

Rapidly Progressive Dementia – Clinical Aspects and Management

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Abstract

Although no precise definition for rapidly progressive dementia (RPD) exists, this term is generally used to refer to cases with significant and progressive cognitive impairment that occurs over weeks or months. RPD represents an unusual but severe condition that causes distress not only for patients and their relatives but also for the clinicians involved, as multiple investigations and decisions about management must be made urgently to avoid misdiagnosing a treatable condition and to preserve as much of the neural tissue as possible from definite damage. While Creutzfeldt-Jacob disease (CJD) has for a long period of time been regarded as the prototype of RPD, this infrequent but severe condition can be produced by an extensive variety of causes such as various endocrine, metabolic or toxic disorders, central nervous system (CNS) infections, primary or secondary CNS neoplasms, various CNS vasculitides and various autoimmune conditions in which autoantibodies against neural tissue are produced, whether in the presence of a neoplasm or not. However, even in the more common and usually slowly progressive dementias such as Alzheimer's disease, frontotemporal lobar degeneration, dementia with Lewy bodies and other degenerative dementias, as well as vascular dementia, establishment and progression of the disease is occasionally surprisingly accelerated, leading to a clinical presentation of RPD. The few published case series of RPD have shown that the relative frequency of underlying diseases depends mainly on the clinical setting. Thus, CJD has been found to be the most prevalent cause in referral centres for spongiform encephalopathies, while secondary causes are more prevalent in general referral centres for dementia diagnosis. In clinical practice, for the cases presenting with RPD, the diagnostic procedure must be exhaustive, starting with a detailed clinical evaluation and proceeding to a complete laboratory work-up and sophisticated neuroimaging studies. There has been recent enormous progress in imaging, with sensitive new sequences of magnetic resonance imaging and immunology; as a result, a plethora of antibodies against the CNS can now be detected in cases of autoimmune dementias, which has dramatically changed the diagnostic approach and early management of cases of RPD. The same favourable effect in clinical practice comes from the accumulated knowledge of the complex clinical picture of various causes of RPD, associated specific neurological features (pyramidal signs, ataxia, myoclonus) and systematic features (weight loss, hyponatraemia, hepatic disorders) and their mode of progression.

Keywords

Rapidly progressive dementia, Creutzfeldt-Jacob disease, autoimmune encephalopathies, central nervous system infections

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The term rapidly progressive dementia (RPD) is used to describe cases with a progression course which usually ranges between weeks and months.^{1–4} The subacute nature of RPD excludes other conditions with fulminant progression such as infectious or metabolic acute encephalopathies, which progress within hours or days and typically commence as an acute confusional state.

In most cases, the cognitive decline observed in RPD can be attributed to a single underlying disorder. Nevertheless, a rapid course might also represent the aggravation of an undiagnosed disease attributable to a secondary cause, usually an infection or a metabolic dysregulation. Various conditions involving the central nervous system (CNS) can emerge as RPD, including Creutzfeldt-Jacob disease (CJD) and other spongiform encephalopathies, vascular disorders, autoimmune and paraneoplastic encephalopathies, subacute infections, metabolic and toxic disorders and systemic diseases (see *Table 1*). However, it is important to point out that

even neurodegenerative disorders such as Alzheimer's disease (AD), dementia with Lewy bodies and frontotemporal dementia present in rare cases as a subacute dementia instead of a slowly progressive deterioration of higher functions.⁵ CJD is the prevailing cause of RPD in most related studies. Regarding the relative frequency of other disorders which account for cases of RPD, there is marked variability among scientific groups.^{1–3} In cases of RPD with an early age of onset, the possibility of an infection, hereditary metabolic disorder or autoimmune encephalopathy should be considered.^{6,7}

The early diagnosis of the underlying disorder in a patient exhibiting an RPD can be particularly demanding owing to the paucity of clinical signs during the early stages of many disorders and to overlapping laboratory findings. The pattern of cognitive deficits is crucial for clinical assessment. Selective memory, executive function and language deficits might favour one potential diagnosis and exclude others. Thus, a detailed neuropsychological evaluation is crucial.^{2,3}

The evaluation of behavioural alterations and neuropsychiatric symptoms is of high importance, since the initial symptoms can be exclusively a depressive-like or a disinhibited behaviour. Associated signs and symptoms, either neurological or systematic, can unveil an undetermined underlying disease. Ataxia, parkinsonism and specific motor or sensory deficits might herald the clinical expression of an otherwise obscure disorder during the progression of various forms of RPD.

Further investigation comprises laboratory testing, which includes routine serological studies (blood cell count, electrolyte levels, liver and renal function assessment, erythrocyte sedimentation rate and C-reactive protein, thyroid function evaluation including antithyroid autoantibodies, vitamin B12, folic acid, basic rheumatological screening and testing for HIV) and urine analysis. Cerebrospinal fluid (CSF) analysis of cell count, glucose and protein level, immunoglobulin G index and oligoclonal bands, 14-3-3 and τ -protein is also required. Brain magnetic resonance imaging (MRI), including fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences, is required for the diagnosis as in many instances it can be highly indicative of the underlying disorder (e.g. CJD and autoimmune encephalopathies). The electroencephalogram (EEG) can also be helpful, albeit inconsistently, as a number of EEG findings (such as the periodic triphasic discharges observed in CJD) have relatively high specificity for certain disorders.^{4,6}

A high proportion of RPD patients undergoing the routine assessments mentioned above will presumably receive a diagnosis during the initial stages of the investigations. However, the remaining cases might require additional serological or imaging testing. Given the rapid progression of the disease, there is high risk in restricting the initial evaluation. In most cases, it might appear rational to run investigations in parallel from the very beginning so as not to miss the early stages of a potentially treatable cause, as an important proportion of people with RPD disorders may benefit from therapy but only if treated before permanent neurological deficits are established.²

Neurodegenerative Disorders with a Rapid Course

A number of neurodegenerative diseases that usually progress gradually can also present as RPD. AD is the most common cause of dementia. The brains of affected patients exhibit hippocampal and temporoparietal cortical atrophy and the most common histological findings are senile plaques and neurofibrillary tangles. The median survival of AD patients is approximately 12 years, but occasionally the deterioration course can be rapid, mimicking CJD, especially when combined with amyloid angiopathy. Although CJD is the most frequent cause of RPD,⁸ AD represents a major non-CJD cause and in our centre was the third most common cause.³ However, AD was much less common in the University of California, San Francisco series, which came from a major prion disease referral centre.¹

In a recent study, researchers attempted to trace the clinical features, CSF biomarkers and genetic polymorphisms that distinguish individuals exhibiting slow and rapid progression of AD.⁹ Most AD patients with a rapidly progressive course experienced psychiatric symptoms, myoclonus (75 %) and sleep disturbances together with weight loss. Moreover, motor signs including tremor, rigidity and gait disturbance appeared to be predictors of a poor outcome of AD. Similarly, according to Chui et al.,¹⁰ extrapyramidal signs and behavioural symptoms such as agitation and hallucinations trigger a

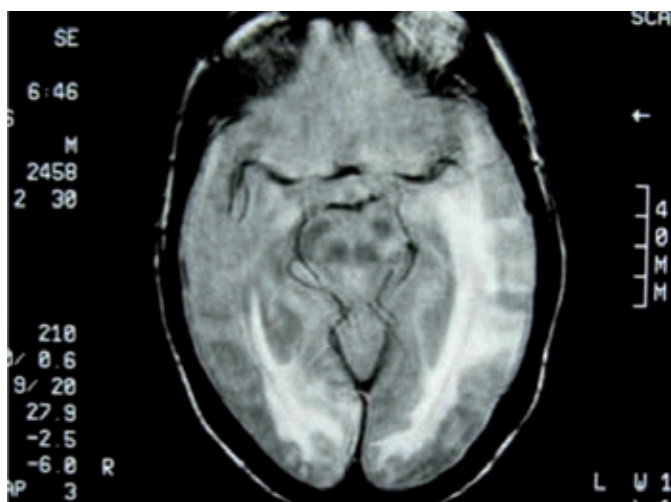
Table 1: Summary of the Possible Causes of Rapidly Progressive Dementia

Neurodegenerative disorders	CJD Alzheimer's disease Frontotemporal lobar degeneration Corticobasal degeneration Progressive supranuclear palsy Lewy body dementia Parkinson's disease dementia Multiple system atrophy
Autoimmune disorders	Paraneoplastic limbic encephalitis (anti-Hu, anti-CV2, anti-NMDA) Anti-VGKC encephalitis Anti-GAD encephalitis Hashimoto encephalopathy Systemic lupus erythematosus Sjogren's syndrome Primary or secondary CNS vasculitis Coeliac disease Inflammatory bowel disease Neurosarcoidosis Behcet's disease
Infections	Viral infections (HSV1, HSV2, HIV) <i>Treponema pallidum</i> <i>Mycobacterium tuberculosis</i> Fungal/parasitic infections Whipple's disease
Malignancies	Metastatic tumours Primary CNS lymphomas
Metabolic/toxic disorders	Inherited metabolic disorders (leukodystrophies, lysosomal, Wilson's disease, mitochondrial) Vitamin deficiency (niacin, thiamine, B12) Hypothyroidism Hyperparathyroidism Severe liver/renal disorders Heavy metals (mercury, lead, aluminium, arsenic, bismuth, lithium) Anticancer drugs (e.g. methotrexate) Benzodiazepines
Vascular dementias	Multi-infarct dementia Strategic isolated infarcts Hyperviscosity syndromes
Normal pressure hydrocephalus	
Psychiatric disorders	Major depression

CJD = Creutzfeldt-Jacob disease; CNS = central nervous system; GAD = glutamic acid decarboxylase; HSV = herpes simplex virus; NMDA = N-methyl D-aspartate; VGKC = voltage-gated potassium channel.

faster cognitive decline in AD patients. Alterations in biogenic amine systems, the administration of neuroleptic drugs or the presence of an underlying diffuse Lewy body disease may account for the rapid course. Low level of education, extrapyramidal signs and delusions, but not hallucinations, were correlated to a rapid progression rate of AD in the study by Mangone et al.¹¹ Finally, Viatonou et al.¹² assessed the factors predicting a rapid cognitive decline among demented patients over 75 years of age and demonstrated that nutritional status, the initial Mini Mental State Examination score and mood state predict a rapid cognitive decline. Surprisingly, high socioeconomic status also represented a risk factor for rapid decline, but this can be explained by the fact that well-educated people can compensate for early memory deficits for a long time, exhibiting AD signs only when their disorder has already progressed. Regarding genetic factors,

Figure 1: A 57-year-old Female Patient with a History of Uveitis and Rapidly Progressive Dementia



The patient presented bilateral occipital lesions in successive brain magnetic resonance imaging scans. Lesion biopsy revealed malignant lymphoma.

PRNP gene polymorphisms appeared to be correlated to the rate of cognitive decline. The data concerning apolipoprotein E (ApoE) type 4 allele polymorphisms are rather contradictory. Martins et al.¹³ showed an influence of ApoE type on disease progression, while other studies failed to demonstrate any correlation.¹⁴ Interestingly, Schmidt et al.⁹ concluded that the absence of ApoE type 4 alleles might predict a shorter survival in AD patients. The reverse correlation between the presence of ApoE type 4 gene and the development of motor signs partially accounts for the protective effect in terms of disease progression observed in carriers.¹⁵

Frontotemporal lobar degeneration (FTLD) occurs earlier in life than AD. In our centre,³ FTLD was the third most common cause of RPD, accounting for 16.2 % of the studied cases, and FTLD was also among the most common non-CJD causes of RPD in the UCSF study.¹ Of the three main clinical forms – primary progressive aphasia, semantic dementia and behavioural variant frontotemporal dementia (bv-FTD) – the latter progresses more rapidly to death.¹⁶ bv-FTD is marked by profound personality alterations, apathy, disinhibition and social awkwardness. Cognitive decline usually occurs as the disease progresses. Overlapping FTLD–motor neuron disease and FTLD–parkinsonism syndromes are relatively common and predispose to a fast progression of the disorder. A mean survival of 2.3 years has been observed for FTLD–motor neuron disease compared with approximately eight years for FTLD alone.^{17,18} It is possible that motor impairment contributes to the cognitive decline of the affected patients. As far as the molecular basis of FTLD is concerned, tau-positive FTLD appears to have a better prognosis compared with tau-negative pathologies. By contrast, FTLD with ubiquitin and/or TDP-43-positive inclusions and FTLD associated with neurofilament inclusion body disease often exhibit a more rapid course and present as early-onset and rapidly progressive dementias.¹⁹

Other tau-related pathologies, such as corticobasal degeneration (see Figure 1) and progressive supranuclear palsy, may progress as RPD and have been marked as potent causes of rapid cognitive decline by many studies.^{1–3} The motor symptoms associated with these pathologies, including myoclonus and parkinsonism, can easily be misdiagnosed as CJD.

Dementia with Lewy bodies is characterised by a fluctuating course, extrapyramidal motor disorders and visual hallucinations and is among the most common neurodegenerative entities presenting a rapid cognitive decline.²⁰ Dementia with Lewy bodies may mimic CJD symptoms, although it lacks its typical MRI imaging properties.¹ Single photon emission computed tomography with ¹²³I-ioflupane can facilitate the diagnosis of dementia with Lewy bodies. Other synuclein-related disorders, such as Parkinson's disease dementia and multiple system atrophy, may also occasionally exhibit an RPD course.³

In any case, given the fact that any neurodegenerative dementia can follow an accelerated course in the presence of an underlying infection, metabolic deregulation or drug toxicity (e.g. benzodiazepines), such disorders should be thoroughly ruled out during clinical assessment.

Creutzfeldt-Jakob Disease

Spongiform encephalopathy (CJD) is caused by the transformation of the normal neuronal prion protein, resulting in its abnormal accumulation within the neurons. The disease can have a sporadic form (sCJD), a familial/genetic form and a variant form (vCJD). sCJD, which is the most common form of all – accounting for approximately 85 % of cases – is still a rare disease affecting 1–1.5 people/million/year.²¹ The clinical presentation of sCJD is characterised by an extremely variable picture of cognitive disturbances (attentional deficits, amnesia, aphasia, apraxia) that lead rapidly to dementia (in weeks or months), cerebellar ataxia, extrapyramidal symptoms, myoclonus and multiple behavioural/psychiatric disturbances (hallucinations, delusions, misidentifications, anxiety, aggression, etc.).²² Posterior cortical symptoms – such as cortical blindness, palinopsia, gaze apraxia and optic ataxia – are also commonly found and, when encountered at disease onset, characterise the Heidenhain variant of the disease.²³ sCJD usually occurs at 50–70 years of age and affects both sexes equally.¹ Survival is very short and 85 % of patients are dead by the end of the first year after onset.¹ Genetic forms of CJD are attributable to various mutations of the prion protein gene and include familial CJD, Gerstmann–Sträussler–Scheinker and fatal familial insomnia. Genetic forms of CJD tend to have a slower course, although they often have the same clinical presentation as sCJD.²⁴ More than half of genetic cases do not have a known family history of CJD.²⁵ Initially, focal or diffuse slowing is seen on the EEG but, with disease progression, pseudo-periodic and, eventually, periodic 1–2 Hz triphasic sharp waves appear. Although this periodic EEG pattern is highly characteristic of sCJD, it takes its typical form only in the late stages of the disease and not in all patients.^{26,27} In addition, the same EEG findings can be encountered in various other disorders, mainly of toxic or metabolic cause (e.g. lithium encephalopathy) or in herpetic encephalitis. CSF protein level can be mildly increased and oligoclonal bands may be present.²⁸ By contrast, cell count is always normal. Several CSF protein levels, mainly 14-3-3, neuron-specific enolase and τ -protein, have been shown to be increased in CJD,^{28,29} and thus have been proposed as diagnostic markers for this disease. However, the use of these markers has been criticised as they lack sensitivity and specificity, especially in the initial stages of the disease.^{21,29} Novel MRI techniques have altered the diagnostic approach in CJD to a considerable degree. Early in the disease course, FLAIR and DWI sequences demonstrate hypersignals in the striatum (caudate and putamen) and thalamus as well as 'cortical ribboning' (hypersignal delineating the cortex) in the parietal, temporal and frontal cortices (see Figure 2). MRI with these sequences (DWI being more sensitive

than FLAIR) is highly sensitive and specific (92 and 94 %, respectively) for the diagnosis of CJD.^{1,30} The above characteristic findings can be seen well before the EEG periodic abnormalities and the positivity of the 14-3-3 protein test. Similar MRI findings generally characterise the inherited prion diseases.¹ These abnormalities are highly specific for the diagnosis of CJD and have been seen only exceptionally in other pathologies, such as neurofilament inclusion body disease,¹ Wilson's disease, Wernicke's encephalopathy, CNS vasculitis, anti-CV2-associated paraneoplastic conditions and voltage-gated potassium channel (VGKC) encephalopathy.¹ The diagnosis of CJD is based on the WHO clinical diagnostic criteria, which have recently been updated to include the above-described typical MRI findings.⁸ However, a definitive diagnosis of CJD can be made only after the demonstration of prions in the brain. Clinical criteria for probable sCJD require the existence of dementia with a progressive course and at least two of the following: pyramidal and/or extrapyramidal symptoms, visual or cerebellar symptoms, myoclonus, akinetic mutism and positivity in at least one out of three tests (EEG, 14-3-3 protein and MRI). No treatment has been found to be effective even for delaying the course of this rapidly fatal disease. Palliative treatment for the control of seizures and myoclonus includes sodium valproate and clonazepam.

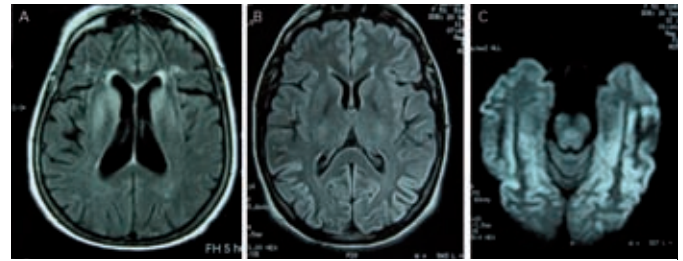
vCJD affects much younger individuals, with a mean age of 27 years.^{31,32} This disease has been encountered mainly in the UK following the epidemic of bovine spongiform encephalopathy in the 1980s. Psychiatric disturbances are the most common presenting features of vCJD and typically last for months before other neurological symptoms arise, mainly cerebellar ataxia, dysesthesias, cognitive deficits leading rapidly to dementia, variable extrapyramidal disorders (dystonia, chorea) and myoclonus. The duration of the disease is somewhat longer than that of sCJD. Although MRI findings are similar to those for sCJD, more marked hyperintensity of the pulvinar compared with the anterior putamen (the 'pulvinar sign') is the characteristic finding.³³ EEG rarely shows the typical pattern of sCJD. Diagnosis of vCJD is based on clinical, EEG and MRI findings. The WHO diagnostic criteria have been shown to be highly sensitive and specific in a recently published validation study.³¹

Secondary Causes of Rapidly Progressive Dementia

Infectious Diseases

Although infectious CNS diseases usually present acutely, in certain cases the course is less prominent, resembling a chronic encephalopathy.^{1,34} An early diagnosis is of high importance, as most cases of infection-related dementias are treatable. The possibility of a viral infection affecting the brain should be thoroughly investigated. Herpes simplex virus (HSV) infection can rarely exhibit a chronic course with cognitive decline, but even a clinical suspicion of such a diagnosis must lead to intravenous treatment with aciclovir. HSV encephalitis can then be confirmed by means of polymerase chain reaction for HSV 1 and 2 in the CSF.³⁵ HIV infection is associated with cognitive decline either during the seroconverting period or during a later stage of advanced immunosuppression (AIDS–dementia complex).³⁶ The mechanism of the disorder involves both a direct action of HIV and the coexistence of opportunistic infections (including JC infection). Measles may result in subacute sclerosing panencephalitis, a syndrome comprising progressive dementia, ataxia and seizures.³⁷

Figure 2: Brain Magnetic Resonance Images of Two Patients with a Diagnosis of Sporadic Creutzfeldt-Jacob Disease



A: fluid-attenuated inversion recovery (FLAIR) sequences demonstrate hyperintense signal in the striatum (caudate and putamen, R>L); B: FLAIR and C: diffusion-weighted imaging sequences demonstrate 'cortical ribboning' (hyperintense signal delineating the cortex) in the parietal, occipital and temporal cortices, bilaterally (B and C are of the same patient).

As far as bacterial infections are concerned, the possibility of neurosyphilis as a cause of RPD should always be excluded. Cognitive decline may coincide with psychiatric symptoms and focal neurological signs. All patients must undergo rapid plasma reagin and venereal disease research laboratory testing in the blood and CSF.³⁸ *Mycobacterium tuberculosis* and other atypical *Mycobacterium* species occasionally cause chronic meningitis.³⁹ In cases of pleocytosis or elevated protein in the CSF, further investigation using Ziehl-Nielsen staining, mycobacterial culture and polymerase chain reaction is required. Lyme disease, caused by *Borrelia burgdorferi*, occasionally presents as an RPD, as do other neurological manifestations such as cranial nerve palsies, polyradiculopathy and psychiatric symptoms.⁴⁰ Chronic fungal and parasitic CNS infections including *Cryptococcus neoformans* may exhibit a course resembling RPD. Whipple's disease is a multisystem disorder caused by *Tropheryma whippelli*. Its clinical spectrum includes gastrointestinal symptoms such as malabsorption, fever, weight loss, arthralgias and lymphadenopathy. Neurological manifestations include ataxia, psychiatric signs and the classic triad of cognitive decline, myoclonus and ophthalmoplegia. Occulomasticatory ophthalmoplegia is pathognomic of the disease. It should be noted that neurological symptoms might occur independently of malabsorption. The diagnosis can be confirmed by the detection of periodic acid-Schiff-positive inclusions on jejuna biopsy or positive polymerase chain reaction.⁴¹ Inflammatory bowel disease involvement in the development of RPD is exceptional.

Malignancies

Both primary and metastatic CNS neoplasms may present with RPD, although focal symptoms are also present in most cases. MRI is the examination of choice to identify a brain tumour, which will appear as a contrast-enhancing lesion. CNS lymphomas, either primary or metastatic, should also be considered during the investigation of a rapid cognitive decline. Primary CNS lymphomas occur often in immunodeficient patients as an outcome of HIV infection or immunosuppressive therapies.^{42,43} However, they may occur in immunocompetent individuals as well, most commonly in older patients. Memory loss, confusion, behaviour alterations, ataxia and gait disorder are among the most common symptoms. MRI findings include isolated or multiple white matter lesions (isointense or hyperintense in T2-weighted images) that typically exhibit contrast enhancement (see Figure 1).⁴⁴ CSF testing will reveal a lymphocytic pleiocytosis and elevated protein. A transient response to corticosteroid administration might be anticipated. In most cases, biopsy is necessary to confirm the diagnosis. Intravascular lymphoma progresses in the form

of blood vessel infiltrations and can present with acute stroke-like attacks or with RPD. Gliomatosis cerebri usually presents a more diffuse infiltrating pattern without enhancement during computed tomography or MRI imaging.⁴⁵

Metabolic/Toxic Causes of Rapidly Progressive Dementia

Although rare, inherited metabolic disorders should also be taken into account during the assessment of RPD, especially in younger patients.⁶ Adult-onset leukodystrophies usually initiate with cognitive decline, psychiatric symptoms, ataxia, dystonia and progressive gait disturbance.^{46,47} The pattern of MRI white matter lesions often facilitates the diagnosis. Adult-onset metachromatic leukodystrophy might emerge as mental deterioration and psychiatric symptoms without movement deficits. Krabbe disease and X-linked adrenoleukodystrophy can present with similar features, although these conditions are usually diagnosed before adulthood.⁴⁸ Lysosomal storage disorders such as Niemann-Pick type C and Fabry's disease often present characteristic systemic symptoms. In the presence of extrapyramidal signs, the possibility of Wilson's or Huntington's disease should be considered. Porphyria is suspected in the presence of painful abdominal attacks or psychiatric symptoms. Finally, mitochondrial disorders often exhibit specific features such as short stature and multiple organ deficits (CNS, peripheral nerve, muscle, heart, kidney, vision and hearing disorders).

Common metabolic disorders related to RPD include vitamin deficiency and endocrine disorders.¹ Niacin deficiency or pellagra is marked by the presence of dementia, diarrhoea and dermatitis. This entity is often an outcome of alcoholism but can also occur in nutritional deprivation, chronic infections and neoplasms, cirrhosis and malabsorption syndromes. Thiamine (vitamin B1) deficiency is common in alcoholics as well and its main clinical feature is Wernicke's encephalopathy (memory loss, ataxia and ophthalmoplegia). Vitamin B12 deficiency stems from gastrointestinal disorders and its manifestations include anaemia, degeneration of the spinal cord dorsal columns, psychiatric symptoms and cognitive decline. All of the situations mentioned above are potentially reversible. Hypothyroidism can initiate as an RPD, with mental deterioration as one of its main features. Thyroid hormone screening should be performed in all patients referred for memory impairment or executive function deficits. Hyperparathyroidism can also mimic CJD and this treatable condition should be excluded in every case of rapid cognitive decline.⁴⁹ Measurement of serum calcium, phosphorus and parathyroid hormone levels is adequate for an initial assessment, occasionally followed by advanced imaging techniques. Encephalopathy in advanced stages of renal or liver dysfunction may resemble RPD and therefore renal and liver function evaluation should be carried out in every patient.

Heavy metal intoxication (mercury, lead, aluminium, arsenic, bismuth and lithium) is a rare cause of RPD. Urine level measurements should be performed in occupationally exposed individuals. Prolonged administration of anticancer drugs such as methotrexate may result in a diffuse type of encephalopathy which is not fully reversible following the discontinuation of therapy.

Vascular Dementias

Vascular disorders are a rather uncommon cause of RPD.^{1,3} Multi-infarct dementia is the result of numerous diffuse minor strokes that eventually lead to memory and executive function impairment. On the other hand, isolated strategic infarcts in the thalamus anterior

corpus callosum and the striatum may lead to rapid cognitive decline as well.⁵⁰ Screening for possible cardiovascular risk factors such as diabetes, hyperlipidaemia, hypertension, smoking and cardiac arrhythmias should be performed. Subcortical vascular dementia (Binswanger's disease) represents an outcome of alterations of small brain vessels and is characterised by gradual memory deterioration, apathy and supranuclear paresis signs. Secondary causes of vessel occlusions such as thrombotic thrombocytopenic purpura and hyperviscosity syndromes (polycythaemia and Waldenstrom's macroglobulinaemia) may cause global cerebral ischaemia with clinical manifestations resembling an RPD. Brain MRI will facilitate the assessment of vascular causes of RPD and discriminate them from CJD or neurodegenerative disorders.¹

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus is an important, and reversible, secondary causative factor of dementia which can take the form of an RPD.³ The clinical spectrum of normal pressure hydrocephalus involves the classic triad of memory impairment, gait disorders and urinary incontinence. Brain MRI will reveal enlargement of the ventricular system. Diagnosis can be confirmed by means of CSF pressure measurement.

Psychiatric Causes of Rapidly Progressive Dementia

Following the exclusion of all neurological and systemic causes of RPD, the possibility of pseudodementia should be considered. Patients with a history of major depression may exhibit symptoms of rapid cognitive decline. Although apathy and other depressive symptoms might prevail, this situation can mimic RPD and the differential diagnosis is often difficult.

Autoimmune Dementias

Although autoimmune encephalopathies were thought to be rare in the past, it appears that they represent a relatively frequent cause of RPD.¹ It should be noted that a number of autoimmune encephalopathies are treatable and therefore an early diagnosis could be of high importance. The hallmarks of the disorders are a rapidly progressive fluctuating course, the detection of autoantibodies in the peripheral blood and indications of inflammation in the CSF (pleocytosis, elevated protein level, increased immunoglobulin G index).⁵¹ A common clinical presentation is limbic encephalopathy initiating with disorders of short-term memory. Behavioural alterations, depression and temporal lobe seizures may accompany the memory deficits. Despite the fact that limbic encephalopathy is often paraneoplastic, even preceding the diagnosis of the underlying malignancy, in many cases the neurological disorder is non-paraneoplastic.⁵² The differential diagnosis of limbic encephalitis includes viral encephalitis (especially HSV), CJD, psychosis and other forms of autoimmune disorders. Affected brain areas may include the anteromedial temporal cortex, the hippocampus and the amygdala, and brain MRI shows non-enhancing signal changes in the mesial temporal lobes (see *Figure 3*). In cases of paraneoplastic limbic encephalitis presenting as an RPD, there is evidence of autoantibodies reacting against tumour proteins.⁵³ It remains unknown whether these autoantibodies have a pathogenic role or represent markers of a T-cell-mediated immune response. It seems that in most cases T-cell immunity determines the neurological outcome in paraneoplastic limbic encephalopathies. CSF possibly presents signs of inflammation and screening for tumour markers in the peripheral blood may be positive. Anti-Hu antibody is the most

common cause of limbic encephalopathy and is usually associated with small-cell lung cancer. Other neurological manifestations include myelitis, non-convulsive status epilepticus and peripheral sensory neuropathy.⁵⁴ Anti-CV2 antibodies (anti-CRMP5) can be observed in cases of small-cell lung cancer and thymoma. Cerebellar degeneration, myelitis, chorea, optic neuropathy and sensory neuropathy may occur as well. Anti-Ma2 antibody is associated with testis germ cell tumours, small-cell lung cancer and breast cancer and, in addition to limbic encephalopathy, affected patients may also present limb rigidity, vertical gaze palsy, sleep abnormalities and orofacial dystonia.^{52,53}

Paraneoplastic encephalitis with N-methyl D-aspartate receptor antibodies occurs in young women with an underlying ovarian teratoma. Memory problems are often combined with psychiatric symptoms, dyskinesias and alterations of the level of consciousness. MRI may reveal an increased signal in the cerebral and cerebellar cortex in FLAIR sequence.⁵⁵

Antibodies against neuronal VGKC may be related to lung cancer or thymoma, but most cases are not paraneoplastic, especially in the absence of other paraneoplastic autoantibodies. VGKC autoantibodies have been correlated with acquired neuromyotonia (Isaac's syndrome).⁵⁶ Patients often exhibit signs of limbic encephalitis, occasionally combined with neuromuscular hyperexcitability. Brain MRI may reveal an increased signal in the mesial temporal lobe. Morvan syndrome includes acquired neuromyotonia, dysautonomia, myokymia, insomnia and encephalopathy with hallucinations and fluctuating cognition. Diagnosis can be confirmed by means of needle electromyography showing spontaneous muscle activity. The disorder exhibits a quick response to corticosteroid treatment or plasma exchange therapy.^{52,57}

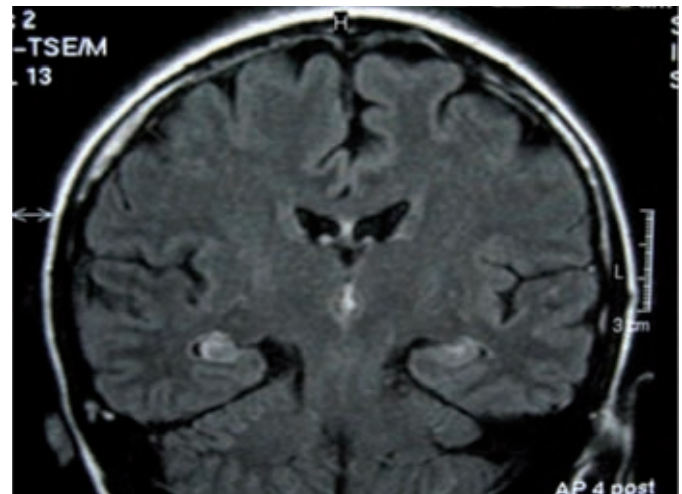
Antiglutamic acid decarboxylase (anti-GAD) antibodies can be observed in various conditions including type 1 diabetes and stiff person syndrome. Occasionally, the presence of anti-GAD antibodies may herald the development of a subacute encephalitis with RDP, ataxia, autonomic instability, myoclonus and trunk rigidity responding to immunosuppressive therapy.⁵⁸

Autoimmune encephalopathies with rapid progression can mimic CJD in terms of clinical and MRI findings. The latter is particularly true for limbic encephalopathy, with anti-VGKC antibodies exhibiting cortical ribboning.⁵⁹ The laboratory investigation for antineuronal autoantibodies (anti-Hu, anti-Ma, anti-CV2 and anti-VGKC) is therefore of high importance. In selected cases, computed tomography of the thorax and abdomen and whole-body positron emission tomography may reveal an underlying tumour such as an early-stage small-cell lung carcinoma.^{4,52}

Hashimoto Encephalopathy

Hashimoto thyroiditis has been implicated in the development of neurological and psychiatric symptoms. Its most severe clinical expression affecting brain function is Hashimoto encephalopathy, a steroid-responsive encephalopathy associated with high titres of serum antithyroid antibodies.^{60,61} The disorder mainly affects middle-aged women. The patient may be euthyroid, hypothyroid or even hyperthyroid, although a return to a euthyroid status is essential to establish the diagnosis. The encephalopathy course is either that of stroke-like relapsing–remitting episodes or that of a progressive cognitive impairment. Myoclonus, generalised seizures, sleep disturbance and psychiatric symptoms, namely visual hallucinations,

Figure 3: A Patient Diagnosed with Limbic Encephalitis



Brain magnetic resonance imaging shows non-enhancing signal changes in the hippocampi.

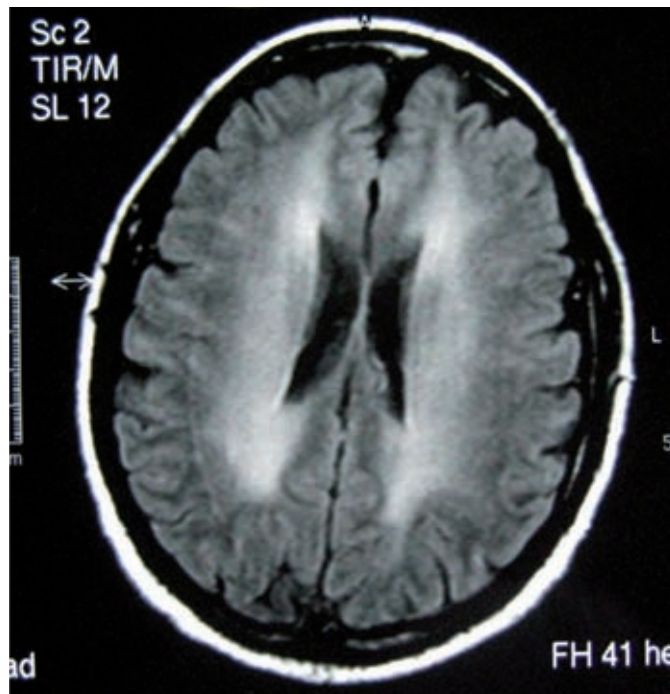
might also be present. Laboratory findings include abnormal EEG, elevated CSF protein and elevated serum antithyroid antibodies (anti-thyroglobulin antibodies [anti-TG] and anti-thyroid peroxidase antibodies [anti-TPO], the latter being more common). However, these markers are not disease-specific and may also be present in other autoimmune disorders. MRI might be normal or present subtle, non-specific findings such as white matter hyperintense lesions (see *Figure 4*).^{62–64} The EEG will show non-specific slowing and occasionally epileptiform discharges suggestive of CJD.⁶⁵ Hashimoto encephalopathy responds well to corticosteroid treatment, which can be prolonged to achieve a full remission.

Other Autoimmune Conditions

Systemic autoimmune disorders such as systemic lupus erythematosus and Sjogren's syndrome can manifest as a rapidly progressive dementia in rare cases. Systemic lupus erythematosus affects the CNS in almost 75 % of cases either by means of antibodies against the CNS parenchyma or indirectly, causing an antibody-mediated vasculitis.⁶⁶ Common CNS findings include cognitive impairment, psychiatric disorders, seizures and stroke episodes. The presence of antiphospholipid antibodies may contribute to this situation. Transverse myelitis and peripheral neuropathy may also be observed during the course of the disease. Despite the fact that Sjogren's syndrome often involves the peripheral nervous system (sensory neuropathy), it can also affect the CNS. On rare occasions it can present as an RPD with cognitive decline and mood disorders. Nevertheless, the most common CNS symptoms of Sjogren's syndrome are recurrent attacks with focal symptoms mimicking multiple sclerosis. Primary or secondary vasculitis of the CNS, such as polyarteritis nodosa or Wegener's granulomatosis, can cause an encephalopathy resembling RPD. Detection of perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (in secondary vasculitis), brain CSF inflammation findings, MRI data (ischaemic lesions, leukoencephalopathy and gadolinium enhancement of the meninges) may facilitate the diagnosis, which is confirmed by means of angiography.

Coeliac disease occasionally presents with cognitive decline, psychiatric symptoms, ataxia, seizures, neuropathy and headaches independently of systematic symptoms (malabsorptive syndrome). Progression of

Figure 4: A 59-year-old Male Patient with a History of Hypothyroidism (under Treatment) who Exhibited Mental Deterioration, Myoclonus and Pyramidal Signs over a Three-month Period



The patient's brain magnetic resonance imaging revealed bilateral hyperintense areas in the deep white matter of the hemispheres. A high titre of anti-thyroid peroxidase antibodies suggested an underlying autoimmune thyroiditis. A diagnosis of possible Hashimoto encephalopathy was adopted and the patient responded favourably to intravenous corticosteroid treatment.

dementia may be rapid. The detection of specific autoantibodies (antigliadin, antitissue transglutaminase and antiendomysial) in the peripheral blood or the CSF can confirm the diagnosis.⁶⁷ A gluten-free diet usually triggers clinical improvement.

Although neurosarcoidosis accounts for only 5 % of patients with sarcoidosis, it can also initiate as an RPD in rare cases. The pathogenic mechanism involves vasculitis of the CNS. Cranial nerve palsy and headache may also be present. The level of angiotensin-converting enzyme in the peripheral blood and the CSF is increased in cases of sarcoidosis, but its sensitivity is low. MRI might reveal hyperintense T2-weighted lesions or enhancing granulomas at the base of the brain.⁶⁸

The main features of Behcet's disease are uveitis and oral and genital ulcerations, but the condition can also present neurological manifestations such as cognitive deficits, behavioural alterations and spinal cord lesions. The development of vasculitis may contribute to the pathophysiology of the disease. Brain MRI reveals T2 hyperintensities.⁶⁹

Conclusions

RPD has a wide differential diagnosis. The evaluation of a patient with RPD must commence with a detailed history. The clinician should pay particular attention to the natural history of the disease and to the exact pattern of cognitive deficits (memory, language, attention, executive, visuo-receptive) together with the associated neurological or psychiatric symptoms. A thoroughly performed clinical examination is of high importance. A detailed history search for inherited familial disorders, other systemic diseases and metabolic, toxic and drug causes is also necessary.

As far as laboratory testing is concerned, it is rational to follow a two-stage procedure. The first stage (basic) includes a number of diagnostic studies that should be carried out in all individuals with RPD as these tests will often reveal the cause: haemogram, serum testing including electrolytes, renal and liver function, screening for rheumatological diseases and cancer, thyroid function tests, vitamin B12 and urine analysis, immunoassays for syphilis and HIV, CSF testing with cell count and type, protein and glucose levels, immunoglobulin G index and oligoclonal band search. Brain MRI including FLAIR and DWI sequences will be very informative in cases of CJD, neurodegenerative diseases, autoimmune disorders and CNS neoplasms. Finally, EEG might reveal rhythm patterns that correspond to certain pathological entities. Given the rapid progression of RPD, it is rational to run investigations in parallel so as not to miss the early stages of a potentially treatable cause.

When the clinician fails to reach a diagnosis following the initial laboratory testing, or when an uncommon cause is highly suspected from the beginning, it is mandatory to proceed to the second stage. This includes paraneoplastic autoantibodies, chest and abdomen computed tomography, whole-body positron emission tomography and immunoassays for specific pathogens. In the event of a diagnostic dead-end, a brain biopsy might be considered to determine the aetiology of the disorder. ■

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