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CIRN
Centro Interuniversitario di Ricerca per le Neuroscienze

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

CRC per la Diagnosi e Sorveglianza delle Malattie da Prioni dell'Uomo

Demenze Rapidamente Progressive

Gianfranco Puoti

CONVEGNO SIN CAMPANIA

Focus su novità diagnostiche e terapeutiche

Napoli, 13 dicembre 2019
Aula Magna G. Salvatore AOU Federico II

Rapidly progressive dementia (RPD)

- **No formal definition exists for what constitutes a rapidly progressive dementia (RPD), generally we use the term when dementia occurs in less than 1–2 years from illness onset, but more commonly over weeks to months.**

- **Prevalence of RPD in a Tertiary care dementia referral center : 2%**

DEMOGRAFICS
- Gender: F=M
- Mean Age: 67,8 yrs ± 11 (41-86)
- Disease duration: 6,4 mth ± 5

Tagliapietra et al, JAD 2013

- **Prion diseases are the prototypical causes of RPD…**

…but reversible causes of RPD might mimic prion disease and should always be considered in a differential diagnosis

At first: exclude delirium !!

DSM-5 criteria for delirium

A) A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

B) The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

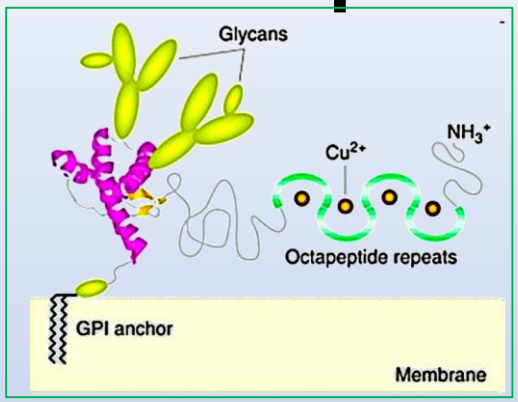
C) An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).

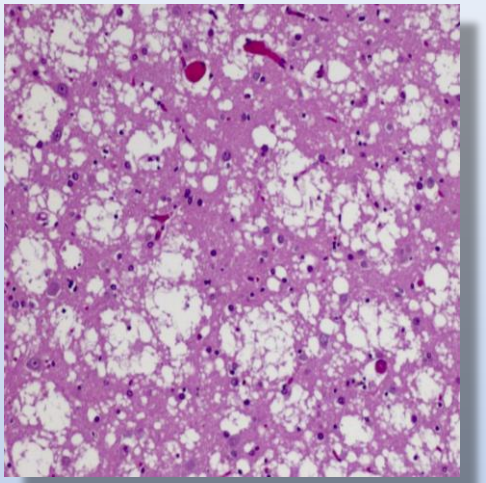
D) The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

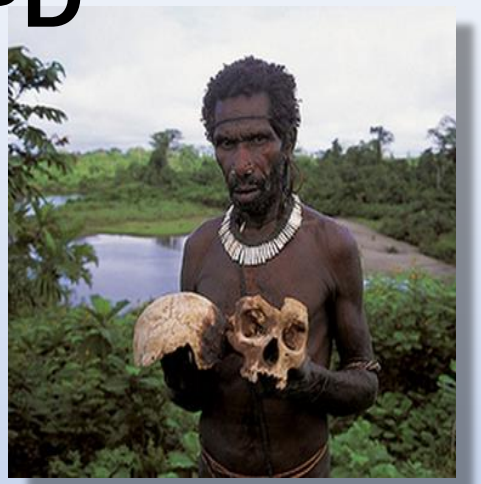
E) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Prion diseases are the prototypical causes of RPD

Prion Protein (PrP)







Human Prion Diseases

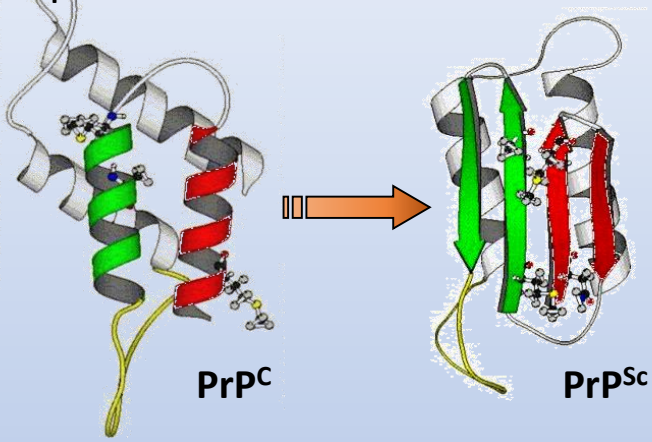
Sporadic (80-85%)
- ✓ Sporadic Creutzfeldt-Jakob (sCJD)
- ✓ Sporadic Fatal Insomnia (sFI)
- ✓ Variably Protease Sensitive Prionopathy (VPSPr)

Genetic (10-15%)
- ✓ Familial Creutzfeldt-Jakob familiare (fCJD)
- ✓ Fatal Familial Insomnia (FFI)
- ✓ Gerstmann-Staussler-Sheinker disease (GSS)

Transmissible (≃1%)
- ✓ Iatrogenic Creutzfeldt-Jakob
- ✓ New variant Creutzfeldt-Jakob disease (nvCJD)
- ✓ Kuru

‘Protein only hypothesis’

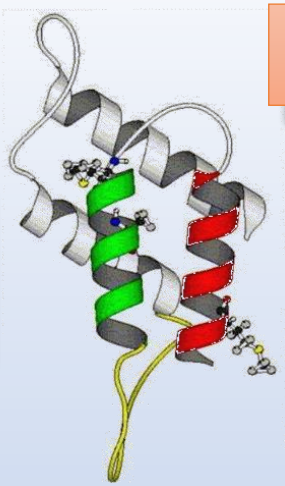
Prions, the causative agents of transmissible spongiform encephalopathies, appear to consist entirely of PrP^{Sc}, an orderly aggregated, β sheet–rich isoform of a ubiquitous membrane protein termed PrP^{C}.



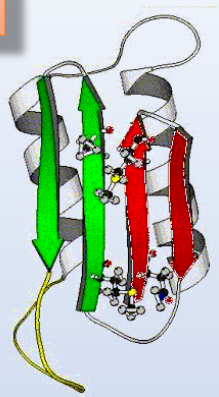
‘Prion’ concept

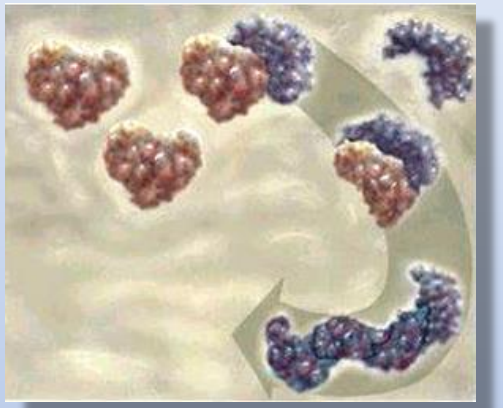
- a self-propagating state of a protein (the prion) that is biologically accessible but rarely formed spontaneously
- Prions replicate themselves by acting on their nonprion substrate protein
- Prions spread to naive hosts and find new substrate pools for replication.
- Prions also cause phenotypic changes in the host.
- Replication can be maintained over multiple serial passages from one animal to another
- Prions are usually partially proteinase K (PK) resistant
- Prions are usually insoluble in nonionic detergents.

PrP conversion…



PrP^{C} ⟹ PrP^{Sc}

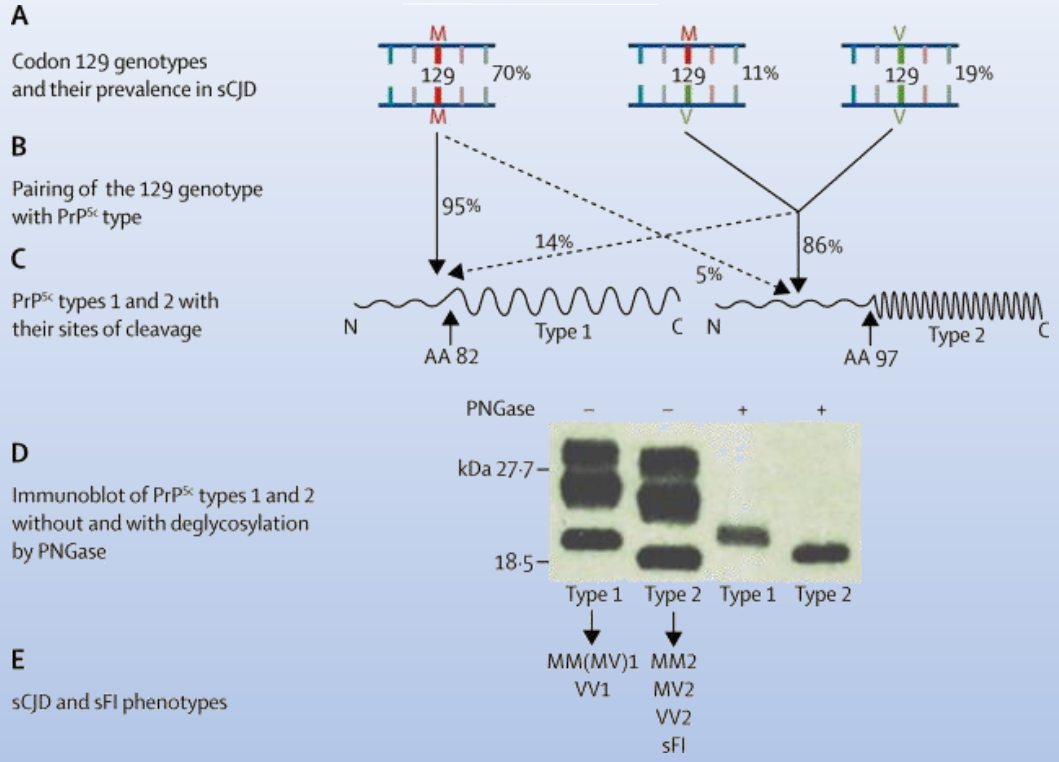




…represents the key molecular event of prion diseases

- stochastic event in the **sporadic** forms
- induced by exogen PrP^{Sc} in the **iatrogenic or transmitted** forms
- as consequence of mutated PrP instability, in the **familial** forms

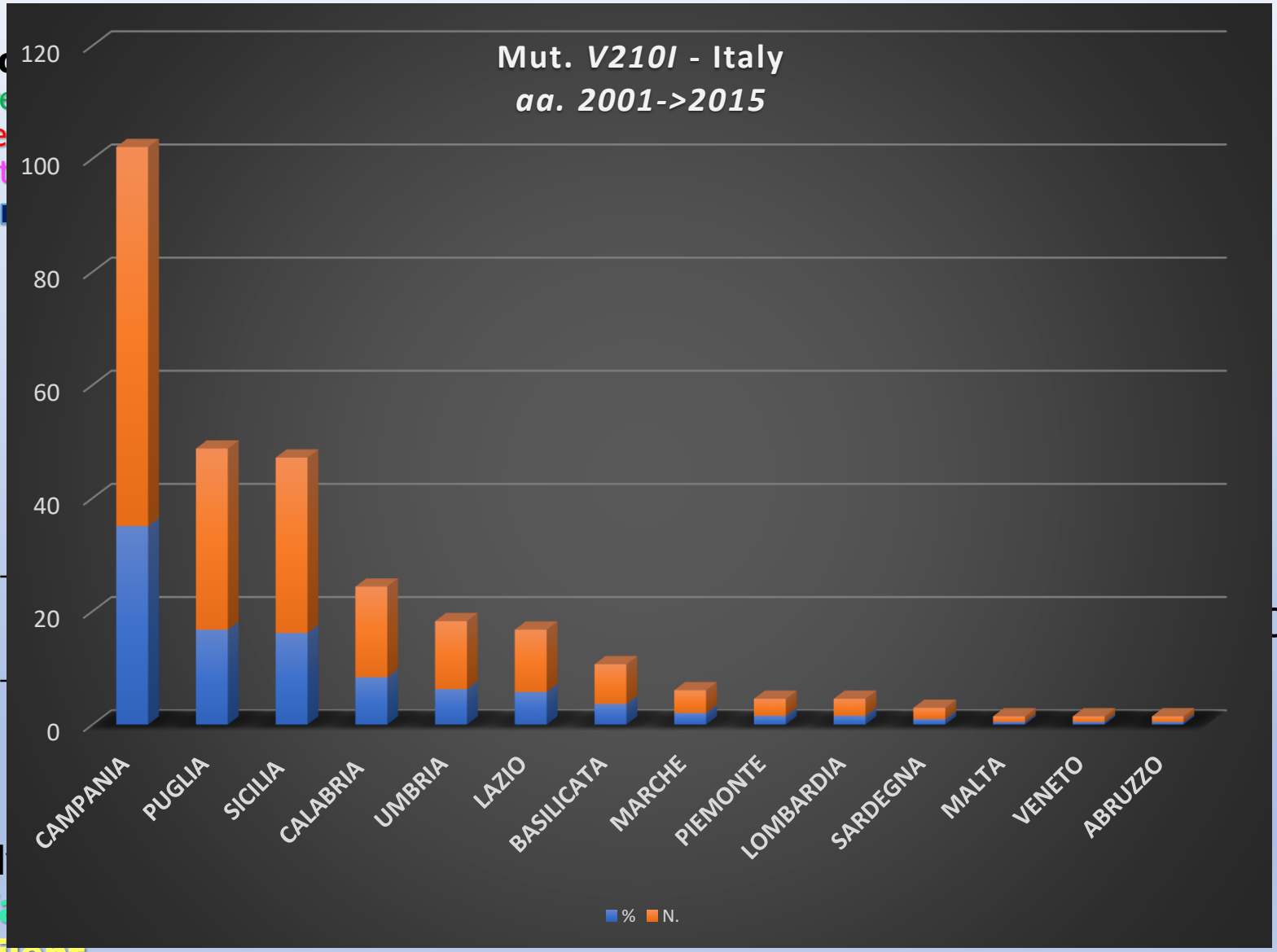
Rerationship between PrP genotype, determined by MV-polymorphism at codon 129, and type 1 or 2 PrP^{Sc}



(A) Diagrammatic representation of each of the three 129 genotypes (MM, MV, and VV) with their average relative prevalence in all subtypes of sCJD.
(B) PrP^{Sc}type 1 is associated with the 129MM genotype in about 95% of cases, whereas MV and VV genotypes are associated with PrP^{Sc} type 2 in about 86% of cases.
(C) Diagrammatic representation of PrP^{Sc} types 1 and 2; each consists of an amino-terminal region (N) of different size that is protease-sensitive and is digested down to amino acid (AA) 82 in type 1 and to amino acid 97 in type 2 (arrows). The different cleavage site is thought to be the result of the different conformation in PrP^{Sc} types 1 and 2.
(D) Types 1 and 2 PrP^{Sc} have distinct electrophoretic mobilities because of the different size of their respective protease-resistant fragments.
(E) Both 129 genotype and PrP^{Sc} types are thought to act as determinants of the phenotypes of sporadic prion diseases that are commonly identified with letters and numbers to indicate the associated genotype and PrP^{Sc} type.

adapted from *Puoti G. et al. Lancet Neurology 2012*

Genetic forms (10-15%)

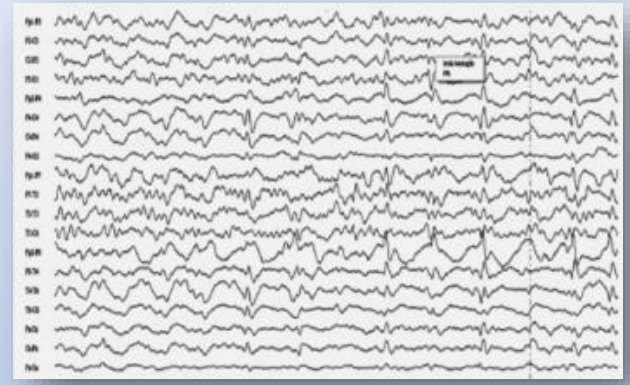


*Mutations with two or more known haplotypes

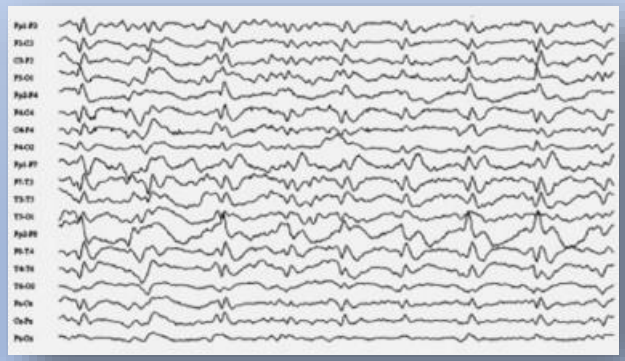
Creutzfeldt-Jakob disease

Diagnosis

EEG

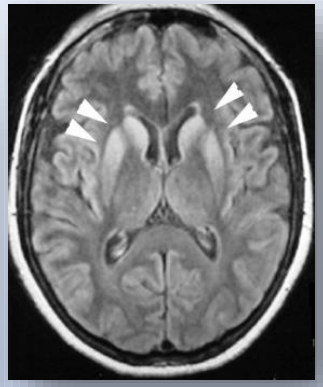


Periodic lateralized epileptiform discharges (PLEDs) in the right hemisphere, with some widespread

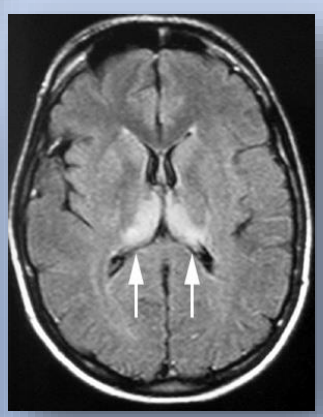


Generalized periodic epileptiform discharges (GPEDs)or periodic sharp-waves complexes

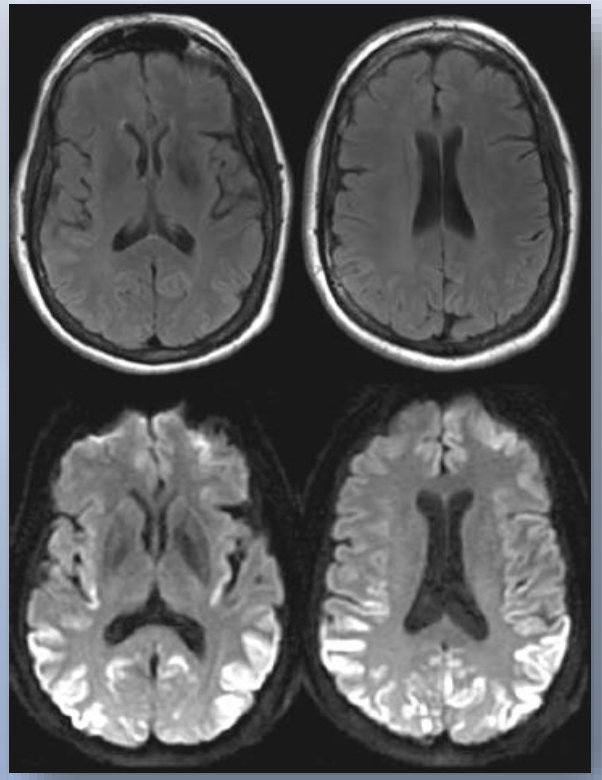
MRI



FLAIR MRI showing bilateral anterior basal ganglia high signaling a sCJDVMM1 patient



FLAIRMRIshowingbilateralandsymmetricalhighsignalinthepulvinarnucleiofthethalamus-the '*pulvinar sign*' of variant CJD



FLAIR MRI (row above) and DWI (row below) in a sCJDVV11 patient. Note the much more prominent signal hyperintensity in the cortical ribbon on DWI c/w FLAIR images.

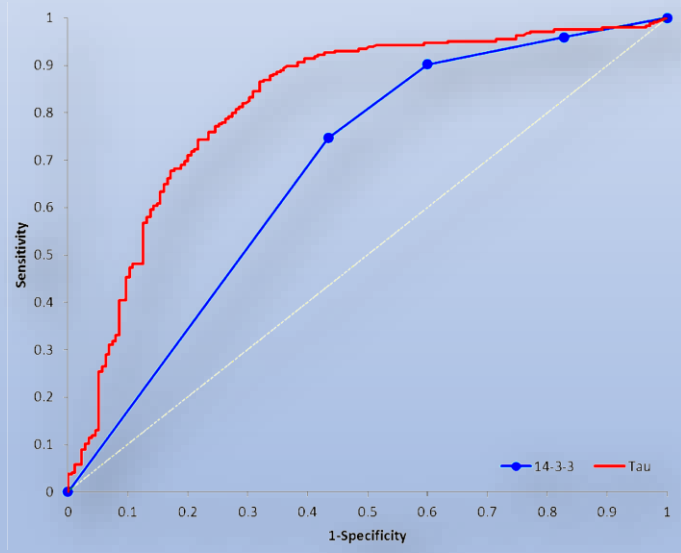
Creutzfeldt-Jakob disease

Diagnosisi

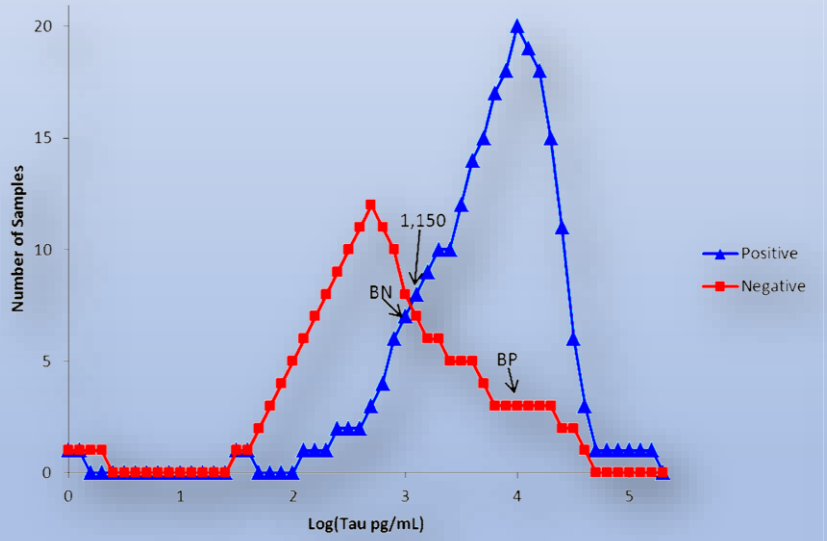
A comparison of CSF Tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease

Hamlin C, Puoti G. Berri S . Neurology 2012

Receiver operating characteristic (ROC) curves for tau and 14-3-3 protein



Histogram of distribution of tau values (log) per 0.1 log unit



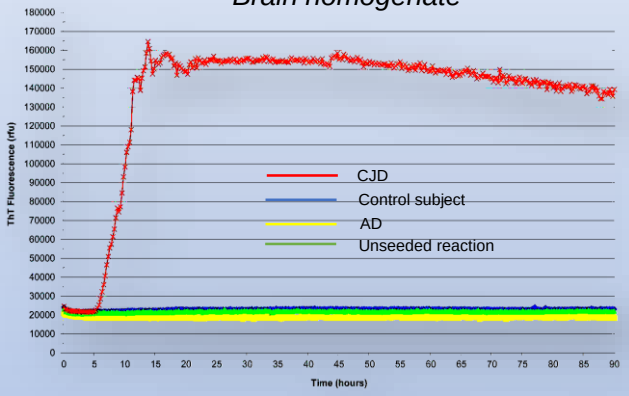
Creutzfeldt-Jakob disease

Diagnosis

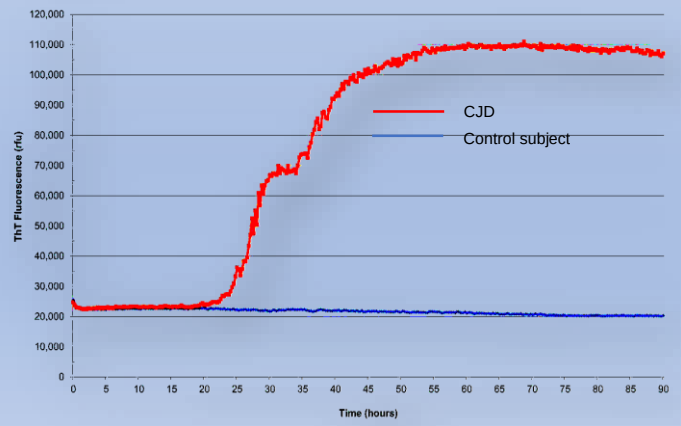
Real-time quaking-induced conversion (RT-QuIC)

This technique exploits the ability of PrPSc to induce PrPC to misfold in a cyclical fashion to form aggregates of PrPSc fibrils. The formation of these aggregates is monitored in real time by their ability to bind a fluorescent dye, namely thioflavin T

Brain homogenate



CSF



Key Points

- CSF RT-QuIC is a highly sensitive and specific test for sporadic Creutzfeldt-Jakob disease (sCJD).
- It is not affected by age at onset of disease or PRNP codon 129; however, it may be less sensitive in the rarer forms of sCJD such as MM2 with cortical changes and VV1.
- Of those patients who are negative for CSF RT-QuIC, 90% have an alternative positive diagnostic investigation, such as CSF Tau or 14-3-3, the presence of cortical ribboning and/or basal ganglia changes on MRI or triphasic waves on electroencephalogram.
- The interpretation of CSF RT-QuIC is hampered by the presence of elevated red cell counts (>1250 x 10^6/L), white cell counts (>10 x 10^6/L) and raised total protein concentrations (>1 g/L).

Creutzfeldt-Jakob disease

Diagnosis

Diagnostic criteria for surveillance of sporadic Creutzfeldt-Jakob disease from 1 January 2017

Mackenzie and will. Verson 1. F1000Res. 2017;6:2053

1.1	DEFINITE:		
	Progressive neurological syndrome AND		
	Neuropathologically or immunohistochemically or biochemically confirmed		
1.2	PROBABLE:		
	1.2.1	I + two of II and typical electroencephalogram[a]	
OR	1.2.2	I + two of II and typical magnetic resonance imaging brain scan[b]	
OR	1.2.3	I + two of II and positive cerebrospinal fluid (CSF) 14-3-3	
OR	1.2.4	Progressive neurological syndrome and positive real-time quaking-induced conversion in CSF or other tissues	
1.3	POSSIBLE:		
	I + two of II + duration <2 years		
I	Rapidly progressive cognitive impairment		
II	A	Myoclonus	
	B	Visual or cerebellar problems	
	C	Pyramidal or extrapyramidal features	
	D	Akinetic mutism	

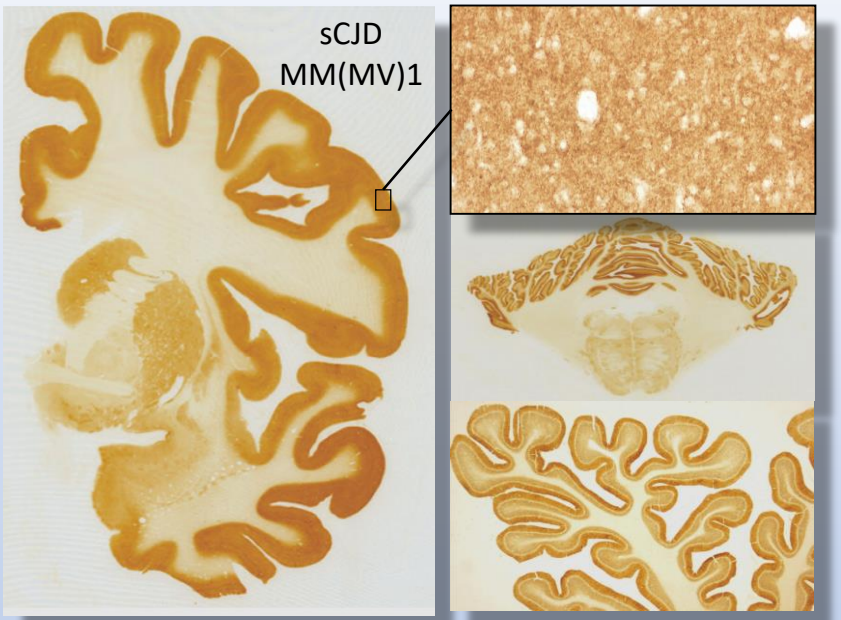
[a]Generalised periodic complexes. [b]High signal in caudate/putamen on magnetic resonance imaging brain scan or at least two cortical regions (temporal, parietal, occipital) on either diffusion-weighted imaging or fluid-attenuated inversion recovery.

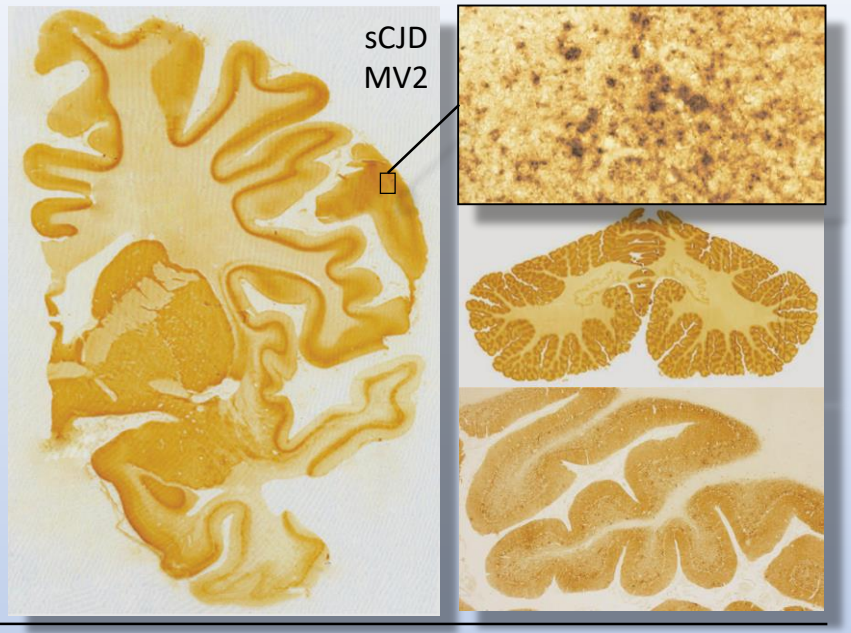
Sporadic prion diseases – Clinical heterogeneity

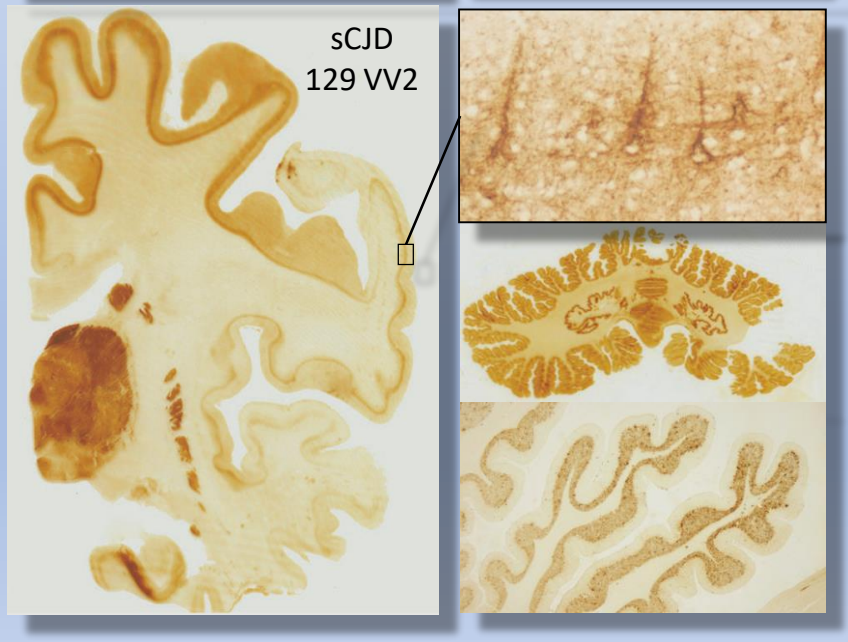
Puoti G. et al. Lancet Neurology 2012

	Sporadic familial insomnia	Variably protease-sensitive prionopathy			
	MM2 (n=31)	VV (n=21)	MV (n=9)	MM (n=3)*	All genotypes (n=33)
Age at onset (years)	46 (13, 24–74)	67 (9, 48–77)	74 (5, 65–81)	78 (12, 64–87)	70 (9, 48–87)
Duration (months)†	24 (13, 10–73)	18 (15, 10–60)	34 (25, 7–73)	41 (9, 10–73)	24 (10, 7–73)
Presentation					
Cognitive decline	13/31 (42%)	12/21 (57%)	6/9 (67%)	0/3	18/33 (55%)
Ataxia	13/31 (42%)	0/21	0/9	1/3 (33%)	1/33 (3%)
Insomnia	9/31 (29%)	..	..	..	..
Psychiatric	8/31 (26%)	14/21 (67%)	6/9 (67%)	1/3 (33%)	21/33 (64%)
Visual signs	7/31 (23%)	..	..	..	..
Dysautonomia	1/31 (3%)	..	..	..	..
Aphasia	..	11/21 (52%)	1/9 (11%)	1/3 (33%)	13/33 (39%)
Parkinsonism	..	2/21 (10%)	0/9	1/3 (33%)	3/33 (9%)
Advanced stage					
Cognitive decline	31/31 (100%)	21/21 (100%)	9/9 (100%)	3/3 (100%)	33/33 (100%)
Ataxia	22/31 (71%)	10/21 (48%)	2/9 (22%)	1/3 (33%)	13/33 (39%)
Insomnia	14/31 (45%)	..	..	..	..
Psychiatric	14/31 (45%)	18/21 (86%)	6/9 (67%)	1/3 (33%)	25/33 (76%)
Visual signs	13/31 (42%)	..	..	..	..
Pyramidal signs	9/31 (29%)	..	..	..	..
Dysautonomia	6/31 (19%)	..	..	..	..
Aphasia	..	12/21 (57%)	1/9 (11%)	2/3 (67%)	15/33 (45%)
Parkinsonism	..	8/21 (38%)	3/9 (33%)	3/3 (100%)	14/33 (42%)
Myoclonus	32% (30)	12% (16)	22% (9)‡	100% (2)‡	22% (27)‡
EEG sensitivity§	7% (27)	0% (16)	25% (4)	50% (2)	9% (22)
CSF sensitivity§¶	13% (15)	37% (8)	0% (4)	50% (2)	21% (14)
MRI sensitivity§‖	8% (26)**	5% (20)	0% (9)	0% (2)	3% (31)

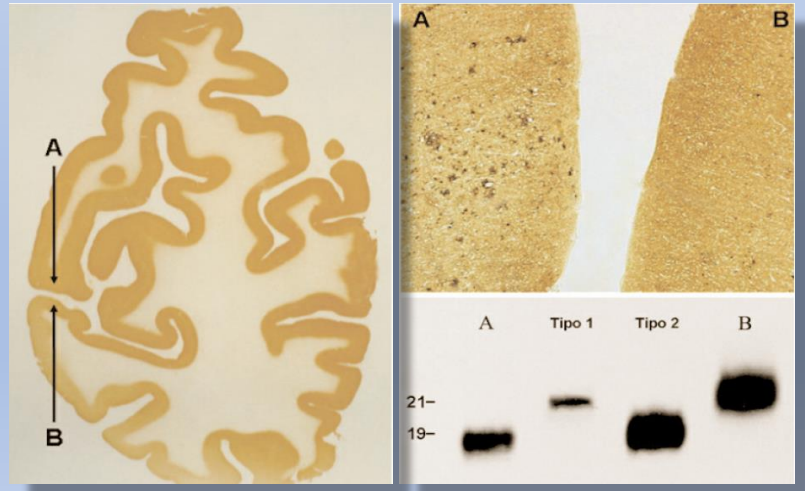
Sporadic prion diseases – Neuropathological heterogeneity





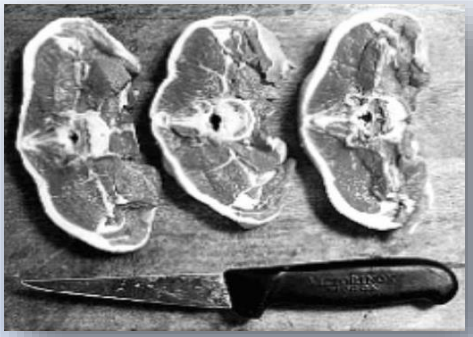


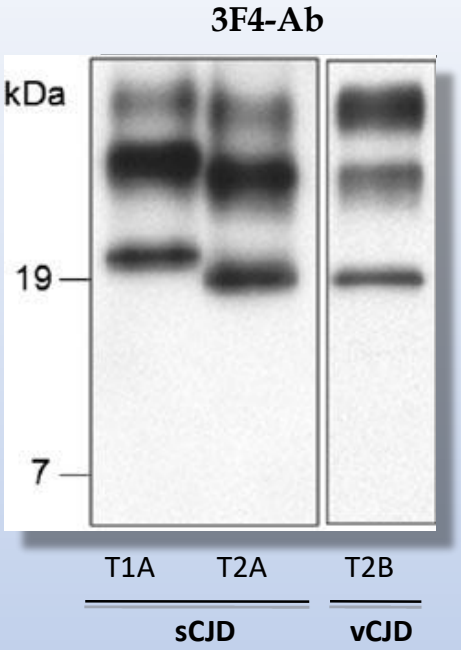
sCJD MM 1+2
(*PrP^{Sc} co-occurrence*)



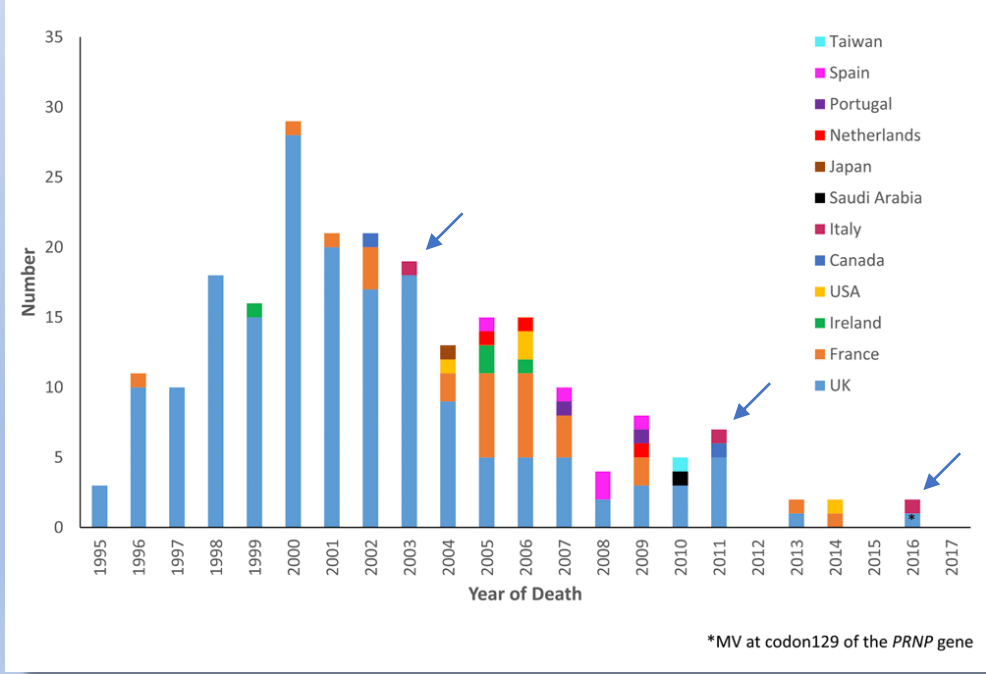
adapted from *Puoti G. et al. Neurology 1999 and J Neuropath Exp Neurol 2005*

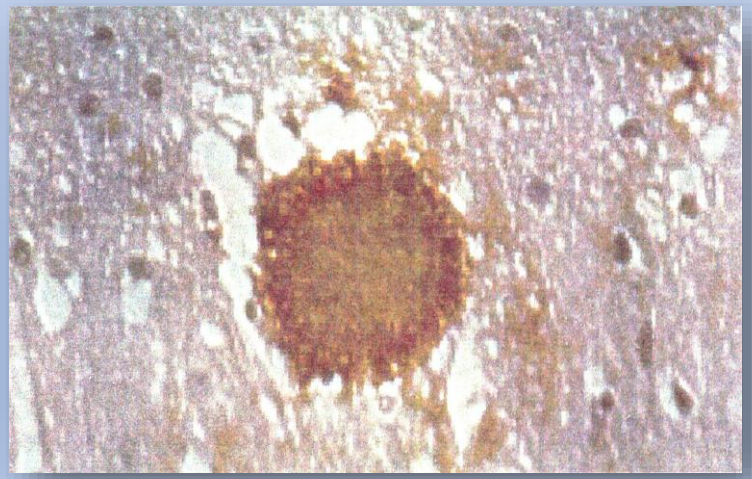
BSE and nvCJD





Variant Creutzfeldt-Jakob disease cases by year and country



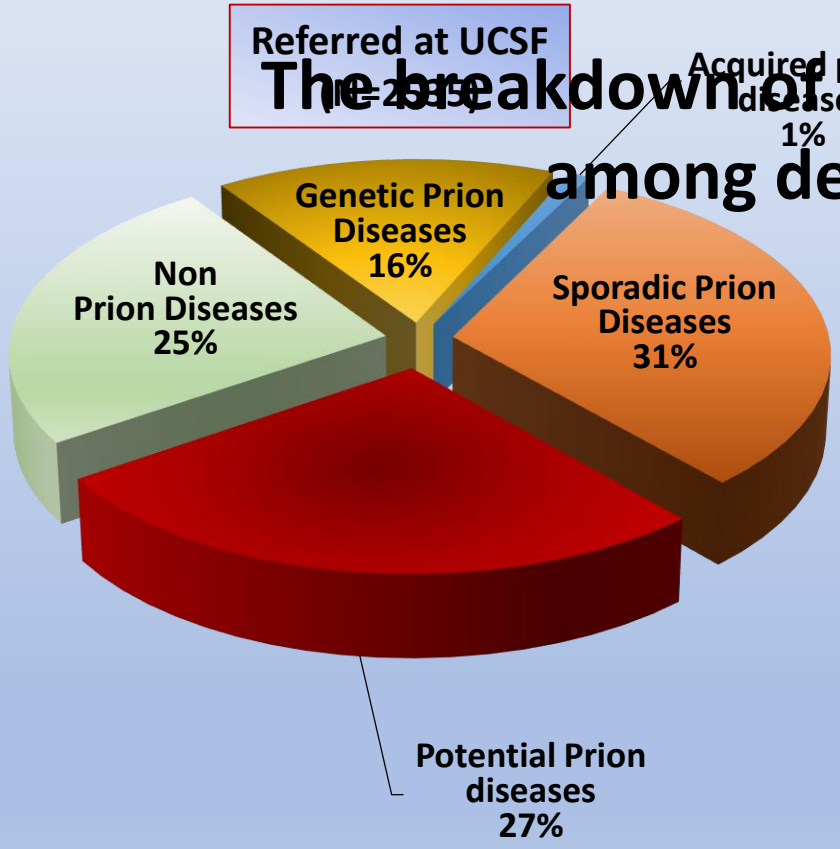


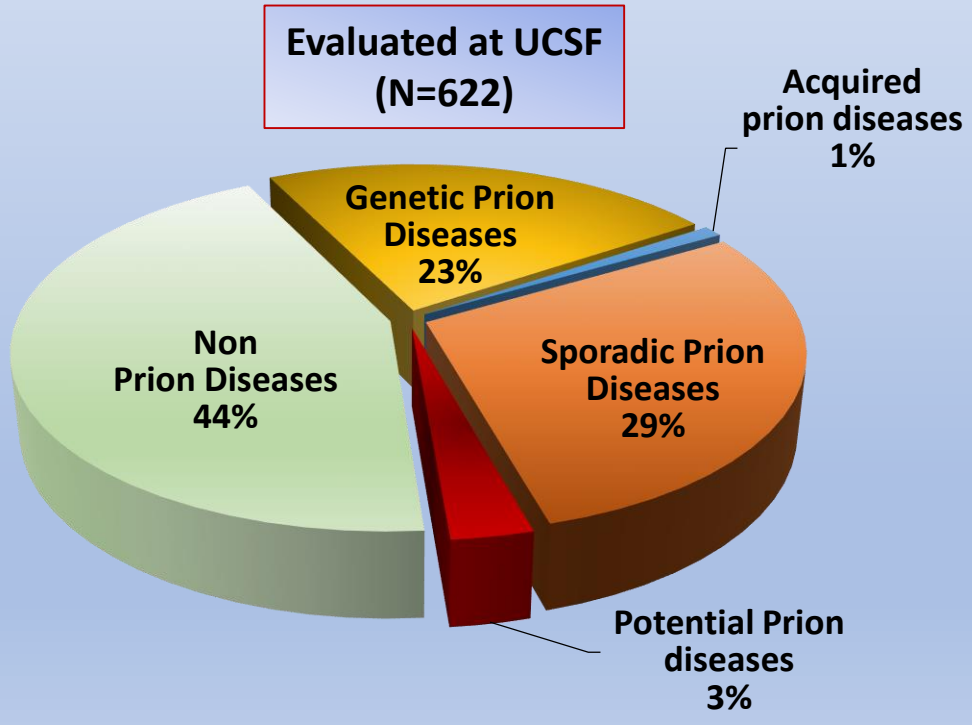
Mackenzie G and Will R. Creutzfeldt-Jakob disease: recent developments [version 1]. F1000Research 2017, 6:2053

Etiologies of RPDs

Major diagnostic categories of patients with rapidly progressive dementia (RPD) referred to, versus evaluated at the University of California, San Francisco (UCSF) rapidly progressive dementia program over 13 years.

The breakdown of etiologies of RPDs varies among dementia centers

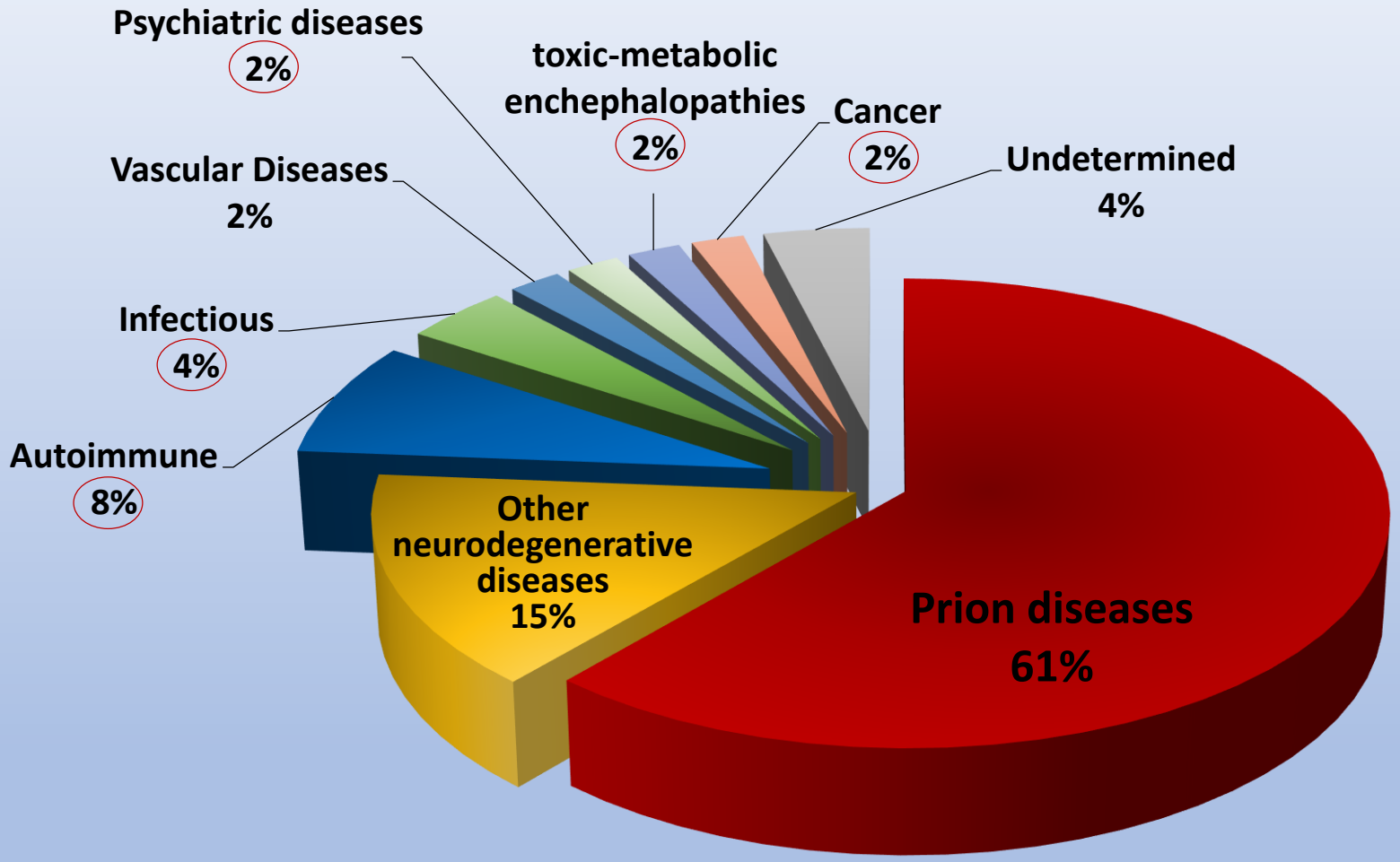




Michael D. Geschwind Continuum 2016

The breakdown of etiologies of RPDs at University of California, San Francisco, Memory and Aging Center

Peterson RW et al. Neurology®Clinical Practice 2012



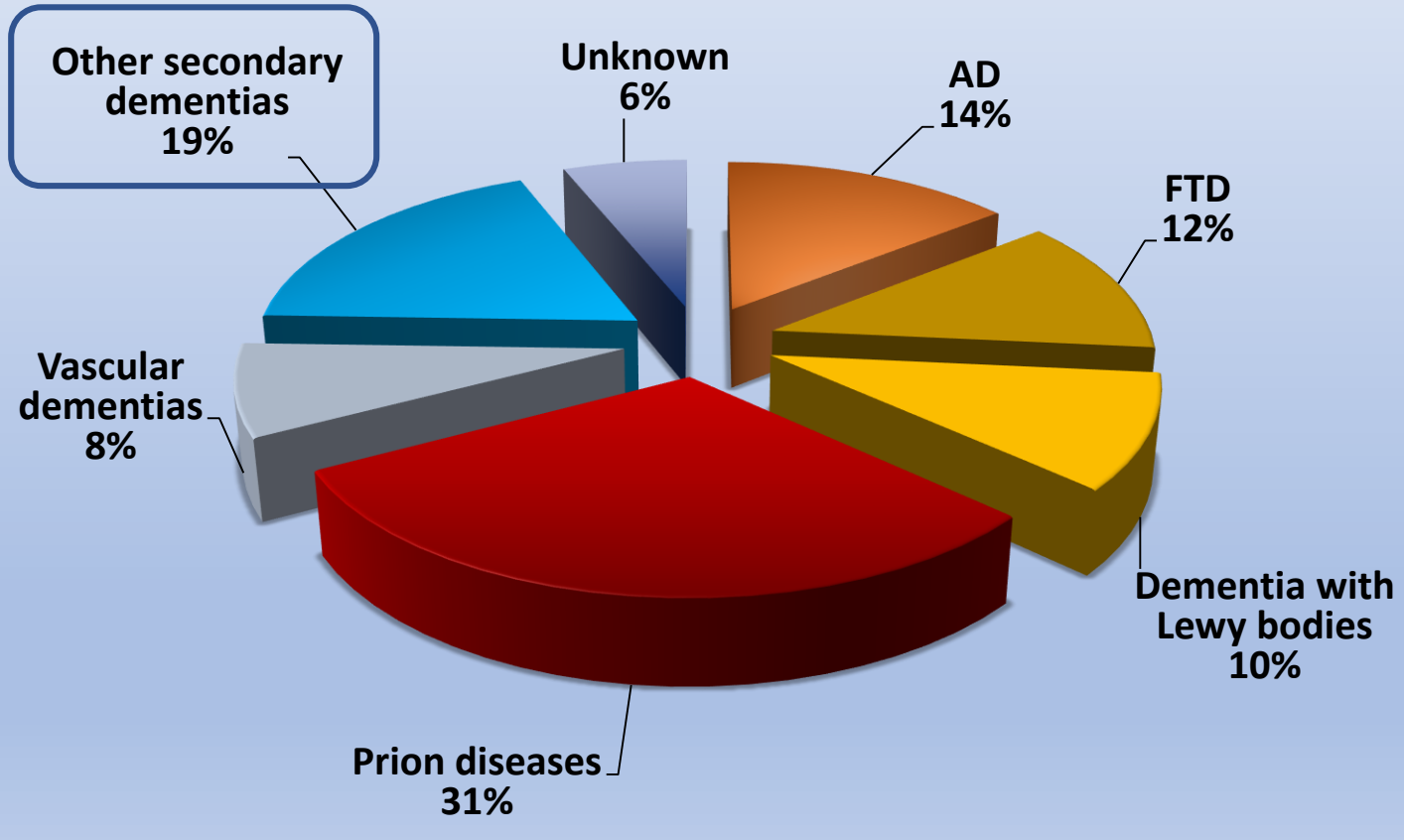
18% had potentially treatable etiologies

(50% autoimmune, 13% each infectious, psychiatric, and cancer, and 10% toxic-metabolic)

Causes of Rapidly Progressive Dementia in a major tertiary care dementia referral center in Spain

Barcelona Cohort (n. 49)

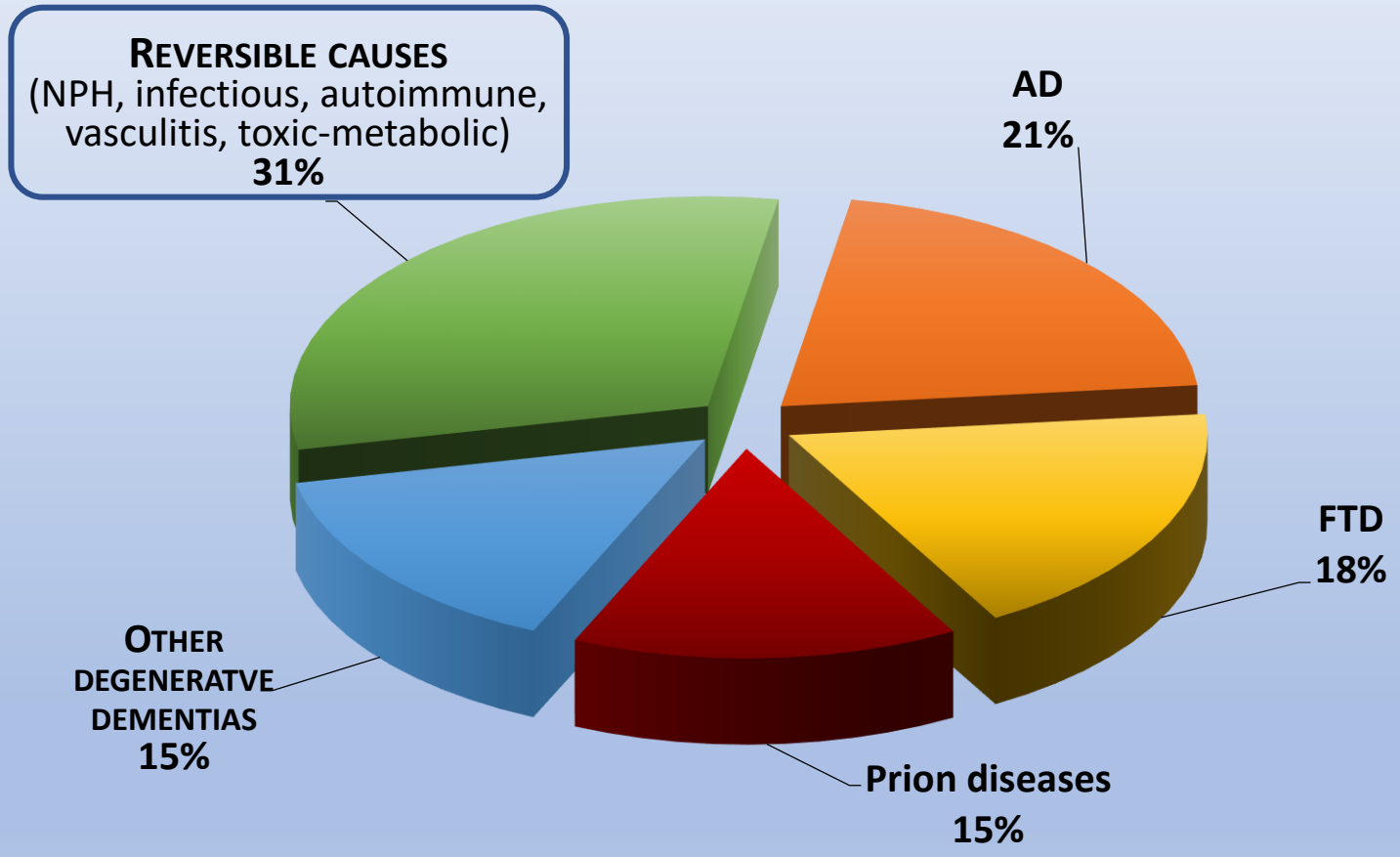
Sala I et al. Alzheimer Dis Assoc Disord 2012



Causes of Rapidly Progressive Dementia in a major tertiary care dementia referral center in Greece

Athens Cohort (n. 68)

Papageorgiou SG et al. Alzheimer Dis Assoc Disord 2009



US National Prion Disease Pathology Surveillance Center (CWRU - Cleveland, Ohio)

…which treatable disorders are most commonly mistaken for CJD

1,106 Patients autopsied *(aa. 2006-2009)*

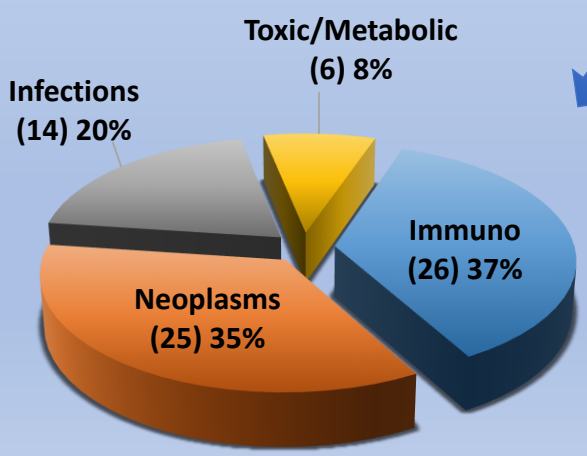
754 prion Positive Cases

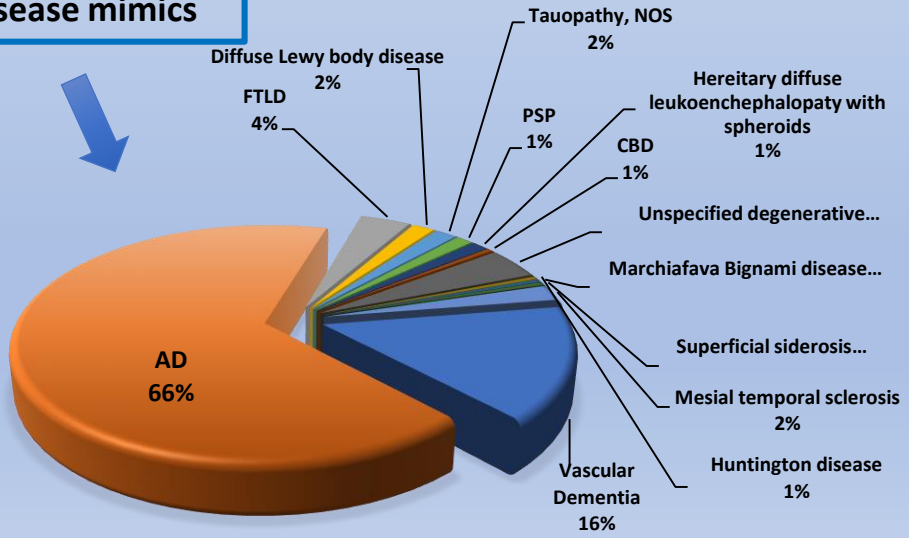
352 Negative Cases

48 Insufficient tissue

71 (23%) with potentially treatable diagnosis

233 (77%) with incurable prion disease mimics



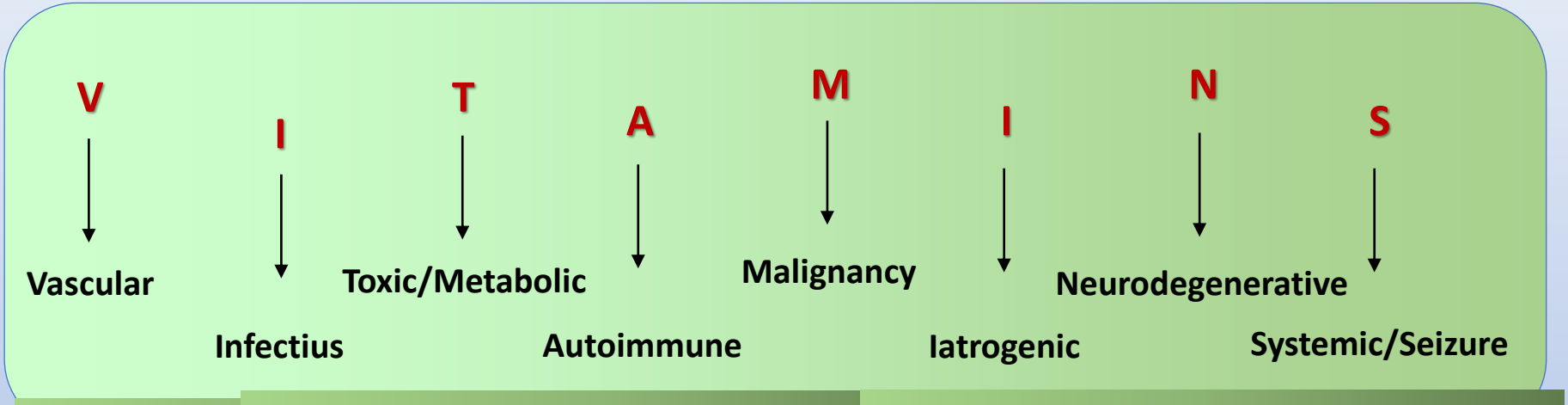


Chitravas et al. Ann Neurol 2011

Rapidly Progressive Dementia

Michael D. Geschwind Continuum 2016

ETIOLOGIC CATEGORY



VAS

- Multi-infarct V
- Strategic Infar
- Inflammatory
- Primary CNS angiitis
- Cerebral venous sinus thrombosis

- Limbic
- NMDA-
- VGKC antibodies encephalopath
- Acute demielinating encephalon

MALIGNA

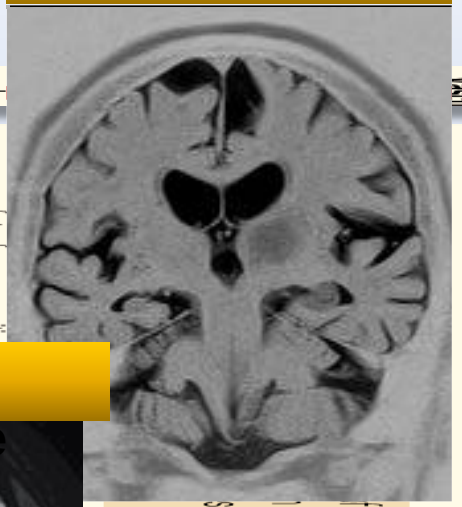
- Primary lymphoma o
- Gliomatosis cerebri

nyria

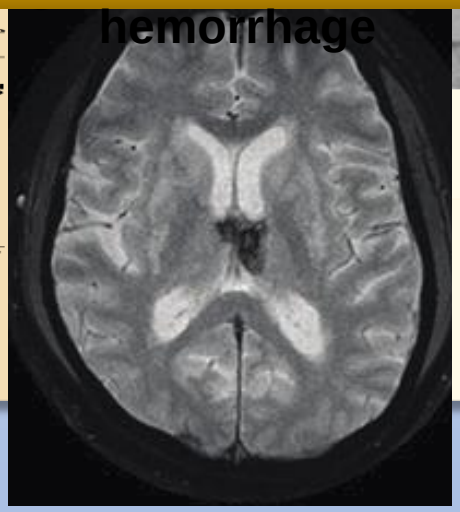
NEURODEGENERATIVE

- Prion diseases
- Alzheimer's disease
- LBD
- FTD
- CBS

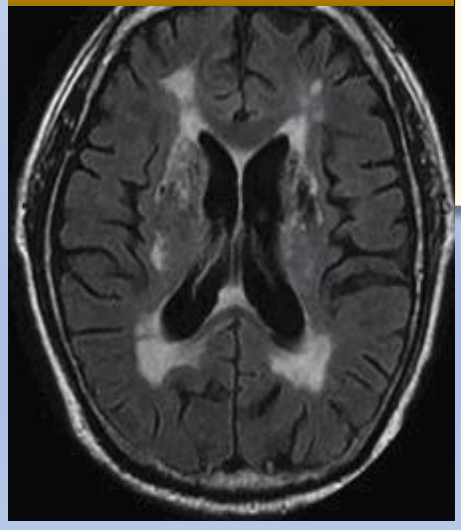
Strategic stroke



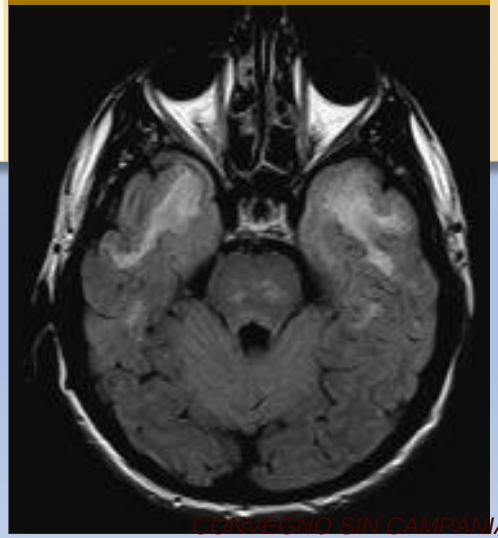
Thalamic hemorrhage



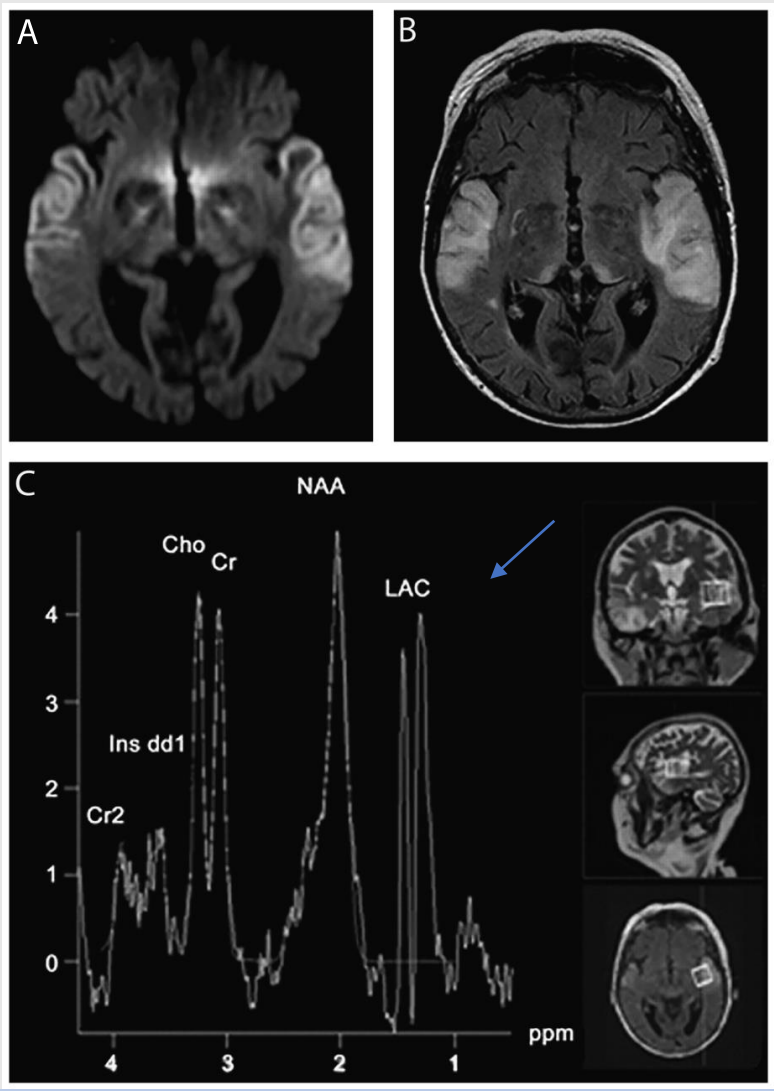
Multi-infarcts



CADASIL



MELAS

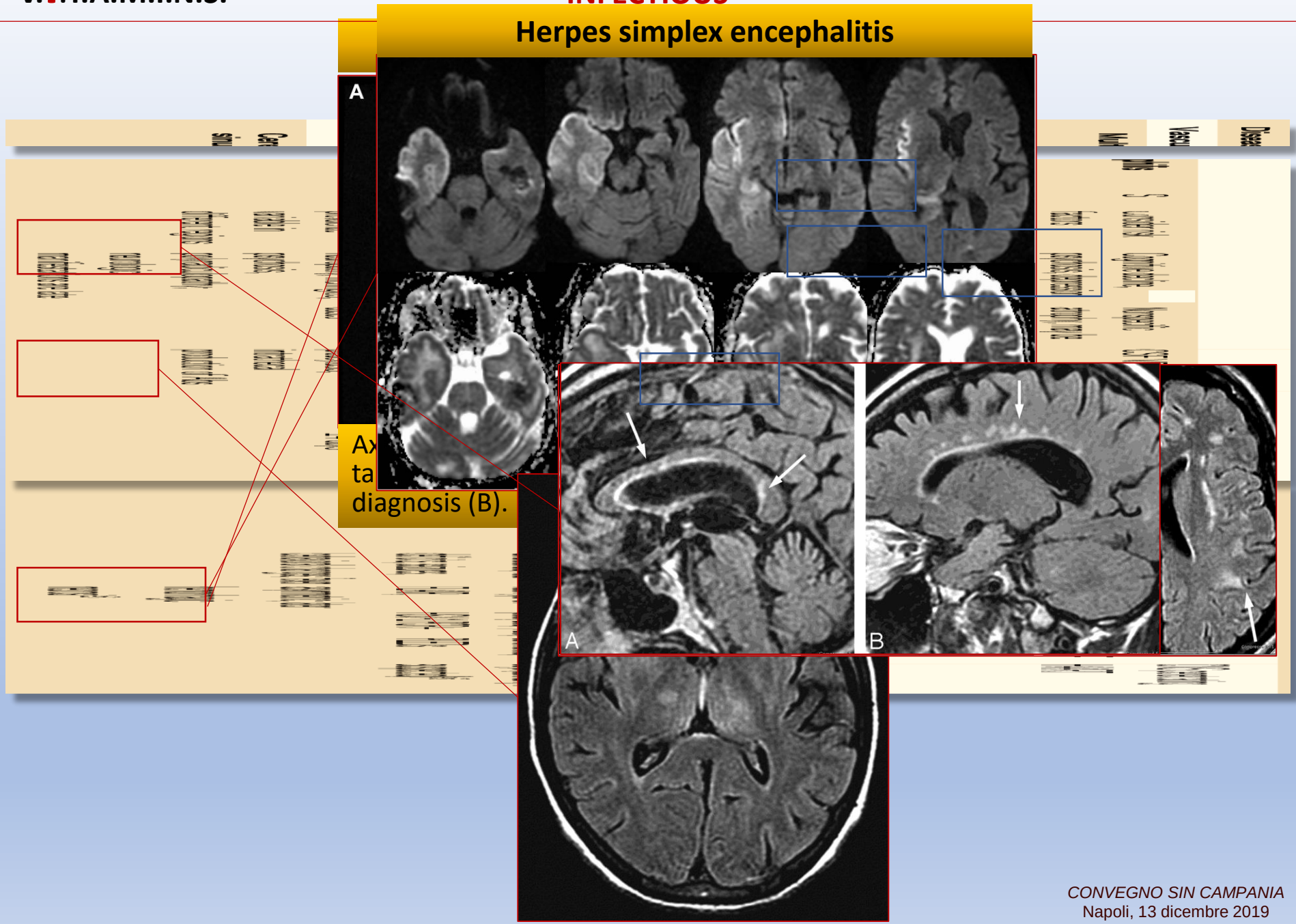


A 59-year-old woman developed confusion, progressive aphasia, mutism, and fluctuations of alertness over 2 weeks.
DWI MRI revealed abnormalities overlapping with CJD (**A**), although the FLAIR MRI (B) with white and gray matter hyperintensity was not consistent with CJD. CSF showed normal cell counts, negative PCR for herpes simplex virus, elevated lactate (4.6 mmol/L), and increased levels of 14-3-3 and tau protein (1300 pg/L), both concerning for CJD . There were no periodic sharp-wave complexes on EEG recordings. MR spectroscopy revealed a lactate signal indicative of mitochondriopathy and genetic analysis confirmed the MELAS A3243G mutation. The DWI (A) displays bitemporal neocortical hyperintense signals. The FLAIR (B) 2 days after the initial MRI scan reveals newly emerging symmetric lesions in the pulvinar thalami. Magnetic resonance spectroscopy (C) displays a strong lactate signal.

M.D. Geschwind Continuum (Minneap Minn) 2016

INFECTIOUS

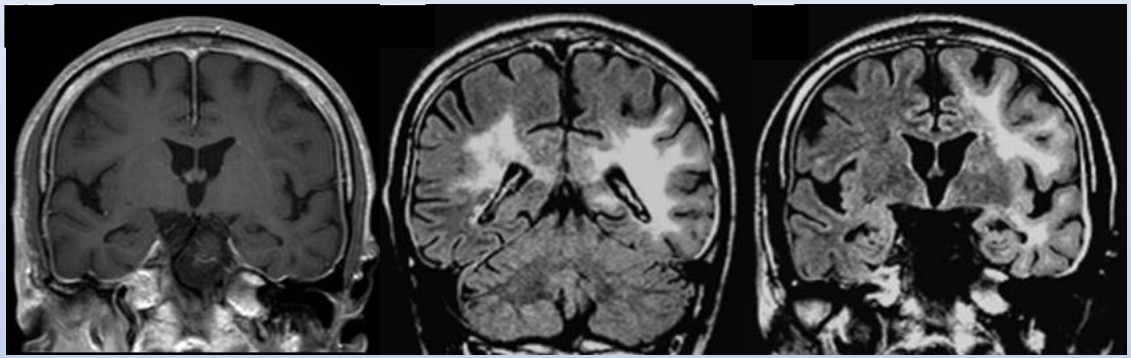
Herpes simplex encephalitis



PML

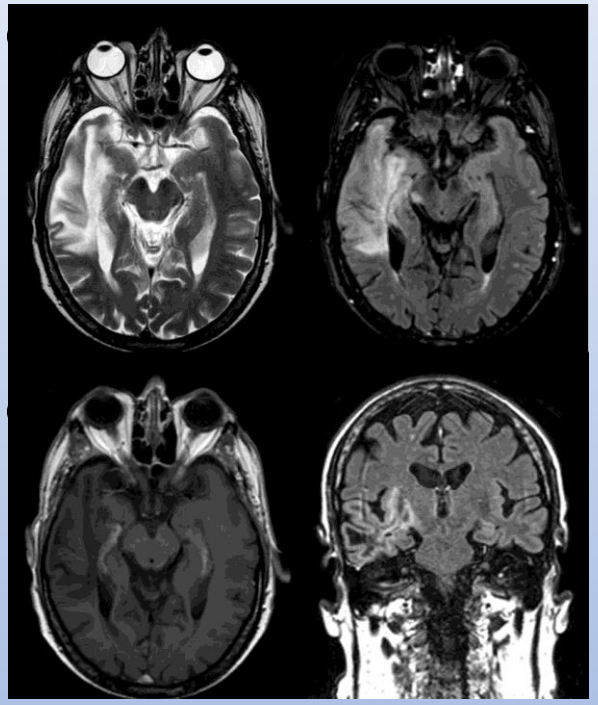
Progressive multifocal leukoencephalopathy associated with borderline idiopathic CD4⁺ T-cell lymphocytopenia

Dato C. et al. Int. J. Neurosci, submitted

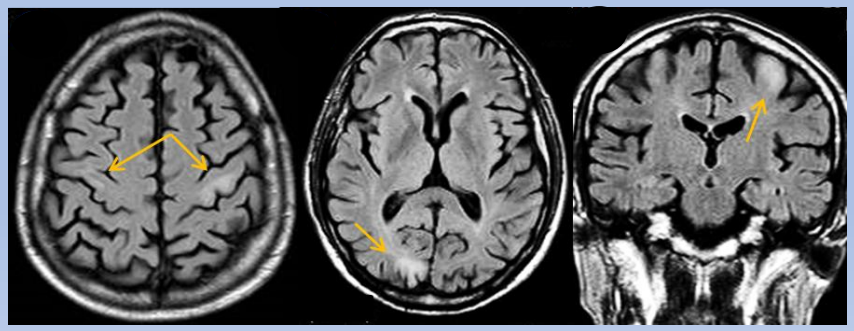


Bilateral FLAIR hyperintense signal of parietal and occipital lobe subcortical and deep white matter, extending to the splenium of the corpus callosum, temporal lobe white matter, and the left external capsula. Slight hypointensity of the same areas on T1W images, without contrast enhancement.

Atypical monofocal PML



Atypical PML with cortical involvement



TOXIC/METABOLIC

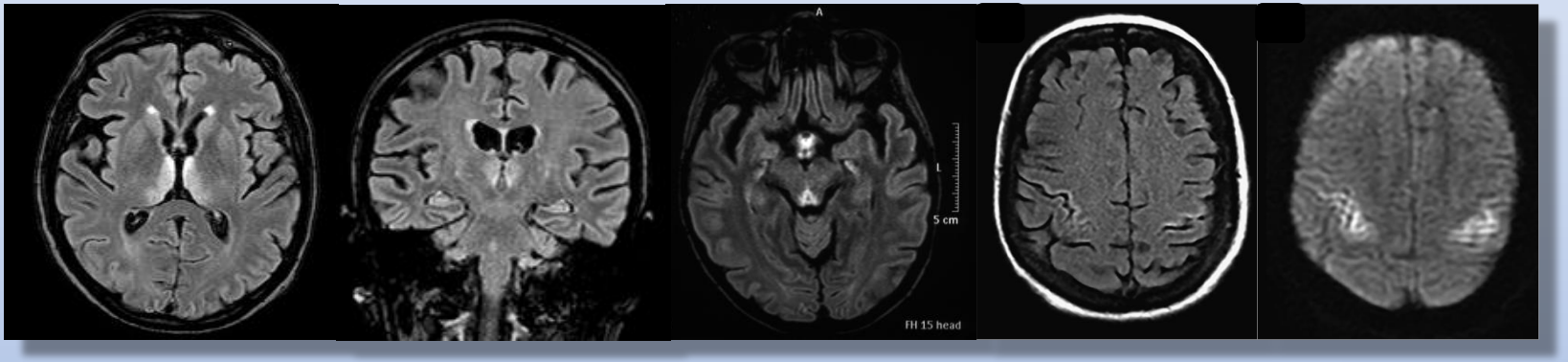
Diseas	tabolic							
Vascu	ke syndrome	A	Risk factors: alcoholism, malnutrition	Cognitive impairment, eye movement abnormalities, ataxia	T2 hyper in medial thalamus and mammillary bodies[7]	Nondiagnostic	-	Thiamine
Nutr								
	ontine olysis	A	Rapid correction of electrolyte disturbance (e.g., hyponatremia)	May take few days to develop symptoms; encephalopathy, movement disorders, para/quadriparesis	Hyper T2 lesions (CE) in pons, cerebellum, basal ganglia, thalamus; may take days to appear[8]	Nondiagnostic	-	Symptomatic
Stra dem								
Infla	n B12 ncy	S	Older adults, pernicious anemia, veganism, fad diets	Cognitive impairment (infrequent, but treatable), sensory ataxia, paresthesias	Nondiagnostic	Nondiagnostic	↓Vitamin B12, ↑MMA, ↑homocysteine	Vitamin B12
Prim	ed cerebral eration	S	Cirrhosis (portosystemic shunting)	Apathy, inattention, parkinsonism, cranial dyskinesia	Pallidal T1 hyper, T2 normal[9]	Nondiagnostic	-	Treatment of liver disease, but might be irreversible; liver transplant
Cere sinu	intermittent ria[10,11]	A/S	20s-30s; F > M	Abdominal pain, autonomic dysfunction, behavioral changes, altered consciousness	Normal	Nondiagnostic	Elevated PBG/ALA in urine	Carbohydrates, intravenous haem arginate; avoid certain medications and metabolic disturbances

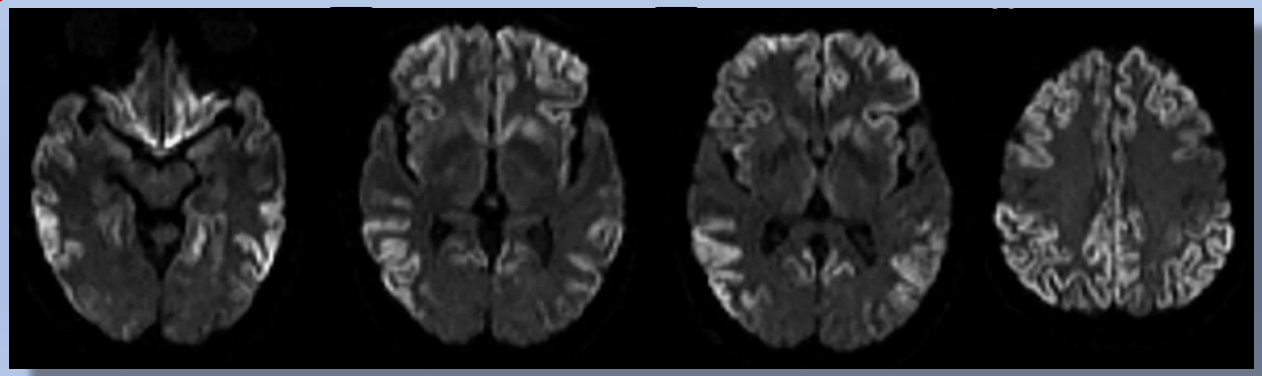
WERNICKE encephalopathy

Modified from Elefante A, Puoti G, Senese. Eur J Radiol. 2012.

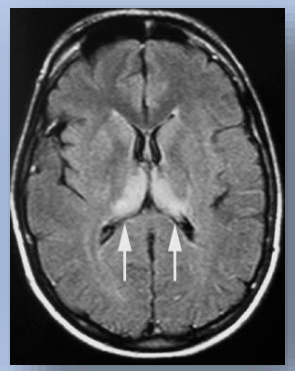
Classic clinical triad :

- Ophtalmoplegia/nystagmus,
- Ataxia
- Rapid cognitve deterioration + Consciousness disturbance



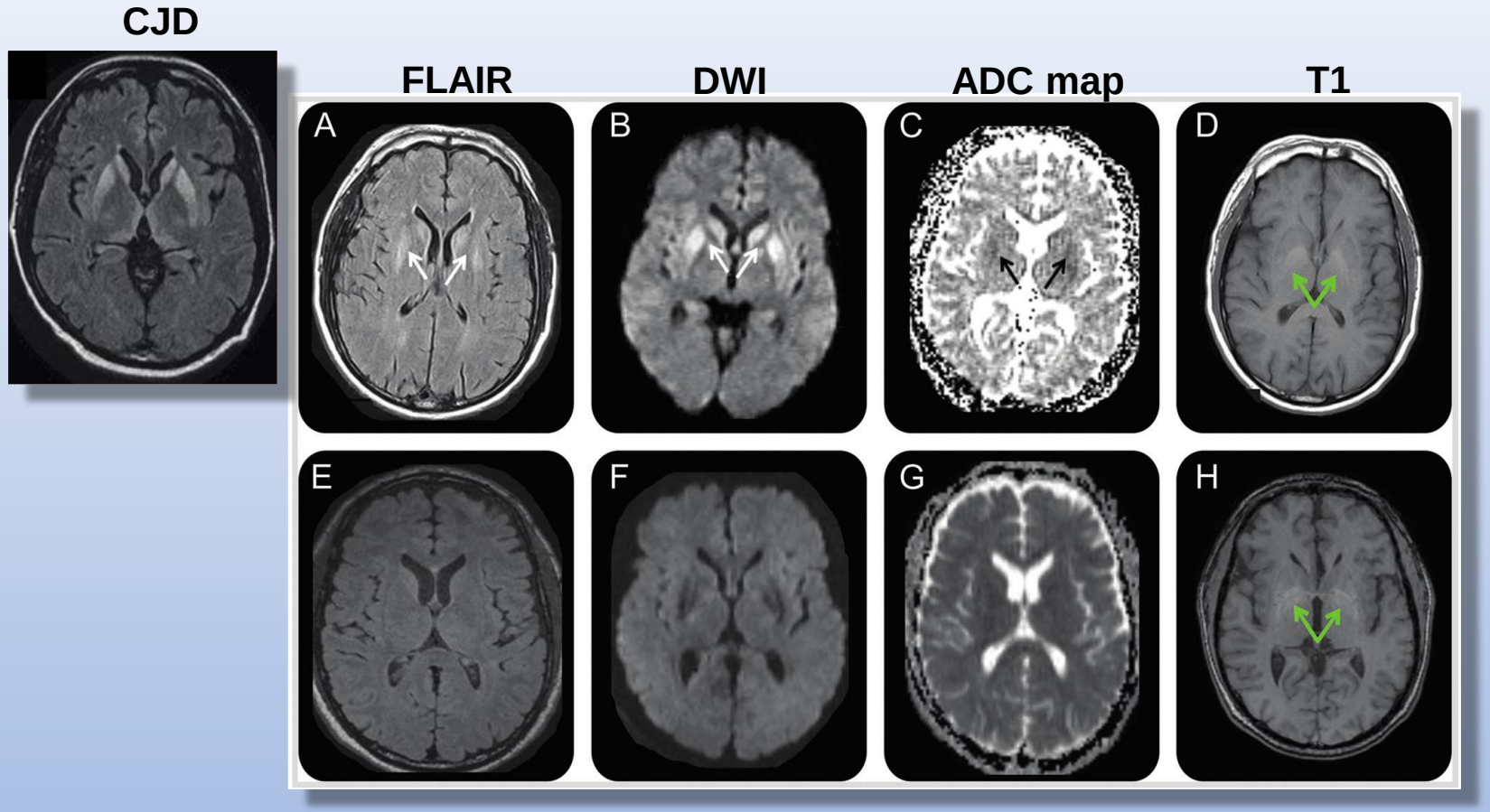


sCJD



variant CJD

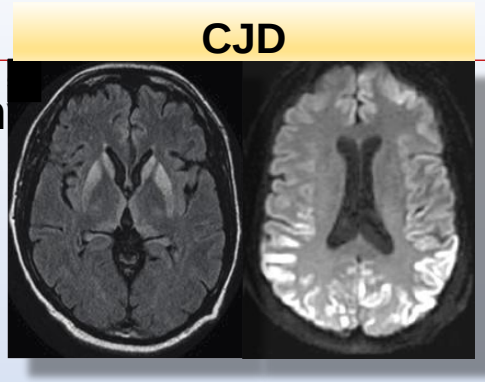
Extrapontine myelinolysis

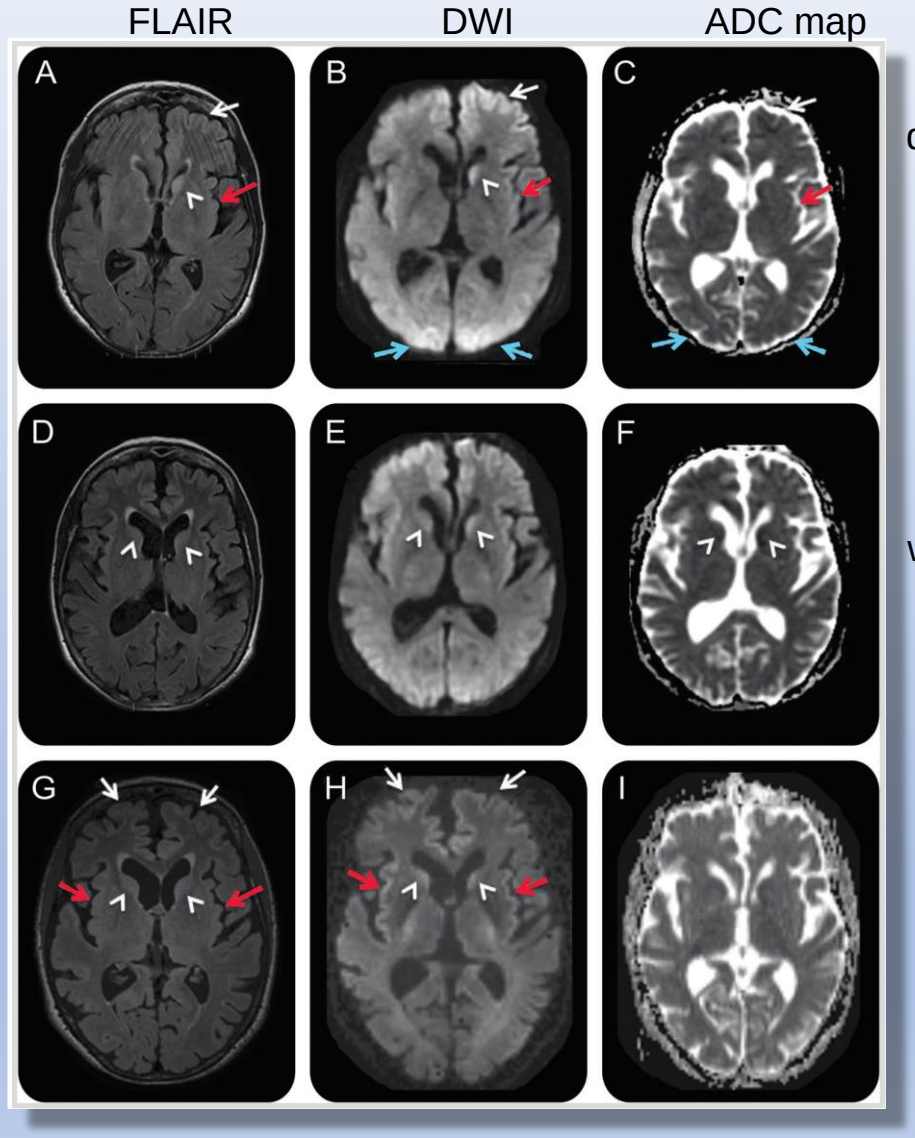


A 50-year-old man. Initial MRI 2 months after onset (A-D) showed symmetric bilateral striatal FLAIR (**A**)/DWI (**B**) hyperintensities (**A**, **B**; white arrows) with corresponding hypointensities on the ADC map suggesting restricted diffusion (**C**; black arrows). Bilateral globus pallidus hyperintensities were present on T1-weighted images **(D**; green arrows). MRI 1 month later, 3 months after onset (E-H), showed resolution of the prior FLAIR (**E**), DWI (**F**), and ADC (**G**) map abnormalities but no change in the globus pallidus T1 hyperintensities (**H**; green arrows).

M.D. Geschwind Continuum (Minneap Minn) 2016

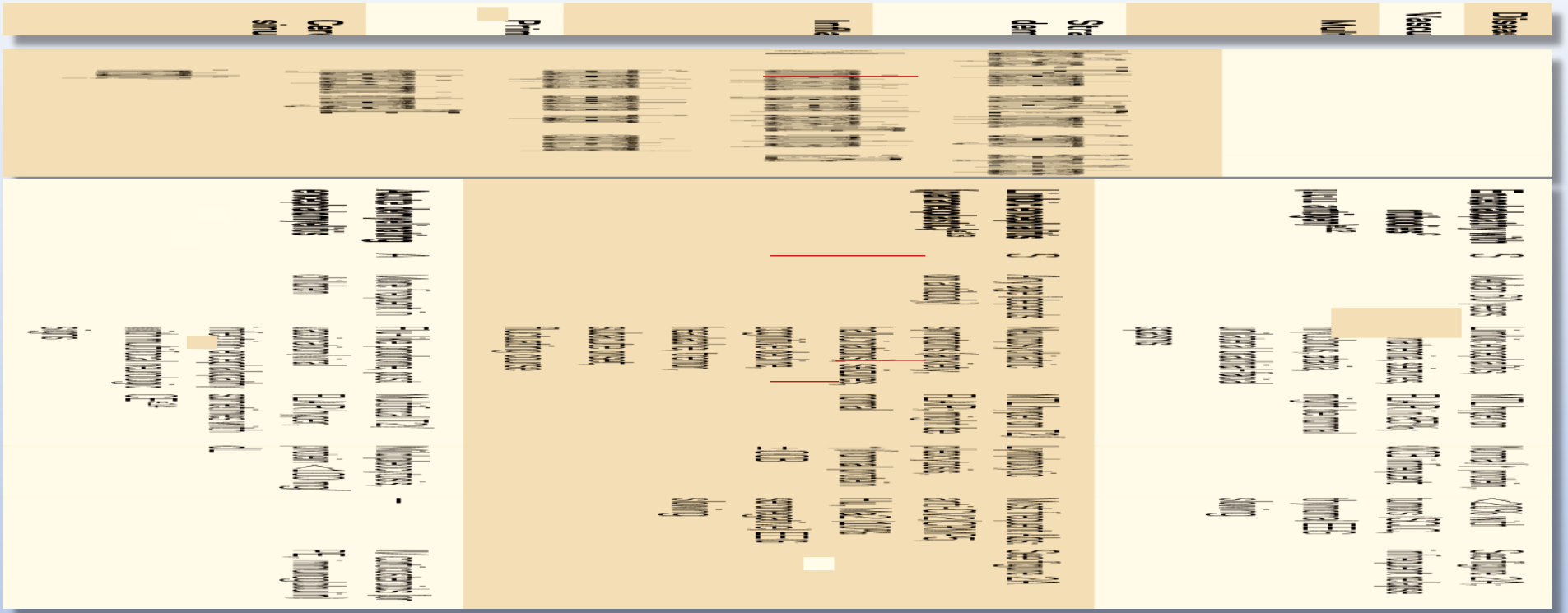
Hypoglycemic encephalopath





Initial MRI (**A-C**) showed left frontal (white arrows), left insular (red arrows), bilateral medial occipital (blue arrows), and left caudate (white arrowhead) FLAIR/DWI hyperintensity with restricted diffusion, which is subtle but definitely appreciable. Repeat MRI about 3 weeks later (**D-F**) showed possible reduced FLAIR/DWI hyperintensity in the left caudate head and medial occipital regions, and possible increased right caudate FLAIR hyperintensity and restricted diffusion (DYF; white arrowheads). A third MRI 1 week later, 1 month after onset (**G-I**), revealed more intense FLAIR/DWI insular (**G**, **H**; red arrows) and frontal cortical hyperintensities (G, H; white arrows) and possible restricted diffusion and FLAIR hyperintensity still present in the caudate heads (**G**, **H**; arrowheads). The resolution of occipital cortical ribboning in such a short time argued against a diagnosis of sporadic Jakob-Creutzfeldt disease.

AUTOIMMUNE

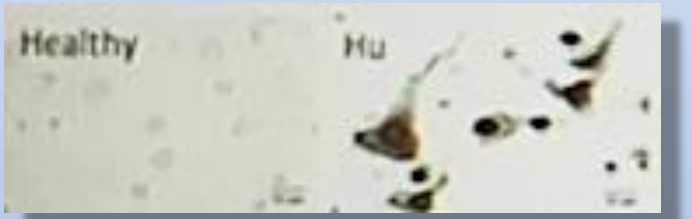


Emerging Paradigm of CNS Antibody Disorders

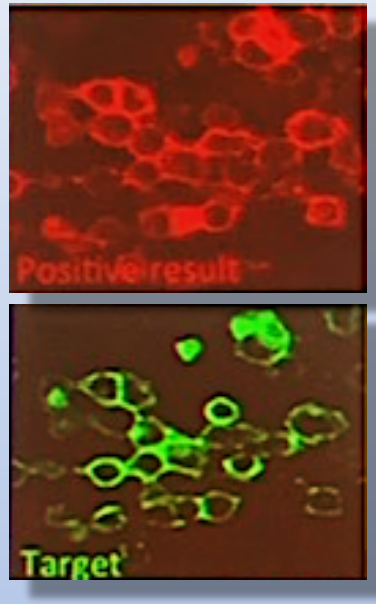
Neuronal Intracellular (Classicsl Paraneoplastic)	Neuronal Cell-Surface/Synaptic (Autoimmune)	Astrocytes	Myelin	Other Brain Proteins
Hu (ANNA-1), Yo, Ri, Ma, CRMP-5, Amphiphysin …	VGKC (LGI-1, CASPR), NMDAm AMPA, GABA-Bm VGCC …	AQP4 (NMO)	MOG (NMO-like syndromes)	A-Beta (CAA-I)
CANCER associated	Usually NOT cancer associated (i.e. autoimmune)	Not Cancer	Not Cancer	Not Cancer
Poor	Good	Good	Good	Poor

Diagnosis

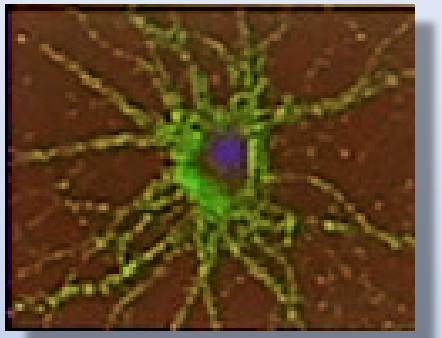
Cell-based Assay



Cell-based Assay
(Hec-293m express known antigen)



Cultured dissociated
hippocampal neurons
(Rat)



Stain against rodent
brain slices

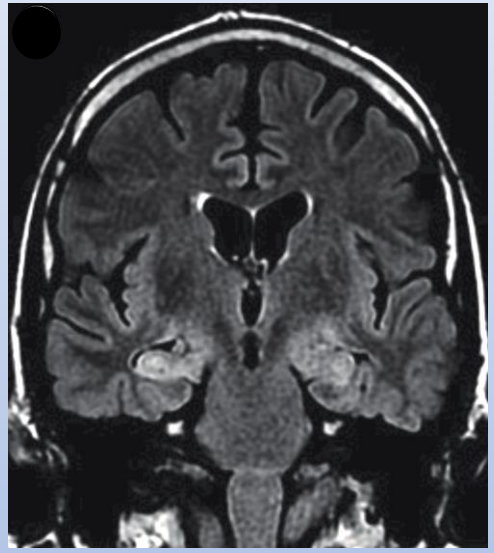
INTRACELLULAR

NEURONAL CELL-SURFACE

Limbic Encephalitis

Clinical criteria

- **Phenotype** (developping over days, weeks, or months)**:**
  - *Cognitive decline (m*emory problems)
  - *Psychiatric (*behavioral changes)
  - *Seizures*
- **Serum***: anti-neuron Abs*
- **CSF***: anti-neuron Abs, mild pleiocytosis and hyperproteinorrachia*
- **EEG***: diffuse or temporal slowing; epileptic activity*
- **MRI***: T2-hyperintensity, T1-atrophy*



Limbic Encephalitis

Antibodies and clinical phenotypes

Anti-neuronal intracellular antigens

- ***Anti-Hu**: classic L.E.+ cerebellar syndrome*
- ***Anti-Ma2**: classic L.E. + diencephalitis*
- ***Anti-CV2**: classic L.E + chorea*

} PARANEOPLASTIC

Anti-neuronal cell surface antigens

- ***Anti-VGKC**: classic L.E.- MORVAN – CJD Like*
- ***Anti-NMDAR**: classic L.E. + brainstem encephalitis*
- ***Anti AMPAR**: recurrent classic L.E.*
- ***Anti-GABAbR**: classic L.E + prominent seizures*

} IDIOPATIC and PARANEOPLASTIC

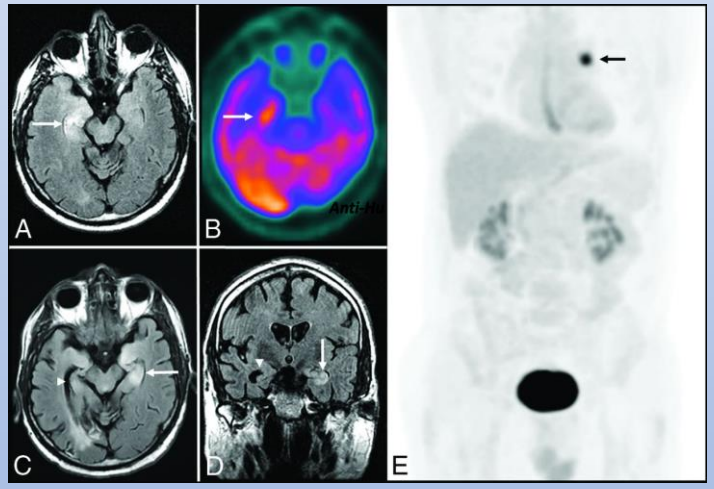
Limbic Encephalitis

Anti-neuronal intracellular antigens

Anti-Hu

Phenotype:

- L.E.+ sometimes extra-limbic involvement (paraneoplastic encephalomyelitis)
- associated with lung microcitoma (>70%)

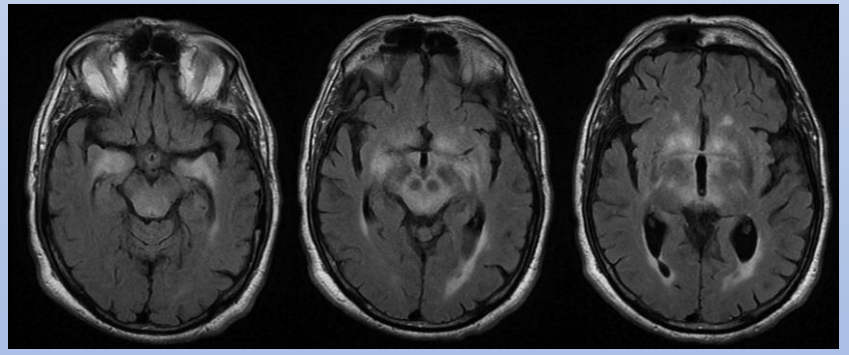


MR imaging of the brain demonstrates T2-FLAIR hyperintensity and mild expansion in the right medial temporal lobe (*A*), right insular cortex (not shown), and left dorsal thalamus (not shown), without restricted diffusion (not shown) or postcontrast enhancement (not shown). FDG-PET of the brain demonstrates a hypermetabolic focus within the right medial temporal lobe lesion (*B*). PET of the body demonstrates a hypermetabolic focus in the left lung (*E*),

Anti-Ma2

Phenotype:

- male, <40 years
- L.E. + frequent brainstem and diencephale involvement, with narcolepsia, SIAD, weight increase
- associated with testicular tumor



Axial slices, FLAIR sequences) in patients with limbic, diencephalic, and midbrain encephalitis associated with anti-Ma antibodies.

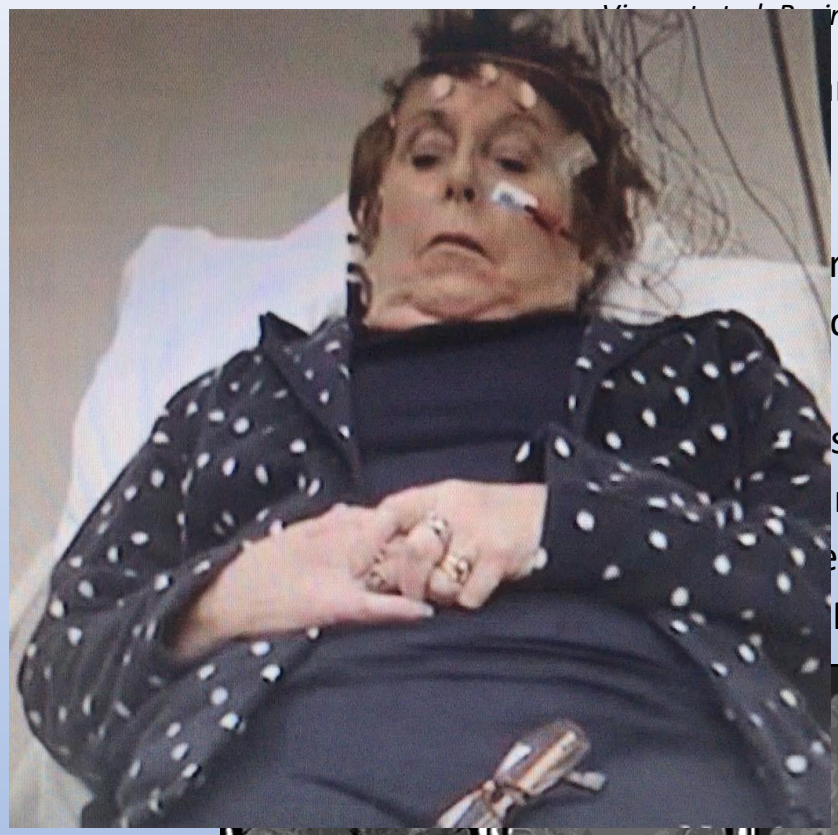
Limbic Encephalitis

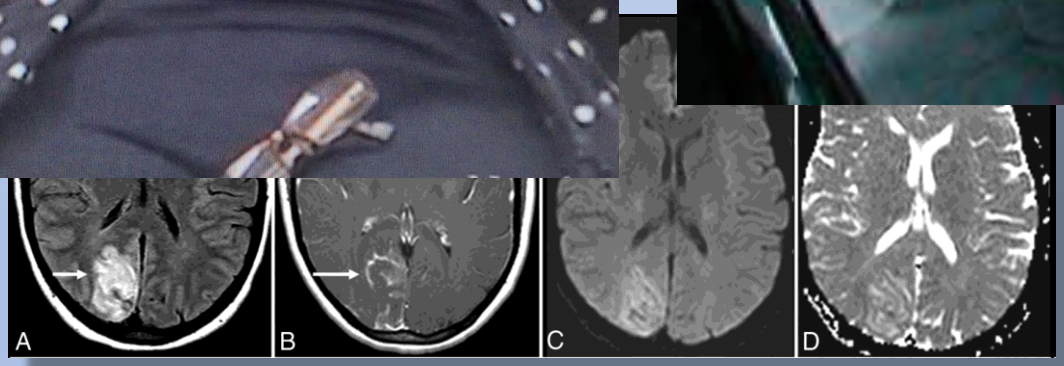
Anti-neuronal cell surface antigens

	NMDAR	VGKC		AMPAR	GABA-b	Glycine
		LGI1	CASPR2			
Approx n. of published cases	>700 in 6 years	250 in 3 years	30 in 3 years	25 in 4 years	30 in 3 years	60 in 5 years
Classic phenotype	Diffuse enchephalitis, psychiatric features, movement disorder, seizures, autonomic	LE: amnesia, seizures, hyponatremia	Morvan's syndrome: dysautonomi, neuropsychiatric, neuromyotonia. Sometimes LE	LE	LE + seizures	Progressive encephalomyelitis with rigidity and myoclonus (PREM)
Tumor	Ovarian teratoma (30%)	<10% (various)	Thymoma (30%)	Lung, breast, thymoma	Lung (50%)	Thymoma (10%)

Adapted and modified from *Irani, Gelfand, Al-Diwani, Vincent, Annals of Neurology, 2014*

VGKC-antibody complex associated Encephalitis





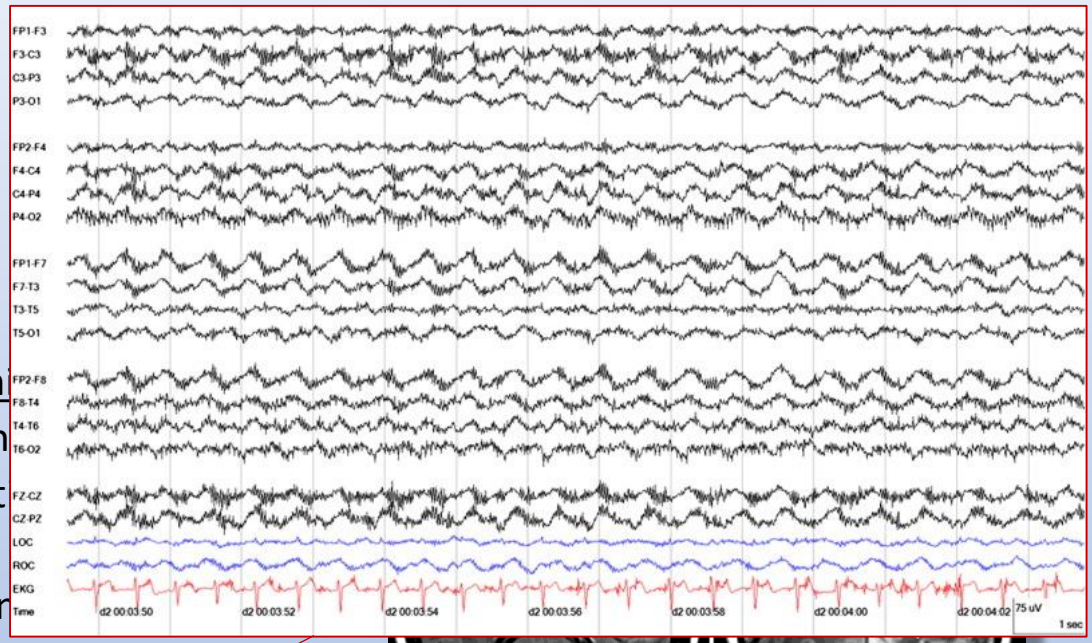
Facio-brachial dystonic seizures

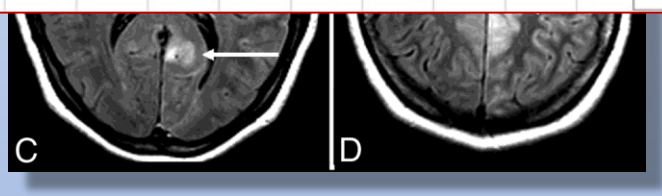
MR imaging of the brain (*A–D*) demonstrates multifocal T2-FLAIR hyperintense lesions in the right parieto-occipital region (*A*), with associated pial/sulcal enhancement (*B*) and mild cortical restricted diffusion and T2 shinethrough within the subcortical white matter on DWI (*C*) and the corresponding ADC map (*D*)

NMDAR Antibody Encephalitis (most frequent one)

- **Disease of the young** (F:M=4:1)
  - **95% <45 years**
  - **37% <18 years**

- **Charcacteristic Clinical Syndrome**
  - Vague progrome (HA, fever,
  - Acute/subacute neuropsych
    sometimes even triage to th
  - Amnesia, language dysfunct
  - Seizures
  - Subset with coma and autor
  - Abnormal movement
  - 58%of affected female patients have an ovarian teratoma
  - Brain MRI is abnormal in 30% of cases
  - EEG: extreme delta brush (**maximal high-voltage beta activity superimposed on frontally maximal delta waves**)
  - Diagnosis is confirmed by CSF abs anti-NMDAR (serum: false negative results in up to 14% of cases)

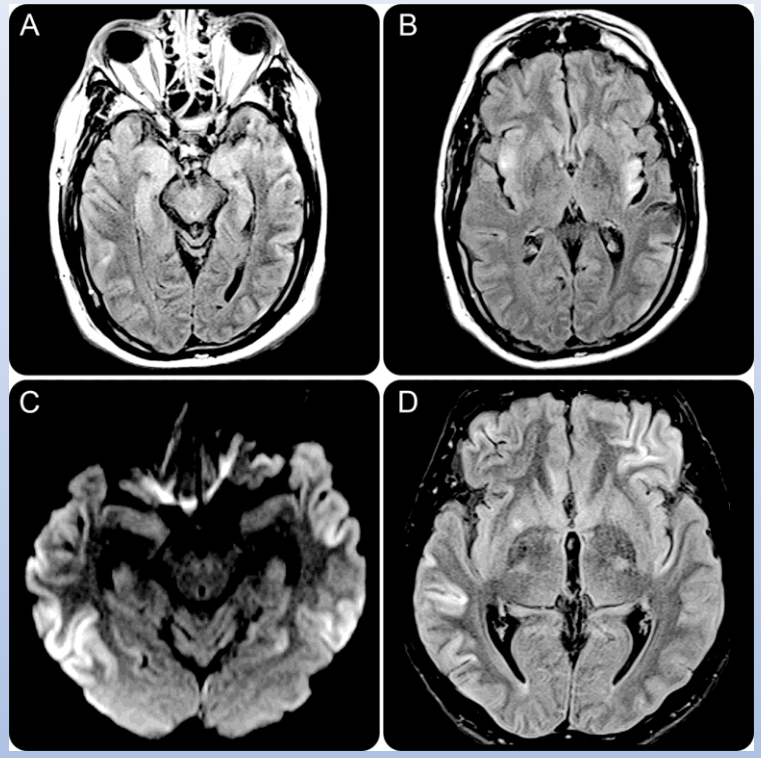




T2-FLAIR hyperintensity in the left inferior temporal lobe (*A*), left > right insular cortex (*B* and *C*), and left > right cingulate gyrus (*B–D*),

AMPAR Antibody Encephalitis

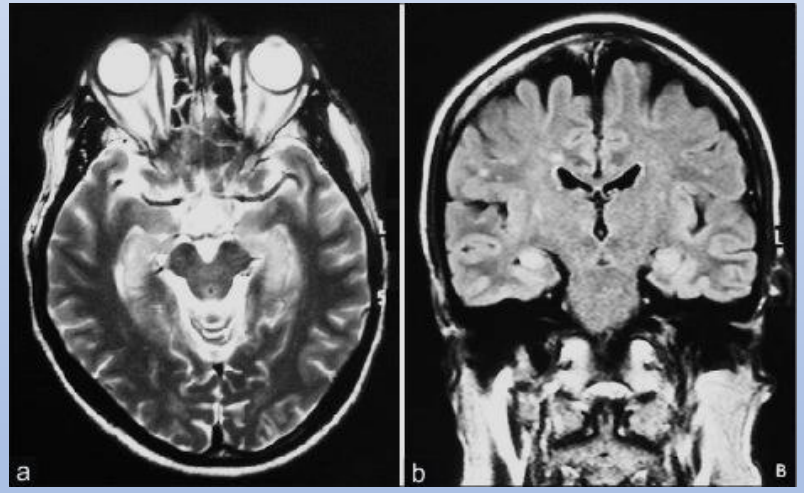
- Median age in the 60s (Female>Male)
- About 70% with an associated cancer (breast, thymus, lung)
- About 70% improve with therapy, but neurological relapses without tumor are frequent and lead to cumulative diysability
- Charcacteristic Clinical Syndrome
  - Limbic encephalitis + prominent psychiatric simptoms and amnesia



Abnormal FLAIR signal involving the cerebral cortex, mainly the medial temporal lobes

$GABA_bR$ Antibody Encephalitis

- Occurs predominantly in children and young adults
- Charcacteristic Clinical Syndrome
  - Limbic encephalitis + prominent seizures
- Associated with small-cell lung cancer and with other autoantibodies (mainly IgG1)



(**a**) T2-weighted and (**b**) FLAIR images of a patient with **$GABA_bR$** abs and limbic encephalitis show increased signal in the mesial temporal lobes

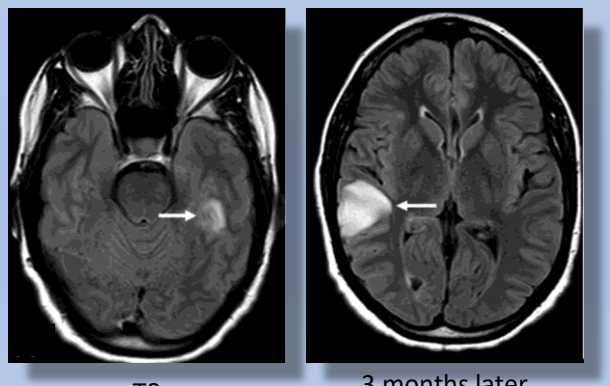
Hashimoto Encephalitis

Prevalence: 2.1/100.000
Age: 45-55 y.; F/M= 5/1
Clinical phenotype:
- Stroke like (aphasia, 65%)
- Progressive cognitive decline (100%) with seizures (70-80%)

Diagnosis:
- Serum: anti-TPO, -TG Abs
- CSF: mild hyperproteinorrachia
- MR images are usually unremarkable

Therapy: I.V. high dose steroids

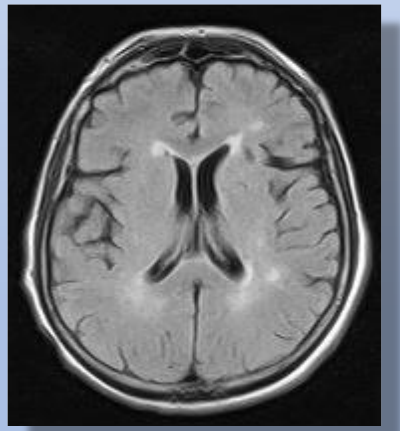
MRI



T0 3 months later

Cellular Inflammation

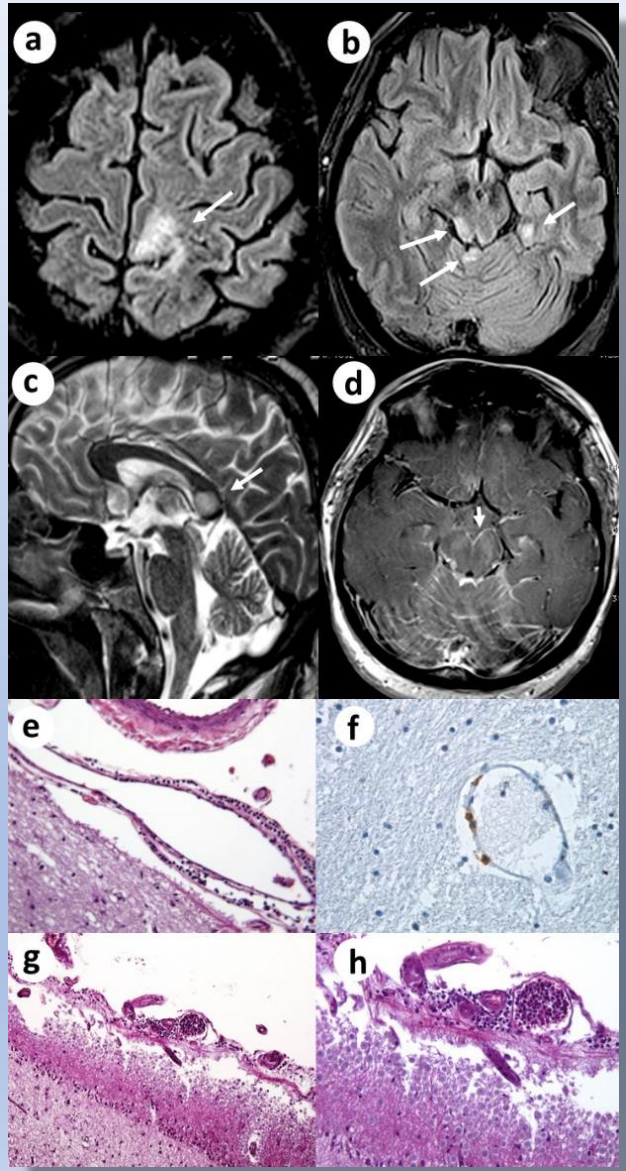
- Neurosarcoidosis
- Primary SNC Angiitis
- Post-infective acute encephalomyelitis
- Behcet



Dramatic neurological debut in a case of Köhlmeier-Degos disease

(malignant atrophic papulosis)

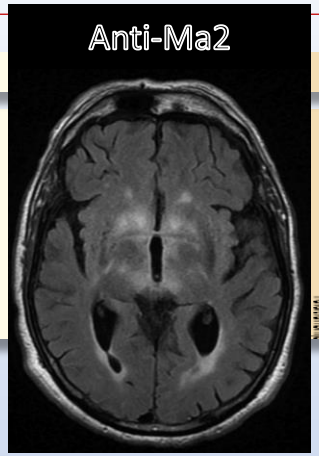
Saracino D. et al. Neurol Sci. 2019



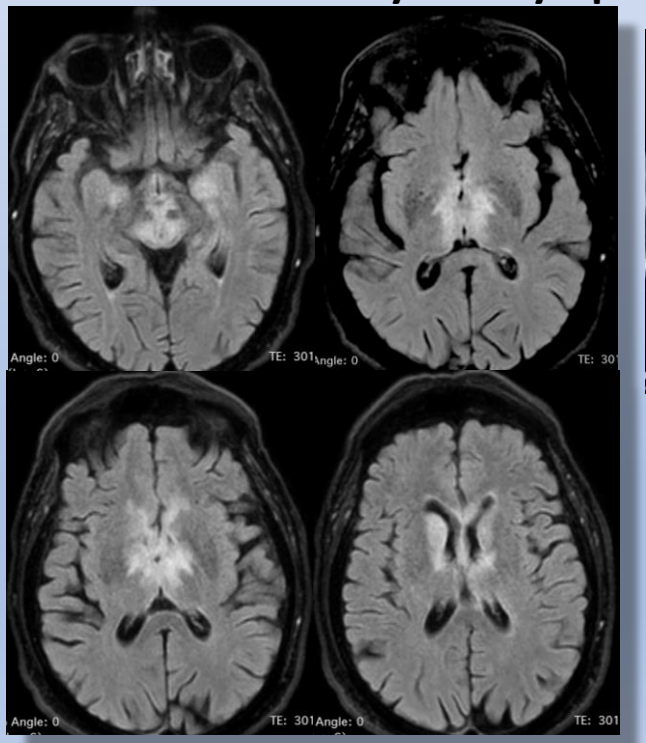
Brain MRI. Axial FLAIR weighted (a, b), Sagittal SE T2 weighted (c) and axial SE T1 post-gadolinium weighted sequences (d). Axial FLAIR MRI sequences show several lesions, namely in paracentral lobule (a) (arrow), right mesencephalic tegmentum, dorsal vermis, left parahippocampal cortex (b) (arrows) and splenium of corpus callosum (c) (arrow).
Axial SE T1 post-gadolinium contrast MRI (d) readily shows diffuse leptomeningeal enhancement (d) especially at the ventral surface of both pons and midbrain, along with obliteration of quadrigeminal cistern (arrowhead).

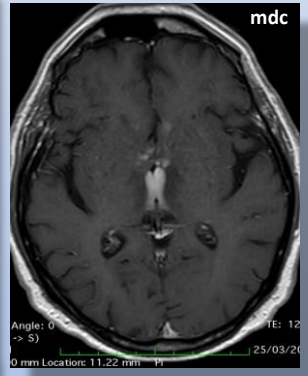
At autopsy, examination of the CNS revealed diffuse **perivenous lymphocytic meningoencephalitis** with few scattered $CD20^{+}$ lymphocytes throughout the parenchyma and the vessel wall (e, f); **laminar necrosis** of cortical neurons with accumulation of glycogen, congestion of neocortical vessels and neutrophil infiltrates was evident (g, and higher magnification in h). No evidence of viral particles or nucleic acids was found. H&E: Hematoxilin and Eosin; EP459Y: Anti-CD20 Antibody.

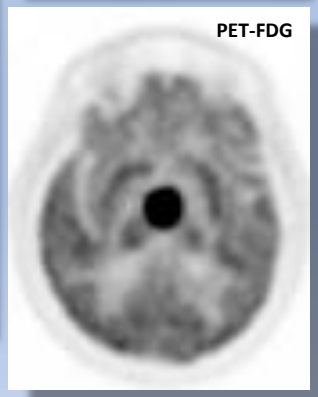
METASTASIS/NEOPLASMS



Primary CNS Lymphoma

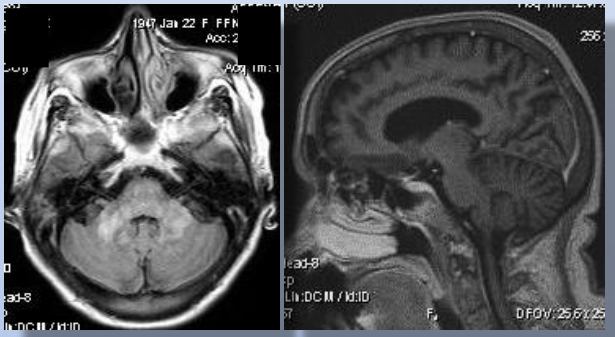




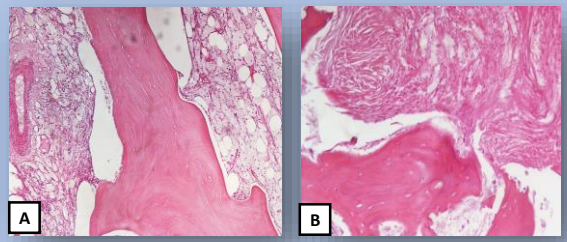


Erdheim-Chester disease

Rare non-Langerhans-cell histiocytosis

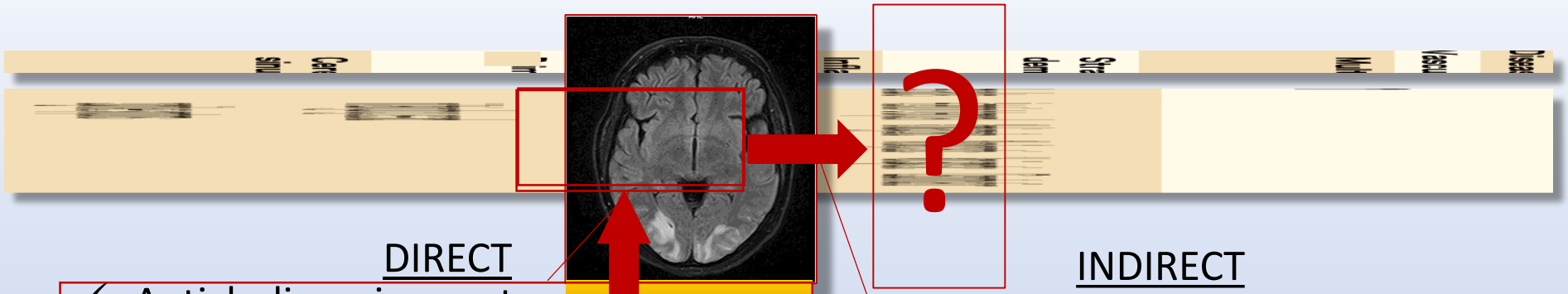


Hyperintense lesions in the pons, bilateral middle cerebellar peduncles and cerebellar hemispheres; (E) Sagittal T1w-Gd MRI sequence showing a homogeneous intense gadolinium enhancement of infundibular stalk



(A) Diffuse bone marrow substutution with foamy hystiocytes and Touton-like multinucleated giant cells along with lymphocytic and eosinophilic infiltration; (B) Bone trabeculae with sclerotic areas.

IATROGENIC



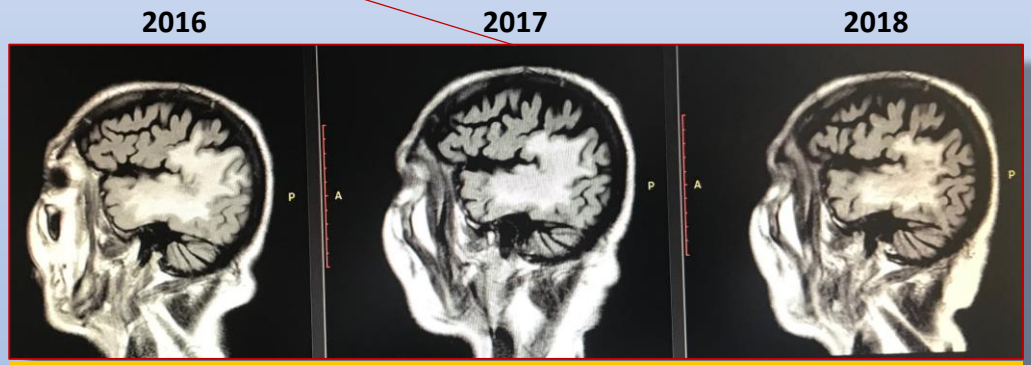
PRES

DIRECT

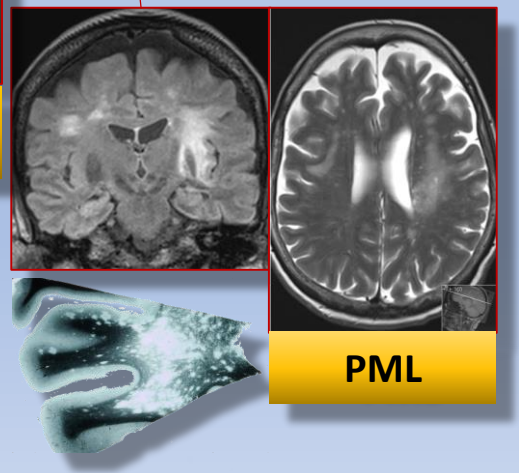
- ✓ Anticholinergic agents
- ✓ Neuroleptics (hypersensitivity in LBD)
- ✓ BDZ
- ✓ Post-irradiation

INDIRECT

- ✓ Cyclophosphamide
- ✓ Corticosteroids
- ✓ Mycophenolate mofetil
- ✓ Monoclonal antibodies
  - natalizumab
  - rituximab
  - alemtuzumab

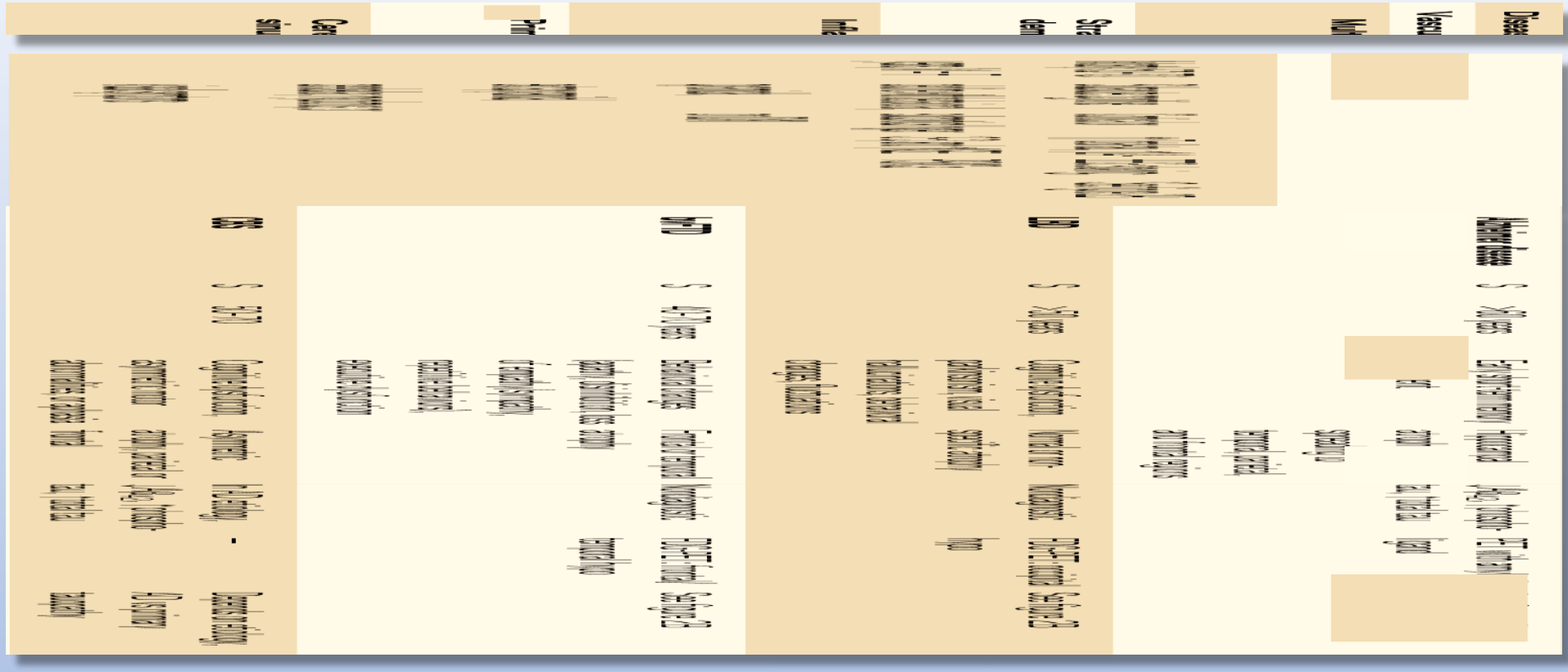


Post-irradiation



PML

NEURODEGENERATIVE



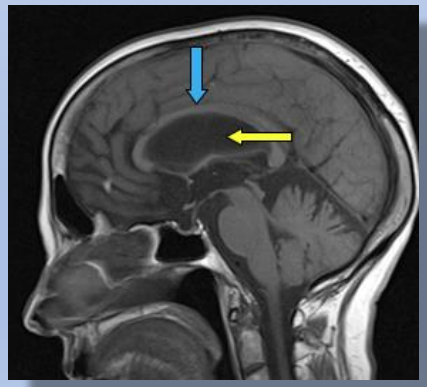
…the diagnosis of neurodegenerative RPD requires above all the exclusion of all potentially reversible forms !!

Normal Pressure Hydrocephale
(NPH)

The ***classic clinical triad***:

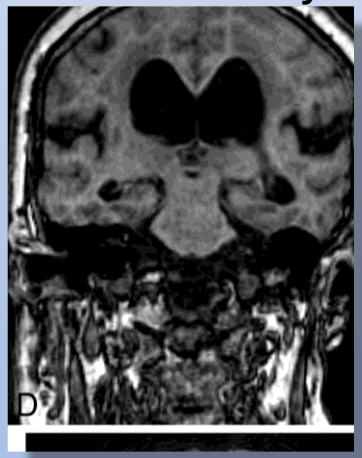
- Cognitive impairment (frontal pattern)
- Gait deviations ("stuck to the floor", or "magnetic" movement)
- Urinary incontinence

Test di Fisher (Tap test)



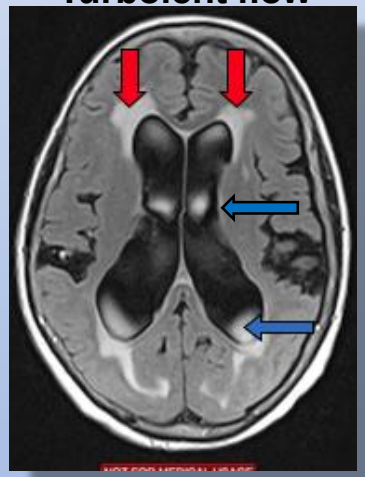
MRI - T1 sequence, lateral view. The corpus callosum is thin (blue arrow) due to dilation of the lateral ventricles (yellow arrow)

Evans index x/y



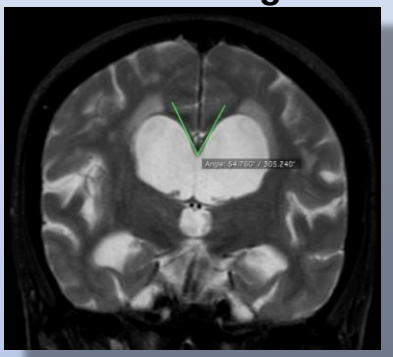
Rmeasures the atio between the maximum diameter of the frontal horns of the lateral ventricles and the maximum inner diameter of the skull in the same section (on trensverse images)

Turbolent flow

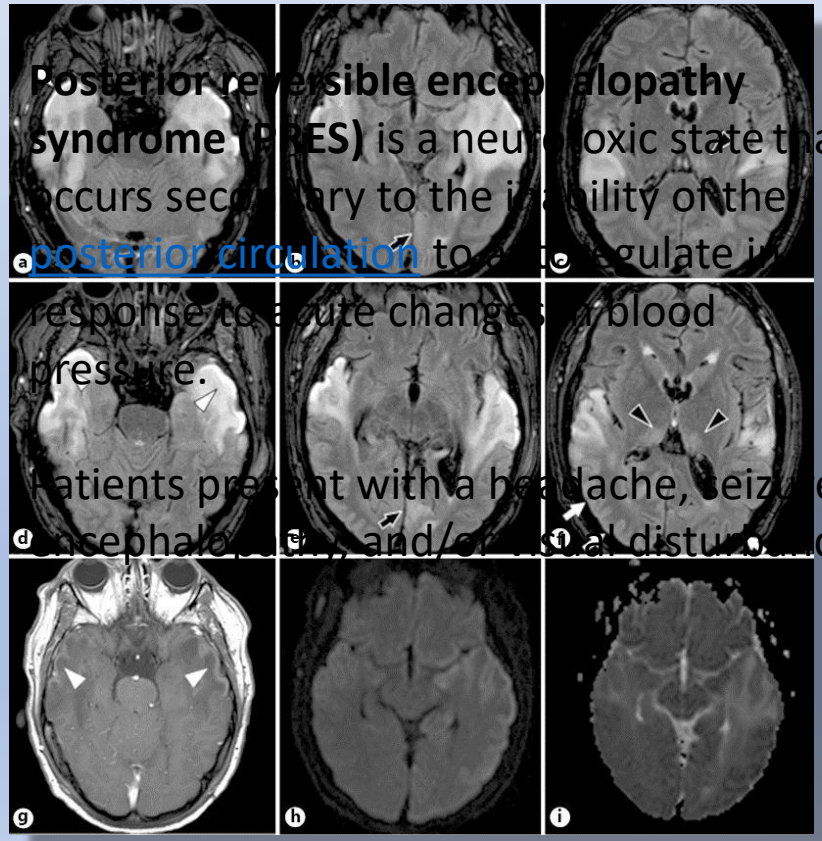


FLAIR sequence in axial projection. The ventricles are large and dilated. Around the ventricles the parenchyma is suffering, the white that looks like a hood (red arrow). The liquor in the ventricles has a turbulent flow: the white patches in the center and the back (blue arrows)

Callosal angle



Patients with NPH have a narrower callosal angle than those with ventriculomegaly linked to atrophy or controls. A normal value is typically between 100-120 °. In patients with NPH the value is lower, between 50-90



Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state that occurs secondary to the inability of the posterior circulation to autoregulate in response to acute changes in blood pressure.

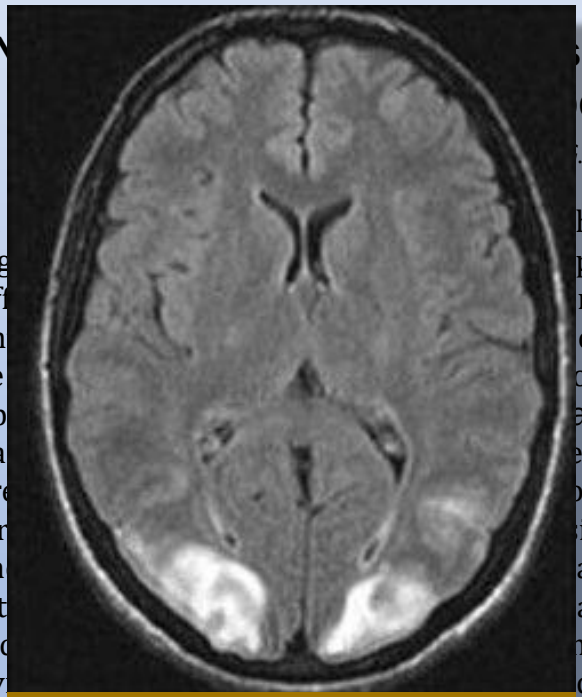
Patients present with a headache, seizures, encephalopathy, and/or visual disturbance

Epilepticus

es Virus

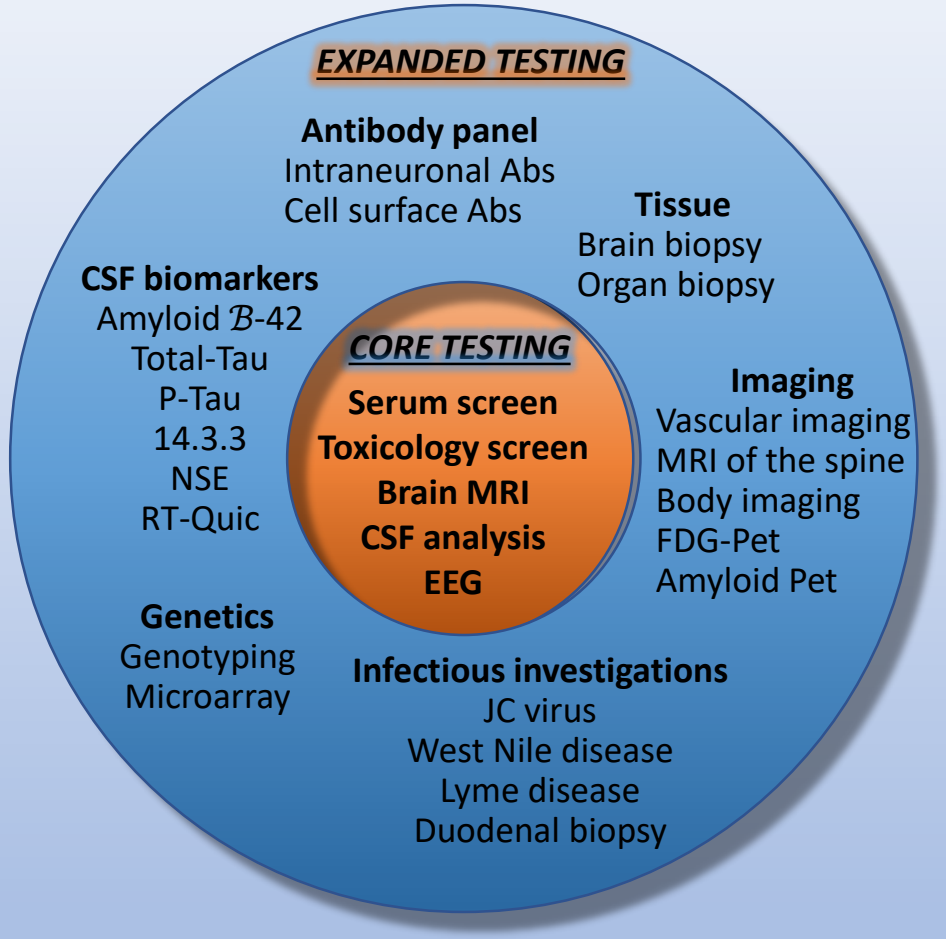
rt al. Case Rep Neurol 2013

MRI hanced T1-weighted
imag pparent diffusion
coeff nset. d–f FLAIR images 1
mon of the entire temporal
lobe oral pole up to the
hipp a, d, white arrowheads),
is ea e edema is significantly
more mpared with 1 month
later ion coefficient map
dem al involvement outside
the t ar of the left precuneus
(blac nd MRI. c, f The left
pulv d 1 month later, with
invo k arrowheads).



PRES
Posterior reversible encephalopathy syndrome

Stratified approach to diagnostic testing in rapidly progressive dementia



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Algorithm for evaluating rapidly progressive dementia

Suspected RPD

- Rule out delirium
- Confirm history of rapid progression (eg, acute decline of slower dementia)

Initial RPD screening

CORE TESTING

Serum screen
Toxicology screen
Brain MRI
CSF analysis
EEG

Second tier RPD workup

EXPANDED TESTING

Antibody panel
Intraneuronal Abs
Cell surface Abs

Tissue
Brain biopsy
Organ biopsy

CSF biomarkers
Amyloid $\mathcal{B}$-42
Total-Tau
P-Tau
14.3.3
NSE
RT-Quic

Imaging
Vascular imaging
MRI of the spine
Body imaging
FDG-Pet
Amyloid Pet

Genetics
Genotyping
Microarray

Infectious investigations
JC virus
West Nile disease
Lyme disease
Duodenal biopsy

Rule out

V **I** **T** **A** **M** **I** **N** **S**

If CSF and MRI are non diagnostic

Infections and lymphoma are ruled out

High dose steroids

If no marked benefit

Brain biopsy

Some diagnostic pearls for rapidly progressive dementia

Verify time course: often symptoms began earlier than records state

Be thorough: try using a mnemonic: VITAMINS

CJD is the great mimicker: it can look like anything (and vice versa)

Do not rely on CSF 14-3-3 for CJD diagnosis: interpret CSF biomarkers with caution

Brain MRI with appropriate sequences: contrast, coronal/axial FLAIR, DWI, ADC

Read your own MRIs: most CJD cases will have DWI-positive cortex "cortical ribboning" that has been missed

If diagnosis not clear, get body imaging w/contrast (or consider PET)

Do not forget the basics: common things are common…

…so if it quacks like a duck, it probably is a duck…

…owever, sometimes, the rare diagnosis is the right one

Acknowledgments

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EEG patterns of interest in rapidly progressive dementia

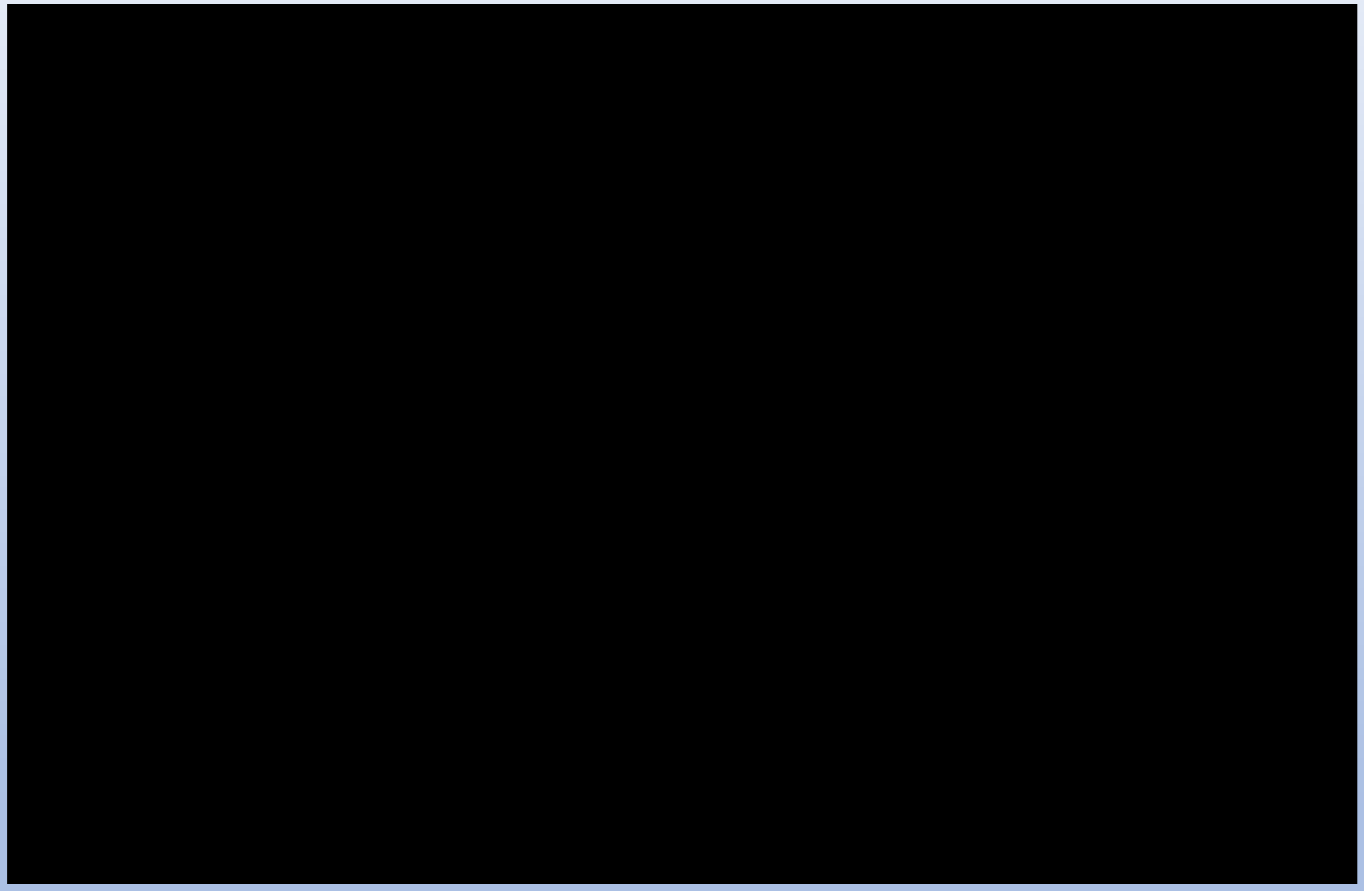
EEG finding	Definition	Potential etiologies
Periodic complexes	Generalized discharges of synchronous high-voltage spikes or sharp waves	CJD SSPE Rarely Alzheimer's disease · DLB
Extreme δ-brush	Rhythmic δ activity (1–3 Hz) with superimposed bursts of 20–30 Hz β-frequency activity riding on each δ-wave	Anti-NMDA receptor encephalitis
Triphasic waves	Synchronous, frontally predominant, rhythmic triphasic waves, usually with background slowing	Metabolic disorders (i.e., hepatic encephalopathy) nonconvulsive status epilepticus
PLEDs	High-voltage sharp potentials over one or both lobes, occurring every few seconds	Herpes simplex encephalitis (temporal PLED) other focal lesions
Frontal intermittent rhythmic δ-activity	Rhythmic, discontinuous high-voltage δ-frequency (1–3 Hz) activity that predominates in frontal regions	Processes involving deep midline structures (i.e., hydrocephalus), other focal lesions

CJD: Creutzfeldt–Jakob disease; DLB: Dementia with Lewy bodies; PLED: Periodic lateralized epileptiform discharge; SSPE: Subacute sclerosing panencephalitis.

Recommended Initial Screening Tests for Evaluation of a Rapidly Progressive Dementia

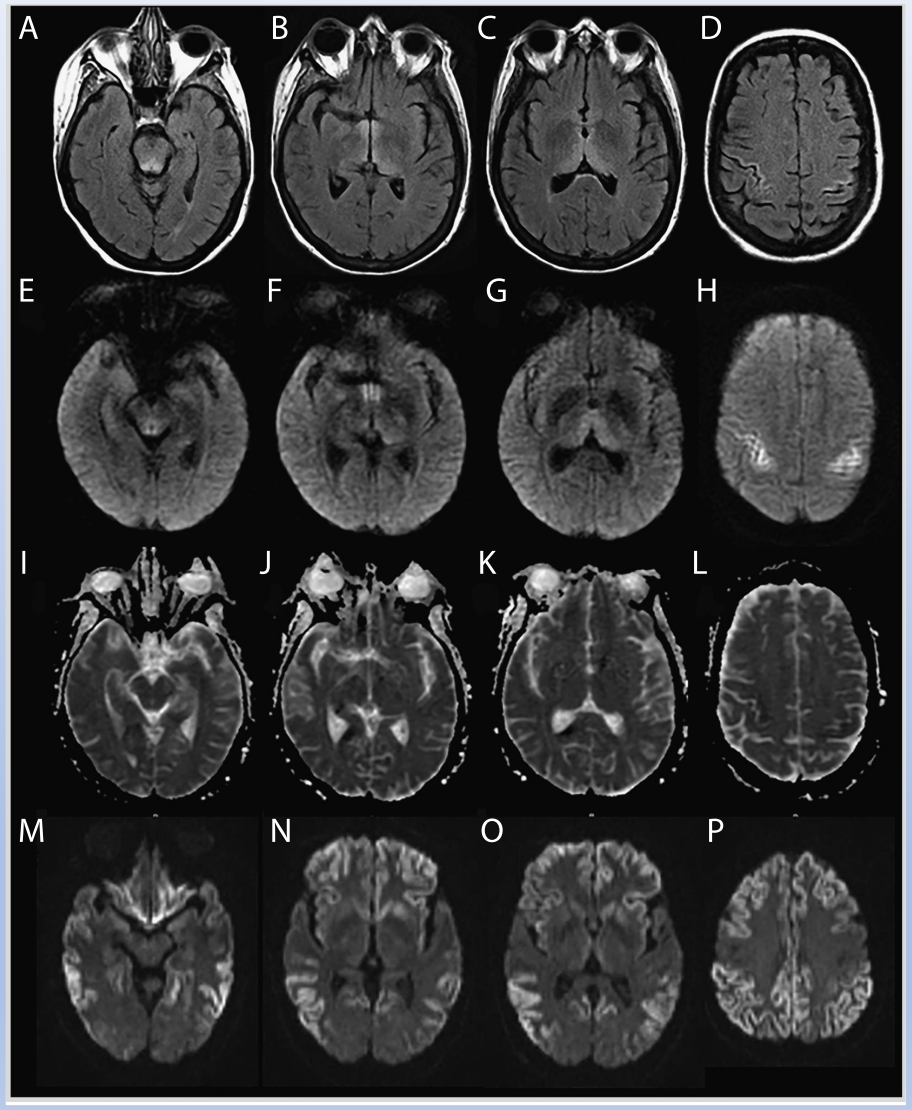
Category	Initial Screen	Secondary Tier (Depending on Initial Screen and Clinical Scenario)
Blood tests	• Complete blood cell count with differential • Basic metabolic panel (including calcium, magnesium, phosphorus) • Liver function tests Rapid plasma reagin (RPR) • Rheumatologic screen (erythrocyte sedimentation rate, antinuclear antibody, and C-reactive protein) • Thyroid function tests (thyroid-stimulating hormone [TSH], free thyroxine) • Vitamin B12 Human immunodeficiency virus • Medication levels as clinically indicated (eg, lithium, phenytoin)	• Cancer screen (eg, serum protein electrophoresis, serum immunoelectrophoresis, cancer antigen 125) • Blood smear Coagulation profile • Hypercoagulability testing Homocysteine Methylmalonic acid • Additional rheumatologic tests (eg, cytoplasmic antineutrophil cytoplasmic antibody, perinuclear antineutrophil cytoplasmic antibody, double-stranded DNA, Smith antigen-ribonucleoprotein, SCL-70, SSA/SSB, rheumatoid factor, C3, C4, CH50) • Antithyroglobulin and antithyroperoxidase antibodies • Lyme antibodies • Paraneoplastic/autoimmune antibodies • Additional endocrinologic tests (eg, cortisol) Lymphoma markers
Urine	• Urine analysis (with or without culture) • Urine toxicology screen (if indicated)	• Urine culture • Heavy metal screen (24 hours)
CSF	• Cell count and differential Protein • Glucose • IgG index • Oligoclonal bands • Venereal Disease Research Laboratory (VDRL) • 14-3-3 protein western blot • Total tau enzyme-linked immunosorbent assay (ELISA) • Neuron specific enolase ELISA • Real-time quaking induced conversion (RT-QuIC) test	• Cryptococcal antigena • Viral polymerase chain reactions (PCRs), antibodies, and cultures[b] • Bacterial, fungal, acid-fast bacilli stains, and cultures • Cytology[d] Flow cytometry • Whipple PCR • Metagenomic deep sequencing (CSF, biopsy tissue) Phosphorylated tau, amyloid-"42 • CSF "2-microglobulin and Epstein-Barr virus PCR (lymphoma)
Imaging	• Brain MRI (including T1, T2, fluid-attenuated inversion recovery [FLAIR], diffusion-weighted imaging, apparent diffusion coefficient map, hemosiderin sequence) with and without contrast • Chest x-ray (if clinically indicated)	• CT head • CT chest, abdomen, and pelvis with and without contrast • Magnetic resonance angiography/magnetic resonance venography • Computed tomography angiography/brain angiogram • Magnetic resonance spectroscopy (for lesions or masses) • Mammogram • Body fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan • Testicular or pelvic ultrasound Carotid ultrasound Echocardiogram
Other tests	EEG	• Electromyogram/nerve conduction study

Real-time quaking-induced conversion (RT-QuIC)



Responses from reactions seeded with cerebrospinal fluid (CSF) from two sporadic Creutzfeldt-Jakob disease (sCJD) cases and a positive sCJD CSF control.
The RT-QuIC from an unseeded reaction and a reaction seeded with brain homogenate from Alzheimer's disease are also shown. Image courtesy of Neil McKenzie, University of Edinburgh, Edinburgh, UK. AD BH, Alzheimer's disease brain homogenate; RFU, relative fluorescence units; ThT, thioflavin T.

WERNICKE encephalopathy



Wernicke encephalopathy (compared to a sporadic Jakob-Creutzfeldt disease case). Fluid-attenuated inversion recovery (FLAIR) (**A-D**), diffusion-weighted imaging (DWI) (**E-H**), and apparent diffusion coefficient (ADC) map (**I-L**)
sequences showing FLAIR and DWI hyperintense signal changes involving the periaqueductal gray and midbrain tectum, medial thalami, and perirolandic cortex in the patient with Wernicke encephalopathy. There is relative sparing of the mammillary bodies across all sequences (**B,F,J**). The ADC sequences (I**-L**) primarily show subtle hypointensity in the perirolandic cortex (**L**), corresponding to hyperintensities on FLAIR (**D**) and DWI (**H**). This pattern preferentially involving the perirolandic cortex is the opposite of what we typically see in sporadic Jakob-Creutzfeldt disease (**M-P**; DWI sequences), in which there is generally sparing of the perirolandic region, particularly the primary motor cortex.

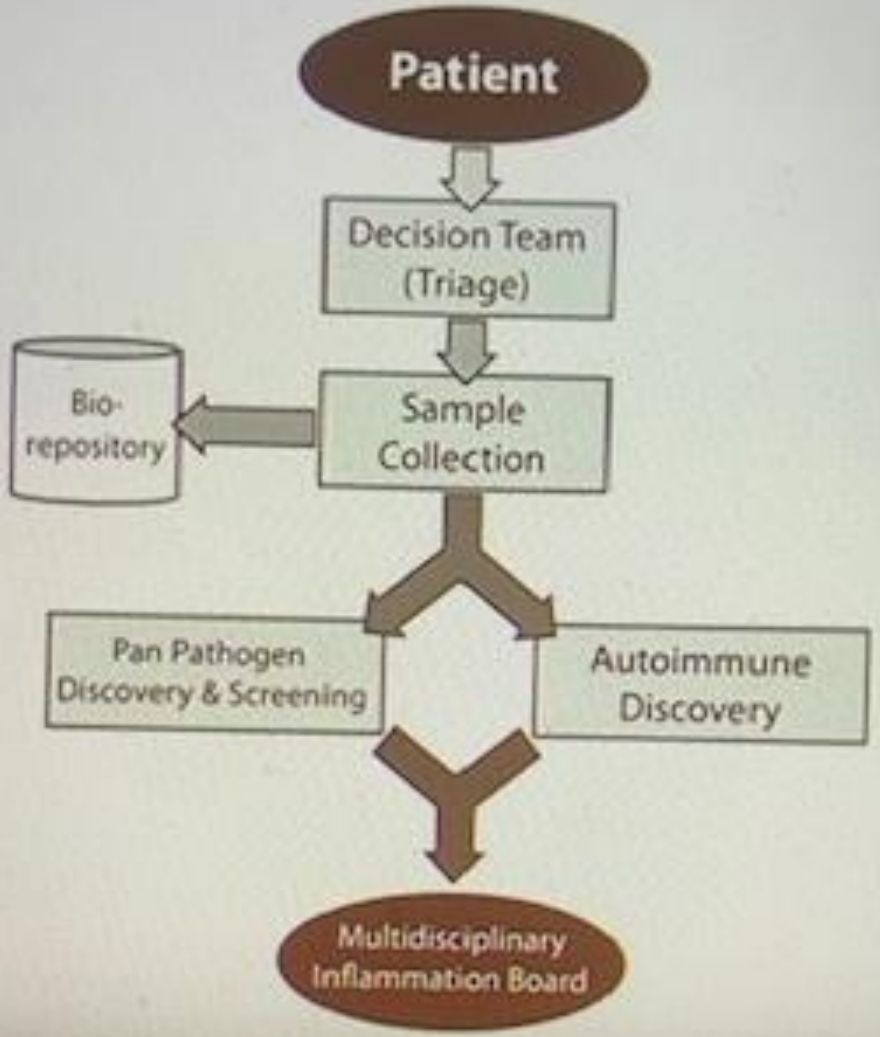
Goals of Immunosuppressive Therapy for Autoimmune Encephalitis

- Improve symptoms acutely
- Induce remission of the pathological inflammatory process
- Maintain remission
- Minimize risk from immunosuppression

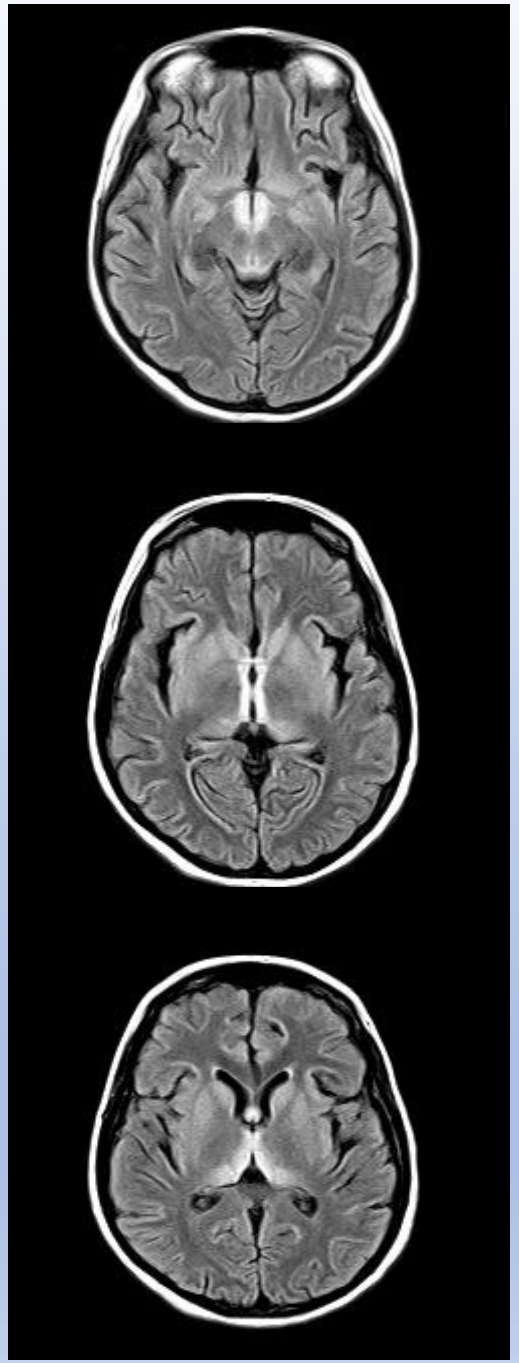
Treat symptoms:

- i.e. neuropsychiatric, seizures, pain, concentration, fatigue, sleep
- Promotion of neurorehabilitation

UCSF Precision Medicine Model: Meningitis and Encephalitis



Wernicke



Neuronal surface antibody associated syndromes

Table 2 Neuronal surface antibody associated syndromes

Syndrome	Antibodies	Particular clinical features	Possible tumours	Immunotherapy response	In vitro evidence of Ab pathogenicity	Frequency or No of cases reported
NMDAR-Ab encephalitis	NMDAR	Dyskinetic movements, decreased consciousness, psychiatric presentation in young women. Epilepsy and abnormal movements more frequent at onset in children	Ovarian teratoma. Rare in children. Up to 50% after age 18 years	Yes	In vitro and in vivo reduction of NMDA receptors	Common syndrome. More than 500 cases reported, mainly in USA
LE	LGI1 CASPR2 (<10%)	Male predominance, hyponatraemia, faciobrachial dystonic seizures, myoclonus	Rare with LGI1-Ab. Thymoma in some with CASPR2-Ab	Yes	In vitro production of epileptogenic activity in brain slices	Common syndrome More than 600 cases reported, mainly in UK
	AMPAR	Possible isolated psychiatric symptoms	70% (lung, breast, thymus)	Yes, frequent relapses	Downregulation of AMPA receptors	14
	$GABA_BR$	Prominent seizures	60% (SCLC)	Yes	None	25
	mGluR5	Ophelia syndrome	Hodgkin lymphoma	Unknown	None	2
Morvan's syndrome	CASPR2	Encephalopathy, peripheral nerve hyperexcitability, dysautonomia	Thymoma	Yes	Not tested	9
PERM	GlyR	Encephalomyelitis with myoclonus, rigidity and brainstem signs	Thymoma	Yes	Not tested	6
Cerebellar ataxia	VGCC	Possible coexistence of LEMS	SCLC	Poor	Not tested	16
	mGluR1	Remote history of Hodgkin lymphoma	Hodgkin lymphoma	Yes	In vivo	3

The frequencies given depend on reported cases. Many cases are being diagnosed but are not reported.
Ab, antibody; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin associated protein 2; $GABA_BR$, gamma-aminobutyric acid B receptor; GlyR, glycine receptor; LE, limbic encephalitis; LEMS, Lambert-Eaton myasthenic syndrome; LGI1-Ab, leucine rich glioma inactivated 1 protein antibody; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; PERM, progressive encephalomyelitis with rigidity and myoclonus; SCLC, small cell lung cancer; VGCC, voltage gated calcium channel.

AUTOIMMUNE

The clinical presentation of autoimmune encephalopathies (AEs) varies greatly and includes cognitive decline and psychiatric changes developing over days, weeks, or months, often associated with seizures.

Myoclonus, extrapyramidal symptoms, ataxia, or signs of hypothalamic or autonomic dysfunction can also be observed.

The term limbic encephalitis (LE) is often used to describe a classic phenotype of AE characterized by subacute onset of behavioral changes, memory problems, and seizures. But frequently the disease is multifocal and other parts of the CNS are affected (such as hypothalamus or brainstem), characterizing an autoimmune encephalomyelitis.

Clinical features and demographics might give clues as to the antibody causing an AE.

Encephalopathy due to VGKC complex antibodies (caused by LGI-1 receptor antibodies) can cause RPD that resembles CJD, though hyponatremia due to SIADH might be a clue as it is not typical of CJD, but is found in about 60% of cases with VGKC complex antibody encephalopathy.

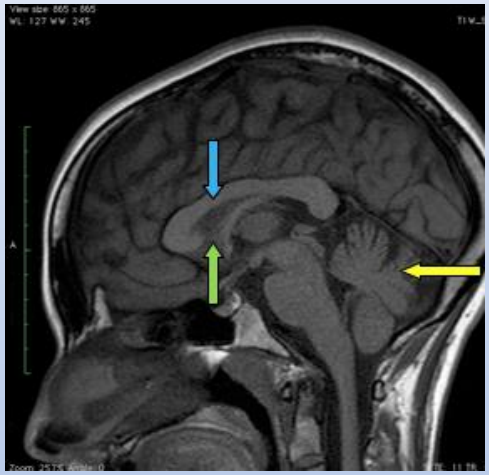
AMPAR antibody encephalitis is more frequent in middle-aged women; in a male under 50, AMPAR antibody encephalitis is associated with SCLC, breast or thymus tumors,
Anti-Ma2 antibodies (usually associated with testicular tumors) and testicular ultrasound should be considered. And

GABA$_B$R antibody encephalitis is associated with LE and frequent seizures.

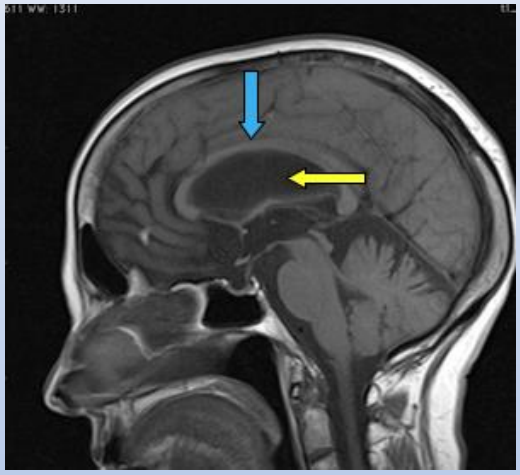
Several excellent reviews on these antibody-mediated encephalo- pathies have recently been published.:

- *Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol 2011;18:19-e3.*
- *Flanagan EP, Caselli RJ. Autoimmune encephalopathy. Semin Neurol 2011;31:144–157.*
- *Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 2011;77:179–189.*
- *Mckeon A, Lennon VA, Pittock SJ. Dementia: immunotherapy-responsive dementias and encephalopathies. Continuum 2010;16:80–101.*

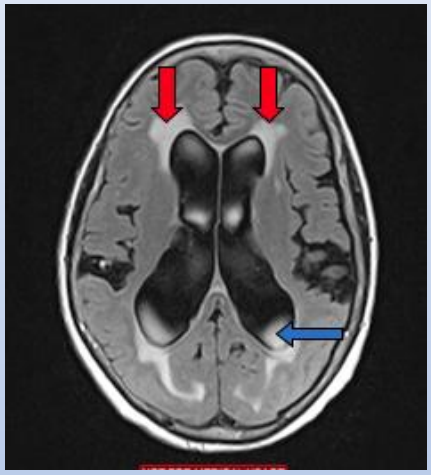
Idrocefalo Normoteso (NPH)



RM in sequenza T1 pesata, in proiezione laterale che mostra un idrocefalo importante. Il corpo calloso è sottile per la dilatazione dei ventricoli laterali (freccia gialla) . Si confronti con la figura precedente.



RM in sequenza T1 pesata, in proiezione laterale che mostra un idrocefalo importante. Il corpo calloso è sottile per la dilatazione dei ventricoli laterali (freccia gialla) .



Sequenza FLAIR in proiezione assiale. I ventricoli sono ampi e dilatati. Attorno ai ventricoli il parenchima è sofferente, il bianco che sembra un cappuccio (freccia rossa), ed è tipico delle situazioni di idrocefalo. Il liquor nei ventricoli ha un flusso turbolento: le chiazze bianche al centro e posteriormente (freccia blu).

Cognitive domains and available screening tests

Tools	Executive function	Memory	Language	Visuospatial	Arithmetic	Praxis	Facial recognition
Localization							
Lobe in the brain	Frontal	Temporal	Dominant hemisphere	Biparietal and occipital	Dominant parietal	Parietal	Right temporal
Sample bedside tests	Modified Trails Making test, digit span, spelling W-O-R-L-D backwards, serial 7s, verbal fluency, letter cancellation, Wisconsin card sorting	Orientation, learning and delayed recall, logical (story) memory, free-cued recall, California adult verbal learning test	Reading, writing, naming, comprehension, repetition, semantic fluency	Cube copy, intersecting pentagons, Rey-Osterrieth complex figure, block design, figure (i.e., clock) construction	Calculations (simple arithmetic)	Completion of cued motor plans/actions, figure (i.e., clock) construction	Identify famous faces [101]
Practical screening tests							
MoCA	+	+	+	+	+	+	
MMSE	+	+	+	+	+	+	
Clock draw	+			+	+	+	
SLUMS	+	+	+	+	+	+	
Short portable mental status questionnaire	+	+			+		

+: Domain assessed by screening test; MMSE: Mini-Mental Status Examination; MoCA: Montreal Cognitive Assessment; SLUMS: Saint Louis University Mental Status examination.

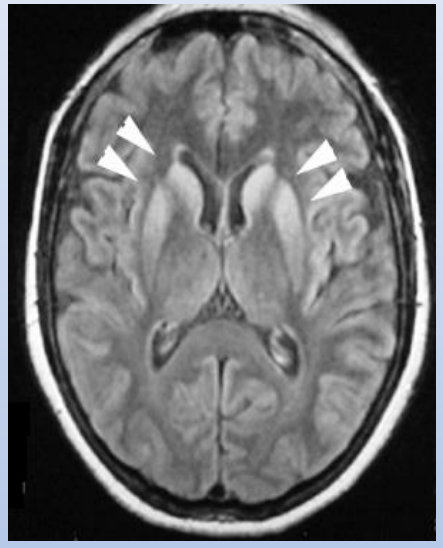
Modified by: Day & Tang-Wai - Neurodegen. Dis. Manage. 2014

Human Prion Diseases

MRI

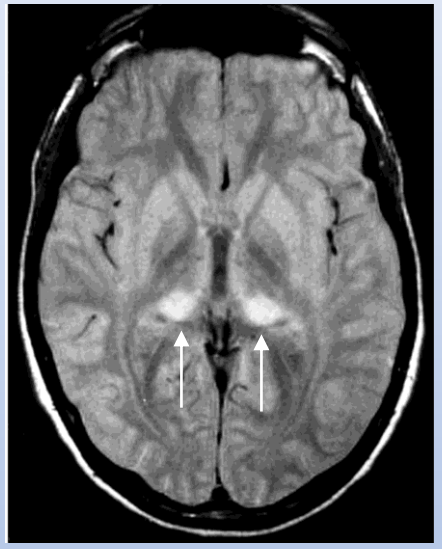
FLAIR

Sporadic CJD



Transverse showing bilateral anterior basal ganglia high signal (arrowheads)

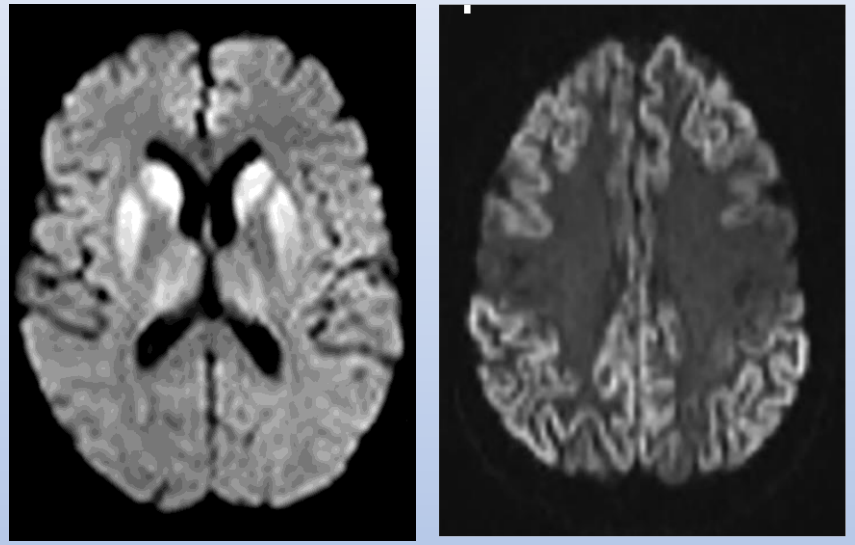
Variant CJD



Bilateral and symmetrical high signal in the pulvinar nuclei of the thalamus - the '***pulvinar sign***' of variant CJD

DWI

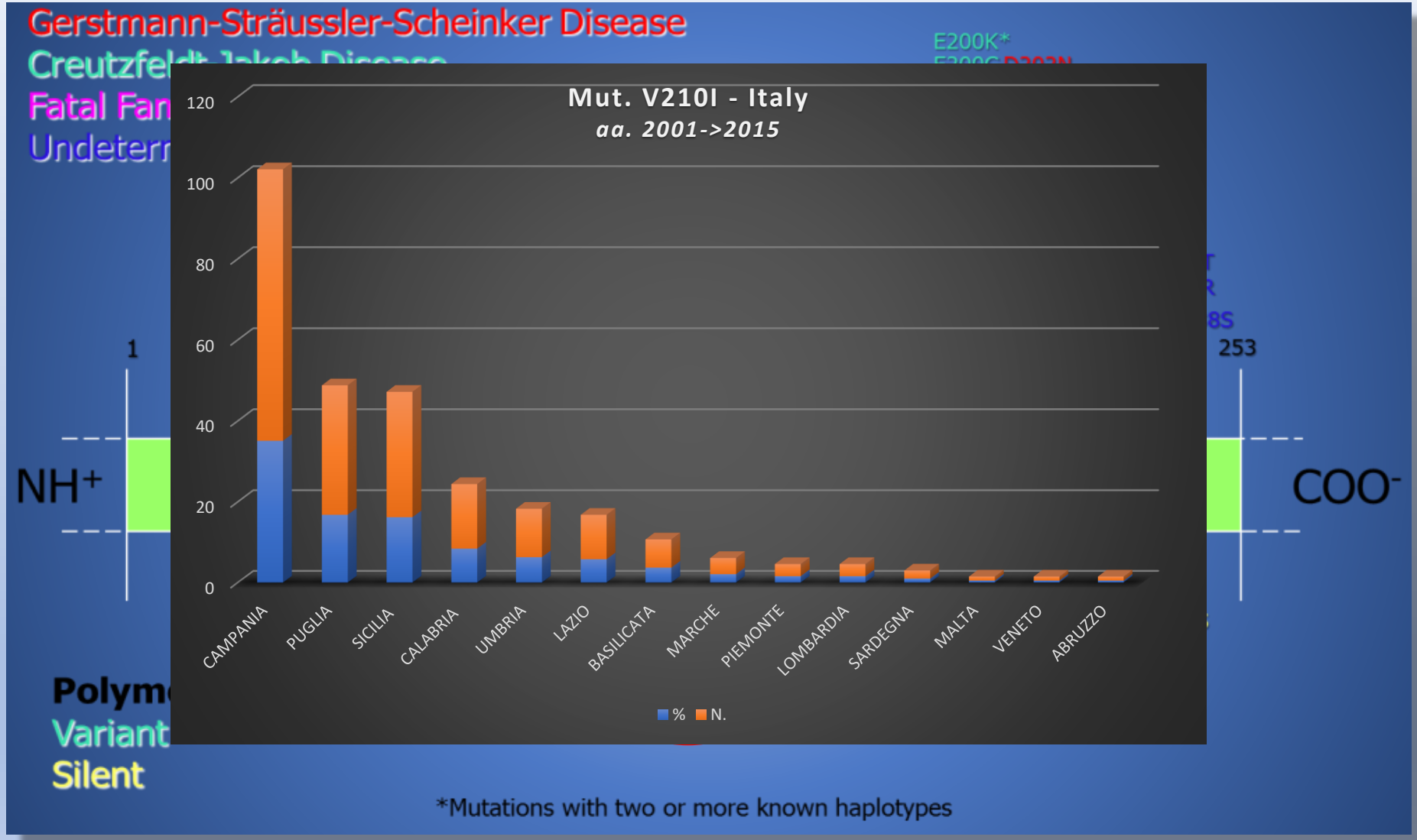
Sporadic CJD



Modified by *Mackenzie G and Will R. Creutzfeldt-Jakob disease: recent developments [version 1]. F1000Research 2017, 6:2053 (doi: 10.12688/f1000research.12681.1)*

Genetic forms (10-15%)

Pathogenic mutations and polymorphisms of the human prion protein



Autoimmune Causes of Brain Dysfunction –
Breaking down barriers between Neurology and Psychiatry

Autoimmune Encephalitis in Postpartum Psychosis

Veerle Bergink, M.D., Ph.D., Thais Armangue, M.D., Maarten J. Titulaer, M.D., Ph.D., Sander Marks, M.D., Josep Dalmau, M.D., Ph.D., Steven A. Kushner, M.D., Ph.D.

-- 2% of women with postpartum ps
women cared for in a dedicated mot
-- Another 2% exhibited abnormal st

One Brain, Two Specia
Neuronal Autoantibodi
Postpartum Psychosis

Jeffrey M. Gelfand, M.D., M.A.S.

Encephalitis and Antibodies to Dipeptidyl-Peptidase–Like Protein-6, a Subunit of Kv4.2 Potassium Channels

Anna Boronat, BS,[1] Jeffrey M. Gelfand, MD,[2] Nuria Gresa-Arribas, PhD,[1] Hyo-Young Jeong, PhD,[3] Michael Walsh, MD,[4] Kirk Roberts, MD,[5] Eugenia Martinez-Hernandez, MD,[6] Myrna R. Rosenfeld, MD, PhD,[1,7] Rita Balice-Gordon, PhD,[8] Francesc Graus, MD,[1] Bernardo Rudy, PhD,[3] and Josep Dalmau, MD, PhD[1,7,9]

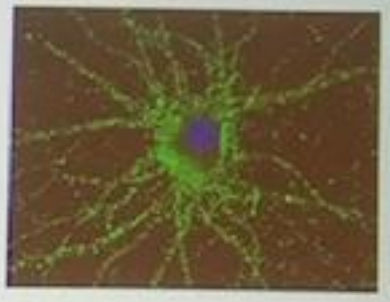
Annals of Neurology, 2013

DPPX potassium channel antibody

Frequency, clinical accompaniments, and outcomes in 20 patients

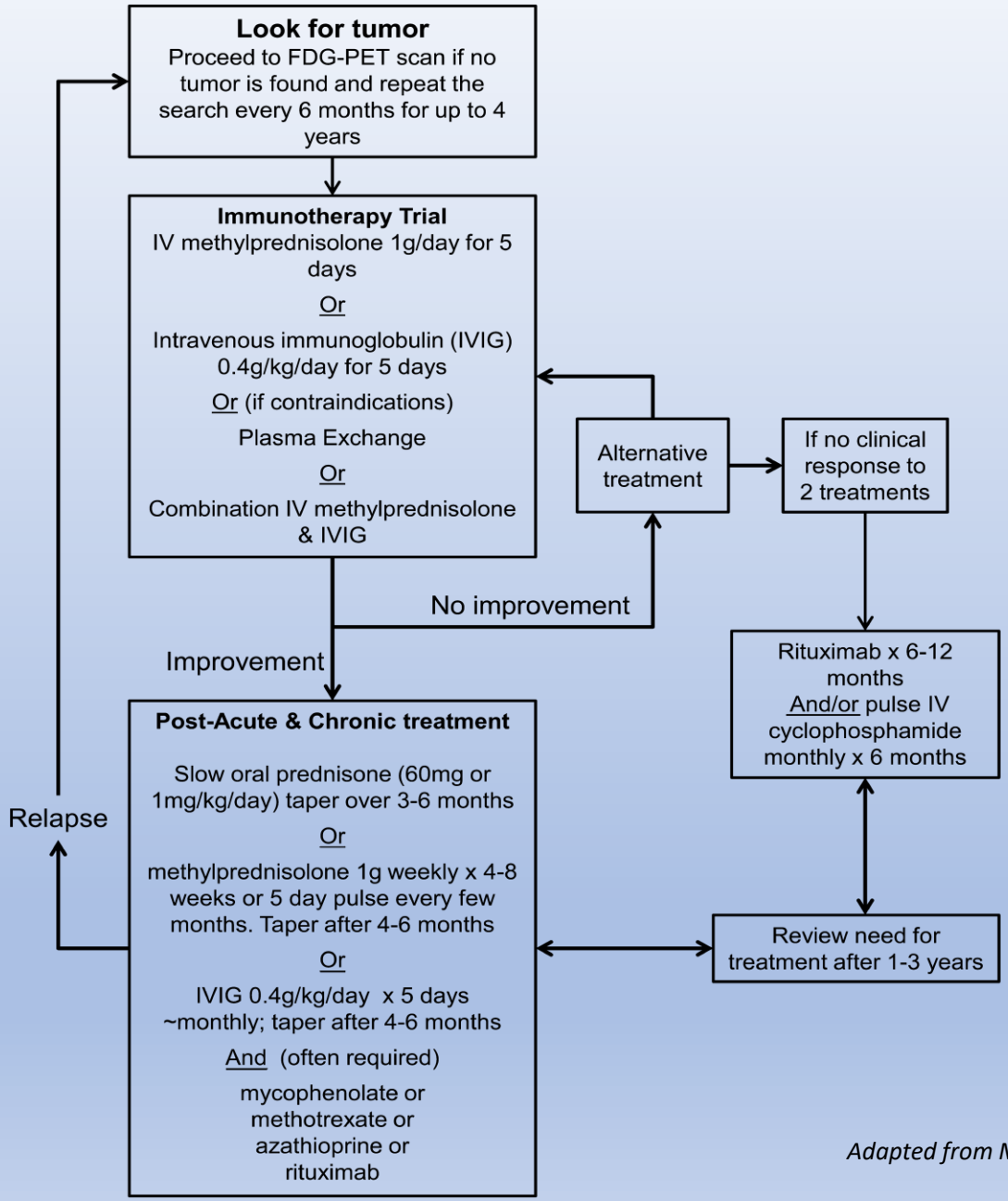
Neurology, 2014

DPPX Encephalitis

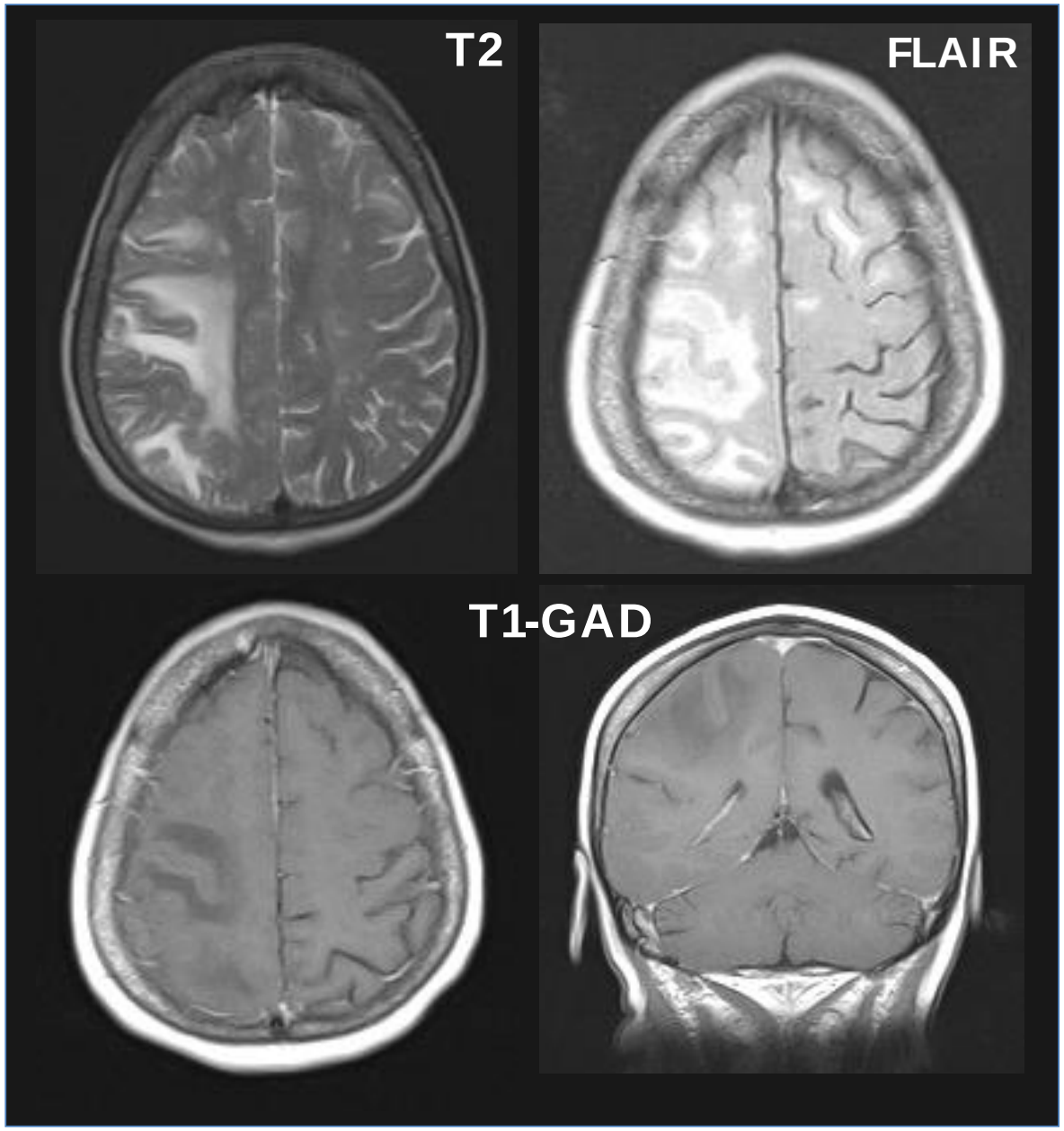


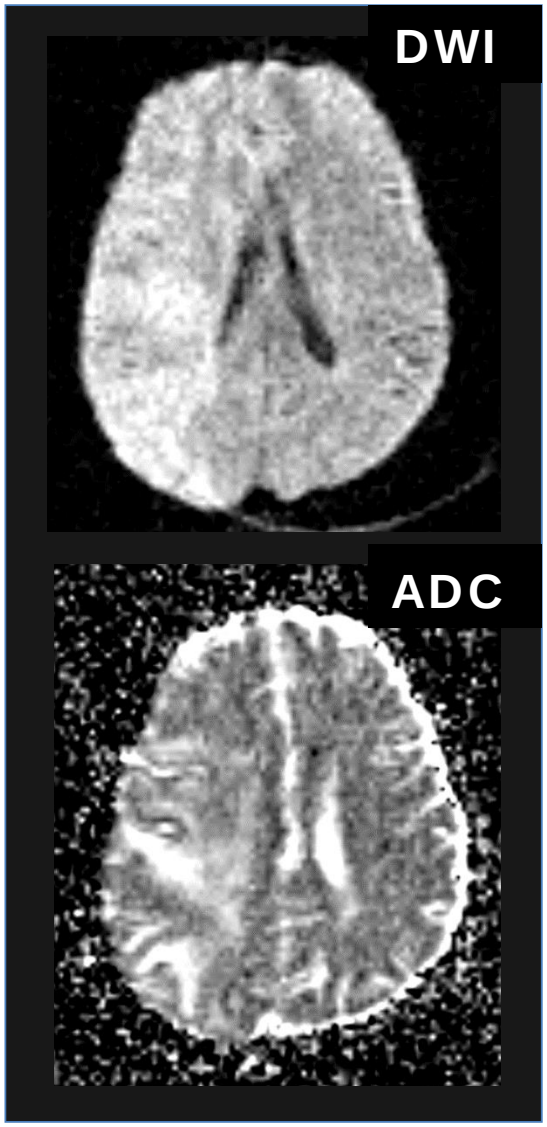
- **GI prodrome with intense diarrhea** (Note that the gut has more neurons than the spinal cord and gut neurons (myenteric plexus) express these antigens)
- **Hyperexcitability** – seizures, myoclonus, exaggerated startle
- **Encephalopathy**

Proposed non–evidence-based treatment algorithm for autoimmune paraneoplastic and non-paraneoplastic encephalopathies

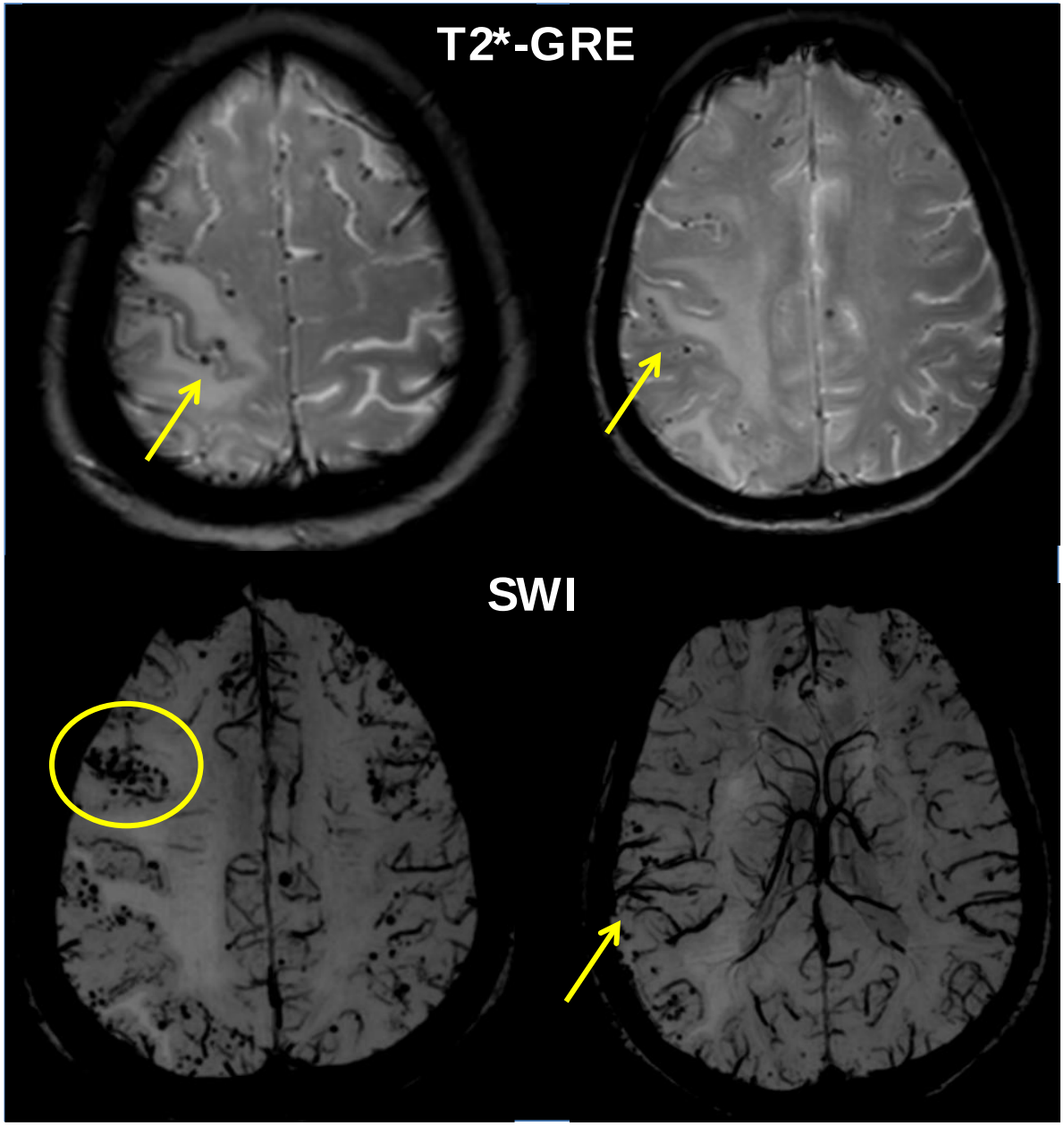


Adapted from Mckeon et al. Continuum 2010





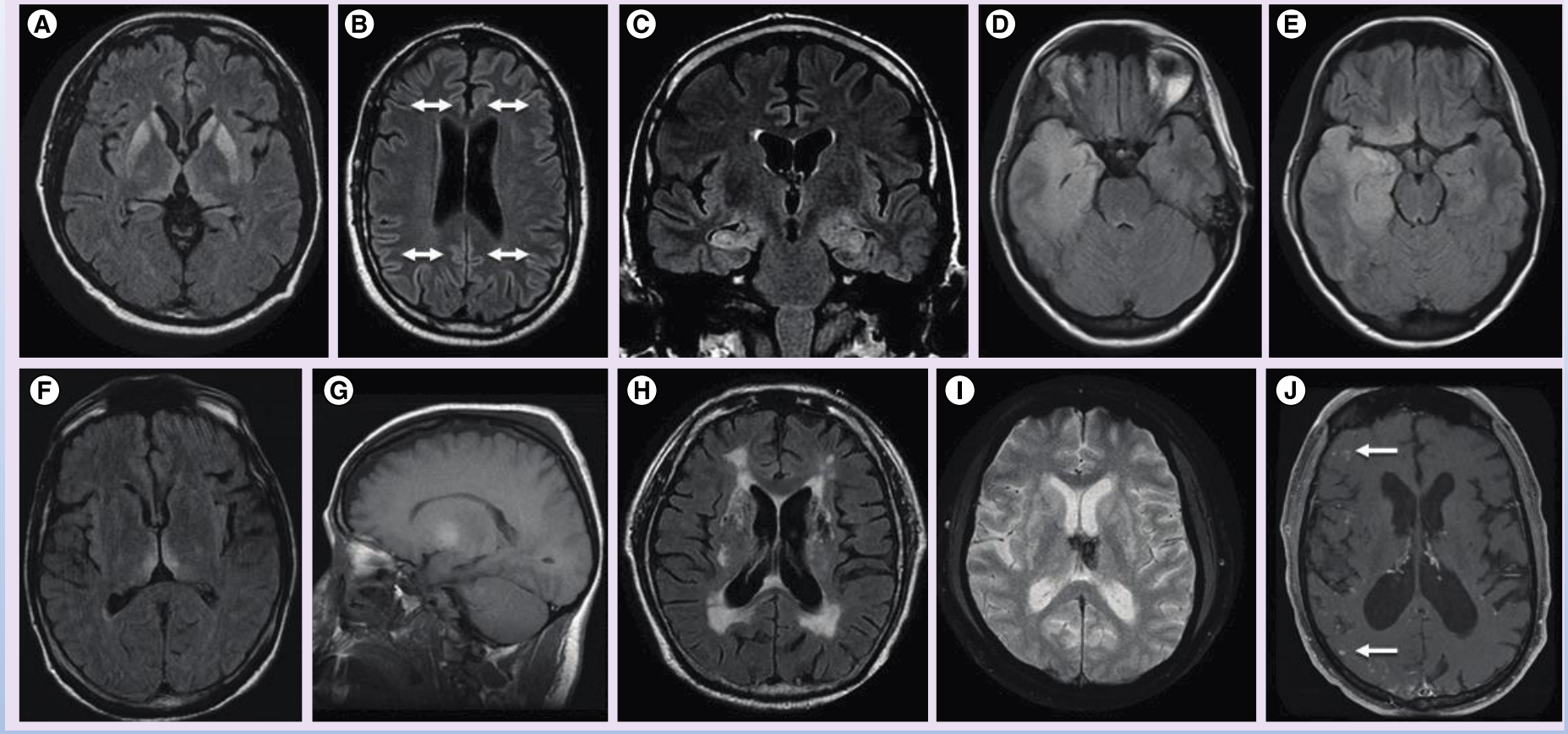
edema vasogenico



Cortical Microbleeds CMBs

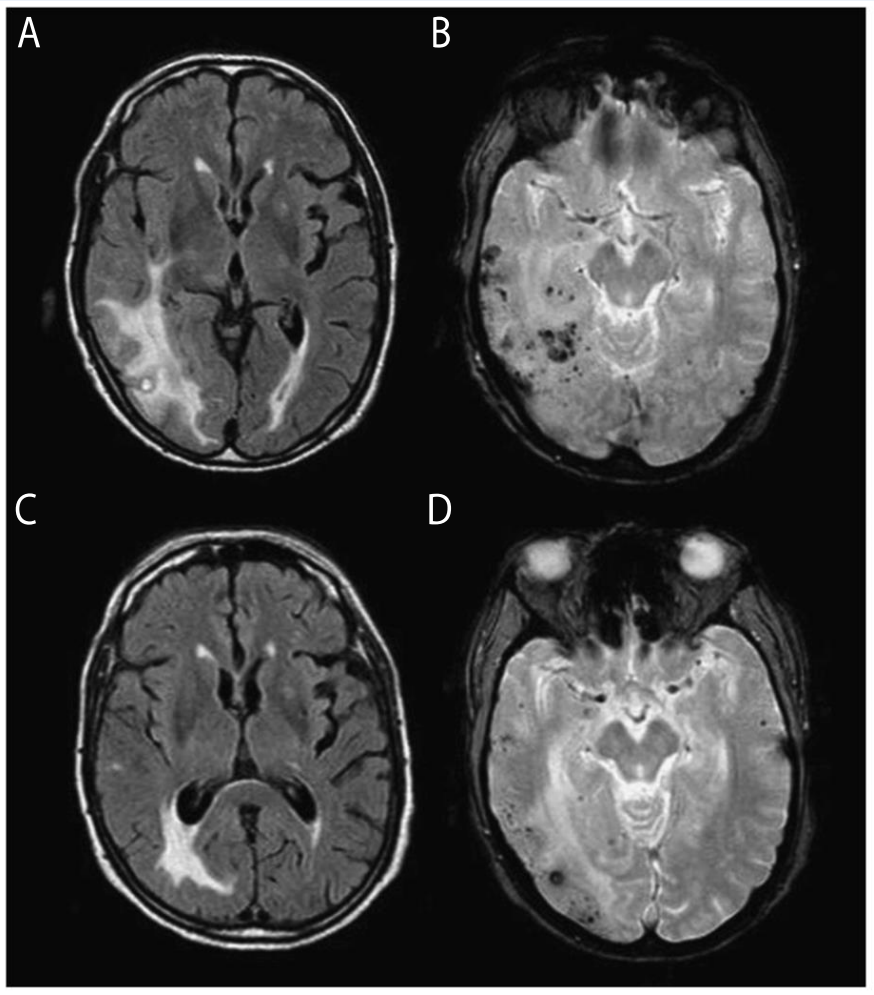
Siderosi Superficiale Corticale

Diagnostic MRI of the brain in select cases of rapidly progressive dementia



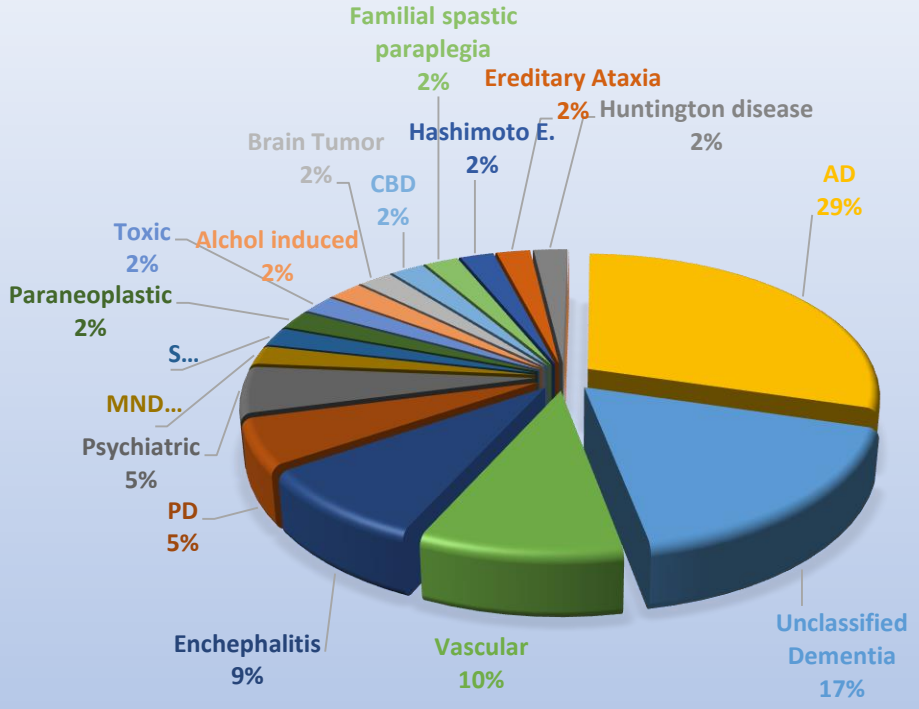
(A & B) CJD: axial fluid-attenuated inversion recovery sequences (FLAIR) images demonstrating striatal **(A)** thalamus and **(B)** cortical (arrows) T2-hyperintensities. **(C) Limbic encephalitis**: coronal FLAIR images demonstrating bilateral limbic/hippocampal T2-hyperintensities.
(D & E) Herpes simplex encephalitis: axial T1-weighted images demonstrating right anteromedial temporal lobe hyperintensities.
(F) Wernicke's encephalopathy: axial FLAIR images demonstrating dorsomedial thalamic T2-hyperintensities. **(G) Hepatic encephalopathy**: sagittal T1-weighted images demonstrating diencephalon hyperintensity. **(H & I) Cerebrovascular disease**. **(H)** Axial FLAIR images demonstrating strokes and diffuse ischemic white matter changes. **(I)** Axial gradient-echo images demonstrating bilateral anterior and dorsomedial **thalamic hemorrhage** causing acute-onset amnesia. **(J) CNS vasculitis**: axial T1-weighted images with gadolinium demonstrating enhancement of vessels in the right hemisphere (arrows).

Cerebral amyloid angiopathy-related inflammation



Modified with permission from Crosta F, et al, Case Rep Neurol Med. www.hindawi.com/journals/crinm/2015/483020/. B 2015 Francesca Crosta et al.

An elderly man presented with relatively acute onset left hemiparesis, left homonymous hemianopia, dysarthria, spatial and temporal disorientation, sensory aphasia, and psychomotor slowness. Cerebral amyloid angiopathy-related inflammation was suspected and the finding of APOE genotype (4/(4 supported the diagnosis. Anti-amyloid-" (A") autoantibody concentration in CSF was elevated at 55.9 ng/mL. Physical therapy and corticosteroid therapy with dexamethasone 24 mg/d were started and the patient showed clinical improvement. Initial axial fluid-attenuated inversion recovery (FLAIR) MRI shows bilateral hyperintense lesions (A) and gradient recalled echo (GRE) image shows cortical and subcortical microhemorrhages (B). After 1 month of steroid therapy, FLAIR MRI (C) and GRE (D) sequence show reduction of both cerebral edema and microhemorrhages.


Familial spastic paraplegia 2%
Ereditary Ataxia 2%
Huntington disease 2%
Hashimoto E. 2%
Brain Tumor 2%
CBD 2%
AD 29%
Toxic 2%
Alchol induced 2%
Paraneoplastic 2%
S...
MND...
Psychiatric 5%
PD 5%
Enchephalitis 9%
Vascular 10%
Unclassified Dementia 17%

Enchephalitis is a major public health problem

UNITED STATES

- $ 2.0 billion USD hospital charges in 2010
- >260,000 U.S. hospitalizations 1998-2010
- About 20,000 hospitalizations per year
- 5.7% fatal, 10.1% if HIV/AIDS, 17,1% transplant

ENGLAND, ITALY, AUSTRALIA

- 5-6/100,000 incidence

Cause of Enchephalitis is often UNSOLVED

	Year	Popuation	Infectious	Inflammatory / Autoimmune	Unknown
Sing et al. Neurology	2015	Adult - Mayo Clinic	48%	22%	**30%**
Pillai et al. Pediatrics	2015	Children - Sydney/NSW	38%	34%	**28%**
Saraya et al. BMC Neurology	2013	Children/Adult - Thailand	24%	25%	**52%**
Granerod et al. Lancet ID	2010	Children/Adult - England	42%	21%	**37%**
Maillers et al. CiD	2009	Children/Adult - France	52%	Not sampled	**48%**
Olsen et al. EiD	2015	Children/Adult - Thailand	36%	Not sampled	**64%**
Glaser et al. CiD	2006	Children/Adult - CA Enceph Project	29%	8%	**63%**

l sistema limbico possiede due componenti:

una parte relativa alla corteccia,
- Giro del cingolo
- Paraippocampo
- Ippocampo
- Corteccia relativa ai nuclei septali

una profonda
- amigdala
- formazione reticolare
- nucleo anteriore del talamo
- parte dell'ipotalamo
- nuclei abenulari

Il sistema limbico opera influenzando il sistema endocrino e il sistema nervoso autonomo. È largamente connesso con il Nucleus accumbens tramite i circuiti cortico-striato-talamici, la cui degenerazione è stata associata all'insorgere di sindromi schizofreniche.
Inoltre il sistema limbico riceve proiezioni dopaminergiche dal mesencefalo che danno vita alla *via dopaminergica mesolimbica* correlata ai fenomeni di gratificazione e quindi all'effetto delle sostanze d'abuso (oppioidi endogeni e alcune droghe trovano un'abbondanza di recettori in queste strutture cerebrali)[16].
Le proiezioni noradrenergiche provenienti dal nucleo pontino del locus coeruleus (così come le fibre serotoninergiche[17]) sono invece responsabili degli attacchi di panico, ansia, paura di morire, senso di soffocamento e derealizzazione[16], tutti sintomi che si rinvengono nelle crisi epilettiche della corteccia limbica[16].
Le proiezioni colinergiche dei nuclei del setto sono invece fondamentali per il mantenimento della memoria: lesioni di tali nuclei portano a disturbi della memoria, come nelle demenze[11].
Il sistema limbico è strettamente connesso alla corteccia prefrontale. Molti scienziati ritengono che questi circuiti limbico-frontali siano coinvolti nei meccanismo di presa di decisione in base a reazioni emozionali.

Diagnostic Breakdown of Non–Jakob-Creutzfeldt Disease Rapidly Progressive Dementia Referrals to Three Jakob-Creutzfeldt Disease Referral Centers

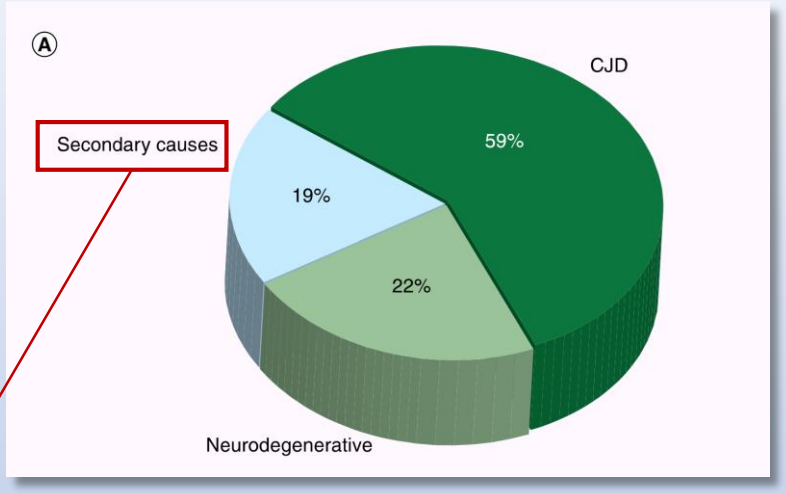
University of California, San Francisco (UCSF), Cohort N = 104 (21)[b]	%	German Cohort[7] N = 124 (37)[b]	%	National Prion Disease Pathology Surveillance Center (NPDPSC) Cohort[8] N = 304 (304)[b]	%
Autoimmune/antibody-mediated[c]	13	Alzheimer disease	27	Alzheimer disease	51
Unclassified dementia	13	Unclassified dementia	16	Vascular disease	12
Psychiatric	12	Cerebrovascular (vascular dementia, cerebrovascular accident)	9	Immune mediated	9
Dementia with Lewy bodies	8	Encephalitis, unknown	8	Neoplasia	8
Encephalitis, not otherwise specified	8	Parkinson disease	5	Infections	5
Neoplasm	8	Psychiatric	5	Unspecified degenerative disease	3
Frontotemporal dementia with or without motor neuron disease	7	Motor neuron disease	2	Frontal lobe degeneration	3
Corticobasal syndrome or corticobasal degeneration	6	Multiple sclerosis	2	Metabolic	2
Alzheimer disease[d]	5	Paraneoplastic	2	Hippocampal sclerosis	2
Central nervous system vasculitis	3	Toxicity	2	Dementia with Lewy bodies	1
Encephalopathy, not otherwise specified	3	Alcohol induced	2	Tauopathy, not otherwise specified	1
Leukoencephalopathy	3	Brain tumor	2	Hereditary diffuse leukoencephalopathy with spheroids	1
Progressive supranuclear palsy	3	Chronic epilepsy	2	Progressive supranuclear palsy	1
Vascular dementia	2	Corticostriatonigral degeneration	2	Other[e]	2
Other[e]	8	Familial spastic paraplegia	2	Total	100
Total	100	Hashimoto encephalopathy	2		
		Hereditary ataxia	2		
		Huntington disease	2		
		Metabolic disorder	2		
		Primary central nervous system lymphoma	2		
		Other[e]	4		
		Total	100		

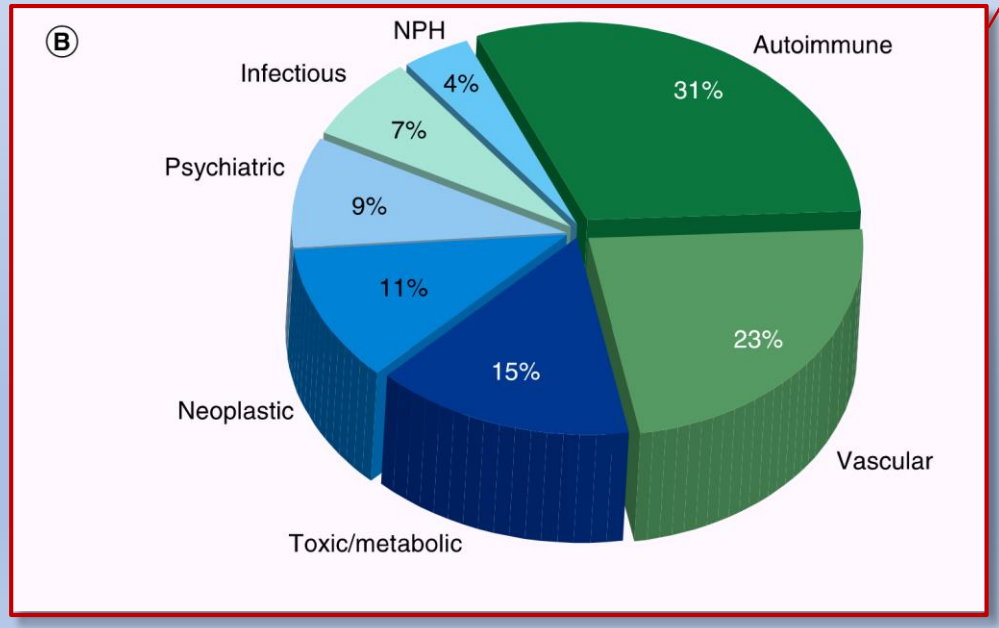
Causes of rapidly progressive dementia.

A definitive cause of RPD was identified in 95.4% (644 out of 675) of patients included in the five largest case series

(A) All causes (n = 644)

(B) Secondary causes (n = 121)





1. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Ann. Neurol. 64(1), 97–108 (2008).

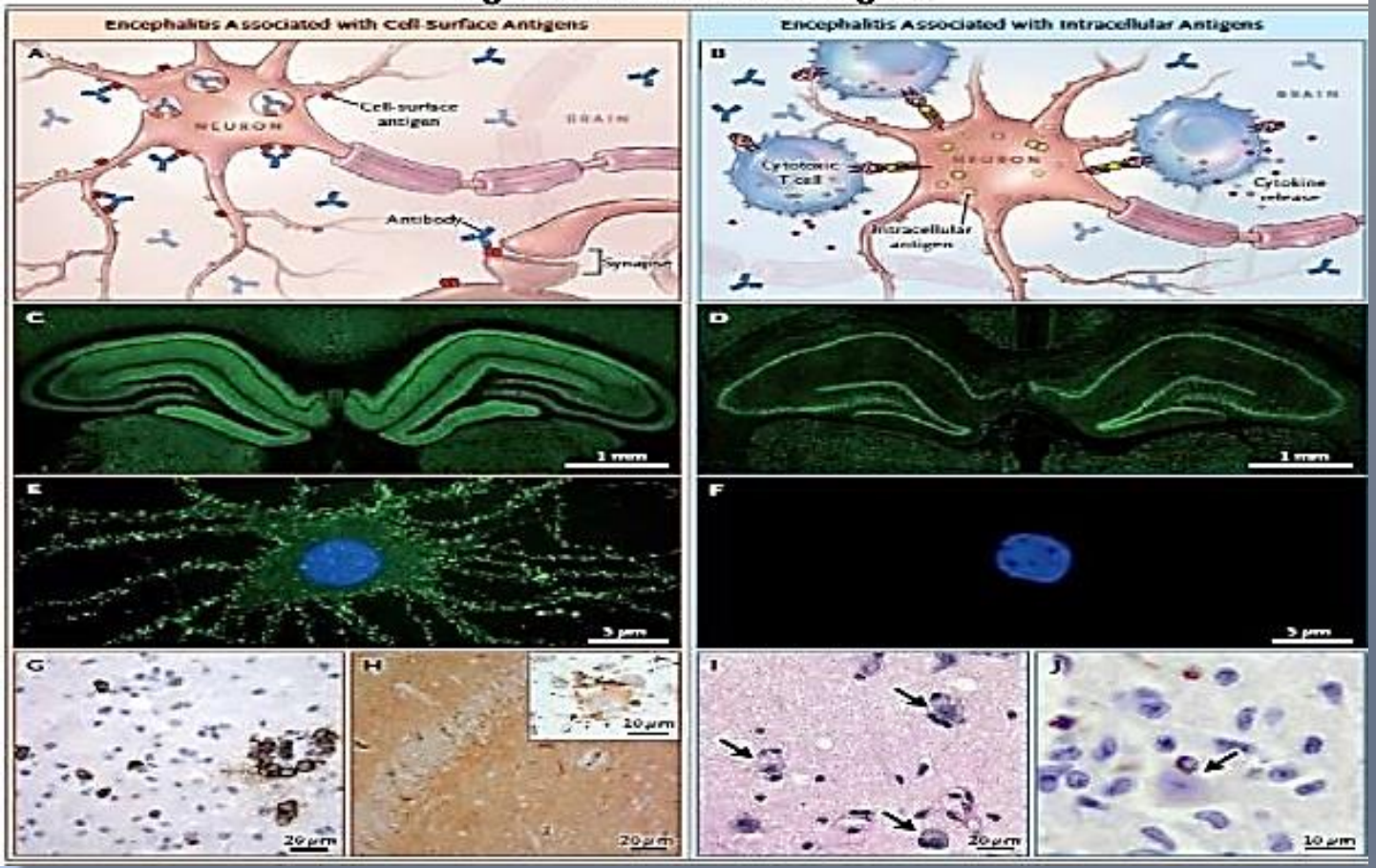
2. Josephs KA, Ahlskog JE, Parisi JE et al. Rapidly progressive neurodegenerative dementias. Arch. Neurol. 66(2), 201–207 (2009).

3. Papageorgiou SG, Kontaxis T, Bonakis A, Karahalios G, Kalfakis N, Vassilopoulos D. Rapidly progressive dementia: causes found in a Greek tertiary referral center in Athens. Alzheimer Dis. Assoc. Disord. 23(4), 337–346 (2009).

4. Poser S, Mollenhauer B, Kraubeta A et al. How to improve the clinical diagnosis of Creutzfeldt–Jakob disease. Brain 122, 2345–2351 (1999).

5. Sala I, Marquie M, Sanchez-Saudinos MB 24 et al. Rapidly progressive dementia: experience in a tertiary care medical center. Alzheimer Dis. Assoc. Disord. 26(3), 267–271

Antibody Reactivity and Pathological Features of Encephalitis Associated with Antibodies against Neuronal Cell-Surface Antigens as Compared with Encephalitis Associated with Antibodies against Intracellular Antigens

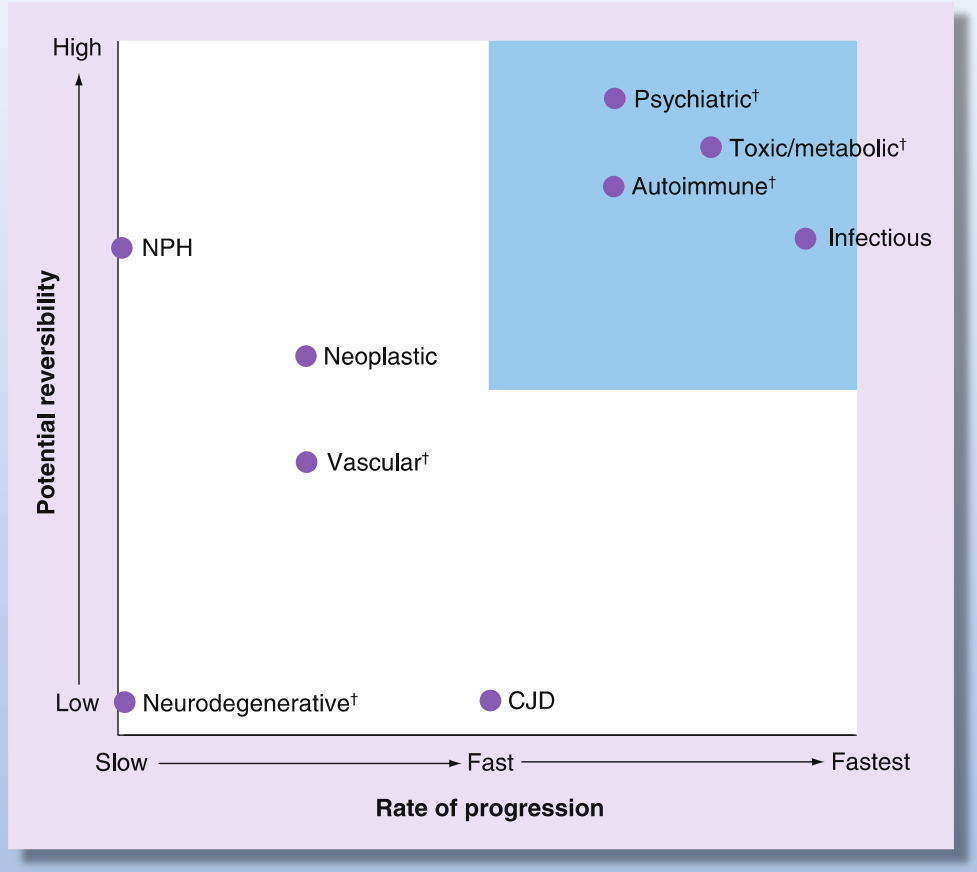


Stain against rodent brain slices

Cultured dissociated hippocampal neurons (Rat)

Dalmau J. and Graus F. N Engl J Med. 2018

Causes of rapidly progressive dementia stratified by rate of progression and potential reversibility



Disease etiologies in the top right quadrant (shaded) are typically associated with the most rapidly progressive presentations and the greatest potential for response to treatment with appropriate treatments.

†Associated with marked fluctuations in course; neurodegenerative disease with prominent fluctuations implies a diagnosis of dementia with Lewy bodies.

Modified by: Day & Tang-Wai - Neurodegen. Dis. Manage. 2014