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The Evaluation of Rapidly Progressive Dementia

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Abstract

Background—Rapidly progressive dementia (RPD) is a unique set of disorders resulting in cognitive, behavioral, and motor decline within 2 years. A variety of etiologies may contribute to RPD including neurodegenerative, inflammatory, infectious, and toxic-metabolic conditions. Jakob-Creutzfeldt disease (CJD) is frequently the most concerning diagnosis on the differential. The challenge for the neurologist is distinguishing prion disease from reversible processes that result in dementia.

Review Summary—This review discusses the clinical aspects and the diagnostic work-up of RPD. Particular focus is given to both CJD and the potentially treatable inflammatory conditions that may cause a similar presentation. Furthermore, a standardized step-wise approach is outlined for patients presenting with RPD.

Conclusion—Neurologists should adopt a standardized approach to the rapidly presenting disease processes that may mimic CJD in their clinical and radiological features.

Keywords

Rapidly progressive dementia; Jakob-Creutzfeldt disease; Immune-mediated dementia; Paraneoplastic syndrome; Hashimoto’s Encephalopathy

Introduction

Dementia is a chronic progressive, irreversible neurodegenerative process compromising cognitive, behavioral, and motor function and ultimately leads to functional impairment. Typical examples of chronic neurodegenerative diseases include Alzheimer’s dementia (AD), vascular dementia (VD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). However, a certain subset of these conditions may also present with a more accelerated decline in function and warrant classification as a rapidly progressive dementia (RPD).

Rapidly progressive dementia (RPD) is distinguished from the more typical dementias by a subacute time course and an accelerated rate of decline that develops in fewer than 2 years. Furthermore, a variety of underlying causes may contribute to a RPD presentation, including neurodegenerative, auto-immune, infectious, and toxic-metabolic processes. The most concerning differential diagnosis in any patient presenting with RPD is Jakob-Creutzfeldt Disease (CJD), a fatal prion-related neurodegenerative illness.

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Whereas the prognosis is relatively well-defined for the chronic dementias, the prognosis in RPD is variable depending on the underlying cause of the symptoms. For instance, infectious or autoimmune processes may be slowed or reversed with appropriate treatment whereas a neurodegenerative condition such as CJD may lead to rapid progression to death within 6 months time. Identification of a reversible RPD is particularly important considering that delay in treatment may lead to permanent functional impairment or death.

Thus, the task of the clinician evaluating RPD is distinguishing an irreversible neurodegenerative process such as CJD from potentially reversible processes such as paraneoplastic disease (PND) or Hashimoto's Encephalitis (HE). Due to the broad differential diagnosis that may lead to a RPD presentation, the clinical evaluation requires a more extensive diagnostic work-up compared to typical dementias, involving a comprehensive history and physical exam, magnetic resonance imaging (MRI), electroencephalography (EEG), and cerebrospinal fluid (CSF) analysis.

The purpose of this review is to provide insight into the differential diagnosis, clinical approach, and potential treatments for RPD. There is particular emphasis on CJD, one of the most common causes of RPD.

Prion Disease Presenting as CJD

Jakob-Creutzfeldt Disease (CJD)—CJD is divided into sporadic CJD (sCJD), familial CJD (fCJD), and variant CJD (vCJD). sCJD is by the far the most common variation, occurring in 85% of patients with CJD. Genetic CJD, defined as prion diseases associated with an underlying mutation of the prion protein gene (PRNP) on chromosome 20, occurs in approximately 10–15% of prion disease whereas vCJD accounts for 1% of cases[1].

sCJD usually presents between the ages of 50 and 70 [2]. sCJD carries one of the gravest prognoses within the field of neurology with a median survival of 5 months and 85% of patients dying within 1 year of onset[2]. In Western countries, CJD occurs at a rate of 1–2 million/year[1].

Variant CJD (vCJD) is an acquired prion disease that predominantly affects young adults with a mean age of 29 years and a range from 12–74 years. vCJD often presents with a psychiatric prodrome lasting more than 6 months, and frequently, these patients may be misdiagnosed as having a primary psychiatric illness. Similarly to sCJD, patients present with a combination of neurological signs including ataxia, cognitive impairment, and extrapyramidal motor findings. Neuroimaging is characterized by the "pulvinar sign" on MRI demonstrating hyperintensities affecting the pulvinar nucleus on T2 and FLAIR sequences[3].

Familial genetic CJD is inherited in an autosomal dominant fashion and results from point mutations and insertions affecting PRNP[4, 5]. The most common mutation is a point mutation affecting E220K[4]. Insertions in PRNP, such as ins24bp, lead to repeated expansions in which the repeat number and size of the insertion directly correlates with clinical phenotype and severity (as in Huntington's disease).[4] Other inherited forms of prion disease include fatal familial insomnia (FFI), characterized by progressive sleep and autonomic disturbances, and Gerstmann-Strauussler-Scheinker disease (GSS), which presents as a progressive cerebellar ataxia.

Sporadic CJD can have a variety of presentations that result in cognitive, behavioral, sensory, or motor dysfunction. The disease has been described as a "great mimicker," compromising cortical, extrapyramidal, and cerebellar function. The accuracy of diagnosing

CJD can be quite variable. Approximately, 15–20% of RPD referrals for suspected CJD are a result of non-prion causes.[6]

When performing the clinical interview, the clinician should inquire about initial symptoms as this information may be diagnostically relevant in terms of functional localization. The most common initial symptoms in sCJD include cognitive (39%), cerebellar (21%), behavioral (20%), consititutional (20%), sensory (11%), motor (9%), and visual (7%).[7].

The World Health Organization (WHO) (see table 1) has defined criteria based on clinical symptoms for possible, probable, and definite CJD.[1] The diagnosis of definite CJD requires either pathological confirmation (by autopsy or biopsy) or demonstration of the disease causing form of the prion protein.[1]

In order to meet the World Health Organization (WHO) criteria for probable CJD, patients must have either an electroencephalogram (EEG) positive for periodic epileptiform disharges or positive 14-3-3 protein as well 2 of the following symptoms: 1. myoclonus, 2. pyramidal/extrapyramidal findings, 3. visual or cerebellar deficits, or 4. akinetic mutism. Furthermore, routine investigations should not suggest an alternative diagnosis.

Unfortunately, the criteria for probable CJD suffer from both a lack of sensitivity and specificity. Akinetic mutism and an EEG showing periodic epileptiform discharges are clinical features that characterize the later stages of CJD. Furthermore, the criteria fail to include signs of cortical dysfunction such as aphasia, apraxia, and alien limb phenomenon. The motor signs of myoclonus, parkinsonism, cerebellar ataxia, and/or spasticity lack specificity and can be found in a variety of other neurodegenerative processes. For instance, myoclonus with extrapyramidal findings is seen in 70% of DLB patients and 50% of AD patients.[8]

All patients with suspected CJD should undergo spinal fluid analysis, EEG, and magnetic resonance imaging (MRI) of the brain.

The typical cerebrospinal fluid (CSF) profile in a patient with CJD shows a mildly elevated protein and normal glucose without leukocytosis.[2] Any signs of inflammation may be indicative of an autoimmune-mediated encephalopathy. 14-3-3 (Gambetti) protein, tau, and neuron specific enolase (NSE) are all recognized CSF biomarkers for CJD. Despite routine assessment of 14-3-3 protein levels in these patients, recent studies have showed that this biomarker has limited sensitivity. In a cohort of 32 pathologically confirmed cases, only 17 (53%) showed elevated CSF 14-3-3 protein levels.[9] Unfortunately, the 14-3-3 protein, tau, and NSE are all indirect indicators of neuronal injury and fail to address the underlying need for a prion-specific biomarker.

EEG is a useful diagnostic tool for looking at cortical irritability in this patient population. Studies in patients during the early stages of the disease may show focal or diffuse slowing and only in the later stages of the illness will the characteristic 1–2 Hz periodic sharp waves be present. However, such findings may also occur in DLB and HE [2]. The sensitivity and specificity of EEG for CJD is variable, ranging from 50–66% and 74–91% respectively.[2]

Recent literature has shown brain MRI to be a relatively sensitive and specific diagnostic tool for CJD. The most useful sequences include fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC). In a study of 26 patients, the detection of DWI hyperintensities within the cortical and subcortical gray matter was 92.3% sensitive and 93.8% specific and considered superior to both EEG, NSE and 14-3-3 protein in the detection of sCJD.[10] In another neuroimaging study, two neuroradiologists, blinded to diagnosis, retrospectively evaluated DWI and

FLAIR images from 40 patients with probable or definite CJD and 53 control subjects with other forms of dementia and rated the likelihood of CJD on the basis of the imaging findings. The use of both DWI and FLAIR sequences was 91% sensitive and 95% specific for CJD. Furthermore, hyperintensities in these sequences was most commonly found in the neocortex and/or deep gray matter (thalamus, striatum, or both)[11]. Thus, the typical MRI findings in a patient with sCJD include FLAIR and DWI hyperintensities involving cortical and subcortical structures. Recent work has shown that the presence of a corresponding apparent diffusion coefficient (ADC) hypointensity is further supportive of sCJD. Of note, patients with sCJD rarely present with predominatly subcortical involvement. While the presence of cortical DWI hyperintensities has a high sensitivity for CJD, it should be noted that such findings may be present in other conditions such as vasculitis or seizures.

The mechanism behind increased cortical and subcortical DWI signal may be related to vacuolation. A case study involving a patient who underwent MRI imaging 15 days prior to death and was subsequently autopsied showed that the DWI hyperintensities correlated best with vacuolation (r=0.78; P=0.0005), followed by PrP load (r=0.77; P=0.0006), and astrogliosis (r=0.63; P=0.0008).[12].

The diagnosis of definite CJD requires pathological confirmation by brain biopsy or autopsy. Confirmation of CJD by biopsy presents a difficult challenge from an infectious disease standpoint given that prion proteins are not removed by standard surgical sterilization methods.[1]

Gross examination of the brain usually shows diffuse atrophy without any further specific findings. There are three histological features that characterize CJD that include 1.) neuronal loss (particularly in cortical layers III-V); 2) Spongiform change; and 3) accumulation of abnormal prion protein.[1] The spongiform change in CJD is characterized by round, 20–50 micron-sized vacuoles located within neurons. While spongiform changes are most commonly seen in CJD, this histological finding is by no means unique to prion disease and can be found in DLB, hypoxic-ischemic encephalopathy, and frontotemporal dementia.[1]

Demonstration of the presence of abnormal prion protein by immunohistochemistry is another key element in the neuropathological confirmation of CJD. The prion protein has a variety of distributions including perivacuolar, diffuse synaptic, and plaque arrangements. The plaque confirmation is most commonly seen in vCJD, Kuru, and Gerstmann Straüssler Scheinker syndrome.[1]

Chronic Neurodegenerative Diseases Presenting as RPD

At the UCSF RPD unit, neurodegenerative disease (non-prion related) was responsible for 14.6% of all patients referred for suspected CJD and represented 39% of the non-prion cases.[2]. Furthermore, a retrospective study of 22 patients diagnosed with RPD showed that 23% of the cases consisted of frontotemporal dementia-motor neuron disease (FTD-MND), 18% consisted of either corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP), 14% consisted of dementia with Lewy bodies (DLB), and 9% consisted of Alzheimer's disease (AD).[13].

Possible factors relating to the misdiagnosis of these typically chronic dementias include atypical time course and multisystem neurological findings. For instance, patients with FTD-MND were most commonly misdiagnosed with CJD, and this disease progresses relatively rapidly with an average survival of 2.3 years from diagnosis.[14]. In addition, these patients may present with diffuse symptoms affecting cognitive, bulbar function, and motor function, a combination that can be seen in CJD. Typically, chronic dementias such as CBD and DLB may occasionally present with an accelerated time course as well as with myoclonus and

extrapyramidal findings, both of which are common signs in CJD. Whenever considering a RPD diagnosis in a patient suffering from a chronic dementia, it is important to keep in mind that such patients are more susceptible to metabolic and infectious disturbances. For instance, the rapidly deteriorating AD patient in the setting of a UTI or dehydration may be misinterpreted as suffering from a RPD.

Non-prion neurodegenerative disease is frequently a diagnosis of exclusion and requires comprehensive serum and CSF analyses and neuroimaging to rule out vascular, toxic-metabolic, infectious, and inflammatory conditions. For reasons mentioned above, CSF biomarkers (14-3-3 protein, tau, NSE) and EEG findings of periodic spike and wave discharges may occur in any disease that results in rapid cortical injury, and positive findings are not conclusive evidence for CJD.

The clinician should first confirm the absence of a metabolic or infectious process superimposed upon the neurodegenerative disease. Thus, a metabolic panel looking at electrolytes, BUN, creatinine, and liver function tests is essential. Mental status change may be the only sign of infection in the demented population, and thus, a screen for pneumonia (chest x-ray) and urinary tract infection (urine analysis and culture) is essential. Finally, a thorough review of centrally acting medications, including non-prescription drugs, may provide clues into contributing factors to abrupt changes in mental status.

Neuroimaging is helpful in distinguishing prion-related from non-prion-related RPD. First of all, CJD is the only neurodegenerative condition resulting in DWI and FLAIR hyperintensities, and the absence of these findings is suggestive of a non-prion related process. Furthermore, the assessment of atrophy patterns on MRI can distinguish various causes of dementia. Recent work has shown that each neurodegenerative syndrome is associated with atrophy within a specific intrinsic functional connectivity network. [15] Thus, defined structures are inherently more susceptible for different neurodegenerative diseases. For example, AD patients will typically have atrophy involving hippocampal, precuneus, and posterior cingulate structures. On the other hand, a patient with CBD will have an atrophy pattern involving dorsal frontal-parietal networks.

Immune-Mediated Dementias Presenting as RPD

Limbic Encephalitis—Limbic encephalitis (LE) is an infectious and autoimmune process the predominantly involves the anteromedial temporal cortex, hippocampus, and amygdala and occasionally the hypothalamus and insular cortex.[16] For the purposes of this review, we will be discussing inflammatory causes of LE. Inflammatory causes of limbic encephalitis include paraneoplastic (PNS) LE and anti-voltage-gated potassium channel associated encephalopathy (VGKC-E), both of which are characterized by a more subacute time course.

PNS is an inflammatory group of conditions that result in antibodies produced within the CSF and serum resulting in focal neurological symptoms.[17, 18] These antibodies react against proteins expressed by the tumor and will precede the neoplasm in 70% of cases.[16] Patients with paraneoplastic antibodies against cell surface antigens generally have a better prognosis than patients producing intraneuronal antibodies.[19] The most common paraneoplastic antibodies associated with cognitive and behavioral symptoms include anti-Hu, CV2, Ma2, and VGKC antibodies, which may or may not be associated with an underlying tumor. Of all the paraneoplastic antibodies, anti-Hu is most commonly associated with limbic encephalitis and is most frequently found in patients with small cell lung cancer (SCLC).[18]. These patients frequently have a history of smoking. Other syndromes associated with Hu antibodies include cerebellar degeneration, myelitis, sensory neuronopathy, epilepsia partialis continua, and central hypoventilation syndrome[20]. CV2 antibody (also

referred to as anti-collapsin response mediated protein 5 [CRMP 5]) is found in patients suffering from either SCLC or thymoma. In addition to LE, CV2 antibody is associated with cerebellar degeneration, uveitis, chorea, optic neuropathy, myelitis, and peripheral neuropathy.[18] Anti-Ma2 is associated with testicular germ-cell tumors, breast cancer, and non-small cell lung cancer and frequently reacts against limbic, diencephalic, and brainstem structures.[21]. Common presentations in addition to cognitive and behavioral changes include vertical gaze palsy, limb rigidity, hypokinesis, and orofacial dystonia.[21, 22] . Furthermore, these patients tend to develop sleep disorders such as daytime somnolence, narcolepsy, and REM sleep disorder. Ma2 antibody syndrome is relatively responsive to treatment with 30% of patients experiencing resolution of symptoms following orchiectomy, immunotherapy (corticosteroids and IVIG), and chemotherapy.[21] A more recently described PNS resulting in reversible LE has been associated with antibodies to the alpa-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid receptor (AMPA-R) and is further characterized by confusion, hypersomnia, visual hallucinations, and combativeness in patients with breast adenocarcinoma.[23]

VGKC-E results in a limbic encephalitis through the production of anti-voltage gated potassium channel antibodies that react against the molecular layer of the hippocampus.[24] Voltage-gated potassium channel autoantibodies have been reported in acquired neuromyotonia, Morvan's syndrome, and autoimmune dysautonomia.[25–27] There is a temporal relationship between a drop in antibody levels and clinical improvement. The presence of hyponatremia is frequently found in VGKC-E patients and aids in the discrimination of this disease from other causes of LE.

Due to involvement of limbic structures such as the hippocampus and parahippocampal cortex, patients typically present with short-term memory loss. Other cognitive and behavioral symptoms such as executive dysfunction, personality changes, panic attacks, delusions, and hallucinations have been described.[28, 29] Furthermore, patients with LE frequently suffer from generalized tonic-clonic seizures, a possible result of an isolated hippocampal lesion.

Due to the rapidly progressive course combined with the abrupt onset of cognitive/behavioral impairment, this condition may present similarly to CJD, and should always be considered in the differential of RPD. A case series showed that 15 patients were erroneously given a diagnosis of CJD, but were subsequently found to have elevated VGKC antibodies[28]. Sixty percent of patients satisfied the WHO diagnostic criteria for CJD.[30] Furthermore, one patient's MRI showed increased DWI and FLAIR signal involving extra-limbic structures such as the anterior cingulate gyrus and insula, which would be more characteristic of findings in CJD[30] as 94% of patients with sporadic CJD showed DWI hyperintensities involving the limbic cortex.[31] Biopsy of the affected region was negative for vacuolation or prion deposition. All patients presented with subacute short-term memory deficits with a majority presenting with myoclonus, seizures, and behavioral and/or affective disturbances.

The evaluation of LE requires distinguishing between infectious and autoimmune causes. An infectious LE is typically associated with fever, elevated white blood count, and nuchal rigidity. Such generalized symptoms with accompanying encephalopathy typically prompt spinal fluid analysis. HSV encephalitis will show both elevated protein and leukocytosis. The diagnosis is confirmed by HSV PCR, which carries a sensitivity of >90%.

Autoimmune LE related to PNS shows a relatively milder leukocytosis with elevated protein. Depending on the underlying neoplasm, patients may manifest elevated Hu, CV2, or Ma2 antibodies in serum and CSF. Finally, patients may have regions of increased glucose

uptake on full body PET scan or structural tumors detected by CT scan of the chest, abdomen, and pelvis. VGKC-E may or may not be associated with an underlying thymoma. This syndrome is distinguished by co-existing hyponatremia detected on serum chemistry. VGKC-E is defined by elevated VGKC antibodies detected in serum or CSF.

The treatment for autoimmune LE further varies depending on the underlying cause. In paraneoplastic disease, the hallmark of treatment should focus on addressing the underlying tumor responsible for the paraneoplastic syndrome. For instance, the optimal intervention for a patient with small cell lung cancer and anti-Hu LE should focus on surgical and chemotherapeutic treatment for the tumor.

Treatment for VGKC-E without an underlying tumor involves immunosuppressive therapy consisting of plasma exchange and/or IVIG followed by oral corticosteroids. A prior case series has shown that some combination of these agents resulted in variable falls of VGKC-Ab to values between 2 and 88% as well as marked improvement of neuropsychological functioning in 6 patients, slight improvement in 3, and none in one.[32]

Steroid-Responsive or Hashimoto's Encephalopathy (SRE/HE/SREAT)

Different names (Hashimoto's Encephalopathy (HE), Steroid-Responsive Encephalopathy (SRE), Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT)) have been used to refer to a heterogeneous, sub-acute to chronic autoimmune-related, encephalopathy syndrome that may present as a dementing disorder associated with abnormally high-levels of thyroid antibodies and which, by definition, responds to treatment with corticosteroids, plasmapheresis or immunosuppressive therapy. Hashimoto's encephalitis, first described in a single-case of a 48 year-old man with hypothyroidism, elevated thyroid antibodies and recurrent episodes of stroke-like encephalopathy by Brain et al[33] is an encephalopathy that is associated with a lymphocytic thyroiditis and typically involves woman (85% of cases).[34] Patients may have co-existing autoimmune conditions such as type 1 diabetes, systemic lupus erythematosus, and Sjogren's disease. Individuals may be euthyroid, hyperthyroid, or hypothyroid, but the diagnosis of HE should only be made once the patient has returned to a euthyroid state.[34] While HE may present with a myriad of symptoms including confusion and cognitive, psychiatric, mood and behavioral symptoms, two main types of presentations have been proposed: one involving a relapsing-remitting course with stroke-like episodes (25–30% of patients) and a second consisting of insidious onset of seizures (70–80% of patients).[34] Other symptoms include tremor, myoclonus, visual hallucinations, ataxia, headache, psychosis, and sleep disturbance.[34]

Contrary to CJD, the MRI findings in HE are relatively non-specific and vary from generalized atrophy, periventricular white matter changes, and diffuse increased T2 signal within subcortical and cortical regions. [34, 35]

Diagnosis involves testing for elevated anti-thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG) antibodies. TPO antibodies are more frequently elevated than TG antibodies.[34, 35] While elevated thyroid antibodies in the setting of encephalopathy is suggestive of HE, the clinician should keep in mind that thyroid antibody levels may be elevated in up to 10% of the population, and the pathogenic role of these antibodies in HE remains unclear.[36] Furthermore, these biomarkers are non-specific for HE and may be found in other autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and even euthyroid patients[37–39] Spinal fluid protein is frequently elevated (78% of patients). EEG most frequently shows nonspecific diffuse slowing, and triphasic or periodic sharp waves suggestive of CJD may also occur.[40]

In a case series of 6 patients compared with 14 patients described previously in the literature, up to 90% of patients responded favorably to some form of immunosuppression that most commonly consisted of high-dose intravenous corticosteroids followed by a slow taper of oral prednisone.[41] Unfortunately, there are no controlled studies or evidence-based guidelines that define indication, choice of immunosuppressive agent, and the optimal duration of therapy. At our institution, we recommend giving a trial of high-dose corticosteroids to patients who present with a significant subacute deterioration in mental status, elevated anti-thyroid antibodies, and in whom other extensive clinical and laboratory investigations (see Figure 5) have failed to reveal a likely cause. In additional to the clinical profile, other non-specific findings that are supportive of HE include thyroid abnormalities (e.g. elevated TSH), elevated ESR or hsCRP, mildly inflammatory CSF (non-infectious and non-neoplastic), mild or moderate (relative to age and cerebrovascular risk factors) T2 subcortical white-matter hyperintensities on brain MRI with minimal atrophy, and abnormal EEG findings including slowing (generalized or focal) and sharp waves (often bifrontal or bitemporal). Depending on the individual's risk-benefit profile, we usually begin treatment with 1 gram IV Solumedrol for 3–5 days followed by a prednisone taper (starting at 60 mg). Initial steroid taper should be slow as patients with HE may experience frequent relapses with steroid withdrawal. Patients who remain asymptomatic do not require ongoing treatment with immunosuppressive agents. However, in cases of recurrent or severe relapses as demonstrated by worsening symptoms and objective findings on neuropsychological or clinical tests, patients may require more frequent and repeated steroid infusions (eg. every 3–6 months) and the addition of further immunosuppression. A case study has suggested that plasmapharesis may also be an effective treatment in patients with suboptimal response to steroids[42]. In many cases, abnormal laboratory findings, including very high levels of antithyroid antibodies, EEG, and inflammatory CSF and serum may normalize (or substantially improve) after clinical response to treatment.

Approach to the Evaluation of RPD

A variety of etiologies may result in RPD (see table 2). The evaluation of any RPD presentation requires a combination of history, neurological exam, neuroimaging, and spinal fluid analysis.

Step 1: The History—The work-up of each RPD presentation begins with a comprehensive history focusing on the time course, nature of symptoms, and potential contributing factors.

Firstly, it is important to assess the patient's premorbid baseline and educational history. As in any disease process resulting in cognitive symptoms, a supplementary history from a reliable informant such as a friend or family member is critical. Such precautions are helpful in avoiding historical inconsistencies regarding time course and progression, which are necessary for distinguishing an atypical from a typical dementia.

RPD should be suspected in any patient presenting with deterioration of cognitive function in fewer than 2 years. In addition, the course of the disease may provide further clues to an underlying cause. For example, Hashimoto's Encephalopathy may have a relapsing-remitting course with stroke-like symptoms whereas the course of sCJD is fulminant, leading to death within 1 year's time in 85% of patients.

The quality of symptoms may provide further insights into possible underlying disease processes. Given that all patients with RPD have primary cognitive or behavioral dysfunction, a detailed history of the affected cognitive modality, specifically memory, executive function, language, or visuospatial ability may help narrow the differential diagnosis. In addition, patients with RPD frequently complain of motor dysfunction and

inquiries should be made to determine whether the problem is related to corticospinal tract, basal ganglia, or cerebellar disease.

Consideration of potential contributing factors and systemic symptoms is especially helpful for reversible causes of RPD. Assessment of toxic exposures is a particularly helpful part of the history. The clinician should ask about alcohol or recreational drug use. Furthermore, centrally-acting medications especially those listed under Beers List (defines medications that are generally considered inappropriate in the elderly) may result in acute-subacute mental status changes.[43] Anti-cholinergic agents commonly prescribed for urinary complaints such as tolterodine have been shown to result in subacute, reversible hallucinations and verbal memory impairment.[44] Even over-the-counter medications such as Peptol-Bismol can cause a clinical presentation of apathy, myoclonus, dysarthria, confusion, and seizures resembling CJD through bismuth poisoning[4]. A consideration of undiagnosed neoplasm is important when considering potential PNS and inquiries should be made regarding tobacco use and weight loss. Small cell lung cancer, thymoma, and breast, ovarian, and testicular cancers have been associated with centrally-acting paraneoplastic antibodies. Patients with celiac disease and Whipple's disease may present with a malabsorption syndrome prior to development of cognitive symptoms. Finally, sleep impairment is a contributing factor to cognitive impairment and in the appropriate context, the clinician should inquire into symptoms of sleep apnea and similar disturbances. A comprehensive family history is important for ruling out potential inherited causes of RPD such as fCJD, HD, mitochondrial encephalopathy, and leukoencephalopathy. Constructing a family tree is a useful aid for determining the pattern of inheritance (eg. autosomal recessive, autosomal dominant, X-linked).

Finally, inquiry into the degree of functional impairment with regards to activities of daily living (taking medications, doing the finances bathing, dressing, etc) is helpful for an appreciating the severity of the cognitive and behavioral consequences. The functional assessment questionnaire (FAQ) is a quick survey assessing basic daily functions that can be completed with the assistance of a caregiver.[45]

Step 2: The Neurological Exam—The neurological exam serves as the second step in the evaluation of RPD. Patients with CJD frequently have cortical-related deficits including apraxia, aphasia, or neglect depending on the cortical region affected by the prion disease. Observation of affect is important as multiple diseases associated with RPD including CJD, VGKC-E, FTD-MND, anti-NMDA paraneoplastic disease, syphilis, etc may be associated with depression, anxiety, apathy, and/or hallucinations. The neuropsychiatric inventory (NPI) serves as a means of quantifying neuropsychiatric and behavioral symptoms. The cranial nerve exam may show oculomotor abnormalities suggestive of PSP or CBD. A funduscopic exam should be performed to rule out increased intracranial pressure. Important initial motor observations include resting asterixis, a finding in metabolic encephalopathy, and myoclonus (with or without startle), which is commonly found in various neurodegenerative condition such as CBD, DLB, or CJD. Extrapyramidal signs including resting tremor, cogwheel rigidity, dystonia and bradykinesia can be found in both metabolic (ie. Wilson's Disease) as well as neurodegenerative (ie. CJD, DLB, PSP, CBD) lesions involving the basal ganglia.

Patients with RPD will frequently have prominent frontal release signs (eg. grasp, palmomentalis, rooting, snout, and suck; Myerson's sign may be found in frontal or extrapyramidal disease). Consequently, the elicitation of the Babinski reflex may be complicated by a lower extremity grasp, and thus, alternative techniques such as the Chaddock (irritation of the skin at the ankle joint around the malleolus) and Oppenheim

(stroking downward on the medial tibia) are recommended for assessing pathological toe extension.

In the evaluation of RPD, neuropsychological testing should be considered an extension of the neurological exam. In such cases, it is recommended that formal neuropsychological testing be performed to assess memory, executive function, language, and visuospatial function. The neuropsychological testing will serve to substantiate the medical history, aid in neuroanatomical localization, and narrow the differential diagnosis. If formal testing is not possible, we recommend an expedited cognitive assessment using the Montreal Cognitive Assessment (MOCA).[46]

Step 3: Diagnostic Studies—Serum chemistry and hematological studies are a helpful first step for ruling out reversible causes of encephalopathy. Dramatic shifts in electrolytes such as with sodium (hyper or hyponatremia) and glucose (hyper or hypoglycemia) can result in sudden mental status changes. Furthermore, an elevated white blood cell count may be a harbinger of a systemic inflammatory process. A reversible dementia panel including TSH, vitamin B12, homocysteine, methylmalonic acid, and urine analysis/culture are all useful to look for contributing factors to a patient's dementia. An RPR is not routinely ordered in patients with suspected dementia, but is helpful for any atypical presentations of cognitive impairment. If a hepatic encephalopathy is suspected, it is recommended to check a serum ammonia. Paraneoplastic antibodies including anti-VGKC should be ordered based on the clinical presentation and can be obtained from either the serum or CSF

One of the most important steps in evaluating RPD is the spinal tap and cerebrospinal fluid analysis. This diagnostic test not only provides initial data about the inflammatory nature of the disease process, but also allows for the measurement of various CSF biomarkers relating to neuronal injury or infectious disease. An opening pressure should always be measured to address the potential for elevated intracranial pressure. Inflammatory markers include CSF protein, leukocyte count, CSF IgG (to be compared with serum IgG for an IgG index), and oligoclonal bands, all of which may be elevated in either autoimmune or infectious disease. The CSF provides infectious disease markers including bacterial gram stain and culture, fungal culture, acid fast bacilli (AFB) staining, VDRL, and Whipple's PCR. One of the important CSF laboratory studies includes 14-3-3 protein, neuronal specific enolase (NSE), and tau, all of which are biomarkers of neuronal injury. An elevated CSF pyruvate and lactate are suggestive of mitochondrial disease. Finally, a CSF sample may be helpful for investigating a neoplastic process such as lymphoma in which abnormal cells can be measured through cytology and flow cytometry.

Brain MRI imaging, a diagnostic intervention that will provide further information regarding vascular, infectious, autoimmune, and neurodegenerative processes, is recommended for all patients presenting with RPD. Any patient suspected of having a vascular-related RPD secondary to ischemic stroke should have accompanying vascular imaging either through magnetic resonance angiography (MRA) or CT-angiography. Expected findings in these patients include focal hyperintensities that obey a vascular distribution on T2, FLAIR, and DWI sequences. MRI showing focal medial temporal lobe T2 and FLAIR hyperintensites may indicate a limbic encephalitis, which has both autoimmune (anti-VGKC-E and paraneoplastic disease) and infectious causes. Occasionally, the neuroimaging may only show non-specific white matter hyperintensities, which is frequently the case in Hashimoto's Encephalopathy. In CJD, patients have characteristic DWI, FLAIR, and ADC findings in both subcortical and cortical regions. Finally, a CNS lymphoma may manifest itself either as a mass-occupying lesion or as diffuse white matter disease and should always be evaluated with and without IV contrast.

Electroencephalography (EEG) is a diagnostic tool with high temporal resolution that is helpful in determining the focality of a lesions and assessing the presence of cortical irritability. EEG is particularly helpful in the patient who may have subacute cognitive impairment related to focal epilepsy or complex partial seizures. This method is useful for uncovering a hepatic encephalopathy through the demonstration of triphasic waves or the characteristic finding of the 1 Hz spike and wave pattern associated with CJD. Of note, non-specific theta and delta slowing on EEG can be found in early CJD as well as in the other neurodegenerative diseases.

Finally, brain FDG-PET is an additional functional imaging modality that may further help narrow the differential diagnosis. This imaging is particularly useful for distinguishing a frontal-anterior process from a temporoparietal-posterior process. Additionally, the presence of regional PET brain hypometabolism in a patient suspected of malingering is helpful for confirming an organic illness.

Step 5: Brain Biopsy—In extreme cases where diagnosis cannot be confirmed by history, exam, neuroimaging, electrophysiological studies, or spinal fluid analysis, a brain biopsy may be indicated to determine the etiology, whether it be neurodegenerative, neoplastic, inflammatory, or infectious.

Conclusion

Due to their relatively infrequent incidence and the sudden, diffuse onset of symptoms, the rapidly progressive dementias represent one of the most challenging groups of diseases facing the neurologist. Consequently, diagnostic evaluation of any patient with RPD is typically more comprehensive than with chronic neurodegenerative conditions such as AD. The overwhelmingly broad differential requires the clinician to take a standardized method to any patient presenting with the rapid onset of dementing symptoms. Such an approach will enable the clinician to efficiently diagnose potentially treatable conditions such as Hashimoto's Encephalopathy, anti-voltage-gated encephalopathy, and paraneoplastic limbic encephalitis and distinguish these conditions from diseases such as CJD, which carry a more grave prognosis. Increased awareness of the RPDs throughout the primary care, geriatrician, and neurologist communities should foster more efficient diagnostic and treatment strategies for this complex set of disorders.

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Table 1

Criteria for Probable Sporadic Jakob-Creutzfeldt Disease (WHO 1998)

A. Progressive Dementia	
B. At Least 2 of the Following 4Symptoms	
	1. Myoclonus
	2. Pyramidal/Extrapyramidal 3. Visual or Cerebellar
	4. Akinetic Mutism
C. Positive EEG (periodic epileptiform discharges)	
D. AND/OR positive 14-3-3 protein result and <2 year disease duration	
E. Routine investigations do not suggest an alternative diagnosis.	

Table 2

Differential Diagnosis of RPD

Vascular	Stroke, Vascular Dementia
	CADASIL
	Thrombotic thrombocytopenic purpura
	Hyperviscosity Syndromes/Paraproteinemias (polycythemia, monoclonal gammopathies)/
	Hypoxic-ischemic encephalopathy
Infectious	Whipple's Disease
	Syphilis
	Lyme Disease
	SSPE
	HIV Associated Dementia
	PML
Toxic/Metabolic	Vitamin B12 deficiency
	Thiamine deficiency
	Niacin deficiency
	Folate deficiency
	Uremic encephalopathy
	Wilson's Disease
	Hepatic encephalopathy
	Porphyria
	Heavy Metals Bismuth Toxicity
	Alcohol toxicity
	Lithium Toxicity
	Mercury Toxicity
	Arsenic Toxicity
	Lead
	Electrolyte abnormalities

	Kuf's Disease
	Methylmalonic academia
	Mitochondrial encephalopathies
Autoimmune	Paraneoplastic limbic encephalitis
	Anti-VGKC-E
	Hashimoto's Encephalopathy
	Lupus cerebritis
	Sarcoid
	CNS vasculitis
	Celiac disease
Metastases/Neoplastic	CNS metastases
	Primary CNS Lymphoma
	Intravascular Lymphoma
	Lymphomatoid granulomatosis
	Gliomatosis cerebri
Iatrogenic/Idiopathic	Central pontine myelinolysis
	Insulin-induced hypoglycemia
	Normal pressure hydrocephalus
Neurodegenerative	AD
	CJD sCJD
	fCJD
	vCJD
	FRONTOTEMPORAL SPECTRUM bvFTD SD PNFA FTD-MND,
	PARKINSON SPECTRUM DLB CBD

	PSP
	PDD
	HD
Systemic	Vasculitis (GCA)
	Sleep apnea