Rapidly Progressive Dementia: A Systematic Evidence Review and a practical approach to diagnosis

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Abstract:

Rapidly Progressive Dementia (RPD) is an uncommon condition for which there is no accepted definition, and for which there are numerous causes.

We conducted a systematic review of published studies to make recommendations about [1] definitions for (a) dementia developing in previously healthy individuals, and (b) where individuals with an existing dementia experience unusually rapid cognitive decline; and [2] a logical diagnostic approach based upon the prevalence of conditions described in case series, which cause RPD.

We describe the process of conducting the review, propose criteria for standard definitions, and the iterative process leading to a recommended diagnostic approach.

Introduction:

Rapidly Progressive Dementia (RPD) is an uncommon condition, characterized by the emergence of cognitive decline leading to dementia at a rate which exceeds that seen in the more common causes of dementia.

The purpose of this systematic review is to (1) define the condition; (2) describe the prevalence of different diagnoses which lead to RPD; and (3) recommend an approach to diagnostic assessment based upon the prevalence of causative conditions in the published literature.

Definitions of Rapidly Progressive Dementia:

Remarkably, many articles entitled "Rapidly Progressive Dementia" do not describe specific diagnostic criteria. We sought to define two trajectories which fall under the umbrella of RPD. The first is a condition where an individual proceeds from cognitive "normality" to definite dementia within a specified time. In published studies, where a definition is offered, this time period varies from 3 – 24 months or even longer.

For example, the University of California at San Francisco definition of RPD reads: A form of dementia in which the time period from first symptom to dementia is less than two years and often less than one year.

The second type of RPD (sometimes called rapid cognitive decline) occurs in an individual who already has an established diagnosis of dementia, but who is declining at a rate which is not commensurate with the usual course of the illness.

Methods:

After consultation with a Health Sciences Librarian, we conducted a systematic review of published studies. We placed no limits on age, but did reject articles which were not written in English or French. We searched Medline, Web of Science, EMBASE, Cochrane database of systematic reviews and PsychINFO, using the headings "rapidly progressive dementia"; "rapidly progressing dementia"; "rapid cognitive decline" and "rapid" tw; "progressive" tw; "dementia" tw. Most publications are case reports which describe ever more exotic diseases which may cause RPD. The initial search identified over 1400 articles. The flow of articles is shown in Figure 1. Each abstract was assessed for relevance by two independent reviewers. If either reviewer deemed an article relevant or possibly relevant, it was

assessed for quality by two independent reviewers using predetermined criteria. For case series, a good article described patient population (and referral bias if any), diagnostic criteria for dementia, and definition of RPD. We aimed to identify large case series to determine the prevalence of different conditions which lead to RPD. If assessed of good or fair quality, data on diagnostic prevalence were abstracted.

We purposefully excluded individual case reports and brief case series as these reports invariably describe rare or unusual conditions, the inclusion of which could greatly distort the estimated prevalence of causes of RPD. Rather, we have listed as an electronic supplement, case reports which illustrate specific conditions, grouped in the broad diagnostic categories which have been associated with RPD, i.e. neurodegenerative, inflammatory (immune mediated and other), infective, toxic-metabolic, vascular, malignant.

After reviewing the prevalence of individual diagnoses in case series, we have attempted to describe a pragmatic diagnostic approach based on the prevalence of those diagnoses, giving emphasis in particular to those conditions where effective treatment or cure might be possible.

Results:

Fourteen case series were identified in the literature searches. Three of these originated from the same centre, each was a review with clinical data quoted in the article. (Gescwind 2007, 2008, 2010). Two of these articles were of poor quality (definition of RPD and clinical evaluation strategy not stated) so we included only the most recent, largest series (Geschwind 2010). The definitions of RPD varied widely. In 3 case series (Chivatras 2010, Tschampa 2001, VanEverbroek 2004) the definition or the implied definition was onset over 6 or 7 months. In one case series (Papaageorgeou 2009) the definition was “development of dementia within 12 months” in another (Kelley 2009) the definition was “progression to severe dementia or death within 18 months of clinical onset”. In the largest case series (Geschwind 2010) the definition was “first symptoms of dementia in less than 1 – 2 years”. In a German case series

the definition was “duration less than 2 years” (Poser 1999) and in the Mayo clinic series (Joseph’s 2009) the “disease duration was less than 4 years”. Thus, the very definition of RPD varies enormously among different case series.

In some case series the subjects included living patients (Papageorgeou 2009, Poser 1999, Geschwind 2010), in some series a mixture of live patients and pathological tissue (Brown 1994) and in the others (Eurelings 2010, Chivatras 2010, Josephs 2009, Tschampa 2001, Will 1984) the samples were from autopsy series. The Belgian series (Van Everbroek 2004) included CSF samples.

Several of the case series emanated from national laboratories, usually focusing on spongiform encephalopathies. These laboratories included the Netherlands (Eurelings 2010), the US National Prion Disease Pathology Surveillance Center at Case Western Reserve University (Chivatras 2010) the Belgian National Laboratory of Neurobiology at the University of Antwerp (Van Everbroek 2004), the German Reference Centre for Spongiform Enephalopathies (Tschampa 2001, Poser 1999) and the UK National Survey (Will 1984).

The articles are described in table 1: the quality of the articles was generally fair. However, those of Chivatras (2010), Papageorgeou (2009) and Poser (1999) were regarded as good, based upon predetermined validity criteria. With regard to the prevalence of diagnostic causes for RPD we considered the case series of Eurelings (2010), Chivatras (2010) Papageorgeou (2009) Van Everbroek (2004) Poser (1999) and Tschampa (2001), Shields (2010) and Geschwind (2010) as the most relevant, as they included a definition of RPD between 6 – 12 months. Case series which define RPD as significantly longer would likely include patients where the time course of the decline exceeded that regarded as “rapid”.

The biggest case series, that of Geshwind (2010) included more than 1400 patients referred for RPD. Of these, 76% were due to probable or potential CJD (32% probable, 20% potential, 15%genetic, 1% acquired). While several of the other case series described patients with RPD in whom CJD had been

excluded, the majority of cases of RPD are likely to suffer from CJD, see table 2. The diagnostic criteria for CJD are show in table 3, although recent studies have cast doubt upon the value of protein 14-3-3, which may be negative in CJD and may be positive in other diseases.(Geschwind 2003) Table 4 summarizes the non CJD cases of RPD assembled from the case series of Eurelings (2010), Chivatras (2010), Papageorgeou (2009), Van Everbroek (2004), Tschampa (2001), Poser (1999), Geshwind (2010) and Shields (2010).

The diagnostic process:

The first step in evaluating a patient with RPD is to rule out a delirium, as recent studies have shown that this condition may persist for months (Cole 2010) in the presence of ongoing medical conditions e.g. organ failure [heart, liver, lung]; toxic metabolic conditions and drug intoxications. (Fong 2009). The next step is to determine whether there is another obvious cause for the RPD. For example, new onset headache and focal symptoms/signs may signal a tumour; changing cough and weight loss in a heavy smoker may indicate metastatic disease or a paraneoplastic syndrome; concurrent chemotherapy may be responsible for an opportunistic infection.

After these initial steps, an organized approach should be undertaken, based upon the prevalence of conditions identified in the case series. In most case series, Creutzfeld Jacob disease (CJD) or its variants are common causes of RPD with prevalence between 13 and 76% (table 2). Table 4 describes other conditions causing RPD in the case series. Prevalence of the broad categories of diagnoses are summarized in table 5.

Of the many incurable neurodegenerative conditions presenting as RPD, Alzheimer's disease is the most common followed by vascular dementia then dementia with Lewy bodies, frontotemporal degeneration, and others .

Infectious causes are particularly important to identify as they may be treatable. Viral causes include HIV, PML, HS-1; bacterial infections include Syphilis, TB, Brucella, Lyme and Whipple diseases. Fungal

and parasitic diseases also occur. The reader is directed to an excellent review of infectious causes by McGinnis (2011)

Toxic metabolic causes include vitamin deficiencies (B12, thiamin, niacin, folate) organ failure (liver, renal) and genetic causes such as Wilson disease and porphyria. Alcohol toxicity and heavy metals (lithium, mercury, arsenic, lead) should be included among toxic causes.

Immunological causes include paraneoplastic limbic encephalopathy, Hashimoto encephalopathy, lupus, sarcoidosis, and CNS vasculitis all of which are all potentially treatable. Rosenbloom and colleagues have published a thorough review of immunologically mediated dementias (Rosenbloom et al 2009).

Malignant diseases such as primary lymphoma or other tumors, metastatic disease and intravascular lymphoma must also be considered.

One should always consider iatrogenic causes such as medication toxicity (e.g. anticholinergic, benzodiazepines, lithium, anticonvulsants). Miscellaneous conditions such as sleep apnea and chronic seizure disorders are occasionally implicated in RPD. Table 5 summarizes a diagnostic approach based upon the most prevalent causes of RPD and those which are potentially treatable.

Rapid cognitive decline in persons with established dementia:

A second type of RPD or rapid cognitive decline occurs in individuals who have been diagnosed with a neurodegenerative condition, but show unusually rapid deterioration. A number of cohort studies have established the mean rate of deterioration in Alzheimer's disease as measured by annual decrements of scores on the Mini-Mental State Examination and other cognitive tools. Different trajectories within these cohorts have been identified, and factors that are associated with more rapid decline have been identified in a number of studies, reviewed by Schmidt (2011). These factors include male gender, presence of subcortical features, apathy, apraxia, psychosis and multiple focal signs including motor features. Poor nutrition and multiple vascular risk factors are also associated with more rapid decline. Different groups have suggested specific rates of change on MMSE as markers for rapid decline. For

example, Soto (2008) noted poorer prognosis when individuals lost 4 or more points during the initial 6 months of dementia; Schmidt (2011) found that a score change of 6 points in one year identified those with a worse outcome. A consensus group met in 2008 and concluded that in Alzheimer's disease a decline of 3 or more points on the MMSE in 6 months predicted worse outcome in terms of death or institutional admission (Soto 2008). Critics of this approach have pointed to the heterogeneity of Alzheimer's disease and what has been argued as a somewhat arbitrary definition for a rapidly decline in AD. However the consensus group performed a systematic review, carefully evaluated the evidence and made a strong case for the 3 points in six months standard. Gauthier et al (2006) have suggested that those with rapid decline be considered for cholinesterase inhibition with rivastigmine, after a study by Farlow (2005).

Conclusions:

1. The definition of rapidly progressive dementia should be defined in a standard manner. The development of a dementia within 12 months of onset of first symptoms is proposed.

2. Using this definition, case series show the most prevalent cause of RPD to be CJD. The next largest category is incurable degenerative diseases, of which AD is most prominent. Rapid cognitive decline in AD is evidently more common than previously thought, and constitutes an important cause of RPD.

3. The diagnostic approach should therefore focus on ruling in or ruling in or out CJD and neurodegenerative conditions (AD is most common of these) while seeking treatable conditions which are most likely to result in a successful outcome. Emphasis is placed upon obtaining clinical data, especially history, and investigations to identify the more common causes of RPD before resorting to tests for rarer disorders.

4. Due to the rarity of rapidly progressive dementia, suspected cases should be referred to physicians who are experienced and have access to the diagnostic facilities able to mount an organized and comprehensive diagnostic procedure.

5. In all suspected cases of CJD, CSF sample should be collected and transferred to the National Spongiform encephalopathy Laboratory in Winnipeg for evaluation of protein 14-3-3, protein 100, and other studies.

6. As RPD is an uncommon condition, and epidemiology in Canada is not well established, a national registry would be valuable.

7. In AD, a decline of 3 points in the MMSE over six months identifies those with a worse prognosis, which necessitates a review of possible comorbid conditions, and consideration of medication review.

Recommendations:

1. It is suggested that RPD be defined as dementia developing in a cognitively normal person within 12 months. Grade 2C

2. It is suggested that individuals suspected of RPD be referred to physicians who are experienced and have access to the diagnostic facilities able to mount an organized and comprehensive diagnostic procedure. Grade 2C

3. After exclusion of *delirium* and *obvious* local or systemic disease, it is suggested that a diagnostic strategy for RPD be based of the prevalence of causes of RPD in case series. Grade 2B

4. Notwithstanding 3 (above) the diagnostic strategy should emphasize the detection of potentially curable conditions, such as infections, immune mediated and toxic metabolic causes. Table 6 outlines such an approach. Grade 2B

5. For individuals with AD, it is suggested that a decline of 3 or more points on the MMSE in 6 months, which identifies a group with a worse prognosis , is a signal to explore comorbid conditions and review pharmacological management. Grade 2B

6. Research recommendation: It is suggested that a national registry be established to study the causes of RPD in Canada. Grade 2C

Figure 1: Flow of articles from literature search

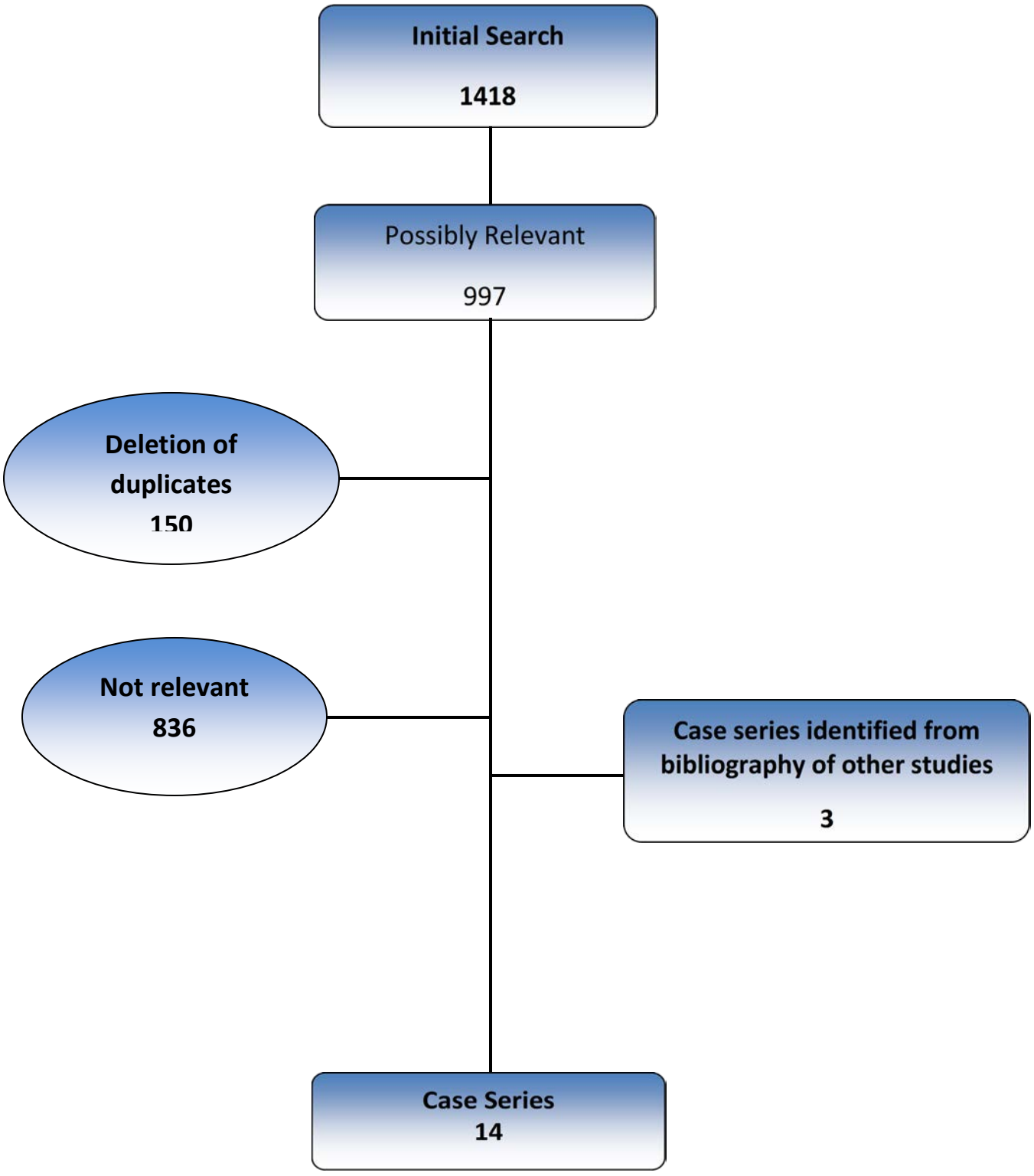

Table 1: Description of Case series

Author	Subjects	Definition	Diagnostic	Referral filter	Quality
Eurelings **2010**	225 brains Suspected CJD 2001-8	Not stated	Clinical, CSF, MRI, pathology	All patients in Netherlands with clinical suspicion of CJD and permission for autopsy are referred to UMC Utrecht	Fair
Chivatras **2010**	352 prion negative brains out of 1106 referred for suspected CJD 2006-9	Median duration 7 months	Pathology in 304 brain autopsies	U.S. National Prion disease Pathology Surveillance Center, Case Western Reserve University	Good
Papageorgeou **2009**	279 patients admitted for diagnostic evaluation of dementia: 68 had RPD 2004-6	Development of dementia within 12 months	AD: NINCDS-ADRDA VaD: NINDS-AIREN DLB: McKeith FTD: Neary CJD: WHO	Tertiary care referral centre, Athens, Greece	Good
Josephs **2009**	96 cases of brain autopsy identified through electronic medical database search using "rapid" plus "dementia" 2000-7	Disease duration less than 4 years Range 0.2-3.5 years	Histological diagnosis of neurodegenerative dementia	Mayo Clinic, Rochester Minnesota, regional and national referrals	Fair
Kelley **2009**	22 cases identified through electronic medical database search for RPD onset age 17-45 1996-2006	Progression to severe dementia or death within 18 months of clinical onset	Clinical, CSF, neuroimaging, pathology	Mayo Clinic, Rochester Minnesota, regional and national referrals	Good

Van Everbroek **2004**	250 CSF samples referred for possible CJD 1998-2003	Not stated , but reference made to CJD median duration of 6 months	CJD: WHO AD: NINCDS-ADRDA DLB: McKeith pathology	Laboratory of Neurobiology University of Antwerp receives all CSF samples for 14-3-3 measurement for the whole of Belgium	Fair
Tschampa **2001**	104 of 413 samples of brain tissue for suspected but disproven CJD 1993-7	Not stated but reference to CJD median duration 7 months	Retrospective medical records, neurological signs, EEG, CSF 14-3-3, NSE; pathology	German Reference Centre for Spongiform Encephalo-pathies Universität Göttingen	Fair
Poser **1999**	364 patients with suspected CJD 1993-6	Duration less than 2 years	Detailed neurological examination, review of medical records, EEG, CT/MRI, CSF 14-3-3	German Reference Centre for Spongiform Encephalo-pathies Universität Göttingen	Good
Geschwind 2010	More than 1400 patients referred for evaluation of RPD 2002-10	First symptoms to dementia in less than 1-2 years	Not stated but diagnostic approach described in this review article	University of California at San Francisco Memory and Aging Center	Fair
Geschwind 2008	178 patients referred for suspected prion disease or RPD 2002-8	RPDs “can develop over months weeks or even days”	Not stated	University of California at San Francisco Memory and Aging Center	Poor
Geschwind 2007	825 patients referred for RPD 2002-7	Not stated	Not stated	University of California at San Francisco Memory and Aging Center	Poor

Shields 2010	Brain tissue from 57 subjects suffering RPD in whom CJD was clinically suspected, but excluded by molecular techniques	Not stated, but referred for suspected CJD	Pathology	University of Maryland, USA	Fair
Brown 1994	1113 cases referred for possible spongiform encephalopathy; CSF	Not stated	Hospital records review; CSF electrophoresis PrP etc	Laboratory of CNS Studies, National Institute of Neurological Disorders and Stroke, NIH USA	Poor
Will 1984	18 cases autopsy of patients certified of death due to CJD: part of national survey 1970-9	Not stated	ICD 8 and 9 criteria. Clinical and EEG. Subsequent autopsy	CJD was reportable in UK. Study was part of national survey. From Oxford, England	Poor

Table 2 Percentage of referrals for RPD which are due to CJD

	Eurelings	**Papageorgeou**	**Kelley**	**Van Everbroek**	**Poser**	**Geschwind**
CJD (all types)	51	13	70	34	56	64-76
Other diagnoses	49	87	30	66	44	24-36

Table 3: Centers for Disease Control Criteria for Spontaneous CJD

· Progressive dementia and

· At least two out of the following four clinical features: myoclonus; visual or cerebellar disturbance; pyramidal/extrapyramidal dysfunction; akinetic mutism and

· Atypical electroencephalogram (EEG) during an illness of any duration, and/or a positive 14-3-3 cerebrospinal fluid (CSF) assay with a clinical duration to death less than two years, and/or magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) and

· Routine investigations should not suggest an alternative diagnosis

Table 4: Prevalence of different causes of RPD in case series

Author	Quality rating	Subjects	Prevalence of causes of RPD
Eurelings 2010	Fair	225 brains Suspected CJD 2001-8	*CJD confirmed in 115 (51%)* *Non CJD diagnoses 110 (49%)* AD with no infarcts 22 (10%) Mixed AD/vascular 10 (4.5%) Multiple infarcts 11 (5%) Autoimmune encephalitis 9 (4.5%) Neoplasia 9 (4%) Lewy body 8 (3.5%) Cerebral amyloid angiopathy 6 (2.5%) Other 35 (16%)
Chivatras 2010	Good	352 prion negative brains out of 1106 referred for suspected CJD: pathology on 304	***Incurable 233*** AD 154 (44%) Vascular dementia 36 (10%) Unspecified neurodegeneration 10 (3%)

		2006-9	FTD 9 (3%) Mesial temporal lobe sclerosis 5 (1%) Lewy body 4 (1%) Tauopathy NOS 4 (1%) Hereditary diffuse leukoencephalopathy 3 (1%) PSP 3 (1%) Other 5 (1%) ***Potentially curable 71*** ***Immune mediated 26 (7%)*** [1º angiitis, limbic encephalitis, sarcoid, paraneoplastic cerebellar degeneration, Wegener's] ***Neoplasms 23 (6%)*** [Lymphoma 16; -1º in 8, intravascular in 8, leptomeningeal in 2; glioma, carcinoma] ***Infections 14 (4%)*** Fungal, viral, parasitic ***Metabolic 6 (2%)*** Wernicke, other
Papageorgeou **2009**	Good	279 patients admitted for diagnostic evaluation of dementia: 68 had RPD 2004-6	***68 patients with RPD*** AD 12 (18%) FTD 11 (16%) CJD 9 (13%) VaD 9 (13%) NPH 4 (6%) DLB 4 (6%) MSA 2 (3%)

			Neurosyphilis 2 (3%) 1 each with: PSP, CBD, scleroderma, sarcoidosis, SLE, 1º vasculitis, limbic encephalopathy, HIV, glioma, Qfever, B12 deficiency, MS, drug intoxication, Chronic psychosis
Josephs **2009**	Fair	96 cases of brain autopsy identified through electronic medical database search using "rapid" plus "dementia" 2000-7	***22 cases RPD with autopsy*** CJD 8 (36%) FTLD with MND 5 (23%) PSP 2 (9%) CBD 2 (9%) DLB 3 (12%) AD 2 (9%)
Kelley **2009**	Good	22 cases identified through electronic medical database search for RPD onset age 17-45 1996-2006	Definite or probable CJD 6 (24%) Unknown neuro degeneration 5 (21%) 1 each with: FTLD-MND, PML, Kuf disease, Fahr disease, iatrogenic CJD, Adult onset leukoencephalopathy, mitochondrial disease, microvascular ischemia, MELAS, paraneoplastic limbic encephalitis
Van Everbroek **2004**	Fair	250 CSF samples referred for possible CJD 1998-2003	***79 patients suspected of possible CJD, but disproven*** AD 45 (57%) VaD 18 (23%) DLB 16 (20%)
Tschampa **2001**	Fair	104 of 413 samples of brain tissue for suspected but disproven CJD	AD 28 (27%) DLB 14 (25%)

		1993-7	
Poser **1999**	Good	364 patients with suspected CJD 1993-6	***Final diagnosis in 321:*** CJD 190 (59%) AD 34 (11%) Unclassified dementia 20 (6%) Cerebrovascular disease 11 (3%) Chronic encephalitis unknown cause 10 (3%) Parkinson's disease 6 (2%) Psychiatric disease 6 (2%) Para neoplastic syndromes 3 (1%) Intoxications 3 (1%) MS 3 (1%) Hashimoto encephalitis 2 (0.6%) Familial spastic paraplegia 2 (0.6%) CBD 2 (0.6%) Lymphoma 2 (0.6%) Huntington 2 (0.6%) Metabolic disorder 2 (0.6%) Chronic epilepsy 2 (0.6%) Hereditary ataxia 2 (0.6%) Alcohol induced 2 (0.6%) Other 7 (2%) Genetic PRION disease 6 (2%)
Geschwind 2010	Fair	More than 1400 patients referred for	***1377 patients referred "most had extensive medical record review***"

		evaluation of RPD 2002-10	Probable CJD 32% Potential CJD (insufficient information) 29% Genetic prion diseases 15% Acquired CJD 1% **Not CJD 23%** ***319 patients evaluated at UCSF*** Probable or definite CJD 34% Genetic prion diseases 26% Potential CJD 3% Acquired CJD 1% **Not CJD 104 (36%)** Unclassified dementia 14 (13% of non CJD cases) Psychiatric 12 (12% of non CJD cases) DLB 8 (8%) Encephalitis 8 (8%) Hashimoto encephalopathy 8 (8%) FTD or MND 7 (7%) CBD 6 (6%) Autoantibody 4 (4%) Metastatic encephalopathy 4 (4%) 1º CNS lymphoma 4 (4%) AD 3 (3%) Encephalopathy 3 (3%) Leukoencephalopathy 3 (3%) PSP 3 (3%) Vasculitis 3 (3%) AD with Lewy bodies 2 (2%)

			Cerebrovascular 2 (3%) Paraneoplastic 2 (3%) Other 8 (8%)
Geschwind **2008**	Poor	178 patients referred for suspected prion disease or RPD 2002-8	Sporadic CJD 46.9% Genetic prion 13.6% Acquired CJD 1.7% ***Non prion diseases 67 (38%)*** Neurodegenerative 26 [CBD 8, FTD 7, DLB 4, AD 5, PSP 2] Autoimmune 15 [Hashimoto 4, MS 1, Sarcoid 1, antibody mediated 9] Unknown 8 Infectious 4 Psychiatric 4 Neoplastic 4 Toxic metabolic 3 Vascular 3
Geschwind **2007**	Poor	825 patients referred for RPD 2002-7	***Prion diseases 54%*** [definite or probable sporadic 37%, genetic 15%, acquired 2%] Undetermined 28% ***Non prion conditions 18%*** Neurodegenerative 265 Autoimmune 15% Infectious 11% Psychiatric 11% Other 9% ***Undetermined 28%***
Shields	Fair	57 subjects suffering RPD in	***Neurodegenerative 25*** (46%) [AD, LBD, FTD, CBD,

2010		whom CJD was clinically suspected, but excluded by molecular techniques	PSP] ***Inflammatory 11*** (19%) [vasculitis, encephalitis, acute disseminated encephalomyelitis, MS] ***Neoplastic 4*** (7%) [lymphoma, carcinoma, glioma] ***No diagnosis 4*** (7%) ***Miscellaneous 13*** (23%) [toxic metabolic, mitochondrial disease ischemic encephalopathy, toxic leukoencephalopathy]
Brown **1994**	Poor	1113 cases referred for possible spongiform encephalopathy; CSF 1963-1993	***Prion disease successfully transmitted to animals 291*** ***Nonspongiform diseases 673*** Unclassified dementia 115 AD 105 ALS 59 Chronic epilepsy 35 Encephalitis unknown cause 29 HIV encephalopathy 25 PD 24 Huntington's 22 Subacute sclerosing panencephalitis 21 MS 17 FTD 15 Schizophrenia 12 Schilder's disease 12 Progressive multifocal leukodystrophy 12 PSP 10 Viliuisk encephalitis 7

			Other neurological disorders 100 Non neurological disorders 53
Will **1984**	Poor	18 cases autopsy of patients certified as death due to CJD: part of national survey 1970-9	***Of 18 cases of suspected CJD autopsy showed:*** AD 3 CBD 3 Nonspecific atrophy 2 MND 1 PD 1 CVD 1 AD plus MS 1 FTD 1 Limbic encephalopathy 1 H. simplex encephalitis 1 Familial spinocerebellar atrophy 1 Multiple cerebral abscesses 1

Table 5: Final diagnostic categories (%) of Rapidly Progressive Dementia not due to CJD

Diagnoses	Eurelings	Chivatras	Papageorgeou	Van Everbroek	Tschampa	Poser	Shields	Geschwind	Kelly
Number of cases in series	**110**	**352**	**57**	**79**	**104**	**321**	**57**	**104**	**14**
Degenerative	**51**	**66**	**60**			**21**	**44**	**45**	**14**
Alzheimers	20	44	21	57	27	11		5	
Mixed AD/vasc	9								
VaD	10	10	16	23		3		2	7
DLB	7	1	1	20	13			8	
FTD		3	20					7	7
PSP		1						3	
PD						2			
Other degen	5	7	2			5		20	
Chronic encephalitis						3		8	
Encephalopathy								6	7

Immune mediated	**8**	**7**	**1**			**2**	**19**	**15**	
Paraneoplastic		2				1		2	7
Malignant	8	7	0.2			0.6	7	5	
Infectious		4	1						
Psychiatric			0.2			2		12	
Metabolic/toxic		2	0.6			2			
Other	32					9	35	8	71

Table 6: Proposed diagnostic approach to Rapidly Progressive Dementia

Procedure	**Tests to be conducted on *all* RPD patients**	**Additional tests to consider**
History	Onset, duration, associated features, comorbid conditions; exposures (tobacco, industrial chemicals, heavy metals, alcohol); complete medication review; past history and symptoms of systemic disease; travel history, sexual, recreational drug or blood products exposure; collateral history from close relatives; hallucinations, psychosis; fluctuating presentation; family history; headache; weight	Collateral history from other sources; previous hospital admissions, other physicians, workplace; other relatives; search for evidence of cognitive "normality" at previous points in time.

	loss; skin rashes etc.	
Examination	Signs of systemic disease (any system, especially cardiovascular, pulmonary, GI, skin, rheumatological); optic fundi; neurological examination for focal signs; rigidity, motor disorders, cerebellar signs, myoclonus; physically examine all medications; cognitive testing	Full neuropsychological testing.
Laboratory	CBC, routine chemistry, Se. B12, Calcium, TSH, electrolytes, ESR, ANA, C-RP Urine analysis	HIV, VDRL, vasculitis screen, anti-thyroglobulin and anti-thyroperoxidase antibodies, paraneoplastic antibodies; drug levels, MMA. P-ANCA, C-ANCA;
Imaging	MRI with and without contrast; FLAIR and DWI Chest X-Ray	MR angiogram; CT chest, abdomen, pelvis PET scanning (FDG, PiB etc.)
CSF	Protein, glucose, IgG, VDRL, oligoclonal banding, cell count and differential	Cultures (bacterial including AFB; fungal) viral studies, protein 14-3-3, PS 100, cytology, Whipple PCR, Lyme serology; amyloid β 1-42, total and phosphorylated tau
EEG	Standard EEG	
Brain biopsy		Biopsy when diagnosis is essential and all above procedures have failed to establish diagnosis

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Electronic appendix of case reports to follow