PRION DISEASE

Disease	Acquisition	Epidemiology	Clinical manifestations	Workup
Sporadic CJD *Cortical & Subcortical*	Sporadic	**Onset**: Peak age is after 50 **Survival**: 50% die in 6 months, 90% die in 1 year **Disability**: inability to perform ADL within 4-8 weeks from onset	**Cognitive**: Memory impairment – aphasia – executive dysfunction **Behavioral**: agitation – irritability – depression – apathy **Cerebellar**: ataxic gait **Motor**: rigidity – dystonia - myoclonus – pyramidal signs **Types** (according to codon 129, either valine or methionine): MM1/MV1 (40%): rapidly progressive dementia, myoclonus VV2 (15%): rapidly progressive ataxia MV2 (8%): Cognitive decline, ataxia, slowly progressive (mean survival 16 months) MM2-thalamic: insomnia (called sporadic fatal insomnia)	**EEG**: 1-2 Hz periodic discharges in 60% **MRI**: cortical ribboning & thalamic, putaminal or caudate restriction, Hockey stick sign (pulvinar + medial nuclei are hyperintense). **CSF**: elevated t-tau, 14-3-3, NSE **RT-QuIC** from CSF or olfactory mucosa positive.
Familial CJD	Inherited (AD) PRNP mutations (E200K mutation, codon 129)	**Onset**: younger 30-50 **Risk factors**: Sephardic (Tunisian/Libyan) Jews & Slovakian ancestry	Same clinical picture as sporadic CJD but younger age of onset.	Same but less prominent cortical ribboning.
Variant CJD (vCJD) *Thalamic* ***Last case was in 2012***	Acquired	**Onset**: **Survival**: average 14 months **Risk factors**: eating meat of infected cattle, mainly in UK and France.	Psychiatric symptoms for 6 months before cognitive decline, ataxia and myoclonus.	**EEG**: usually nonspecific slowing **MRI**: pulvinar sign (posterior thalamic nuclei are hyperintense) **CSF** markers are not elevated **Tonsillar biopsy**: as it spreads through GI lymphatics
Gerstmann-Straussler-Scheinker (GSS) *Subcortical*	Inherited (AD) PRNP mutations (codon 102)	**Onset**: 50s **Risk factors**: only in few families (Indiana Kindred family in USA)	Usually starts with ataxia, parkinsonism then develops dementia, less incidence of myoclonus.	**EEG**: usually nonspecific slowing **MRI**: may be normal **CSF** markers are not elevated **RT-QuIC** positive
Fatal familial insomnia (FFI) *Thalamic*	Inherited (AD) PRNP mutations (D178N mutation, codon 129)	**Onset**: 40s **Survival**: Average 18 months **Risk factors**: only 26 families worldwide	Starts with intractable **insomnia** over several months, followed **psychiatric** features (paranoia, hallucinations) then **dysautonomia** (e.g., tachycardia, hyperhidrosis, and hyperpyrexia).	**EEG**: usually nonspecific slowing **MRI**: may be normal **CSF** markers are not elevated **PET**: thalamic hypometabolism **RT-QuIC** positive
Kuru (means shaking in Fore language) ***Eradicated***	Acquired (due to funerary cannibalism)	Onset: variable Survival: variable Risk factors: Fore tribe of Papua New Guinea	Characterized by ataxia, tremors, bouts of laughter along with rapidly progressive dementia. Disease has already disappeared since the Fore tribe stopped their funerary cannibalism.	
Scrapie (sheep scrape their fleece against rocks)	Not transmissible to humans	Affects sheep	Sheep starts to scrap their fleeces against rocks, abnormal lip movements, later ataxia, anorexia and weight loss.	

Chronic wasting disease (CWD)	Don't know if transmissible	Affects deer and elk Mainly in Colorado, Wyoming & Nebraska	Behavioral changes, decrease interaction with other animals, muscle wasting and weight loss

All inherited prion diseases are caused by mutations in prion-related protein gene (PRNP).

The only prion that can be transmitted from animals: variant CJD.

Familial prion diseases: Familial CJD – GSS – FFI

vCJD start: started because of the practice of feeding cattle with scrapie-infected sheep products. Humans get infected when they eat the brain of affected cattle.

MRI signs: Hockey stick can be seen in all forms of CJD, but pulvinar sign is specific for vCJD

Pronunciation: Prion (pree-ahn)

History: Scrapie was the first discovered prion disease in 1700s, however it was thought it is caused by a slow virus at that time. In 1923 Hans Creutzfeldt described a case of a woman with rapidly progressive dementia then in 1923, Alfons Jacob described a series of similar cases. It was still being thought that it was a slow virus, but the affected tissues couldn't be inactivated by usual techniques used to inactivate viruses, however it can be inactivated by protein denaturation techniques. In 1997 Stanley Prusiner received Nobel prize for confirming that the infectious scrapie agent was a misfolded protein.

Pathophysiology: Normally, living cells have a protein called Prion-related protein in an alpha helical form, abbreviated PrP^{c} (C stands for cellular). In prion diseases the alpha helical structure is switched to B-pleated sheets, abbreviated PrP^{Sc} (Sc stands for Scrapie agent). PrP^{Sc} in its B-pleated sheets can act as a template for other alpha-helical PrP^{c} and convert them into B-pleated sheets of PrP^{Sc} which in turns affect other protein. In sporadic form, a somatic spontaneous mutation may occur in the PRNP gene while in the hereditary form, it is thought that an inherited mutation makes the PrP^{c} more susceptible for conversion.

Epidemiology: prion diseases occur around 1 per million cases per year. In US there is around 400 new cases each year. Of total prion cases, 85% are sporadic CJD, 10% are familial and around 5% are acquired which is 1 per 20 million).

DIAGNOSTIC CRITERIA

Diagnostic Criteria for CJD	
WHO (Probable)	**UCSF**
Progressive dementia with at least 2 of the following:	**Progressive dementia with at least 2 of the following:**
1. Myoclonus	1. Myoclonus
2. Pyramidal or extrapyramidal dysfunction	2. Pyramidal or extrapyramidal dysfunction
3. Akinetic mutism	3. Akinetic mutism
4. Visual or cerebellar disturbance (aphasia, apraxia, neglect)	4. Visual disturbance
	5. Cerebellar disturbance
And either:	6. Higher cortical signs
1. Typical EEG	**Typical EEG or MRI findings**
2. Positive 14-3-3 essay with disease duration to death < 2 years	**Routine investigation doesn't suggest an alternative diagnosis**
Routine investigation doesn't suggest an alternative diagnosis	

DIAGNOSTIC TESTS:

EEG:

- 1-2 Hx periodic sharp-wave discharges (biphasic or triphasic) is present in 60% of patients.
- Appears in advanced stages, so initial EEGs may be negative.

MRI:

- Restricted diffusion in cortical and deep grey matter (cortical ribboning and thalamic, putaminal or caudate diffusion restriction > 90% sensitive and specific).
- Pulvinar sign is characteristic of vCJD where the posterior part of thalamus is hyperintense. Hockey stick sign where the medial part of thalamus in addition to the posterior part is rather non-specific, can be seen with different prion diseases.

CSF: Usually normal but can show mildly elevated protein.

Biomarkers:

- 14-3-3, S100B, NSE (neuron-specific enolase), t-tau (total tau) in CSF: Neither of them is adequately sensitive of specific. Use only if MRI is not helpful.
- RT-QuIC (Real-time quaking-induced conversion) either in CSF or olfactory mucosa brushing: 80% sensitive but 100% specific.