Slow Infections

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* ***long incubation*** (several months ÷ several years).
* ***protracted course*** generally ending in death.
* visada apima CNS (ir tik CNS):
	1. progressive dementia
	2. motor deficits
	3. seizures
		1. **Prion diseases**: [*see below* >>](#Prionoses)
1. Creutzfeldt-Jakob disease (CJD) – most common prion disease!
2. Gerstmann-Straüssler-Scheinker disease (GSSD)
3. kuru
4. fatal familial insomnia
	* 1. **Viral infections**:
5. subacute sclerosing panencephalitis (measles)
6. progressive rubella panencephalitis (rubella)
7. progressive multifocal leukoencephalopathy (JC virus)
8. tropical spastic paraparesis (HTLV-I)

Prion diseases (Prionoses)

- fatal **transmissible spongiform encephalopathies** (noninflammatory neurodegenerative disorders)

[Creutzfeldt-Jakob disease (CJD) 5](#_Toc157279856)

[Kuru 8](#_Toc157279857)

[Gerstmann-Straüssler-Scheinker disease (GSSD) 7](#_Toc157279858)

[Fatal Familial Insomnia 8](#_Toc157279859)

Etiopathophysiology

prion - infectious protein (**prion protein** PrP)

* **PrP gene** (termed *PRNP*) - single copy is located on short arm of chromosome 20.

PrPC (normal cellular isoform of PrP) is normal cell surface glycoprotein:

* developmentally regulated.
* both **membrane-associated** and **secreted** forms exist.
* found in most tissues of body but is expressed at ***highest levels in CNS***, esp. in neurons.
* *PrP knockout* *mice* show no obvious pathological phenotype (but have abnormalities in synaptic physiology and circadian rhythms).

Prion diseases are result of PrPSc (abnormal isoform of PrPC; S for “scrapie”).

* + PrPC exists as α-helical structure.
	+ PrPSc exists as β-pleated sheets (arise from post-translational changes in PrPC conformation) - resists proteolytic digestion → spontaneously aggregates to rodlike or fibrillary particles (***prion rods***).

How PrPSc may appear:

1. conformational change resulting in PrPSc may occur *spontaneously*:
	1. at *extremely low rate* ("de novo") – sporadic prion disease (sporadic CJD).
	2. at *higher rate* if various mutations are present in PrPc – hereditary prion disease (GSSD, familial CJD, fatal familial insomnia).
2. PrPSc may be *inoculated* - infectious prion disease (kuru, iatrogenic CJD).

PrPSc (independent of means by which it originates) facilitates, in cooperative fashion, comparable transformation of other PrPc molecules - PrPSc acts as template that promotes cascading PrPC conversion - ability to replicate! (infectious nature of PrPSc molecules).

**ability to replicate (infectivity)** resides in post-translational tertiary or quaternary alterations in PrP folding!

* ***existence of prion strains*** suggests that PrPSc could adopt multiple distinct pathological conformations.
* material prepared from sporadic or familial cases is infectious when inoculated into appropriate animal hosts.
* each prion strain has *characteristic* *range of infectivity* (e.g. 263K strain is pathogenic for hamsters but does not infect mice) - species barrier (not absolute, as illustrated by emergence of “mad cow disease” in humans).
* *PrP knockout* *animals* are resistant to infection by PrPSc.
* *brain contains highest concentration* of infectious agent; also spinal cord, CSF, and (at much lower levels of infectivity) many peripheral organs, circulating WBCs.
* infectivity has *never been demonstrated* in any external secretion or excretion (urine, feces, tears, saliva).
* prions inoculated by peripheral routes (orally or transcutaneously) replicate in lymphoid organs (esp. spleen and lymph nodes) → hematogenic spread to CNS.

Wide variety of disease-causing mutations have been identified! (e.g. certain families with CJD and fatal familial insomnia are linked to point mutation D178N in *PRNP* gene).

Role of normal Met/Val polymorphism in *PRNP* gene at codon 129:

1. Influences disease pattern:
	1. Met at codon 129 in same allele as D178N point mutation → fatal familial insomnia.
	2. Val at codon 129 in same allele as D178N point mutation → CJD.
2. Many sporadic CJD patients are homozygous at codon 129 (for either Met or Val), while 50% of control populations are heterozygous at this site - heterozygosity at codon 129 is protective against development of disease.



##### C. Histology of CJD - spongiform change in cerebral cortex. Inset (high magnification) - neuron with vacuoles.

D. PAS stain of cerebellar cortex - amyloid (kuru) plaques.

Pathology

Prionoses affect grey matter:

1. membrane bound *intracytoplasmic*\* *vacuoles* in cortical neurons and glia; size 1-50 μm; in advanced cases, vacuolated areas coalesce into cystlike spaces ("status spongiosus").

\*within cell processes (neuropil) and sometimes in perikaryon

Exception - fatal familial insomnia (does not show spongiform pathology)

1. amyloid (kuru) plaques (extracellular deposits of aggregated PrPSc) - common, but not invariable feature;
	* Congo red-positive, PAS-positive.
	* do not stain with anti-β A4 protein (vs. Alzheimer plaques).
	* occur in cerebellum (in GSSD), cerebral cortex (in variant CJD).
2. severe neuron loss → reactive astrocytic gliosis → **cortical atrophy**.
3. brainstem and spinal cord are usually spared.
4. no white matter involvement.
5. no inflammation (imunosupresija įtakos neturi).



Spongiform vacuolation (*arrows*) accompanied by neuronal loss and reactive astrocytosis:



Few small vacuoles:



[Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD) >>](http://library.med.utah.edu/WebPath/webpath.html%22%20%5Ct%20%22_blank)

Vacuoles are coalescing to microcysts:



[Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD) >>](http://library.med.utah.edu/WebPath/webpath.html%22%20%5Ct%20%22_blank)

Numerous vacuoles, along with gliosis and neuronal loss:



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Higher magnification:



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Rounded dark pink plaques, surrounded by prominent spongiform change (features of new variant CJD):



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Diagnosis

N.B. ankstyva diagnostika apsunkinta – pagrinde difkė nuo kitų dažnesnių ligų (e.g. Alzheimer)

**EEG** – paroxysms of sharp waves against slow background. see CJD (below)

**CT / MRI** – cortical atrophy without white matter changes; ventricular dilation.

Diagnosis confirmation – **brain biopsy**.

**Genetic testing** (for familial forms); prenatal diagnosis → elective abortion.

N.B. some mutations are not fully penetrant (e.g. mutations at codons 200 and 210 have penetrance of only 50% - although mutation will be transmitted as autosomal dominant trait, only half of individuals will become sick).

Treatment

- supportive (e.g. suppression of myoclonus or seizures).

"Universal precautions" should be followed in managing patient:

* ordinary surface contact is not hazardous.
* if skin is exposed to blood or CSF → swab with:
	1. 4% NaOH
	2. 10% Na hypochlorite (household bleach)

N.B. įprastos dezinfekcijos nepakanka!

Chirurginiams instrumentams:

1. autoklavavimas 60 min. 134°C.
2. immersion in 1 *N* NaOH for 1 hour at room temperature.

N.B. irradiation is ineffective!

Creutzfeldt-Jakob disease (CJD)

* + described by Creutzfeldt and Jakob in 1920-1921.

Epidemiology

Forms:

* + - 1. Sporadic CJD (90%) – occurs in completely random distribution in all populations of world\* at annual frequency ≈ 1 case per million people;

\*incidence is 60-100 times greater in Libyan-born Israelis and some restricted areas of Slovakia - linked to high prevalence of codon 200 mutations in PRNP gene

* "de novo" events - no antecedent cause or subsequent links to any chain of infection.
* peak of onset - 55-70 yrs.; bell-shaped distribution curve (skewed toward younger age groups, including rare cases in adolescents 17 yrs.).
* disease duration ≈ 8 months (range 1-130 months); > 90% miršta per 1 metus!
	+ significant proportion have more acute courses of 1-2 months;
	+ 5-10% have extended course of ≥ 2 years.
		- 1. Familial CJD (10%) – *autosomal dominant* (> 20 mutations known) – ankstesnė pradžia, bet ilgesnė eiga (≈ 26 months).
			2. Infectious CJD (rare) – transmission (ištirtas nepakankamai):
1. ***human-to-human parenteral*** – via transplants (e.g. dura mater, cornea), cadaveric growth hormone\*, blood transfusions, contaminated brain electrodes – i.e. mainly iatrogenic!
	* incubation period ranges from 2 years (inoculated directly into brain) to > 15 years (inoculated subcutaneously).
	* course (duration) similar to sporadic CJD.

\*now replaced by recombinant GH

1. ***ingestion of beef*** (?) with **bovine spongiform encephalopathy (mad cow disease)** – i.e. new variant CJD!
	* almost all cases occurred in United Kingdom (result of cattle feeding with scrapie\*-infected sheep parts).
	* in August 1999, FDA suggested that those who spent ≥ 6 months in United Kingdom from 1980-1996 should not be accepted as blood donors.
	* young age at onset (average - 28 yrs; no patient > 50 yrs).
	* longer duration (mean – 14 months).

\*prion illness of sheep

Pathology

* + - topographically unpredictable (cortex and basal ganglia are most affected).
		- cortical atrophy (little evidence of brain atrophy in cases of < 6 months duration).
		- spongiform changes > plaques (aptiktos\* tik in new variant CJD).

\*myriad amyloid plaques surrounded by halos of vacuolation (so-called "florid" or "daisy" plaques).

Clinical Features

Symptoms appear over weeks (can occur suddenly!):

1. Rapidly progressive **dementia** → mutism & global dementia.
2. **Cerebellar syndrome** – especially prominent in iatrogenic CJD acquired via peripheral (hematogenous) inoculation.
3. **Visual-oculomotor signs**
4. **Involuntary movements** (esp. ***myoclonus*** provoked by sensory stimuli - startle myoclonus)
5. **Behavioral / psychiatric disturbances** – presenting feature in new variant CJD.
6. Other signs & symptoms (auditory, sensory, pyramidal, extrapyramidal, etc)
* females ≈ males.

Diagnosis

**EEG** (most accessible and most valuable laboratory adjunct to correct diagnosis; negative in new variant CJD):

***Early in course*** - EEG may be normal (or some background slowing)

***Fully developed phase*** (90% patients within 12 weeks of clinical onset):

1. pathognomonic - generalizedbilaterally synchronous **periodic activity**: 0,5-2 cycles per second slow wave **triphasic spiking** activity (resembles ECG).
2. less specific - "burst-suppression" pattern: short runs of high voltage spikes alternate with periods of near electrical silence.

***Terminally*** - background slowing (reflects dying brain).



**CSF**:

1. normal or slight **protein** elevation (never > 100 mg/dl).
2. **CSF immunoassay** for protein 14-3-3 (member of protein kinase C-inhibitor family) - appears in CSF as result of neuronal cell death - high sensitivity and specificity (90-92%) for CJD (present in 90% CJD cases and in only 10% of cases of other neurological disorders).
* negative in new variant CJD.

**MRI**:

1. symmetrical T2 **signal increase** in:
2. cortical ribbon
3. putamen & head of caudate nuclei (10% of sporadic CJD) - "hockey stick" sign.
4. posterior thalami (pulvinar) (> 50% of new variant CJD) - "pulvinar” sign.
5. **brain atrophy** only in late stages of disease (degree of clinical dementia appears disproportionate to amount of tissue loss seen on CT and MRI).

Hyperintensities in region of basal ganglia and caudate bilaterally:



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**Brain biopsy** **with immunostaining for PrPSc** is gold standard for establishing diagnosis (almost never necessary).

* spongiform change is seen in 95% patients.

Gerstmann-Straüssler-Scheinker disease (GSSD)

* 100 kartų retesnė negu Creutzfeldt-Jakob disease.
* autosomal dominant inheritance:

**classic** (incl. Gerstmann's original case) - mutation at codon 102;

**variants** - mutations at codon 105 (with spastic paraparesis), codon 117 (with pseudobulbar signs), codons 145, 198, 217 (with Alzheimer's neurofibrillary tangles).

Pathology

* profusion of multifocal amyloid plaques (in cerebellum) ± spongiform change.
* *pradžioje* spino-olivo-ponto-cerebellar degeneration (atrophic spinocerebellar tracts); *vėliau* generalizuojasi.

Brain stem involvement! (vs. CJD)

Clinical Features

* onset – 40-55 yrs.
* slowly evolving cerebellar dysfunction (ataxia, dysarthria, nystagmus).
* later - dementia, myoclonus, etc.
* longest course of all prionoses (≈ 60 months).
* mirštama po 5-10 metų.

Diagnosis

**EEG** - only diffuse slowing.

Kuru

≈ Creutzfeldt-Jakob disease with prominent cerebellar syndrome.

* buvo paplitusi iki 1960 m. Naujojoje Gvinėjoje dėl *kanibalizmo* - affected 1% of population, with **women** (80%) chiefly affected (women ritualistically ate brains of dead); currently < 10 cases per year are reported.
* *most severe changes are seen in cerebellum* - widespread neuronal loss, neuronal and astrocytic vacuolization, astrocytic proliferation, gross atrophy.
* later – involuntary movements (myoclonus, choreoathetosis), dementia.
* terminates fatally in 4-24 months.

Fatal Familial Insomnia

* autosomal dominant inheritance - *mutation* at codon 178 with *modifying polymorphism* at codon 129. *see above*
* may be no spongiform pathology!!!
* neuronal loss and reactive gliosis in **thalamus** (*anteroventral* and *dorsomedial* nuclei) → disruption of sleep / wake cycle.
* also cerebellar cortex and inferior olives.

Clinical Features

Mean age at onset – 49 yrs (18-61 yrs):

* 1. intractable **insomnia** - loss of slow-wave and REM phases, accompanied by daytime somnolence, complex hallucinations with characteristics of "enacted dreams".
	2. **dysautonomia** - sympathetic hyperactivity (hyperhidrosis, hyperthermia, tachycardia, hypertension)
	3. **motor dysfunction** (ataxia, myoclonus, pyramidal and extrapyramidal)
	4. not prominent **dementia**.
* mirštama per 1-2 metus (6-36 months).

Diagnosis

**EEG** – only diffuse slowing.

[Viktor’s Notes℠ for the Neurosurgery Resident](http://www.neurosurgeryresident.net/)

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