A Practical Approach to the Evaluation of a Rapidly Progressive Dementia

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Disclaimer:
The following is neither an absolute list nor absolute categorical schema since many disorders have overlapping signs/symptoms/lab tests. The following illustrates the most common findings per category.

Definition of a rapidly progressive dementia (RPD):
1. A condition that progress from the first symptom to dementia in less than 1-2 years.
2. A person with dementia that is declining at an accelerated rate that is not commensurate with the usual course of the disease

Diagnostic categories that cause a RPD:

1. Degenerative	2. Inflammatory	3. Vascular	4. Toxic	5. Metabolic	6. Neoplastic	7. Infectious

The Approach:

Step 1: History & Examination								
		Degenerative	**Inflammatory**	**Vascular**	**Toxic**	**Metabolic**	**Neoplastic**	**Infectious**
History	Age - young		**X**			**X**	**X**	**X**
	Age - old	**X**	**X**	**X**			**X**	**X**
	Onset - *acute* (days to weeks) & *subacute* (weeks to months)		**X**	**X**	**X**	**X**	**X**	**X**
	Onset - *chronic* (years)	**X**		**X**				
	Is it really rapidly progressive	**X** if answer is no						

Step 1: History & Examination								
		Degenerative	**Inflammatory**	**Vascular**	**Toxic**	**Metabolic**	**Neoplastic**	**Infectious**
	Relapsing-remitting course	**X** (DLB)	**X** (SRE)				**X** (NMDARE)	
	Are the symptoms consistent with a limbic encephalitis[1]?		**X**				**X** (NMDARE)	**X**
	Seizures?	**X**	**X**				**X**	
	Presence of systemic signs	**X** (weight loss)	**X**				**X**	**X**
	Immuno-compromised?							**X**
	Exposure to certain agents via travel/ insect/animal contacts?							**X**
Cognitive Testing		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neurological Examination	UMN signs		**X**	**X**		**X**		
	Parkinsonism	**X**		**X**		**X**		**X** (SSPE)
	Myoclonus	**X**			**X**	**X**		**X**
	Asterixis	**X**				**X**		

Step 1: History & Examination								
		Degenerative	**Inflammatory**	**Vascular**	**Toxic**	**Metabolic**	**Neoplastic**	**Infectious**
	Peripheral neuropathy				**X**	**X**		
Physical Examination	Fever, meningismus							**X**
	Vascular signs (bruits, hypertension, etc)			**X**				

[1]***Limbic encephalitis signs:*** short-term memory loss, confusions, seizures, irritability, depression, sleeping problems, psychiatric symptoms
DLB = dementia with Lewy bodies
SRE = steroid responsive encephalopathy
NMDARE = NMDA receptor encephalitis (a paraneoplastic syndrome)
SSPE = subacute sclerosing panencephalitis (due to measles)

Step 2A: Laboratory/Blood Tests								
		Degenerative	**Inflammatory**	**Vascular**	**Toxic**	**Metabolic**	**Neoplastic**	**Infectious**
CBC	Hb, WBC, MCV, smear					**X**	**X**	**X**
Electrolytes	Na, Ca, Mg					**X**		
Liver profile	AST, ALT, GGT, alk phos, bili, NH4				**X** (alcohol)	**X**	**X** (alk phos)	
Renal profile	Cr					**X**		
Thyroid function & antibodies	TSH, anti-TPO, anti-Tg		**X** (NAIM)			**X**		
Rheumatology screen	ESR, CRP, ANA, RF, ANCA, hypercoagulability panel, SPEP		**X** (vasculitis)	**X** (vasculitis)			**X** (lymphoma if positive SPEP)	
Vitamin B12						**X**		
Infectious	syphilis, Lyme serologies, HIV, CSF analysis							**X**
Paraneoplastic	anti-Hu, CV2, GAD65, NMDA, Ma2,VGKC						**X**	

NAIM (nonvasculitic autoimmune inflammatory meningoencephalitis)
anti-TPO (anti-thyroid peroxidase antibody); **anti-Tg** (anti-thyroglobulin antibody)
anti-Hu (small cell lung cancer [SCLC]); **anti-Ma2** (testicular germ-cell tumours); **anti-CV2/CRMP5/VGKC** (SCLC, thymoma); **NMDA** (ovarian tumour)

Step 2B: Spinal Fluid (CSF) Examination							
	Degenerative	**Inflammatory**	**Vascular**	**Toxic**	**Metabolic**	**Neoplastic**	**Infectious**
Cell count & differential		**X** (vasculitis)				**X** (lymphocytic pleocytosis - normal)	**X** (lymphocytic pleocytosis)
Protein & glucose		**X** (vasculitis - high protein, normal glucose)			**X**	**X**	**X** (high protein, low-normal glucose)
IgG Index		**X** (autoimmune - high)			**X**	**X** (paraneoplastic)	**X**
Oligoclonal bands		**X** (autoimmune - high)			**X**	**X** (paraneoplastic, esp NMDA)	
Cytology					**X**	**X**	
Gram stain/ cultures/ PCR/ VDRL							**X**
Other	• AD-Abeta (low) & tau (high) • CJD - 14-3-3, NSE, tau (all high)		• mitochondrial - lactate & pyruvate		• mitochondrial - lactate & pyruvate		• PCR • CJD - 14-3-3; NSE; tau (all high)

NSE (neuron specific enolase);

Step 3: Imaging							
	Degenerative	**Inflammatory**	**Vascular**	**Toxic**	**Metabolic**	**Neoplastic**	**Infectious**
MRI brain ± gad - with help of a neuroradiologist, look for specific findings for a disorder	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CT chest, abdomen, pelvis						**X** (if suspect paranoplastic/ neoplastic)	**X** (if need to find source)
Ultrasound			**X** (TTE or TEE to determine cardiac cause of stroke)			**X** (testes or ovaries if paraneoplastic)	
PET/SPECT	**X** (brain - look for specific patterns)					**X** (whole body if positive paraneoplastic antibody but negative scans to search for primary)	

Possible Etiologies: (Compiled from Woodruff BK. *Sem Neurol* 2007; **27**:363-375; Geshwind MD. *Continuum* 2010; **16(2)**: 31-56; McGinnis SM *Sem Neurol*. 2011; **31:** 266-285)

Degenerative	Inflammatory	Vascular	Toxic	Metabolic	Neoplastic	Infectious

• Prion disease
• Alzheimer's disease
• Dementia with Lewy bodies
• Frontotemporal dementia
• Corticobasal degeneration
• Progressive supranuclear palsy
• Neurofilament inclusion body disease
• Progressive subcortical gliosis
	• Hashimoto's encephalopathy, nonvasculitic autoimmune inflammatory encephalopathy (NAIM)
	• Sjögren's syndrome
	• anti-GAD autoimmunity
	• Sarcoidosis
	• CNS vasculitis
	• Paraneoplastic limbic encephalitis
	• Celiac sprue
	• Multiple sclerosis
	• Acute disseminated encephalomyelitis
	• Beçet's disease
		• CNS vasculitis
		  • primary & secondary causes (infectious, neoplastic intravascular lymphoma, systemic vasculitides, connective tissue disease, drug-induced, antiphospholipid syndrome, Susac's syndrome [retinocochleo-cerebral vasculopathy])
		• Hereditary
		  • CADASIL
		  • MELAS
		• Sudural hematoma
		• Strategic infarction or hemorrhage
		• Cerebral amyloid angiopathy (CAA)
			• Radiation-induced leukoencephalopathy
			• Chemotherapy-induced leukoencephalopathy
			  • PRES (reversible posterior leukoencephalo-pathy)
			  • drugs (methotrexate, 5-fluorouracil, cisplatin, cyclosporin A, tacrolimus, levamisole)
				• Wilson's disease
				• NBIA-1 (Hallervorden - Spatz syndrome)
				• mitochondrial diseases
				• cerebrotendinous xanthomatosis
				• neuronal ceroid lipofucinosis
				• metachromatic & adrenoleukodystrophies
				• adult-onset Tay-Sachs disease
				• neuroacanthocytosis
				• Nutritional (Wernicke's encephalopathy/ Korsakoff's psychosis, B12 deficiency, Vitamin E deficiency, folate deficiency, niacin deficiency)
				• Environmental (metal toxicity [lead, arsenic, mercury, manganese, bismuth)
				• Endocrine abnormalities (TSH, calcium etc)
				• Electrolyte abnormalities
				• Liver failure
				• Renal failure
				• Porphyria
				• Extrapontine myelinolysis
					• Primary CNS neoplasms
					• gliomatosis cerebri
					• metastatic encephalopathy
					• metastases
					• primary CNS lymphoma
					• Intravascular lymphoma
					• Paraneoplastic limbic encephalitis, including NMDARE
					• Lymphomatoid granulomatosis
						• Viral (HIV, HSV, PML [JC], SSPE [measles], WNV, EBV, VZV, HHV6)
						• Bacterial (spirochete [syphilis, Lyme], Bartonella, mycoplasma, , Whipple's, mycobacteria [TB, nontuberculous mycobacteria], rickettsial)
						• Fungal (coccidioides, aspergilus, histoplasma, cryptococcus, blastomyces)
						• Prion (s/v/iCJD)
						• Parasites (toxoplasmosis, trypanosomiasis, granulomatous amoebic encephalitis)

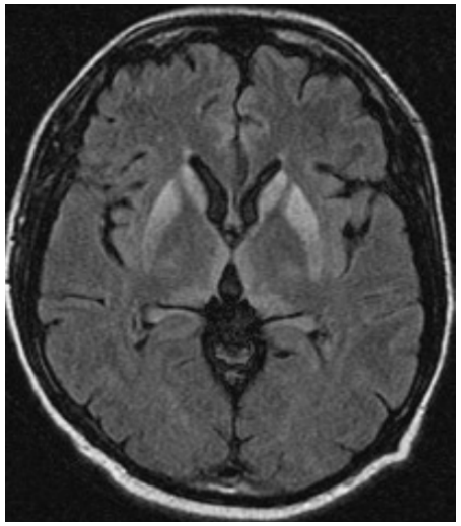
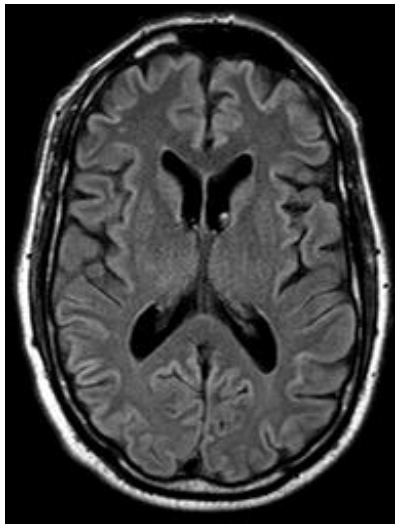
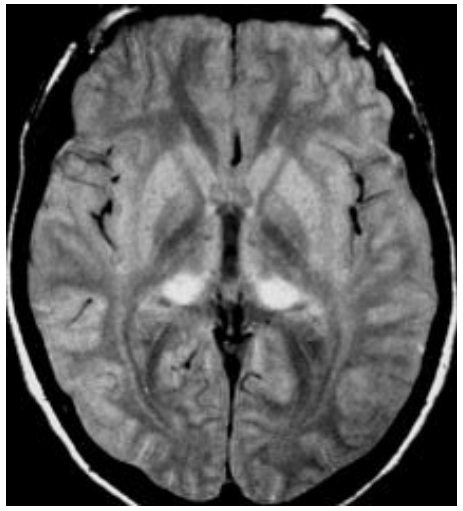
Creutzfeldt-Jacob Disease Summary Sheets			
	Sporadic (sCJD)	**Familial (fCJD)**	**Variant (vCJD)**
Cause	occurs spontaneously	due to autosomal dominant mutations in the PRNP gene encoding the prion protein (PrP)	due to iatrogenic or oral transmission of an abnormally shaped prion protein from an affected individual or animal to a person
Frequency (%)	85	15	<1
Peak age of onset (median age of onset)	50-70 (68)	???	12-74 (28)
Survival (years)	1	1 to several years	1.5

Clinical presentation	CJD can look like many other entities early in the course of the disease
	• cognitive/cortical (memory > executive dysfunction > dysphasia > confusion) (39%)
	• cerebellar (gait/balance changes>limb ataxia) (21%)
	• behavioural (20%)
	• constitutional (dizziness, fatigue, sleep disorders)(20%)
	• sensory (11%)
	• motor (9%)
	• visual (7%)
		• Familial CJD
		  • symptoms similar to sCJD
		• Fatal familial insomnia (FFI)
		  • progressive sleep and autonomic disturbances
		• Gerstmann-Strauussler-Scheinker disease (GSS)
		  • progressive cerebellar ataxia
			• usually presents with a psychiatric prodrome lasting >6 months (can be diagnosed with a primary psychiatric illness)
			• then develops ataxia, cognitive impairment, extrapyramidal motor findings

Testing - EEG **Sensitivity: 50-66%** **Specificity: 74-91%**	Early in disease • normal or focal slowing Early-Moderate Stages • diffuse slowing Moderate-Late Stages • 1-2-Hz periodic epileptiform discharges		Does ***not*** show the 1-Hz periodic epileptiform discharges

<table>
<tr><th colspan="4">Creutzfeldt-Jacob Disease Summary Sheets</th></tr>
<tr><th></th><th colspan="2">Sporadic (sCJD)</th><th>Familial (fCJD)</th><th>Variant (vCJD)</th></tr>
<tr><td>Testing - Spinal Fluid

Sensitivity: 64% (for total tau)
Specificity: 95% (for total tau)</td><td colspan="3">None of these biomarkers are prion specific and do not identify prions - they are markers of neuronal injury
• 14-3-3
• Neuron-specific enolase (NSE)
• Total tau</td><td></td></tr>
<tr><td rowspan="3">Testing - Neuroimaging

Sensitivity: 91%
Specificity: 95%</td><td colspan="2">  </td><td>  </td><td>  </td></tr>
<tr><td colspan="4">Hyperintensities seen in the following structures (best seen on DWI and FLAIR sequences)</td></tr>
<tr><td colspan="3">In decreasing frequency:
• cortical ribboning - abnormal hyperintensity in the cortical gyri
• basal ganglia - caudate & putamen
• thalamus</td><td>pulvinar sign - hyperintensity of the posterior thalamus</td></tr>
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References:

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