ประชุมวิชาการประจำปีกองอายุรกรรม ครั้งที่ 16

Rapidly Progressive Dementia

For Internist

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Topic Outlines

1. Definition
2. Three steps assessment
3. Common diseases
4. Rapidly progressive dementia during COVID-19 pandemic

Overview

- 43.8 million people lived with dementia in 2016
- First mention in the 1950s
- Definitions usually consider less than 1 or 2 years

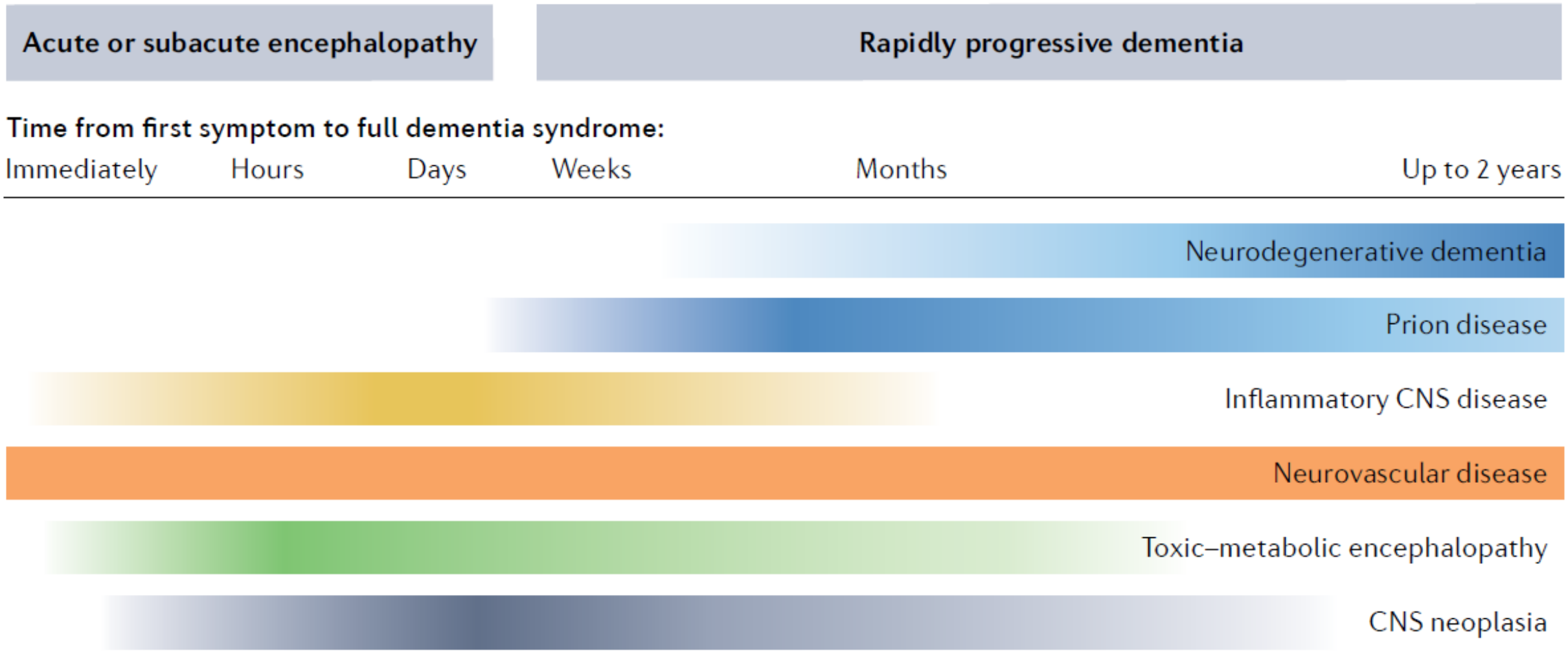
Geschwind, M. D. Rapidly progressive dementia. Continuum 22, 510–537 (2016).
GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol.18, 459–480 (2019).

Table 1 | **Definitions of rapidly progressive dementia**

Study	Type of RPD	Definition of RPD	Additional diagnostic characteristics
Geschwind (2016)[2]	General definition of RPD	Symptom onset to dementia: <1 or 2 years	NA
Degnan and Levy (2014)[22]	General definition of RPD	Symptom onset to dementia: <6 months	NA
Josephs et al. (2009)[19]	Rapidly progressive neurodegenerative dementia	Symptom onset to death: <4 years	Neuropathological diagnosis of neurodegenerative disease
Soto et al. (2008)[5]	Rapidly progressive AD	Reduction of ≥3 points per 6 months in MMSE score	Clinical diagnosis of AD
Schmidt et al. (2011)[20]	Rapidly progressive AD	Reduction of ≥6 points per year in MMSE score	Clinical diagnosis of AD
Gaig et al. (2011)[21]	Rapidly progressive DLB	Symptom onset to death: ≤1.5 years	Neuropathological diagnosis of diffuse Lewy body disease
Garcia-Esparcia et al. (2017)[23]	Rapidly progressive DLB	Symptom onset to death: ≤2 years	Neuropathological diagnosis of diffuse Lewy body disease
Zerr et al. (2009)[18]	Possible sporadic CJD	Total duration <2 years	CJD typical clinical syndrome

AD, Alzheimer disease; CJD, Creutzfeldt–Jakob disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; NA, not applicable; RPD, rapidly progressive dementia.

Hermann, P., & Zerr, I. (2022). Rapidly progressive dementias—aetiologies, diagnosis and management. Nature Reviews Neurology, 18(6), 363-376.



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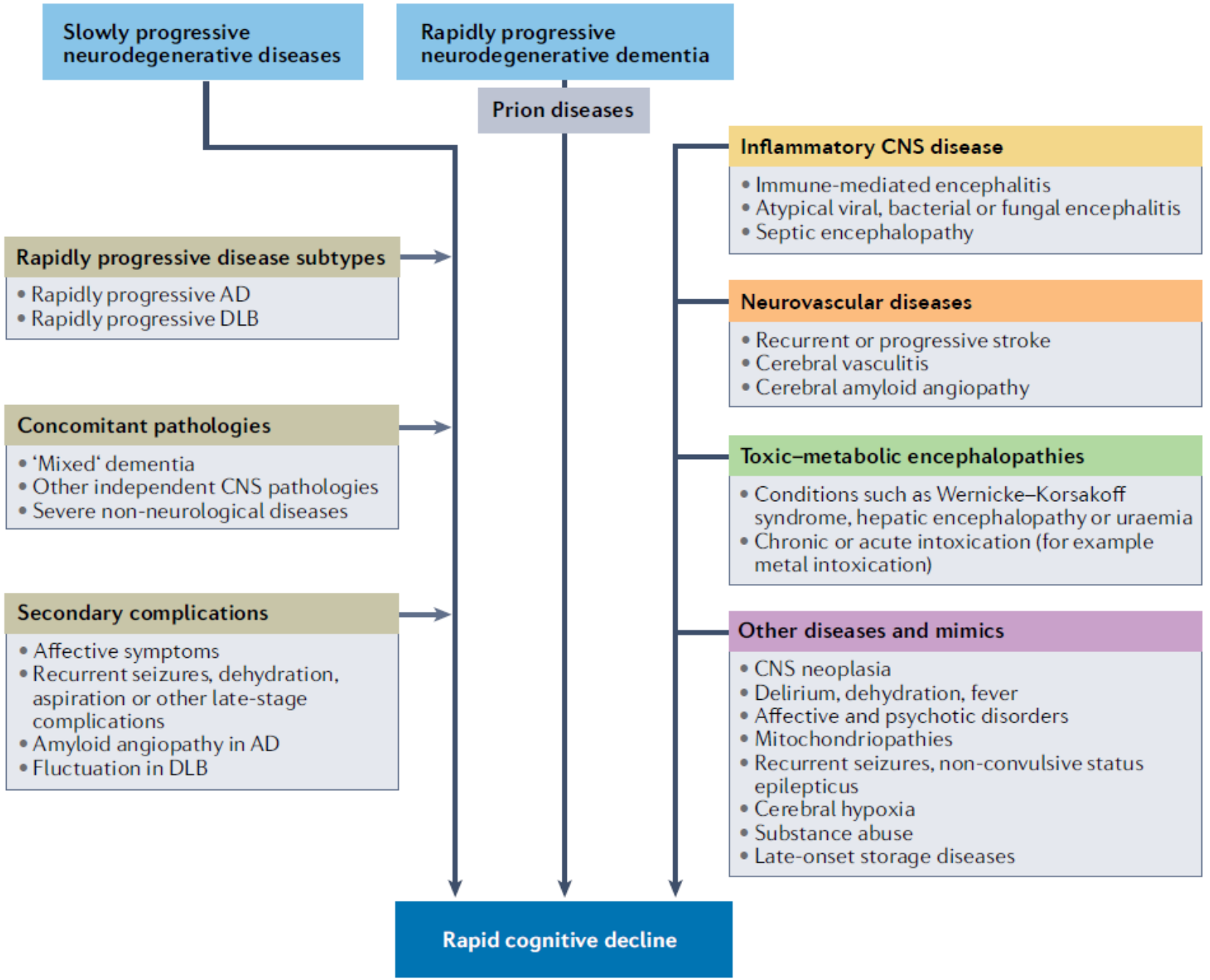

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Treatment

History and physical examination

Standard Investigations

Advanced Investigations

History and physical examination

Patient history

- Age at onset
- Speed of cognitive decline
- Medical history
- Type of cognitive deficit
- Other specific symptoms

Physical examination

- Level of consciousness
- Focal neurological signs
- Other systemic illness

Look for specific characteristics

Identify acute conditions such as delirium, intoxication or stroke

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Standard Investigations

Blood tests:

- Inflammation
- Infection : HIV, syphilis or other pathogens
- Metabolic include kidney and liver functions
- Thyroid hormones
- Vitamin B

Imaging:

- Inflammation, vascular, tumours, metal deposition
- Atrophy
  - CT brain: exclude IICP
  - MRI with gadolinium

Cerebrospinal fluid:

- Infection / Inflammatory processes
- Specific autoantibody
- Protein biomarkers
  - Alzheimer disease: tau, phosphorylated tau and amyloid- β_{42}
  - Creutzfeldt–Jakob disease: 14-3-3 protein and real-time quaking-induced conversion (RT-QuIC))
- Cytopathology

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Advanced Investigations

EEG:

- Abnormal patterns
- Non-convulsive status epilepticus

Biomaterials:

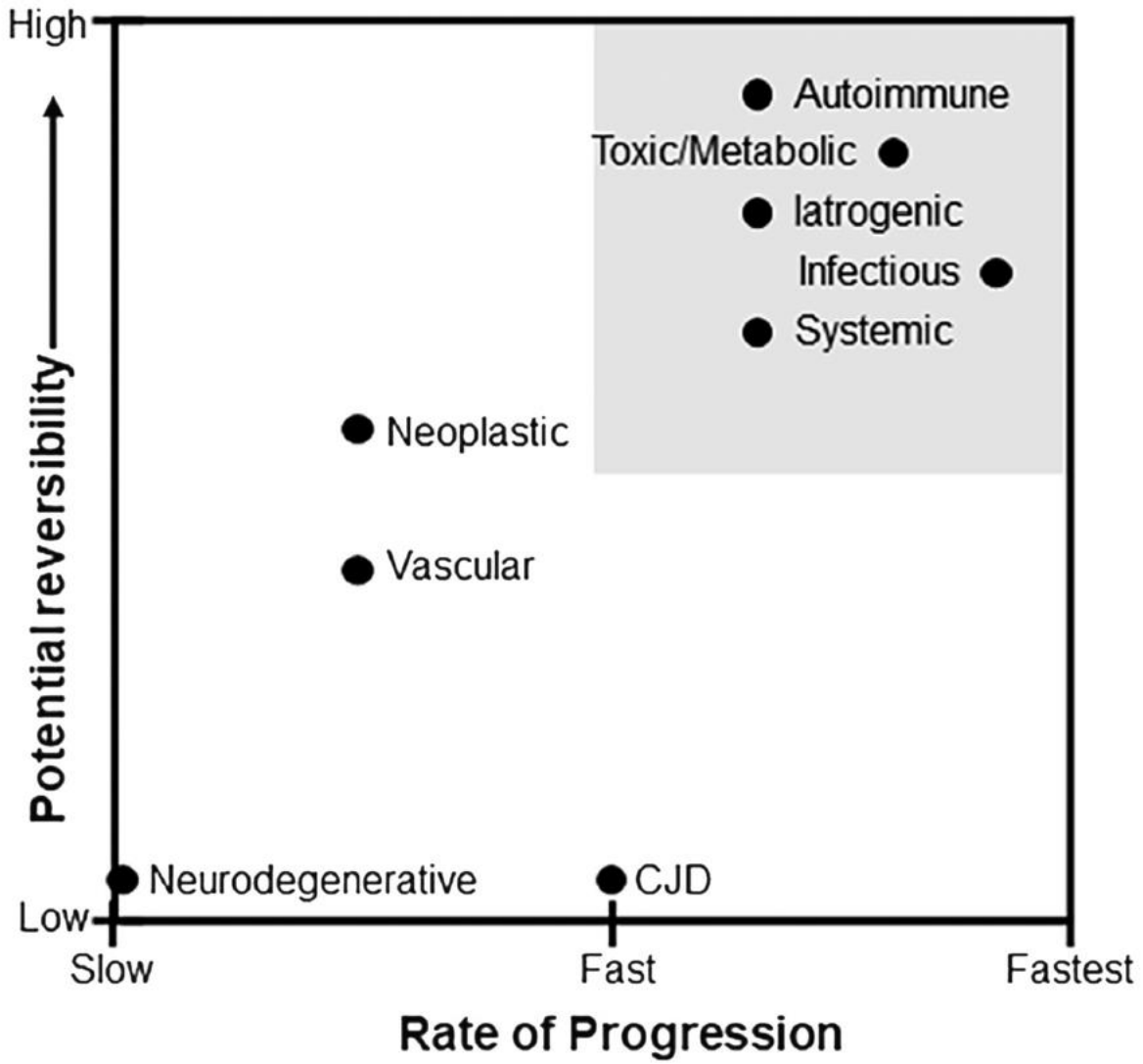
- Rare storage and other hereditary diseases
- Skin biopsy, genetic or enzyme

Imaging:

- 18F- Fluorodeoxyglucose PET
- Amyloid and tau PET
- Whole- body PET−CT to detect non- CNS neoplasia

Tissue pathology:

- Brain, leptomeningeal, skin



Day, G. S. (2022). Rapidly progressive dementia. CONTINUUM: Lifelong Learning in Neurology, 28(3), 901-936.

Rapidly progressive dementia etiology	General abnormalities on examination	Neurologic abnormalities on examination						
		Focal cranial nerves	Upper motor neuron signs[a]	Lower motor neuron signs[b]	Extrapyramidal[c]	Myoclonus	Sensory	Ataxia
Vascular	Stigmata of systemic vasculitis	+	++	-	-	+	+ (cortical)	+
Infectious	Fever, vital sign changes, meningismus, rigors, lymphadenopathy, other organ dysfunction	++	++	+	-	+	+	-
Toxic-metabolic	Cachexia/weight loss, prominent psychosis, stigmata of liver disease, myxedema, asterixis, other organ dysfunction	+	-	-	+	++	+	++
Autoimmune/ inflammatory	Stereotyped movements (eg, faciobrachial dystonic seizures), joint inflammation, skin rash/ ulceration, other organ dysfunction	-	++	+	-	++	+ (cortical)	+

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		Focal cranial nerves	Upper motor neuron signs[a]	Lower motor neuron signs[b]	Extrapyramidal[c]	Myoclonus	Sensory	Ataxia
Metastases/ neoplastic	Cachexia/ weight loss, lymphadenopathy, other organ dysfunction	+	++	+	-	-	+	+
Iatrogenic	Other organ dysfunction	-	+	-	+	-	-	+
Neurodegenerative	Cachexia/ weight loss	-	+	-	+	+	+ (cortical)	+
Systemic/ seizures/structural	Stereotypical gait changes (hydrocephalus), involuntary movements, unexplained alterations in consciousness	-	+	-	-	-	-	-

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Results of Routine CSF Tests and Diagnostic Associations

Etiology	Routine CSF tests			
	Nucleated cells	Protein	Glucose	Oligoclonal bands/ IgG index
Vascular				
Ischemic	↔	↑	↔	↔
Hemorrhagic	↑	↑	↔	↔
Vasculitis	↑↑	↑	↔	↔
Infectious				
Bacterial	↑↑↑	↑↑	↓↓	↑/↔
Viral	↑↑	↑↑	↔	↑/↔
Fungal	↑↑	↑	↓↓	↑/↔
Toxic-metabolic	↔	↑/↔	↔	↔
Autoimmune/inflammatory	↑↑	↑/↔	↔/↓	↑/↔
Metastases/neoplastic	↑/↔	↑/↔	↔	↔
Iatrogenic	↔	↔	↔	↔
Neurodegenerative	↔	↑/↔	↔	↔
Systemic/seizures/structural	↔	↑/↔	↔	↔

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CJD

- Prion is virus-liked organism
- Infectious prion attack nerve cell
- Mode of transmission : contaminated medical equipment & nervous tissue
- Incidence 2 per million person-years
- Sporadic CJD (sCJD) is the most common prion diseases
- sCJD is characterized clinically by RPD with ataxia, myoclonus or other neurological signs, and neuropathologically by the presence of aggregates of abnormal prion protein (PrPSc), spongiform change, neuronal loss and gliosis
- The most common subtypes are MM1/MV1 and VV2
- MM1/MV1 include rapid cognitive decline and cortical anopsia (the so- called Heidenhain variant), followed closely by ataxia, myoclonus or other involuntary movements
    - Death within 4–5 months.
- CSF analysis, MRI and EEG
- EEG : periodic sharp and slow wave complexes
- MRI : hyperintensities in FLAIR / DWI
- Biomarker : 14-3-3 protein and the phosphorylated tau (p- tau) to tau ratio as markers of neuronal damage.

Rapidly progressive dementia during COVID-19 pandemic

- Mimic RPD
- Worsening of pre-existing cognitive deficits
- Increased risk of severe COVID-19 among patients with dementia

Common manifestations

1. Delirium
2. Toxic–metabolic encephalopathies
3. Post-infectious and para-infectious encephalitis
4. Cerebral hemorrhage / thrombosis
5. Encephalomyelitis

Helms, J. et al. Neurologic features in severe SARSCoV-2 infection. N. Engl. J. Med. 382, 2268–2270(2020).
Paterson, R. W. et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 143, 3104–3120 (2020).
Frontera, J. A. et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 96, e575–e586 (2021).
Numbers, K. & Brodaty, H. The effects of the COVID-19 pandemic on people with dementia. Nat. Rev. Neurol.17, 69–70 (2021).

Take Home messages

- Definitions vary
- Prion disease, neurodegenerative diseases, inflammatory (immune- mediated and infectious), vascular, metabolic and neoplastic CNS diseases are important and frequent causes
- Identify treatable causes → MRI and analyses of blood and CSF
- Therapeutic options could become option in the near future