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Disclosures

- Boston Scientific, Inc – Education Faculty, Consulting

2

Outline

- Review terminology pertinent to rapidly progressive dementia (RPD)
- Describe the clinical findings and supportive diagnostic testing for common and/or treatable causes of RPD
- Outline the diagnostic approach for RPD
- Highlight pitfalls along the way

3

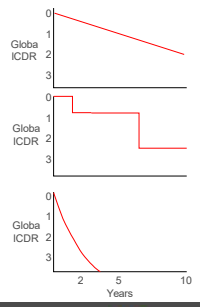
Cognitive Impairment

- Mild neurocognitive disorder
  - formerly *mild cognitive impairment*
  - A modest decline in cognitive function that **DOES NOT** significantly interfere with daily life, though it may require increased effort or compensatory strategies.
- Major neurocognitive disorder
  - Formerly *dementia*
  - *Substantial decline in cognitive function that* **DOES** *interfere with daily life.*
  - **Dementia has a cause**

4

Temporal Profile

- Paramount importance to accurately define the temporal file
  - *What's the story?*
- Chronic, Subacute, Acute, Pseudo-acute
- Rapid
  - Reliable informant
  - Clinical Dementia Rating (CDR)
    - Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, Personal Care
  - Global CDR of 0 to ≥1 in ≤1 year
  - Global CDR of 0 to ≥2 (moderate dementia) in ≤2 years



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What company does it keep?

- Thorough history (revisit & revisit)
- Systemic exam
  - Scleral changes
  - Skin changes
- Detailed neurological examination
  - Mental status
  - Cranial nerves
  - Motor assessment
    - Strength/Tone/Bulk
  - Movement/Coordination
    - Ataxia
    -

6

It's rapid, now what?

- Etiology
  - Vascular
  - Infection/Inflammatory
  - Toxin
  - Autoimmune
  - Metabolic/Malignancy
  - Iatrogenic
  - Neurodegenerative
  - Systemic/Seizures/Structural

Finding	Prion	Neurodegenerative	Metabolic	Vascular	Infection	Toxin	Neoplastic	Autoimmune
Age (years): Young (<50 y old) / Old (≥50 y old)	vCJD / sCJD	X	X / X	X / X	X / X	X / X	X	X / X
Onset: Days–weeks / Months–years	X / X	X	X	X	X	X	X	X
Fluctuations		X (DLB)	X	X	X	X		X
Symptoms of limbic encephalitis*							X	X
Systemic symptoms*					X		X	X
UMN signs	X	X	X	X	X		X	
Parkinsonism	X	X	X	X	X (SSPE)	X		
Myoclonus	X	X	X		X	X		X
Asterixis	X	X	X		X	X		
Peripheral neuropathy			X			X		
Hyponatremia			X			X		X
Eye movement abnormalities		X	X	X				
Visuospatial impairment	hCJD	X		X				

DLB (Dementia with Lewy bodies), vCJD (variant Creutzfeldt-Jakob disease), sCJD (sporadic CJD), hCJD (Heidenhain variant of CJD), SSPE (subacute sclerosing panencephalitis)

Tipton PW et al. Neurol. 2021 Dec;41(6):686-698.

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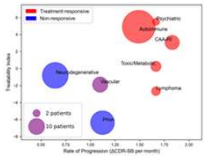
Why make a big deal out of terms?

- Many causes (55.5%) of RPD are **treatable**
- Missed opportunities for treatment in 5–7% of cases of RPD.
- $STAM_3P$
  - *Seizures at presentation*
  - *Disease associated tumor*
  - *Age <50 years*
  - *MRI suggestive of autoimmune encephalitis*
  - *Mania*
  - *Movement abnormalities*
  - *CSF pleocytosis (≥10 cells/mm3)*

$STAM_3P$ score	1	2	3
PPV	0.759	0.913	1.000
NPV	0.915	0.660	0.519
Accuracy	0.806	0.755	0.587



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Ceutzfeldt-Jakob disease

- Invariably fatal spongiform encephalopathy
- Common cause of RPD
- Sporadic CJD
  - Most cases (85-95%)
- Familial
  - 5-15%% of cases
  - *PRPc* mutation
- Variant & Iatrogenic CJD
  - Bovine to human transmission ("mad cow disease")
  - Human to human transmission (e.g., blood transfusion, corneal transplant)

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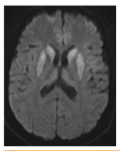
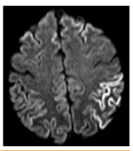
Sporadic CJD

- Clinical symptoms & signs
A. Progressive cognitive impairment
B. Additional symptoms & signs
  1. Myoclonus
  2. Visual or cerebellar signs
  3. Pyramidal or extrapyramidal signs
  4. Akinetic mutism
- EEG may show generalized periodic sharp or sharp-wave complexes
- MR brain
  - Restricted diffusion in the caudate, caudate-putamen, or caudate-putamen-thalamus or ≥2 temporal, parietal, or occipital cortical regions.

Definite sCJD
Detection of abnormal protease-resistant prion protein

Probable sCJD
A + 2 of B + (typical EEG or MRI or positive CSF 14-3-3)
OR
A + 1 of B + positive CSF RT-QuIC

Possible sCJD
A + 2 of B + duration < 2 yrs & exclusion of other causes

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Cortical Ribboning

- Refers to temporal, parietal, or occipital cortical regions.
  - Similar artifact often seen in medial frontal lobes
- Cortical ribboning is not specific to CJD
  - Subacute sclerosing panencephalitis
  - Autoimmune encephalitis
  - Herpes simplex encephalitis
  - High-grade glioma (& other malignancies)
  - Seizures
  - Hypoglycemia & other metabolic derangements.

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Autoimmune Encephalitis

- Growing number of antibodies
  - Mayo Clinic Laboratories serum test (ENS2) screens for 24 different autoantibodies

Most common abs targeting cell-surface epitopes	Most common abs targeting intracellular epitopes	Paraneoplastic
• Leucine-rich glioma inactivated protein 1 (LGI1)	• Glutamic acid decarboxylase 65 (GAD65)	• Antineuronal nuclear antibody type 1 (ANNA-1, anti-Hu)
• NMDAR	• Glial fibrillary acidic protein (GFAP)	• Collapsin response mediator protein-5 (CRMP-5)
• CASPR2		
• $GABA_A$		
• $GABA_B$		
• Myelin oligodendrocyte glycoprotein (MOG)		

Irani SR. Continuum (Minneap Minn). 2024 Aug 1;30(4):995-1020.

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NMDA Receptor Encephalitis

- Median age of onset is 21 years
- More common in females
- "Brain on Fire"
- Symptoms
  - Encephalitis with prominent neuropsychiatric symptoms
  - Movement symptoms: **orofacial-lingual dyskinesias**, dystonia, chorea, stereotypies, catatonia, tremor, myorhythmia, ataxia, bradykinesia (less common)
  - Dysautonomia
- Imaging
  - MR brain may be normal
- EEG
  - Slowing (most), epileptiform abnormalities (some), extreme delta brush (rare)
- CSF
  - Lymphocytic pleocytosis, unpaired oligoclonal bands, NMDA-R antibodies

Li H et al. Front Neurol. 2024 Mar 1;15:1357697.

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NMDA Receptor Encephalitis

- Associated with **ovarian teratoma** in 60% of young females
- May occur after HSV infection
- Most improve with first- or second-line immunotherapy
  - 1st: IVIG, corticosteroids, plasma exchange

Li H et al. Front Neurol. 2024 Mar 1;15:1357697.
Nosadini M et al. JAMA Neurol. 2021;78(11):1333–1344.

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LGI1 Antibody Associated Encephalitis

- Median age of onset is mid 60s
- More common in males
  - 238 patients included 89% carried **HLA-DRB1*07:01** and 10% DRB1*04:02
  - DRB1*07:01 younger and less commonly males
- Neurological symptoms: focal seizures (**faciobrachial dystonic seizures**)
- Bloodwork: hyponatremia is common, LGI1 antibodies (more sensitive than CSF)
- MRI
  - T2/FLAIR hyperintensities in the temporal lobe, without diffusion restriction or contrast enhancement, robustly distinguished LGI1- and CASPR2-antibody encephalitis from other conditions (Kelly 2024)
- CSF
  - Minority with pleocytosis and elevated protein; LGI1 antibodies (more specific than blood)
- EEG
  - Some may have focal slowing or epileptiform abnormalities (Faciobrachial dystonic seizures usually lack electrographic correlate)

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LGI1 Antibody Associated Encephalitis

- Corticosteroids are most effective acute therapy
  - May add IVIg or plasma exchange for severe cases
- Rituximab to decrease risk of relapse, which may occur in roughly 40% of cases
- **Usually not paraneoplastic, but screen** especially if patient presents atypically and/or lacks common associated HLA alleles (HLA-DR7 or HLA-DRB4).

Irani SR. Continuum (Minneap Minn). 2024 Aug 1;30(4):995-1020.
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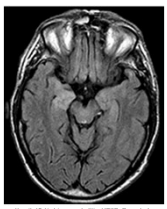
CASPR2 Ab-Related Encephalopathy

- Median age of onset is mid 60s
- Much more common in **males**
- Symptoms
  - Limbic encephalitis
  - Peripheral nerve hyperexcitability
  - Morvan syndrome
  - Movement: ataxia, myoclonus, tremor
- Bloodwork: CASPR2 antibodies (more sensitive than CSF)
- MRI: 30% have T2 hyperintensities in the medial temporal lobes or hippocampal atrophy but can also show multifocal lesions including brainstem involvement.
- CSF: 30% lymphocytic pleocytosis, elevated protein, +/- oligoclonal bands, **CASPR2 antibodies (especially if encephalitis is present)**



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CASPR2 Ab-Related Encephalopathy

- EEG: 70% abnormal including 40% with epileptiform abnormalities
- EMG: fasciculation potentials, myokymic discharges, neuromyotonia
- "In men older than 50 years, otherwise unexplained seizures, cerebellar ataxia, and/or neuropathic pain are suggestive of early-stage CASPR2-encephalitis, especially if they coincide with recent asthenia, mood disorders, or insomnia." (Benoit 2022)

Irani SR. Continuum (Minneap Minn). 2024 Aug 1;30(4):995-1020.
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CASPR2 Ab-Related Encephalopathy

- HLA-DRB1*11:01
- Usually not paraneoplastic
  - Thymoma in 20% of cases so SCREEN
- Prompt immunotherapy with corticosteroids, IVIG, plasma exchange, rituximab
  - Half of patients respond well to therapy (immunotherapy +/- tumor resection)
  - Nearly half with partial response
- 30% relapse rate

Irani SR. Continuum (Minneap Minn). 2024 Aug 1;30(4):995-1020.

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GAD65 Antibodies

- Associated with autoimmune encephalitis & target intracellular aspects of neuroglial proteins.
- Likely nonpathogenic
  - Association ≠ causation
  - GAD65 abs present in 8% of population (especially those with diabetes)
- Low titers are typically not neurologically relevant (serum & CSF)
  - <10,000 IU/mL measured by enzyme-linked immunosorbent assay
  - <20 nmol/L measured by radioimmunoassay
- GAD antibody spectrum disorders
  - Stiff-person syndrome (50%)
  - Cerebellar ataxia (43%)
  - Autoimmune epilepsy (29%)
  - Limbic encephalitis (16%)

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GAD-positive Limbic Encephalitis

- Symptoms:
  - Impaired working memory
  - Neuropsychiatric symptoms
  - Seizures
  - Altered level of consciousness
- Bloodwork: GAD65 abs (if low, investigate other potential causes)
- CSF: Oligoclonal bands and GAD65 abs (if low, investigate other potential causes)
- EEG: +/- epileptiform abnormalities
- EMG: impaired muscle relaxation; specialized measures of stimulus responsiveness (SPS)

Budhram A et al. J Neurol Neurosurg Psychiatry 2021;92(6):645-654.

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Thyroid peroxidase (TPO) antibodies

- TPO antibodies are not specific to disease.
  - Present in the general population (up to 13% overall and 20% in those over 60).
- Hashimoto's encephalitis
  - Steroid-response encephalopathy associated with autoimmune thyroiditis (SREAT)
  - Symptoms are variable including subacute confusion, psychosis, depression, catatonia, and mood disorders, hallucinations, delusions, seizures, movement disorders.
  - Most patients are euthyroid or have mild thyroid dysfunction at presentation
  - **Diagnosis of exclusion**
    - TPO abs serve only as a nonspecific marker of autoimmunity rather than a diagnostic tool.
    - TPO abs should not be used as a stand-alone diagnostic marker for HE or to distinguish it from other autoimmune encephalitides.
  - *Dramatic* improvement with steroids
    - TPO abs do not predict steroid responsiveness

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Misdiagnosis of autoimmune encephalitis goes both ways

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Red Flags in Autoimmune Encephalitis Diagnosis

- Clinical
  - Insidious onset
  - Multiple comorbidities that cause cognitive deficits
  - Examination consistent with functional neurologic disorder
  - Normal neuropsychological test results
- MRI brain
  - Normal
  - Progressive atrophy without signal abnormalities/enhancement
  - Lesion(s) continuing to expand despite immunotherapy
- CSF
  - Noninflammatory (nml WBC & no O bands)

Flanagan EP, et al. JAMA Neurol. 2023;80(1):30-39.

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Red Flags in Autoimmune Encephalitis Diagnosis

- Serology
  - TPO abs of any titer
  - Low titer-positive GAD65 abs
  - Voltage-gated potassium channel complex antibodies negative for LGI1/CASPR2
  - Low-titer antibody positives by older generation techniques (radioimmoprecipitation assay)
  - Isolated serum NMDAR antibody negative in CSF
  - Immunoblot or line blot antibody positivity in isolation
  - Low titer positive CASPR2 abs
  - Antibody detection in noncertified laboratories

Flanagan EP, et al. JAMA Neurol. 2023;80(1):30-39.

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CNS Lymphoma (CNSL)

- Primary or secondary
- 4% of all primary brain tumors
- >90% are large B cell lymphomas
- 60% primary CNSL present as solitary brain lesions
  - Eye involvement (15-25%)
  - CSF 7-42%
  - Spinal cord (rare)
- Lesions are very sensitive to corticosteroids
- Dx: MR brain w/wo contrast, CSF, biopsy

Shah T et al. Semin Neurol. 2023 Dec;43(6):825-832.
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Intravascular lymphoma

- Large B-cell lymphoma that selectively grows in the lumen of small and medium-sized blood vessels
- Variants
  - "Classic" with multi-organ involvement
  - Cutaneous
  - Hemophagocytic (bone marrow involvement)
- Nonspecific symptoms in the absence of a tumor mass make diagnosis difficult often leading to delays in treatment
  - Systemic symptoms (e.g., fever of unknown origin) present in 50% of cases.
- No specific blood lab tests
- CSF: elevated protein (often), pleocytosis (usually), atypical cells & oligoclonal bands (rarely), usually fail to catch tumoral cells.
- Treatable with chemotherapy & immunotherapy

Bentivenga GM, et al. Eur J Neurol. 2024 Jan;31(1):e16068.
Berthet E, et al. Ann Neurol. 2025 Mar;97(3):435-448.

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Intravascular lymphoma

- Clinical Red Flags
  - Acute-onset & recurrent focal neurological deficits, with frequent clinical fluctuations
  - Rapidly progressive encephalopathy
  - Early alternation of general status, asthenia, fever
- Biological Red Flags
  - Early-onset inflammatory syndrome (CRP, fibrinogen), anemia, increased LDH & β2 macroglobulin
  - Elevated CSF protein, mild/inconstant meningitis, increased IL10/IL6 ratio

Bentivenga GM, et al. Eur J Neurol. 2024 Jan;31(1):e16068.
Berthet E, et al. Ann Neurol. 2025 Mar;97(3):435-448.

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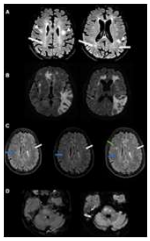
Intravascular lymphoma Imaging Red Flags

- Combination of lesion patterns with FLAIR hyperintense areas associated with infarct-like lesions
- Hemorrhagic lesions, leptomeningeal enhancement
- Accumulation of multiple lesions over time
- Atypical characteristics of infarct-like lesions:
  - DWI-positive lesion localized within broader FLAIR hyperintense area
  - DWI-positive cortical lesion adjacent to subcortical white matter FLAIR hyperintensities
  - Increasing size of FLAIR hyperintensities associated with a stable DWI-positive lesion
  - Increasing size of DWI-positive lesion
  - Prolonged DWI-positive lesion lasting >1 month
- Inconstant distal intracranial arterial steno-occlusive lesions
- Association with medullar lesions, sometimes asymptomatic



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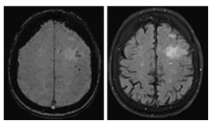
Cerebral Amyloid Angiopathy Related Inflammation (CAA-RI)

- Possible autoimmune reaction to cerebrovascular amyloid β deposits.
- Subacute cognitive decline, seizures, focal neurological symptoms, headaches
- MRI
  - Lobar microhemorrhages, cortical superficial siderosis
  - Asymmetric patchy/confluent subcortical white matter edema
- Similar findings in a patient with Alzheimer disease who is receiving anti-amyloid immunotherapy.



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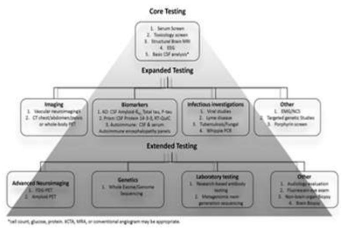
Initial Diagnostic Testing

1. Serum screen
   - CMP, CBC, Thyroid studies, Vit B1/3/12, folate, heavy metals, ceruloplasmin, toxicology, autoimmune panel
2. Urine
   - Heavy metals, toxicology, +/- porphyria
3. Brain MRI with gadolinium
4. Neurologist now or sooner
5. EEG
6. CSF testing



Tipton PW et al. Neurol. 2021 Dec;41(6):686-698.

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Conclusions

- Rapidly progressive dementia (RPD) is a specific descriptor of symptom severity and rate of progression
  - https://www.mdcalc.com/calc/10160/clinical-dementia-rating-cdr-scale
- Accurately diagnosing RPD can result in symptom improvement or complete resolution in some cases
- Choosing the right diagnostic testing should account for most likely cause & treatable conditions
  - Antemortem dx > postmortem dx, even if it isn't treatable
- **Time is brain**

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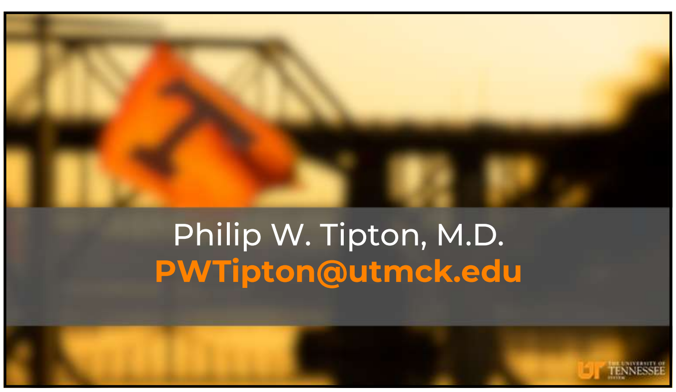

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