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Rapidly Progressive Dementia

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Abstract

In contrast with more common dementing conditions that typically develop over years, rapidly progressive dementias can develop subacutely over months, weeks, or even days and be quickly fatal. Because many rapidly progressive dementias are treatable, it is paramount to evaluate and diagnose these patients quickly. This review summarizes recent advances in the understanding of the major categories of RPD and outlines efficient approaches to the diagnosis of the various neurodegenerative, toxic-metabolic, infectious, autoimmune, neoplastic, and other conditions that may progress rapidly.

New and dramatic advances related to the diagnosis and treatment of conditions that present as rapidly progressive dementia (RPD) have led to more precise classification schemas and diagnostic approaches. Improved magnetic resonance imaging (MRI) techniques allow delineation of most patients with Creutzfeldt–Jakob disease (CJD) from those with other RPDs. Also, a better understanding of neurodegenerative conditions has helped to delineate non-CJD RPDs from each other and from CJD. Previously nonendemic infectious disorders, such as West Nile virus, have appeared in the United States and must be considered in the differential diagnosis of RPD. Finally, an explosion of research related to autoimmune brain disorders, caused by neoplasms or unknown precipitants, has led to the discovery of antibodies associated with an eminently treatable group of RPDs. This review emphasizes these advances and offers a new and modern classification schema for RPDs. In addition, this article emphasizes the MRI features of CJD versus other RPDs, delineates the common infectious causative agents for RPD, and describes new findings related to autoimmune entities that cause RPD.

Experience in a Rapidly Progressive Dementia Referral Center

In 2001, Stanley Prusiner's laboratory at the University of California, San Francisco (UCSF) [1] demonstrated the potential therapeutic efficacy of both quinacrine and chlorpromazine in an experimental model of prion disease. This finding led to a dramatic increase in referrals for suspected prion disease to UCSF, and over the past 6 years we have conducted comprehensive evaluations on 178 cases of suspected prion disease or RPD (Fig 1). We made a conclusive diagnosis in 95.5% of these patients, whereas in 4.5%, the diagnosis was dementia, leukoencephalopathy, or encephalopathy of unknown origin. Sixty-two percent of all patients had prion disease, which was sporadic in 75% (72% were pathology proved), genetic in 22%, and acquired in 3% (variant or iatrogenic). In 38% of the RPD patients, we diagnosed a nonprion condition; typically, these cases were diagnostically complex, defying diagnosis

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despite evaluations by multiple physicians before assessment at UCSF. The breakdown of specific diagnoses for these non-prion RPD cases is shown in Table 1.

The largest group of nonprion patients in the UCSF cohort had neurodegenerative diseases, which were found in 14.6% of all cases, accounting for 39% of all nonprion cases. These nonprion dementing conditions included frontotemporal dementia (FTD), corticobasal degeneration (CBD), Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and progressive supranuclear palsy. All of these dementias can resemble CJD because of the overlap of motor, behavioral, psychiatric, and cognitive manifestations. These disorders sometimes present in a fulminant form, developing over months, with death occurring in less than 3 years.[2–4] For nonprion disorders, dementia of unknown cause was the third most common diagnosis, accounting for 4.5% of all and 12% of nonprion cases.

Autoimmune conditions were the second most common group, representing 8.4% of the entire cohort (22% of nonprion cases), and included antibody-mediated limbic encephalitis (LE) associated with cancer (paraneoplastic) or occurring without cancer (non-paraneoplastic), Hashimoto's encephalopathy (HE), multiple sclerosis, and neurosarcoidosis. HE was diagnosed by identification of highly increased anti-thyroglobulin or anti-thyroperoxidase antibodies in the serum and exclusion of other diseases (including untreated thyroid disease). Antibody-mediated autoimmune syndromes were associated with antibodies directed against the brain. Patients in the autoantibody group often had antibodies in their cerebrospinal fluid (CSF) and/or serum, several of which may not yet be available through commercial testing but can be identified in academic research laboratories. Four RPD patients had encephalitis, but the agent (enterovirus) was identified in only one.[5] In the other three patients, the cause was presumed to be viral, but despite thorough evaluation, no virus could be identified. We identified toxic-metabolic causes of RPD in three cases, including methylmalonic academia, encephalopathy secondary to alcohol intoxication, and methotrexate toxicity.

In four patients, we identified encephalopathies associated with cancer (three had lymphoma) but without evidence of autoantibodies. These cases did not immediately suggest cancer or lymphoma, but they had MRI, T2-weighted, white matter hyperintensities that often were contrast enhancing. Virtually all the lymphomas (systemic or central nervous system [CNS]) required biopsy for diagnosis, because CSF evaluation (cytology) and other studies were nondiagnostic. The main subtypes of RPD and the varied conditions that led to a misdiagnosis of CJD are discussed in the following section.

Categories of Rapidly Progressive Dementia

Prion Diseases

Typically, sporadic CJD (sCJD) presents with a mixture of dementia and cerebellar, extrapyramidal, and behavioral or psychiatric symptoms.[6] sCJD usually occurs between the ages of 50 and 70 years, with a median age of 68, and it affects woman and men equally.[7,8] Median survival is 5 months; approximately 85% of patients die within 1 year of symptom onset.[7,9–11] Pyramidal, extrapyramidal, cerebellar, and focal cortical dysfunction (eg, aphasia) are common. In one third of patients, vague complaints of fatigue, headache, sleep disturbance, vertigo, malaise, weight loss, pain, depression, or behavioral changes precede the dementia by weeks to months.[6,12] Genetic forms are generally slower, but several mutations can lead to a classic sCJD presentation.[13,14]

Variant CJD (vCJD) affects young adults, with a mean age of 29 years and a range of 12 to 74 years.[15–17] In contrast with sCJD, typically vCJD begins with a prodrome of profound psychiatric illness lasting more than 6 months. Neurological symptoms, including ataxia, dysesthesia, dementia, or a movement disorder (chorea, myoclonus, or dystonia), appear later.

Only rarely does the electroencephalogram (EEG) in vCJD show the periodic sharp waves typical of sCJD.[15,18] Although MRI in vCJD shares features with sCJD, vCJD is distinguished by the presence of the pulvinar sign (ie, hyperintensity of the pulvinar relative to the anterior putamen).[19] Three cases of vCJD have been identified in the United States and one in Canada; all patients likely acquired the disease before coming to North America.[20]

Definitive diagnosis of CJD requires demonstration of prions in the brain (or tonsillar tissue in vCJD).[21] Until recently, probable sCJD was diagnosed by the presence of progressive dementia and at least two of the following clinical symptoms: pyramidal/extrapyramidal symptoms, visual or cerebellar disturbance, myoclonus, or akinetic mutism and either a characteristic EEG or an increased CSF 14-3-3 protein level. Initially, EEG shows focal or diffuse slowing, but in about two thirds of cases, EEGs eventually evolve to periodic 1 to 2Hz triphasic sharp waves, which are highly characteristic of sCJD. This EEG finding is seen with other disorders, including toxic-metabolic conditions, HE, and rarely, during the end stages of AD or DLB. This EEG pattern usually appears in only the later stages of CJD.[7,22–24] Therefore, despite the long-standing use of periodic sharp complexes on EEG for diagnosis, the EEG lacks sensitivity and misses many early and some late cases.

In contrast with many other RPDs, CSF cell counts in prion disease are typically normal, but CSF protein level may be mildly increased and oligoclonal bands can be present.[25] Increases in several CSF protein levels, including 14-3-3, neuron-specific enolase (NSE), and tau, have been proposed as diagnostic for CJD,[24,26–29] but all lack sensitivity and specificity.[28–35] With the advent of fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) techniques, brain MRI is supplanting other diagnostic methods. Shiga and colleagues[36] found that the 92% sensitivity and 94% specificity of DWI MRI for CJD is far more sensitive than EEG, 14-3-3, and NSE. In most patients, MRI suggests CJD well before EEG shows periodicity. In our experience, the combination of FLAIR and DWI MRI had 91% sensitivity and 94% specificity. DWI was more sensitive than FLAIR. Two thirds of patients had DWI or FLAIR abnormalities in cortex and deep gray matter (striatum, thalamus, or both), one fourth had cortical changes only, and 5% had isolated changes in deep gray matter structures (Figs 2A–C). Similar MRI findings are evident in some of the inherited prion diseases.[36–39]

With few exceptions, these changes do not occur in other conditions that mimic CJD. Striatal or thalamic hyperintensities on T2, FLAIR, or DWI have been described in neurofilament inclusion body disease,[40,41] Wilson's disease,[42] Wernicke's encephalopathy,[43] vasculitis,[44] and anti-CV2–associated paraneoplastic conditions.[45] Cortical ribboning on DWI sequences may occur with seizures[46] and vasculitis,[44] and with some autoantibody syndromes, but the hyperintensity pattern is usually easy to differentiate from the pattern seen in CJD. Notably, CJD does not show contrast enhancement and is associated only rarely with T1-weighted signal intensity[47] or white matter abnormalities.[48] The presence of any of these findings suggests other causative factors.

Other Degenerative Dementias

AD usually progresses slowly but can progress rapidly.[49,50] AD associated with cerebral amyloid angiopathy can be subacute.[51] Other neurodegenerative diseases, including DLB, CBD, and sometimes FTD, are more likely than AD to present in a fulminant fashion. Myoclonus and extrapyramidal signs are common in CBD, DLB, and in the later stages of AD, and thus their presence does not automatically suggest CJD.[35,49,52] CBD was the most common neurodegenerative dementia misdiagnosed as CJD referred to UCSF. The typical features of CBD, dementia, parkinsonism, myoclonus, and alien limb are also seen in CJD; when these findings evolve rapidly, CJD should be considered.[53] FTD patients often experience development of prominent extrapyramidal syndromes or motor neuron disease;

when FTD progresses rapidly, CJD should be part of the differential diagnosis.[54,55] DLB is associated with dramatic fluctuations in cognitive function, persistent, well-formed visual hallucinations, and parkinsonism,[56,57] and rarely may show periodic sharp waves on EEG, leading to its misdiagnosis as CJD.[23,49,52,58] Importantly, none of these conditions manifests the typical MRI findings of CJD. The MRI pattern of CJD is so sensitive that this disorder should rarely be considered when the MRI is negative.

Other Causative Factors for Rapidly Progressive Dementia

Paraneoplastic and Other Autoimmune Causative Factors

Autoimmune diseases of the brain associated with antineuronal antibodies that cause limbic encephalopathy (LE) were the second most common nonprion diagnostic group in our cohort. Many cases occurred without any identifiable malignancy.[59] Symptoms of LE, the most common syndrome presenting as RPD, include memory loss, often accompanied by behavioral changes. Depression, personality changes, anxiety, and emotional lability often precede cognitive dysfunction and seizures.[59,60] Paraneoplastic syndromes should be considered when there is a subacute or even more rapid development of dementia, extrapyramidal or cerebellar symptoms, other neurological symptoms, inflammatory CSF, cancer risk factors, or a family history of cancer. These syndromes are confirmed when paraneoplastic antibodies are found in the serum or CSF, although antibodies are not always identified.[61,62]

Commercial testing is available for several antibodies associated with LE, but new antineuronal antibodies associated with encephalopathy and paraneoplastic syndromes continue to be defined,[59,63] including the recently described antibodies specific for cell membrane antigen.[64,65]

Identification of these antibodies confirms the diagnosis of a paraneoplastic syndrome, and helps to guide diagnosis and treatment of the underlying malignancy. Specific antibodies tend to cluster with certain types of cancer. For instance, anti-Hu and anti-CV2 antibodies are associated with small-cell lung cancer, anti-Ma2 with testicular cancer, and anti–*N*-methyl-D-aspartate receptor with ovarian teratomas.[66,67] Detection of these antibodies in the proper clinical context should prompt an aggressive investigation for the corresponding tumors. Several patients in our RPD cohort had LE associated with voltage-gated potassium channel antibody. Most had hyponatremia attributable to the syndrome of inappropriate antidiuretic hormone secretion, facial and/or limb twitching or spasms, complex partial seizures, and medial temporal lobe T2-weighted hyperintensity on brain MRI. Some cases have been associated with thymomas or other cancers, but usually no cancer is ever found.[60] Localization of antibody reactivity on the cell membrane, such as in voltage-gated potassium channel LE, is a good predictor of response to therapy, compared with paraneoplastic antibodies that react with intracellular antigens (eg, Hu, Ma2, CV2, and amphiphysin).[59,64] Most of our patients with antibodies to cell membrane antigens recovered dramatically with therapy.

HE is a rare, but treatable, autoimmune disorder associated with Hashimoto's thyroiditis.[68–70] Patients often present with neurological symptoms, including altered or fluctuating levels of consciousness, seizures, extrapyramidal signs, ataxia, or even strokelike episodes. Psychiatric features are frequent.[68,69] HE is more common in women (70 – 85% of cases).[68,69] Markedly increased levels of antithyroid autoantibodies (anti-thyroglobulin or anti-thyroperoxidase) should be present to confirm this diagnosis. Patients may be euthyroid, subclinically or clinically hypothyroid, or even hyperthyroid, but the diagnosis of HE can be made only after correction of the thyroid abnormality.[68] Triphasic or periodic sharp waves on EEG can occur, as in CJD.[69,71] MRI does not show the typical findings of CJD, which helps to separate HE from CJD.[69,72,73] Immunosuppressive treatment can cure HE.[69]

Primary CNS vasculitis often presents with headache, altered mentation, focal neurological signs, and CSF pleocytosis.[74] Other vasculitic considerations include granulomatous angiitis of the CNS, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, hypereosinophilic syndrome, and even mitochondrial disease.[44,75–81] Serological testing typically is normal in CNS vasculitis.[74,82] Vasculitides are distinguished from other RPDs, including CJD, by the presence of systemic manifestations or by specific abnormalities on brain MRI, such as multiple infarctions of different ages or the presence of brain hemorrhage.[44,74] Cerebral angiogram or brain and meningeal biopsy of the affected area may be required for diagnosis. Treatment requires immunosuppression.

Celiac disease ("gluten ataxia") has been reported to cause ataxia, neuropsychiatric symptoms, seizures, headaches, neuropathy, and dementia, even in the absence of gastrointestinal symptoms. MRI may show T2-weighted posterior white matter hyperintensities. Diagnosis is made by detection of increased antien-domysial or antigliadin immunoglobulin A (IgA) or IgG. Treatment is a gluten-free diet.[80,83]

Sarcoidosis can mimic many neurological conditions, and the clinical syndromes and brain MRI findings seen with neurosarcoid are highly variable. With MRI in neurosarcoid, the following changes have been reported: (1) normal; (2) enhancing granulomas; (3) enhancing or nonenhancing, T2-weighted, white matter hyperintensities; (4) thickening of basilar leptomeninges (typical of chronic meningitis)[84]; and also (5) DWI hyperintensities resembling CJD (see Fig 2E). Systemic manifestations or hilar lymphadenopathy on chest computed tomography can aid with diagnosis. CSF can be normal, but increased protein and pleocytosis are common. CSF angiotensin-converting enzyme lacks specificity and sensitivity, and is seen in only 50% of cases. Definitive diagnosis requires biopsy of affected tissue.[85]

Vascular Causative Factors

Rarely, strokelike clinical presentations occur in CJD, initially suggesting a vascular event.[86,87] Conversely, strokes from cerebrovascular disease, including large-vessel occlusions, thalamic or multifocal infarcts,[88,89] and microangiopathic thromboses from thrombotic thrombocytopenic purpura can lead to RPD. Also, diminished cerebral perfusion secondary to hyperviscosity syndromes with polycythemia or monoclonal gammopathies or venous thrombosis and dural arteriovenous fistulas can have clinical features suggestive of CJD, including rapid onset of dementia, parkinsonism, or ataxia. Neuroimaging distinguishes these conditions from each other and from CJD.[90,91]

Infectious Causative Factors

Most CNS infections resulting in altered mental status present acutely, but some emerge more slowly. Infectious causative factors of RPD include viral, bacterial, fungal, and parasitic organisms. CNS infections are usually accompanied by other hallmarks of infection. Therefore, the presence of fever, peripheral leukocytosis, or CSF pleocytosis in an RPD patient should prompt investigation for an infectious agent. Viral encephalitides are sometimes insidious. Herpes simplex viruses 1 and 2, cytomegalovirus, Epstein–Barr virus, and enterovirus, although typically presenting as acute encephalitis, do present with more gradual behavioral and mental status changes.[92–94] West Nile virus has become the most important cause of epidemic viral encephalitis in North America.[95] Rabies virus usually produces a fulminant illness early in its course that is characterized by prominent behavioral and neuropsychiatric features, including agitation, bizarre behavior, hallucinations, and extreme excitability followed by swift progression to coma.[96] Polyomaviruses, including JC and BK viruses, present more frequently as progressive multifocal neurological deficits or meningoencephalitis, but they do cause RPDs in the immunocompromised population.[97,98] Another viral cause of RPD is human immunodeficiency virus (HIV). AIDS-dementia complex

tends to occur in later stages of HIV infection; its incidence has decreased since the introduction of highly active antiretroviral therapy.[99] RPD can develop during HIV seroconversion and even during immune reconstitution. In addition to direct HIV CNS involvement, various HIV-associated subacute and chronic opportunistic infections or other immunocompromised states need to be considered and are also discussed.

Bacterial agents, which more frequently produce suppurative meningitis with a rapid decrease in consciousness, can sometimes present as RPD. *Bartonella henselae*, the agent causing "cat-scratch disease," is typically associated with acute encephalitis, particularly in younger patients, but may present as a rapid, progressive dementia, especially in immunocompromised persons.[96,100–102] Meningitis is the hallmark of CNS infection with mycobacterium species, but a recent report found an atypical acid-fast bacillus in postmortem brain tissue from a patient with RPD. This article highlights the possibility that undiagnosed RPDs are due to infectious organisms not detected by standard microbiological techniques.[103] Infection with *Mycoplasma pneumoniae* and *neoaurum* has been associated with a number of neurological syndromes, including RPD with elevated 14-3-3 protein levels.[100,104,105]

Whipple's disease is a rare bacterial *(Tropheryma whippelii)* infection that often begins as a malabsorption syndrome, but 5% of cases start as a neurological syndrome with dementia, movement disorder (myorrhythmia and ataxia), or psychiatric signs. The triad of dementia, ophthalmoplegia, and myoclonus occurs in only 10% of cases, but this combination strongly suggests Whipple's disease, whereas oculomasticatory myorrhythmia is pathognomonic. Diagnosis is made by the demonstration of periodic acid-Schiff–positive inclusions, *T. whippelii* on jejunal biopsy, or polymerase chain reaction from jejunal biopsy or CSF.[106]

No workup for RPD is complete without an evaluation for neurosyphilis attributable to *Treponema pallidum.* Cognitive dysfunction is usually a late complication of syphilis, but it is the most common neurological syndrome and is particularly virulent in immunocompromised patients.[107] Lyme disease can present as an RPD[108] and is often accompanied by cranial nerve palsies, meningitis, polyradiculopathy, depression, and/or psychosis.[109]

Fungal and parasitic infections of the nervous system, particularly among the immunocompromised population, should be considered in the RPD differential diagnosis. *Cryptococcus neoformans* more typically occurs as progressive meningitis; however, it may cause rapidly progressive neurological dysfunction and altered mental status.[94,110]

In the returning traveler, two parasitic infections that must be considered are trypanosomiasis and malaria. Cerebral trypanosomiasis caused by infection with the parasite *Trypanosoma* is acquired through insect vectors, often sandflies. Although infection with *Trypanosoma cruzii* in the Americas (Chagas' disease) is rarely associated with neurological involvement, infection with *Trypanosoma* species found in Africa causes sleeping sickness and profound neurological consequences. After the fly bite, a skin lesion or a chancre develops, followed in weeks by headache, generalized weakness, and altered mental status. Sleep/wake cycle alterations and progressive mental deterioration can be mistaken for neurodegenerative causes of RPD.[111] Malaria infection from *Plasmodia falciparum* is typically associated with relapsing fevers and other systemic signs but sometimes results in cerebral involvement.[112,113] Cerebral malaria accounts for approximately 10% of inpatient malaria infections in endemic regions. Acute loss of consciousness or convulsions are typical features, but RPD is another manifestation of cerebral malaria, usually accompanied by other signs of organ involvement, including anemia, jaundice, and severe hyperpyrexia. The amoeba *Balamuthia mandrillaris* has caused a few cases of fatal encephalitis in the United States. These patients had CSF pleocytosis and increased protein levels, whereas MRI showed a mass lesion. All diagnoses were made by indirect immunofluorescence antibody staining; without this procedure, the

patients likely would have been misdiagnosed as having tumor, neurocysticercosis, tuberculosis, or viral encephalitis.[114,115]

When faced with an unknown encephalitis, it may be helpful to use the diagnostic resources of specialized encephalitis referral centers funded by the US Centers for Disease Control and Prevention (CDC), such as the California Encephalitis Project.[100,115] Figure 2D shows a FLAIR MRI of a patient referred with possible CJD who was found to have enteroviral meningoencephalitis.

Malignancies (Nonautoimmune Paraneoplastic)

Primary and secondary malignancies cause RPD, but those that are associated with readily identifiable mass lesions with MRI T2-weighted hyperintensity and contrast enhancement are not discussed in this article. Four malignancies to consider are primary CNS lymphoma (PCNSL), intravascular lymphoma (ie, angiotropic lymphoma), gliomatosis cerebri,[116] and lymphomatoid granulomatosis (angiocentric immunoproliferative lesions).[117] Diffusely infiltrating PCNSL (lymphomatosis cerebri) can present as a subacute dementia. PCNSL is usually of the non–Hodgkin B-cell type and often occurs in the setting of immunosuppression.[118] CSF shows lymphocytosis, increased protein, and often low glucose. In immunocompetent individuals, brain MRI typically shows an isointense to mildly hyperintense T2-weighted signal, often involving the basal ganglia, periventricular white matter, and/or corpus callosum with variable contrast enhancement (see Fig 2F).[118] When PCNSL occurs as lymphomatosis cerebri, imaging shows progressive, diffuse signal abnormality of white matter without enhancement or mass effect, likely from a diffusely infiltrative process without interruption of the blood–brain barrier.[119,120] CSF cytology is often negative, and diagnosis usually requires brain biopsy.[82,121]

Intravascular lymphoma often presents with stroke-like and systemic symptoms but also with subacute dementia. Skin or organ involvement should be investigated, and serum lactate dehydrogenase is often increased. Brain MRI typically shows regions of T2-weighted hyperintensity with variable enhancement and sometimes edema. Brain biopsy is needed for diagnosis because on angiography this lymphoma can look like CNS vasculitis. Most cases are diagnosed postmortem.[122]

Toxic-Metabolic Conditions

There are many toxic-metabolic causes of RPD. A workup should begin with the assessment of routine electrolytes, calcium, magnesium, phosphorus, vitamin B_{12}, and renal and liver function. Porphyria can cause psychosis or unexplained pain (particularly abdominal). Vitamin deficiencies (eg, thiamine and vitamin E) occur in patients with a history of alcoholism or malabsorption. Heavy metal intoxication with arsenic, mercury, aluminum, lithium, or lead can cause cognitive decline.[123] Bismuth intoxication (eg, from excessive ingestion of bismuth subsalicylate [Pepto-Bismol]) presents with confusion, ataxia, myoclonus, or psychosis.[124,125] Recently, we identified a case of adult-onset neuropsychiatric syndrome that progressed over several months with gastrointestinal disturbance that was associated with increased serum and urine methylmalonic and malonic acid, but with a normal homocysteine level (M. Geschwind, unpublished data). Adult presentations of childhood metabolic diseases are probably an underrecognized form of RPD.[126]

Nonorganic Causes

Pseudodementia of depression often begins precipitously in a patient with a history of major depression, although most patients with “pseudodementia” probably have an underlying dementia. Nondepressive psychiatric syndromes associated with RPD include conversion

disorders, psychosis, and malingering.[127] In our cohort, the most common psychiatric syndrome leading to RPD was patients who self-diagnosed CJD.

Diagnostic Methods

Algorithms

A practical approach to the evaluation of a patient with RPD is shown in Table 2. Most cases of RPD in the elderly are due to metabolic perturbations or acute infections (pneumonia or urinary tract infection). Tests listed as "first line" should always be done in cases of RPD without an obvious diagnosis. The order in which these are performed will differ, depending on the clinical presentation. An EEG can help to rule out seizures, particularly nonconvulsive status epilepticus,[128] or to diagnose other conditions, such as CJD. Tests listed as "sometimes helpful" may be necessary, depending on the condition suspected.

If initial basic blood and urine tests results are unrevealing, testing for HE should be done. The pattern of MRI abnormalities can provide a diagnosis or help prioritize other diagnostic tests. CSF analysis is usually required, and some CSF should be saved in case other diagnoses are considered later. To every rule, there are exceptions: Lymphomas do not always show enhancement; sarcoid does not always have increased CSF protein level and pleocytosis; and CJD does not always have MRI striatal, thalamic, or cortical hyperintensity.

Brain Biopsy

Despite a thorough evaluation, brain biopsy is sometimes necessary. Diagnostic sensitivity of brain biopsy in dementia ranges from 20 to 65%.[82,129] In a UCSF study, biopsy was diagnostic in 83% of RPD patients.[82] DWI MRI has obviated the need for brain biopsy in most cases of CJD.[36,37] Beyond the risks for hemorrhage, seizures, postbiopsy delirium, and death associated with brain biopsy, there is a legitimate risk for prion spread from neurosurgical equipment. At our institution, we incinerate neurosurgical equipment used for patients with potential prion disease (www.ucsf.edu, Infection Control Department). Improved methods for removal of prions from surgical equipment may soon be available, thus significantly decreasing the risk for iatrogenic transmission and possibly avoiding disposal of costly surgical tools.[130]

Conclusion

RPDs represent one of the most challenging neurology referrals. The differential diagnosis is often wide ranging, and CJD represents one of many disorders to consider. A fresh but systematic approach is required for every patient. FLAIR and diffusion-weighted abnormalities in the cortex and striatum can help to confirm CJD and eliminate other conditions. Common nonprion conditions include neurodegenerative, autoimmune, infectious, and neoplastic disorders. Even after a systematic assessment, a minority of patients will still remain undiagnosed.

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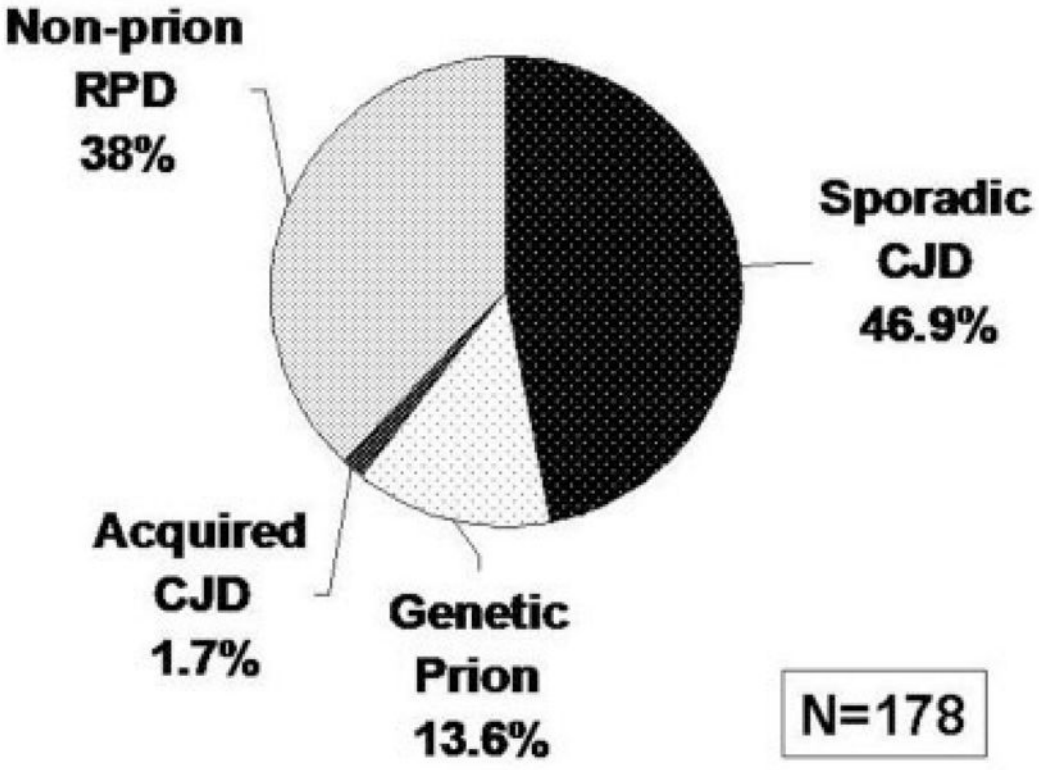

Fig 1.

Diagnosis of University of California, San Francisco (UCSF)–evaluated rapidly progressive dementia (RPD) referrals (N =178) from August 2001 to September 2007. Pie chart showing the percentile of broad categories for final diagnoses of patients with suspected Creutzfeldt–Jakob disease (CJD) or other RPDs. Note that in many cases referred with suspected prion disease, a nonprion diagnosis was made.

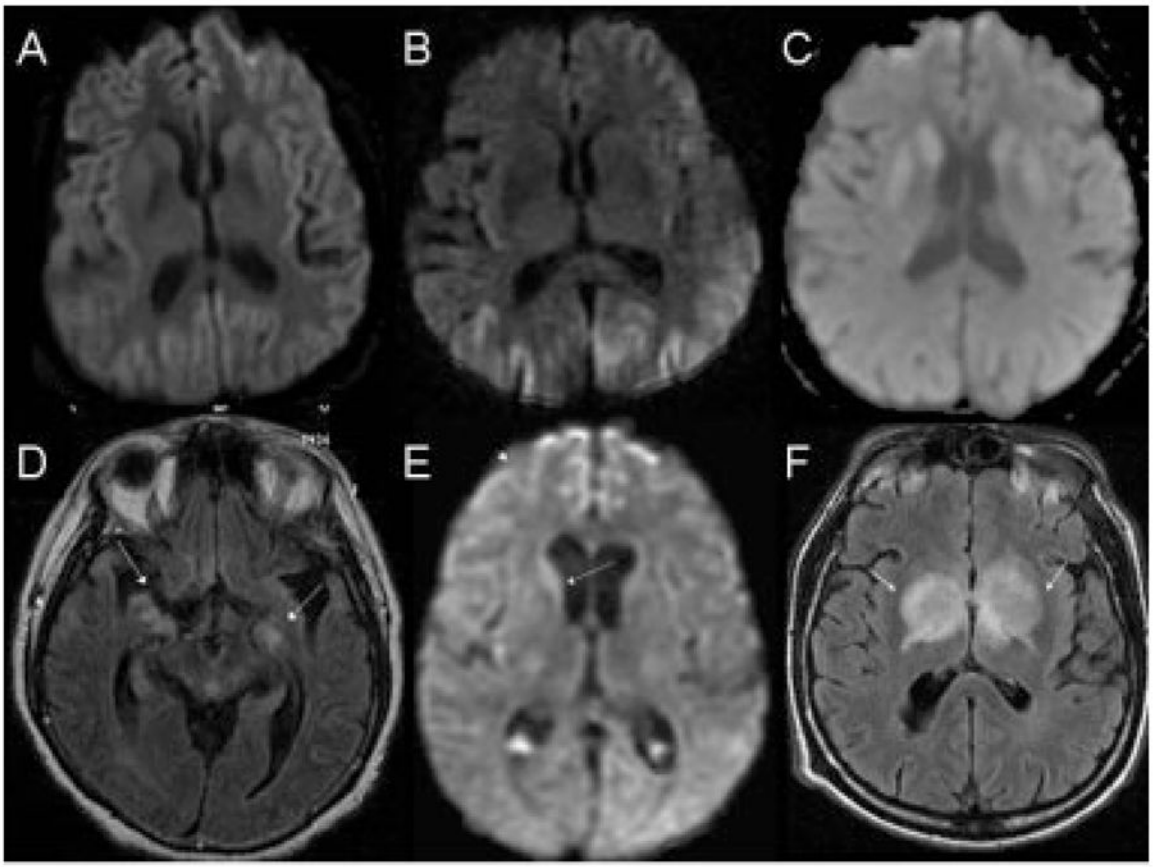

Fig 2.

Brain magnetic resonance images (MRIs) in sporadic Creutzfeldt–Jakob disease (CJD) (A–C) and nonprion rapidly progressive dementias (RPDs) (D–F). Sporadic CJD axial diffusion-weighted imaging (DWI) with both cortical and striatal hyperintensity (A), only cortical (cortical ribboning) hyperintensity (B), and only striatal hyperintensity (C). Fluid-attenuated inversion recovery (FLAIR) MRIs (not shown) showed less hyperintensity than DWI sporadic CJD. Axial FLAIR MRI of patient with pathology-proved meningoencephalitis (D) showing extensive, patchy, T2-weighted white matter hyperintensity (arrows) that was variably contrast enhancing (not shown). Enterovirus was identified through the California Encephalitis Project by reverse transcription-polymerase chain reaction of brain biopsy tissue. DWI axial MRI of a patient with systemic sarcoid (E). Initial diagnosis suggested CJD because of caudate hyperintensity (arrow) and right frontal cortical ribboning (arrowhead). The apparent diffusion coefficient map (not shown), however, did not suggest restricted diffusion, and a lung node biopsy showed sarcoid. Axial FLAIR MRI of an RPD patient with parkinsonism (F). Arrows point to the masses in the bilateral deep nuclei. Note the mass effect with edema (arrows). The lesions were hypodense on T1 and showed some gadolinium enhancement (not shown). Brain biopsy showed a B-cell primary central nervous system lymphoma.

Table 1

Nonprion Diagnoses of Patients in University of California, San Francisco Cohort Initially Suspected of Having Creutzfeldt–Jakob Disease

Condition	Cases (n)	Percentage of Nonprion RPDs
Neurodegenerative		
Corticobasal degeneration	8	
Frontotemporal dementia[a]	7	
Dementia with Lewy bodies	4	
Alzheimer's disease[b]	5	
Progressive supranuclear palsy	2	
Subtotal	26	39
Autoimmune		
Hashimoto's encephalopathy	4	
Multiple sclerosis	1	
Sarcoid	1	
Antibody mediated		
VGKC	2	
Yo and Hu	1	
Ma[c]	1	
CV2[c]	1	
GAD65	1	
Neuropil[c]	1	
Adenylate kinase 5	1	
Glial	1	
Subtotal	15	22
Unknown causative factor[d]	8	12
Infectious[e]	4	6
Psychiatric	4	6
Malignancy[f]		
PCNSL	2	
Non–antibody-mediated paraneoplastic	2	
Subtotal	4	6
Toxic/metabolic		
Ethanol toxicity	1	
Methylmalonic academia	1	
Methotrexate toxicity	1	
Subtotal	3	4
Vascular	3	4
Total	67	100

[a] Includes two frontotemporal dementia/acute lateral sclerosis and one progressive subcortical gliosis PSG patient.

[b] Includes one familial subject.

[c] Includes one paraneoplastic patient.

[d] Includes one leukoencephalopathy, one pathology-proven astrogliosis, and one suspected cerebral amyloid angiopathy patient.

[e] Includes two pathology-proved meningoencephalitis and two viral encephalitis patients (unknown agent; patients recovered).

[f] Includes one thymoma and one systemic lymphoma with encephalopathy patient and two central nervous system lymphoma patients. RPD =rapidly progressive dementia; VGKC =voltage-gated potassium channel antibody; PCNSL =primary central nervous system lymphoma.

Table 2

Recommended Initial Screening Tests for Evaluation of a Rapidly Progressive Dementia

Category	Required Tests	Sometimes Helpful
Blood tests	CBC	Cancer screen
	Chemistry panel (including calcium, magnesium, phosphorus)	Blood smear
	LFTs	Hypercoagulability testing
	RPR	Copper and ceruloplasmin
	Rheumatological screen (ESR, ANA, and CRP)	Methylmalonic acid levels
		Additional rheumatological tests
	Thyroid function	Coagulation profile
	Anti-thyroglobulin and anti-thyroperoxidase antibodies	
	Vitamin B_{12}	
	Homocysteine	
	HIV	
	Lyme	
	Paraneoplastic/autoimmune antibodies	
Urine	Urine analysis	Urine culture
		Copper (24 hours, if Wilson's disease suspected)
		Heavy metal screen (24 hours)
CSF	Cell count and differential	Cryptococcal antigen
	Protein	Viral PCRs and cultures
	Glucose	Bacterial, fungal, AFB stains, and cultures
	IgG index	Cytology
	Oligoclonal bands	Whipple's PCR
	VDRL	14-3-3 test
		Total and phosphorylated tau
Imaging	Brain MRI (including FLAIR and DWI) with and without contrast	CT head
		CT chest, abdomen, and pelvis with and without contrast
		Brain angiogram
		Mammogram
		Body PET scan
		MRS
		Carotid ultrasound
		Echocardiogram
Other tests	EEG	EMG/NCS
		Brain biopsy (especially if procedures listed earlier are nondiagnostic)

CBC =complete blood cell count; LFT =liver function test; RPR =rapid plasmin reagin (test); ESR =erythrocyte sedimentation rate; ANA =antinuclear antibody; CRP =C-reactive protein; IgG =immunoglobulin G; HIV =human immunodeficiency virus; CSF =cerebrospinal fluid; VDRL =Venereal Disease Research Laboratory (test); PCR =polymerase chain reaction; AFB =acid-fast bacilli; MRI =magnetic resonance imaging; FLAIR =fluid-attenuated inversion recovery; DWI =diffusion-weighted imaging; CT =computed tomography; PET =positron emission tomography; MRS =magnetic resonance spectroscopy; EEG =electroencephalogram; EMG =electromyogram; NCS =nerve conduction study.