathy. PNDs that involve the CNS often are divided into two forms: those with isolated involvement of one part of the nervous system (eg, limbic encephalitis/encephalopathy, cerebellar syndromes, or retinal degeneration) or those with more diffuse, multifocal symptoms, sometimes referred to as paraneoplastic encephalomyelitis (PEM). PLE can occur as an isolated syndrome or as PEM with involvement of other parts of the nervous system (ie, brainstem, cerebellum, or peripheral nerves). The most common symptoms are a subacute amnestic syndrome, presenting as problems with short-term anterograde memory or more variable retrograde amnesia. Depression, personality changes, anxiety, and emotional lability often precede the cognitive dysfunction. Seizures are common [52,53]. PNDs occur in patients who have a known diagnosis of a cancer or may precede the detection of the cancer by weeks, months, or, rarely, a few years. In patients who do not have a known cancer diagnosis, various signs or symptoms may suggest a PEM or PLE, including subacute development of multifocal neurologic symptoms, CSF evidence of inflammation, elevated tumor markers (carcinoembryonic antigen, cancer antigen 125, prostate-specific antigen, and so forth), a family history of cancer, unexplained anorexia or weight loss or other symptoms suggestive of cancer, and the presence of certain paraneoplastic antibodies in the serum or CSF [52,53].

The most common tumors associated with PLE are small cell lung cancer (SCLC) (75% of cases), germ-cell tumors (ovarian or testicular), thymoma, Hodgkin's lymphoma, and breast cancer [52,53], whereas the most common antibodies associated with PLE are anti-Hu (ANNA-1), anti-Ma2 (also called anti-Ta; antigen is Ma2), CV2 (anti–CMRP-5), Yo (PCA-1), and probably antineuropil [52,54–56]. Anti-Hu antibodies are found in 50% of cases of PLE with SCLC. Identification of antineural antibodies is highly suggestive of an underlying neoplasm. Furthermore, the type of autoantibody may suggest the tumor type rather than the neurologic syndrome [52,57]. Almost one third of patients who have a neurologic syndrome and autoantibodies have more than one autoantibody [57,58]. In PLE associated with anti-Ma2 (Ta) antibodies and testicular cancer, approximately half of patients have dramatic improvement of their neurologic syndrome after treatment of their cancer [56,59]. This may be in part because of the ability to remove all the cancer through orchiectomy [60]. Hypothalamic involvement is common in patients who have anti-Ma2 antibodies [56]. Antibodies to CRMP-5 (anti-CV2 or anti–CRMP-5), a protein in the collapsin response-mediator protein family, often are associated with PNDs, including PLE. Peripheral neuropathy (47%) and autonomic neuropathy (31%) are the most common neurologic signs. Subacute dementia and cerebellar ataxia each occur in approximately one quarter of patients, followed by neuromuscular junction disorders (12%), chorea (11%), and cranial neuropathy (17%, including optic neuropathy and loss of taste). Spinal fluid often is inflammatory. Anti-CV2 is seen most often with SCLCs, followed by thymomas [61,62]. FLAIR MRI in anti-CV2 antibody syndrome often shows caudate, anterior putamen with or without medial temporal lobe hyperintensity [58], although thalamic T2-weighted hyperintensity also can occur (M. Geschwind, MD, PhD, unpublished data, 2007). The striatal and thalamic involvement can appear similar to findings in CJD; however, unlike CJD, the T2-weighted hyperintensity may extend beyond the deep gray nuclei into adjacent white matter, and there are no diffusion-weighted abnormalities. Most patients who have limbic encephalopathy and thymoma (often anti-CV2 or anti-VGKC antibodies) have significant neurologic improvement after tumor removal and treatment [63]. Table 1 summarizes some of the major antibodies, with their clinical phenotypes, that are associated with limbic encephalopathy.

Recently, there has been increasing awareness of several immune-mediated encephalopathies that not always are associated with cancers [54,64]. In some of these syndromes, antibodies, and sometimes their antigens, have been identified. Two such syndromes of limbic encephalopathy are due to anti-VGKC antibodies and to antineuropil antibodies. Patients who have anti-VGKC antibodies present along a spectrum of nervous system involvement, from the peripheral to the CNS. Involvement of the peripheral nervous system alone may manifest as neuromyotonia (Isaacs syndrome). Isolated CNS involvement may present as a seizure disorder or limbic encephalopathy [54,65–69]. Combinations of peripheral and central involvement, however, such as in Morvan's syndrome, also occur. Some of these patients have limbic encephalopathy in isolation, whereas others also are shown to exhibit different degrees of Morvan's fibrillary chorea, a syndrome characterized by neuromyotonia, myalgias, hyperhydrosis, and disordered sleep [70]. Anti–glutamic acid decarboxylase (anti-GAD)

Table 1
Paraneoplastic and nonparaneoplastic antibodies often associated with limbic encephalopathy

Antibodies	Tumors	Usual age of onset	Gender	Associated symptoms
Anti-Hu	SCLC, neuroblastoma, prostate	55–65	F> = M	PEM, subacute sensory neuropathy
Anti- Ma2 (anti-Ta)	Germinoma, testicular, lung cancer	22–45	M> >F	PLE, brainstem, cerebellar, hypothalamic
Anti-CV2 (anti–CRMP-5)	Thymoma, lung cancer, renal cell	50–70	F = M	Neuropathy, cerebellar, PLE, chorea
Anti-VGKC	80% none, 20% tumor thymoma, lung	Variable	???	Isaac's and Morvan's syndromes, neuromyotonia, cramps, hyperhydrosis, sleep disorder, seizures PLE
Anti-amphiphysin	Breast, SCLC			PEM, stiff-person syndrome, opsoclonus-myoclonus
Anti-Yo	Gynecologic and breast, adenocarcinoma	26–85	F> >M	Paraneoplastic cerebellar degeneration, limbic encephalopathy
Anti-nCMAg (some antineuropil)	Teratomas, thymus	20–50s	F>M	Acute PLE, abnormal movements, decreased consciousness
Anti-Ma1	Lung, other (breast, parotid, colon)	60	F	Paraneoplastic cerebellar degeneration, brainstem
Anti-Ri (ANNA-2)	Breast, gynecologic, lung, bladder			Ataxia, opsoclonus/myoclonus

Abbreviations: >, greater than; > > much greater than.

antibodies, although commonly associated with stiff-person syndrome, also can cause subacute ataxia, sometimes with mild cognitive complaints [71]. Novel antibodies against components of the CNS continually are identified [54]. If autoimmune syndrome is strongly suspected, because of CSF or serologic findings or concurrent or family history of autoimmune disorders, one should have a low threshold for sending serum and CSF to a research laboratory that specializes in identifying such antibodies.

HE is a rare but probably underdiagnosed, treatable autoimmune disorder associated with chronic lymphocytic Hashimoto's thyroiditis [72,73].

Often, it begins with a prodrome of depression, personality change, or psychosis and progresses into a cognitive decline associated with myoclonus, ataxia, pyramidal and extrapyramidal signs, stroke-like episodes, altered levels of consciousness, confusion, or seizures. Hallucinations or other psychoses are common [72–74]. It often is confused with CJD because of their overlapping clinical profile [5,74]. Compared with CJD, HE is associated more frequently with seizures and tends to have a more fluctuating course [74]. For unclear reasons, more women (85%) than men have been diagnosed with HE [74]. Patients may be euthyroid, hypothyroid, and even hyperthyroid, although the diagnosis cannot be made until patients are euthyroid [74]. Elevated levels of either antithyroglobulin or antithyroperoxidase (anti-TPO) and neurologic and psychiatric symptoms when patients are euthyroid, in the absence of other possible causes, suggest the diagnosis. The EEG frequently shows nonspecific abnormalities with asynchronous background slowing and intermittent diffuse or focal slow activity; however, as in CJD, triphasic waves or periodic sharp waves may occur [72,75]. MRI is not specific but commonly shows increased T2-weighted subcortical, mesial-temporal, or white matter signal, which may disappear after treatment [72,76–78]. CSF often has increased protein, a nonspecific finding that occurs in many other RPDs, including CJD [13,72,73]. The cause of HE may be the result of the presence of a shared antigen in the brain and thyroid [72,73,79]. More than 90% of patients respond favorably to immunosuppression, typically high-dose steroids followed by a long, slow taper, although some patients may have persistent symptoms or a fluctuating course [72,75,80]. Plasmapharesis also may be helpful [81].

Many other autoimmune disorders present as RPDs and are important to consider because of potential for reversibility with immunosuppression. A new clinicopathologic entity, called ‘‘cerebral amyloid inflammatory vasculopathy,’’ has been described recently. These patients show acute or rapid onset of dementia. MRI shows evidence of amyloid-related hemorrhages and sometime large confluent white matter hyperintensities. Brain biopsy revealed Aβ amyloid cerebral angiopathy associated with chronic nongranulomatous vasculitis. With two 4 mg doses of dexamethasone, a patient made a rapid and nearly complete recovery over a few months [82].

Collagen vascular and granulomatous diseases also affect the CNS through mechanisms other than vasculitis. Several of these disorders may cause an encephalopathy or RPD, including primary angiitis of the CNS, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, Sjögren’s syndrome, celiac disease (sprue), Behçet’s disease, and hypereosinophilic syndrome [83–89]. Some investigators group these encephalopathies of nonvasculitic origin under the term, nonvasculitic autoimmune inflammatory meningoencephalopathies; this group includes HE and Sjogren’s encephalopathy, which almost uniformly have abnormal EEGs and respond to high-dose steroids [90]. The heralding features of the disorder may be neurologic sarcoid, a systemic illness of unknown origin characterized by the formation of non-necrotizing granulomas, and can be treated successfully, like other autoimmune conditions, with immunosuppression. Only approximately 5% of patients who have sarcoidosis have involvement of the nervous system, but when it involves the CNS it sometimes presents as a RPD. When there is brainstem involvement, cranial neuropathies may occur. MRI is highly variable and may be normal and show enhancing granulomas (often at the base of the brain) or nonenhancing T2-weighted white matter hyperintensities consistent with a leukoencephalopathy. CT of the chest may reveal hilar lymphadenopathy. CSF may be normal but often shows elevated protein and a mild to severe pleiocytosis. CSF angiotensin-converting enzyme levels are elevated in only 33% to 58% of cases and this test also lacks specificity. Biopsy of affected tissue is needed for diagnosis. Steroid treatment or other immunosuppression may be helpful, as are plasmapheresis and intravenous immunoglobulin. It is important to rule out other granulomatosis diseases, in particular tuberculosis, before initiating immunosuppression (M. Geschwind, MD, PhD, unpublished data, 2007) [91].

Vascular etiologies of rapidly progressive dementia

Depending on the location, strokes can present as RPD. Large vessel occlusions and thalamic, anterior corpus callosal or multiple diffuse infarctions in particular all have presented as RPDs [92,93]. Thrombotic thrombocytopenic purpura can cause microangiopathic thromboses producing global cerebral ischemia, resulting in an encephalopathy. Hyperviscosity syndromes from blood dyscrasias, such as polycythemia, or gammopathies, such as Waldenström's macroglobulinemia, can present as RPDs by causing global cerebral microvessel ischemia.

Although it is an autoimmune condition, CNS vasculitis is discussed in this article because of its direct effect on the vasculature as the cause of RPD. Criteria for classification of certain vasculitides largely are based on a combination of clinical symptoms or signs and laboratory findings [94,95]. A vasculitis may be limited to the CNS without any systemic or peripheral nervous system signs or may present initially as a systemic disorder with accompanying fever, weight loss, rash, neuropathy, and other organ involvement. Urinalysis may contain red cells as a sign of renal involvement. Ophthalmologic examination may identify uveitis, scleritis, or signs of ophthalmic artery vasculitis. If a rash is present, a skin biopsy can be diagnostic. There may be signs of a hemolytic anemia. A basic rheumatologic screen may include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement (C3), complement (C4), total complement (CH50), antinuclear antibody (ANA), rheumatoid factor (RF), anti-SSA, anti-SSB, perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA), and cytoplasmic ANCA (c-ANCA) with other testing depending on results of this initial screen. Serologic testing likely is abnormal in systemic forms of vasculitis, but in primary CNS vasculitis, patients typically have normal nonspecific tests, such as ESR, ANA, and CRP [96]. Vasculitides often are distinguished from other RPDs by brain MRI abnormalities, such as strokes or hemorrhage involving the white or gray matter [96]. Similarly, body imaging for systemic involvement may be helpful [97]. When primary CNS vasculitis is suspected, cerebral angiogram or brain and meningeal brain biopsy of the affected area may be required for diagnosis. Intravascular lymphoma sometimes mimics CNS vasculitis on angiogram; if this condition is suspected (based on an elevated serum lactate dehydrogenase or MRI findings), then one should avoid the angiogram and go directly to biopsy [98,99].

Infectious Etiologies

AIDS-dementia complex, HIV encephalopathy, or HIV-associated dementia is a neurologic complication of acquired immunodeficiency syndrome, eventually occurring in one fourth of patients who have AIDS. It typically occurs in the later stages of HIV infection [100] and has diminished since the introduction of highly active antiretroviral therapy (HAART). Some individuals, however, develop RPD during seroconversion or immune reconstitution. In general, more rapid neurologic impairment is associated with symptomatic HIV seroconverting illness [101]. Concomitant use of methamphetamine or cocaine also may synergize with HIV infection to cause an accelerated course of HIV dementia [102]. As dementia can be a presenting feature of AIDS [103], HIV testing should be considered in the evaluation of every RPD.

Subacute and chronic opportunistic infections associated with HIV infection and other immunocompromised states always must be considered in the differential diagnosis of RPD. Cryptococcus and JC virus infections typically present with meningitis or progressive focal neurologic deficits, respectively; however, they also can present with rapid progression of dementia [104]. CNS infection with mycobacteria may present as an inflammatory meningitis. A recent case report identified an atypical acid-fast bacillus, *Mycobacterium neoaurum*, by polymerase chain reaction (PCR) in autopsy brain tissue from a patient who had RPD and was on low-dose steroids. CSF cell count, mycobacterial culture, and Ziehl-Neelsen staining all failed to demonstrate the presence of mycobacterium. It is possible that many undiagnosed RPDs could be caused by infectious organisms that escape detection using standard microbiologic techniques [9,105,106]. (For a review on diagnosis and etiology of encephalitis, see Glaser and colleagues [106]).

Spirochete infections are unusual causes of cognitive impairment but important to consider as they are treatable. No workup for dementia, including RPD, is complete without an evaluation for CNS infection with *Treponema pallidum*, or neurosyphilis. Cognitive dysfunction is the most common neurologic syndrome, although usually a late complication, of syphilis [107]. It occasionally presents with rapid progression, particularly in immunocompromised patients [108]. Serologic testing with rapid plasma regain and VDRL and CSF VDRL suggest the diagnosis. The CSF in neurosyphilis usually shows a pleiocytosis and an elevated protein [107]. Lyme disease is a systemic infection with the spirochette, *Borrelia burgdorferi*, which is transmitted to people from a tick bite. Neurologic manifestations are rare in Lyme disease but can include cranial nerve palsy, meningitis, polyradiculopathy, depression, psychosis, and dementia [109]. Although RPD caused by Lyme disease is reported, it is rare [110,111], but it is important to consider because it responds readily to treatment [112].

Subacute sclerosing panencephalitis is a chronic CNS infection from the virus that causes measles and still occurs in individuals from countries where measles infections are common. It typically occurs in children but can occur in adults [113]. Patients develop progressive dementia, seizures (focal or generalized), myoclonus, ataxia, rigidity, and visual disturbances. In the late stage of the illness, patients are unresponsive, with spastic quadriparesis, brisk deep tendon reflexes, and positive Babinski's signs. EEG often reveals periodic slow-wave complexes with associated sharp waves every 3 to 10 seconds that often are associated temporally with myoclonus. Definitive diagnosis is made with elevated antibody titers to the measles virus in the blood and CSF in the appropriate clinical setting [114].

Whipple's disease is a rare bacterial (*Tropheryma whippelii*) infection, involving many organ systems, that can present as a neuropsychiatric syndrome that, although typically insidious, can progress rapidly over months. More than 80% of the cases have been diagnosed in men. Although the age range varies from childhood to the elderly, onset typically is in the fifth through seventh decades, with an approximate mean age of onset of 50. Clinical presentation is varied. It most commonly presents as a malabsorption syndrome with diarrhea, abdominal pain, weight loss, arthralgias, wasting, fever, and lymphadenopathy; but as many as 15% of cases do not exhibit gastrointestinal symptoms. CNS involvement occurs in 5% to 45% of cases, with 5% of cases having neurologic presenting symptoms [115]. Dementia or mental status changes occur in more than 50% of the cases with neurologic involvement [115,116]. Cognitive impairment occurs in 71% and psychiatric signs in 44% of cases of CNS Whipple's [117]. Eye movement abnormalities, myoclonus or other abnormal involuntary movements, headache, and abnormal hypothalamic function frequently are seen. Seizures, aseptic meningitis, ataxia, and focal cerebral signs may occur [46,77,115–117]. Ataxia has been reported to occur in 45% of CNS Whipple's cases [118]. Approximately 10% of cases have a triad of dementia, ophthalmoplegia, and myoclonus, which is highly suggestive of this condition [115], Oculomasticatory myorrythymia is uncommon but pathognomic [46,118]. Clinically, Whipple's may be mistaken for CBD or PSP [35]. Brain imaging is nonspecific. CSF shows elevated protein or pleiocytosis in approximately half of cases with CNS involvement. Diagnosis is made by identification of PAS-positive inclusions or *T whipellii* in foamy macrophages on jejunal biopsy or by *T whipellii* PCR of CSF or jejunal biopsy. PCR in serum probably is less sensitive. Diagnosis can be challenging, as many of the symptoms are nonspecific, and is particularly difficult when Whipple's presents as an isolated neurologic syndrome without gastrointestinal symptoms [115]. Although rare, Whipple's is important to recognize, as it is readily treatable with antibiotics [115,117,119,120].

Malignancies causing rapidly progressive dementia

Several primary and secondary malignancies can cause an acute or subacute RPD. RPDs that can be identified readily by MRI are not discussed in detail in this article, as once identified, the work-up is somewhat routine. Three malignancies that often present as RPDs and present with varied abnormalities on MRI are PCNSL, intravascular lymphoma (ie, angiotropic lymphoma), and lymphomatoid granulomatosis (also known as angiocentric immunoproliferative lesions). Only the first two are discussed in this article.

PCNSL is an extranodal form of non-Hodgkin's lymphoma. It typically presents with symptoms of intracranial mass lesions, such as headaches, seizures, and focal neurologic deficits, but can present as a RPD [121]. A diffusely infiltrating PCNSL, sometimes called lymphomatosis cerebri, also occurs [122]. Symptoms of PCNSL include personality changes, irritability, memory loss, lethargy, confusion, disorientation, psychosis, dysphasia, ataxia, gait disorder, and myoclonus [121–124]. CNS lymphoma can mimic CJD [5,96,125]. PCNSL accounts for 2% to 3% of all CNS neoplasms. The vast majority of PCNSLs are non-Hodgkin's diffuse large B-cell type, but T-cell, Burkitt's lymphoma, and poorly characterized forms also occur [121,126]. The incidence increased from the mid-1970s to the mid-1980s because of an escalating number of immunocompromised patients from transplants, chemotherapy, and patients who had HIV before the era of HAART but seems to have stabilized during the past decade [126]. This article focuses on PCNSL in immunocompetent individuals. PCNSL occurs most commonly in the sixth to seventh decades but can occur at any age, with a slight male predominance [123]. Uveitis or vitreitisis present in approximately 10% of cases, sometimes preceding the tumor by months, in approximately 75% of cases; identifying the uveitis or vitreitis may allow earlier diagnosis of the cancer [127]. In immunocompetent individuals, brain MRI may show isointense to mildly hyperintense T2-weighted signal consistent with mass lesions with minimal to moderate edema, often involving the cerebral hemispheres, basal ganglia, periventricular white matter, or corpus callosum. Lesions may be isolated or multiple and generally show contrast enhancement [128]. When presenting as lymphomatosis cerebri, imaging reveals progressive, diffuse white matter signal abnormality without significant (or any) enhancement or mass effect—likely from a diffusely infiltrative process without interruption of the blood-brain barrier [122,123]. CSF can show a lymphocytosis, increased protein, and low glucose. Serial CSF cytologic evaluations typically are required to identify the lymphoma [126]. EEG may show symmetric or asymmetric nonspecific diffuse slowing [122,123]. Unfortunately, definitive diagnosis often requires brain biopsy. In cases of ocular involvement, diagnosis sometimes can be made by vitrectomy. When possible, avoid giving corticosteroids before biopsy, as steroids can cause tumor cell necrosis, resulting in temporary shrinkage of the tumor but preventing tissue diagnosis [96,126]. Prognosis is poor with patients surviving only a median of 4 months or fewer without treatment and 12 to 18 months with whole-brain radiation therapy (WBRT) alone; however, survival is upwards of 40 or more months with a combination of aggressive chemo- and radiotherapy. Chemotherapy includes high-dose systemic methotrexate. The use of chemotherapy alone versus chemotherapy plus WBRT is controversial. Because of the increased risk of neurotoxicity, WBRT in patients over 60 is not recommended. Neurotoxicity presents as a RPD with dementia, ataxia, and incontinence, with median onset just over 1 year post WBRT [126,129].

Intravascular lymphoma can occur in almost any organ but commonly has one of four presentations: CNS, skin, reticuloendothelial, or fever of unknown origin. It is caused by the proliferation of clonal lymphocytes within blood vessels, with relative sparing of parenchyma [130]. The more acute form of CNS intravascular lymphoma typically presents in middle age as an acute or subacute dementia, often with transient ischemic attacks or strokes. Systemic symptoms (eg, fever and weight loss) may be present. The tumor cells are believed to be activated or transformed lymphocytes and typically are an angiotropic large B-cell lymphoma, although cell-type forms also occur. These clonal lymphocytes preferentially bind endothelium. Imaging in CNS intravascular lymphoma is variable. MRI may show multiple areas of T2-weighted hyperintensity with patchy enhancement on T1 weighting, with or without edema [131]. Unfortunately, most cases reported in the literature were diagnosed post mortem; therefore, a high index of suspicion, and a low threshold for brain biopsy, is required for patients who have a RPD and focal T2-weighted abnormalities on MRI [99,127,132]. Laboratory findings can include elevated ESR, serum lactate dehydrogenase, CSF pleiocytosis, and increased protein [132,133]. Survival in intravascular lymphoma usually is poor, especially without treatment. Aggressive treatment is needed for PCNSL and intravascular lymphoma. The combination of chemo- and radiotherapy is better than radiotherapy alone [127,130,132].

At the authors' center, several patients referred with potential CJD were determined to have encephalopathy resulting from metastatic cancers, including lymphoma. A recently published case of a 79-year-old woman who had a RPD presenting with early visual hallucinations, followed by severe memory impairment, and extrapyramidal signs was believed to be CJD because of her course and a positive 14-3-3. Unfortunately, the diagnosis of miliary adenocarcinoma was only made at autopsy [134].

Toxic-metabolic conditions

Metabolic causes of RPD include vitamin deficiences, endocrinologic disturbances, and adult presentations of inborn errors of metabolism. Vitamin deficiencies can result in significant neurologic deficits, including cognitive impairment. Pellagra ("rough skin") results from niacin deficiency and classically is described by the three Ds: *d*ermatitis, *d*iarrhea, and *d*ementia (on a historical note, the original term, nicotinic acid, was changed to niacin because of its confusion with nicotine). Niacin deficiency causes abnormalities of the skin and gastrointestinal tract, peripheral neuropathy, myelopathy, and cognitive dysfunction. With a careful history, the dementia of pellagra typically is found to be insidious, not rapid. In industrialized nations, niacin deficiency should be considered in patients who have nutritional deficiency, such as alcoholics and patients who have anorexia nervosa, and in those taking isoniazid [135–138]. Although diagnosis can be made by finding nicotinic acid metabolites in the urine, given the ease of treatment with niacin (40 to 250 mg per day), diagnosis usually is based on clinical suspicion. Treatment often results in rapid resolution of symptoms [135,139]. Deficiency of thiamine (vitamin B_1), a necessary cofactor in oxidative metabolism, can cause Wernicke's encephalopathy, which presents classically as a triad of ophthalmoparesis (with vertical or horizontal nystagmus), ataxia, and memory loss. DWI MRI can show diffusion abnormalities in mammilary bodies and dorsomedial nucleus of the thalamus, areas in which hemorrhagic necrosis is found pathologically. The thalamic involvement on DWI MRI can appear similar to that seen in CJD [40,140–142]. All patients who have dementia should be screened for vitamin B_{12} deficiency, as potentially it is reversible.

Adult presentations of metabolic disorders that typically afflict children in rare instances also can present as dementia in adults. These dementias usually are associated with a constellation of symptoms, such as weakness, spasticity, and ataxia, and tend to be more slowly progressive. They can present with rapid cognitive decline. In the proper clinical context of gastrointestinal disturbance, fluctuating course, an unexplained pain syndrome, or worsening after use of new medicines, porphyria should be ruled out. Adult-onset metachromatic leukodystrophy presented as a RPD in a woman who developed psychiatric symptoms and severe cognitive decline over 18 months with no weakness or ataxia [143]. Other leukodystrophies also can present as RPD. Orthochromatic leukodystrophies are a heterogeneous group of metabolic disorders in which the specific enzymatic defects have not been found. Most are sporadic, but dominant inheritance is reported. One report describes two family members (57 and 38 at presentation) who had a dominantly inherited orthochromatic leukodystrophy and developed rapid dementia progressing to death over 2 to 3 years [144]. Finally, Kufs' disease, the rare adult form of neuronal ceroid lipofuscinoses, can present as RPD. Kufs' is an autosomal recessive lysosomal storage disease in which acid phosphatase-staining ceroid and lipofuscins accumulate in neurons, causing a progressive encephalopathy. Kufs' disease typically presents in early adulthood. Patients who have type A Kufs' disease present with a progressive myoclonic epilepsy, whereas those who have type B present with dementia, which often begins with psychosis. A case reported in 1997 involved a 49-year-old woman who presented initially with alternating catatonia and acute psychosis over 5 months before the development of dementia over the next 2 months. Diagnosis was made by acid phosphatase staining of brain and skin biopsies [145]. The authors recently diagnosed a 50-year-old woman who had a methylmalonic (and malonic) academia who had developed significant cognitive impairment after a several months prodrome of gastrointestinal disturbance and psychiatric disturbance. She had low normal vitamin B_{12} levels and normal homocysteine. Despite thorough evaluation of her vitamin B_{12} pathways, the cause of her metabolic disorder still is unknown (M. Geschwind, MD, PhD, unpublished data, 2007).

Several toxins can cause RPD. Exposure to heavy metals, such as arsenic, mercury, aluminum, lithium, or lead, can lead to cognitive decline, particularly after acute exposure. Most cases of acute exposures result in florid encephalopathies that progress over hours to days and thus would not be confused with RPDs, which progress over weeks to months. Manganese toxicity, found usually in miners, can present with significant parkinsonism [138].

Bismuth is a metal used to treat gastrointestinal disorders, principally peptic ulcer disease and diarrhea. Bismuth intoxication, typically caused by overdosing on bismuth-containing products, such as Pepto-Bismol, can cause a disorder mimicking CJD. Patients initially manifest with apathy, mild ataxia, and headaches, which progress to myoclonus, dysarthria, severe confusion, hallucinations (auditory and visual), seizures, and, in severe cases, even death [146–149]. Blood levels of bismuth, greater than 50 μg/L, are considered in the toxic range [147,149] . The condition usually is reversible; however, extremely prolonged use can result in permanent tremors [146,147]. A careful history may be needed to make the diagnosis.

Nonorganic (psychiatric) causes of rapidly progressive dementia

Psychologic processes sometimes can mimic RPD, although it is essential to rule out a neurologic cause in these cases. Pseudodementia, resulting from depression, occurs in patients who have a past history of major depression. There usually are signs that patients are severely depressed, and cognitive dysfunction, particularly on testing, is found to be the result of decreased effort. Many of the features of patients who have true dementia are seen in atypical psychiatric disorders, including personality disorders, conversion disorders, psychosis, and malingerers [150], and a full assessment is required to rule out potentially treatable or organic disorders. These cases can have many of the features of a true dementia. Furthermore, psychiatric features may be an early symptom of many neurodegenerative conditions, including CJD, DLB, CBD, and others [12].

Summary

Although the evaluation of patients who have RPD may seem daunting, it can be facilitated greatly through a structured approach. Common things being common, most cases of RPD in elderly persons probably are the result of urinary infection or pneumonia causing a delirium. When simple causes are ruled out, however, it is helpful to consider various categories of potential etiologies and rule out each category systematically. As many tests may be necessary, an inpatient evaluation can expedite the process. The authors often find that a body CT with and without contrast is of assistance in diagnosing many difficult cases, helping to identify such conditions as sarcoid, malignancies, and paraneoplastic conditions. Unfortunately, in many cases, a standard laboratory evaluation is not sufficient and brain biopsy may be necessary. If prion disease is in the differential, prion precautions must be used in the operating room and when handling brain tissue.

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