Prion diseases or transmissible spongiform encephalopathies (TSEs)

• rare progressive neurodegenerative disorders that affect both humans and animals.

• They are distinguished by long incubation periods, characteristic spongiform changes associated with neuronal loss, and a failure to induce inflammatory response.
Prion diseases

- Normal prion protein \( \text{PrP}^c \) – encoded by the prion gene (PRNP) on human chromosome 20
- The function of \( \text{PrP}^c \) role in anti-oxidant systems cellular copper metabolism
Prion diseases

- Prion disease – normal gene produces normal PrP<sub>c</sub>, post-translational confirmational change to a disease related form – PrP<sub>sc</sub>
- PrP<sub>sc</sub> - insoluble and protease resistant protein → accumulates in tissues forming amyloid structures
Prion diseases

- $\text{PrP}^{sc}$ deposition → neuronal loss, astrocytic gliosis, spongiform change
Prion diseases

• In human prion diseases – common polymorphism at codon 129 → important effects on susceptibility to disease
• At codon 129 of PRNP an individual may encode for methionin or valin
• 80% of UK sporadic JCD – MM
Prion diseases

- Creutzfeldt-Jakob Disease (CJD)
  - Sporadic CJD
  - Genetic CJD
  - Variant Creutzfeldt-Jakob Disease
- Gerstmann-Straussler-Scheinker Syndrome
- Fatal Familial Insomnia
Creutzfeldt – Jakob Disease
sporadic form

- Mortality rate – 1-1.5 /million/ per year
- Middle age (55-70 years)
Creutzfeldt – Jakob Disease sporadic form (sCJD)

- **Probable sCJD**
  - rapidly evolving dementia (<2 years)
  - EEG: periodic sharp wave complexes (PSWC) with triphasic morphology
  - and/or CSF: 14-3-3 protein

  and

  + (at least two of the following 4) clinical signs:
    - myoclonus
    - ataxia
    - visual signs and symptoms
    - extrapyramidal and/or pyramidal signs and symptoms
    - akinetic mutism

- **Definite sCJD**

  histopathologic the presence of spongiform degeneration and gliosis and/or Western blot presence of protease-resistant PrP.
The typical periodic EEG seen in many cases of sporadic CJD.
(A) **sCJD**: axial FLAIR image at the level of the basal ganglia showing symmetrical high signal in the caudate head and anterior putamen (arrows).

(B) **vCJD**: axial FLAIR image at the level of the basal ganglia showing symmetrical high signal in the pulvinar and dorsomedial nuclei of the thalamus (arrows).
(A) Brain MRIs - PRNP polymorphisms. The top three are DWI images and the bottom three are T2-FLAIR images. The white arrow indicates a lesion with a high signal.
Creutzfeldt – Jakob

- CSF – protein 14-3-3
- Normal protein being released to CSF following neuronal damage
- Not specific for JCD
- Sensitivity – 94%
- Genetic testing – most common mutation – E200K present in genetic CJD
Definite sCJD histopathologic the presence of spongiform degeneration and gliosis and/or **Western blot presence of protease-resistant PrP.**
Gerstmann-Sträussler-Scheinker sy (GSS)

- Begins between the ages of 45 and 50
- Slowly evolving ataxia
- Mental deterioration
- Dementia, myoclonus, duration 5-10 years
- Point mutation at codon 102, 105 (spastic paraparesis), 117 (pseudobulbar signs), 145, 198, 217 (GSS + AD)
Fatal familial insomnia (FFI)

- Autonomic and endocrine dysfunction
- Insomnia (during day - somnolence)
- Unexplained disorders of temperature, cardiovascular and respiratory regulation
- Later – pyramidal, extrapyramidal signs, cerebellar ataxia, myoclonus
- Duration 1 – 2 years
- Mutation at codon 178
Creutzfeldt – Jakob
iatrogenic – accidentally transmitted

• Accidentally introduced into the body
• Length of incubation – 2 years in cases when infection introduced directly into the brain, 15 years – after s.c. inoculation
• Now - rare
• Corneal graft, stereotactic EEG
Creutzfeldt – Jakob new variant (vCJD)

- Due to consumption of beef contaminated by the agent of bovine spongiform encephalopathy (BSE)
- Young age at onset of illness (27-50)
- Psychiatric or sensory disturbance
- Long duration of illness (14 months)
- Clinical feature – like sporadic form (dementia, myoclonus, multisystem neurological deficits)
MRI – pulvinar sign
Creutzfeldt – Jacob variant (vCJD)

- There are no changes on EEG
- There is no protein 14-3-3 in CSF
- **MRI** – abnormally high symmetrical signal in *pulvinar talami* – strong diagnostic clue
- Neuropathological examination – diffuse spongiform changes, especially in BG, posterior thalamus and cerebellum
Bovine spongiform encephalopathy

No. of BSE cases reported each year during the epidemic

- Years: 86, 87, 88, 89, 90, 91, 92, 93, 94
- No. of cases: 63, 663, increasing trend
Acquired immunodeficiency syndrome (AIDS)  
Human immunodeficiency virus (HIV)  

- Neurological complications  
- Aseptic meningitis  
- Cognitive disturbances – adults  
- Progressive encephalopathy – children  
- Myelopathy  
- Neuropathy (inflammatory demyelinizing polyneuropathy, brachial plexopathy, mononeuritis)  
- Myopathies — myopathy, myositis
AIDS

- tumors
- Primary lymphoma of CNS (PCNSL) most frequent, children, adult – 5%
  clinical feature – headache, confusion, impaired memory, seizures, cran. nn.
  Dg.: MRI
- MTS non-Hodgkin lymphoma into CNS
- Kaposi sarcoma
AIDS

- **Oportune infections**
- **Bacterial** – *(Mycobacterium tuberculosis, Treponema pallidum, Nocardia, ...)*
- **Viral** – *(Cytomegalovirus, Herpes simplex, Varicella zoster, JC, ...)*
- **Fungal** – *(Cryptococcus neoformans, candida, ...)*
- **Protozoa** – *(Toxoplasma gondii, ...)*
AIDS dementia complex (ADC)
brain atrophy, wide ventricles and subarachnoid space
AIDS dementia complex (ADC)

- **T2- MRI:**
  - Enlargement of ventricles,
  - Hyperintensity in subcortical white matter of both frontal lobes