### Prion Diseases

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>acquired</td>
<td>kuru, iatrogenic CJD</td>
<td>infection from outside, exogenous</td>
</tr>
<tr>
<td></td>
<td>scrapie, BSE, FSE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vCJD/svCJD/CWD</td>
<td></td>
</tr>
<tr>
<td>sporadic</td>
<td>CJD (90%)</td>
<td>spontaneous change</td>
</tr>
<tr>
<td></td>
<td>(~1:1,000,000 worldwide)</td>
<td>PrP conformation (?), endogenous</td>
</tr>
<tr>
<td>genetic</td>
<td>CJD (~10%), GSS, FFI</td>
<td>germline mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PrP, endogenous</td>
</tr>
</tbody>
</table>

**CJD**: Creutzfeldt-Jakob disease (1921)

**GSS**: Gerstmann-Sträussler-Scheinker syndrome (1936)

**Kuru**: “laughing dead…” (1957; C. Gajdusek +2008)

**FFI**: fatal familial insomnia (1986)

**vCJD**: variant CJD (BSE) (1996)

**svCJD**: iatrogenic vCJD (blood) (2004)

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**Disorders of the central nervous system**

**Compartmentalisation**

yet:

all 3 forms are at the end infectious!!!

- transmissible within species
- transmissible between species

**SPECIES BARRIER!!!**
## Nomenclature

<table>
<thead>
<tr>
<th>Prion: infectious particle</th>
<th>yes</th>
<th>???</th>
</tr>
</thead>
<tbody>
<tr>
<td>without nucleic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(proteinaceous infectious particle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrP&lt;sub&gt;c&lt;/sub&gt;: cellular isoform</td>
<td>no</td>
<td>α-helical</td>
</tr>
<tr>
<td>PrP&lt;sub&gt;Sc&lt;/sub&gt;: pathol. isoform</td>
<td>yes</td>
<td>β-sheet</td>
</tr>
</tbody>
</table>

### Prion Protein (PrP<sub>c</sub>)

- **PK-sensitive**
- **PK-resistant** (rel.)
- **No aggregation**
- **Not infectious**

### Biochemical Properties

<table>
<thead>
<tr>
<th>PrP&lt;sub&gt;c&lt;/sub&gt;</th>
<th>PrP&lt;sub&gt;Sc&lt;/sub&gt;</th>
<th>Prions</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-helical</td>
<td>β-sheet</td>
<td></td>
</tr>
<tr>
<td>Soluble</td>
<td>Insoluble</td>
<td></td>
</tr>
<tr>
<td>PK sensitive</td>
<td>PK resistant (rel.)</td>
<td></td>
</tr>
<tr>
<td>Not aggregating</td>
<td>Aggregation</td>
<td>Infectious</td>
</tr>
</tbody>
</table>

### Conversion of PrP<sub>c</sub> into PrP<sub>Sc</sub>

- Ongoing conversion of PrP<sub>c</sub> (1-2%) into PrP<sub>Sc</sub>
- Recycling/Degradation
- Comparison of Conversions
  - Direct physical contact

- PrP<sub>c</sub>
- PrP<sub>Sc</sub>
- PrP<sub>Sc</sub>
- Lysosome
- Nucleus
Discussed functions:
- synaptic transmission
- circadian rhythm
- copper transport/release
- LRP ligand
- SOD activity
- anti-oxidant...
- many more.....
- signalling!!!

Neuropathology

Spongiform Degeneration:
- intracellular vacuolisation ("holes")
- loss of neurons
- astrocytic gliosis
- ev. amyloid plaques (PrP Sc)
  ("deposits")

Histo-pathology

Plaques
Vacuoles
More than one route leads to CNS

Direct invasion via nerves

Oral or i.p. infection with prions

Replication of prions in lymphatic organs

Secondary invasion via nerves

Secondary invasion via blood???

Transport of PrP<sup>Sc</sup>/prions in spinal cord

Inoculation (i.p.) with buffer

PyP<sup>Sc</sup>

Connection nervous system/lymphatic system

Bruce et al., 2001
Removal of risk materials

BSE infection: disease of aged animals...
- Infection calf (7)
- Cattle: BSE
- Infectivity rises with age
- Removal of risk materials
- Life span
- Mean incubation time: 3 - 5 years
- No detection of BSE possible
- Detection BSE in brain: Rapid testing

Human Prion Diseases
(sporadic, genetic, acquired)
- Sporadic CJD (1: 1,000,000 worldwide)
- Familial CJD/GSS/FFI (1:10,000,000)
- Acquired cases (e.g. hGH, dura)
- Kuru (ritualistic cannibalism)
- vCJD (BSE exposition)

- Long incubation, short clinical phase, always lethal
- No preclinical diagnosis, no therapy

Manifestation, clinical phase and incidence

- Sporadic CJD:
  - Sporadic: progressive dementia (cortex) 1:10^6 worldwide
  - EEG (final) pos.
- Familial CJD/GSS/FFI:
  - Genetic: progressive ataxia (cerebellum) ~1:10^7
- Iatrogenic CJD (e.g. GH, Dura):
  - Acquired: progressive ataxia (cerebellum) >200 cases
- Kuru:
  - Acquired: progressive ataxia (cerebellum) 2500-5000 cases
- vCJD:
  - Acquired: psych. symt./progr. ataxie >220 cases
### Long incubation – short clinical phase

**always lethal**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incubation Time</th>
<th>Clinical Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic CJD:</td>
<td>&gt;40 years: peak ~ 60 years;</td>
<td>2-4 months clinical phase</td>
</tr>
<tr>
<td>Familial CJD/GSS/FFI:</td>
<td>&gt;40 years: peak ~45-50 years;</td>
<td>&gt;1 year clinical phase</td>
</tr>
<tr>
<td>Iatrogenic CJD:</td>
<td>4 years minimal up to &gt;30 years</td>
<td>months to years</td>
</tr>
<tr>
<td>Kuru:</td>
<td>4 years up to &gt;40 years</td>
<td>months</td>
</tr>
<tr>
<td>vCJD:</td>
<td>&gt;10 years??</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>

### Diagnostics

**- ante mortem -:** (exception: genetic forms!)

- **Biopsy:** Histology (Vacuoles /Plaques); Immune-histology (PrP<sub>c</sub>); Westernblot (PrP<sub>Sc</sub>);
- **EEG; MRT (vCJD);** CSF markers (14-3-3, NSE, S100)

**- post mortem -:**

- **Autopsy:** Histology /Immune-histology/Western-B.
- **histoblot:** animal study…

### PK resistance

- **PrP<sup>c</sup>**
- **PrP<sup>Sc</sup>**

### Insolubility

- **Ultra-centrif.**
  - 1 h, 100,000 g
  - 1% Sarc.

### Infectivity

- **Bioassay (incubation)**
  - PrP-overexp. mice
  - wt mice
  - Syr. Hamster
- **Endpoint/Dilution:**
  - ID<sub>50</sub>/g (10<sup>6</sup>-10<sup>10</sup>)

**No blood test!!!**

- **Cell culture infection**

**New test:** PMCA
Scrapie
ataxia
itching!

BSE
ataxia

Scrapie
not infectious for humans
BSE in sheep???
- infectious for humans?
- different from scrapie?

Scrapie in Germany
formerly: 1-2 flocks/a
now testing (EU):
much higher prevalence!

CWD
Chronic Wasting Disease
deer/elk Northern America (South Korea)
free living/captured
initially Wyoming/Colorado...
>70% prevalence (>45 free rang.)
risk for humans???
zoonotic potential...
CWD: Late E.S. Williams
Williams & Young, 1980
Epicenter SE Wyoming

extreme horizontal transmission
most infectious prion disease!
Saliva!!! Urine/feaces

CWD in North America

Wyoming Chronic Wasting Disease (CWD)
Percent Positive Deer 1978-2009 by Hunt Area
"Man-made" Prion Diseases

Kuru (Cannibalism)
Iatrogenic CJD (Dura, EEG electrodes, Cornea...)
growth hormones (hGH; cadaveric pituitary glands)
vCJD (BSE); svCJD

scrapie (1930)
BSE (1980...): "Neo Cannibalism"

BSE epidemics U.K.

vCJD
sec. vCJD

atypical BSE
atypical scrapie

NB: clinically ill animals
Features vCJD (acquired)

>220 cases (02/2011)
(U.K. (174), Ire (4), F (25), USA (3), Neth5, Por2, Spa5, I, Jap, Can, Saudi)
- Young age (14-54 (74) a)
- Atypical clinical course
- Longer clinical phase, LRS!!!
- Pathology: always florid plaques
- Genetics: always Met/Met codon 129
- Prion strain pattern: =BSE
- exponential increase???: no…
Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study

Prevalence U.K.: 1 : 20,000?

Transmission by blood products? vCJD yes!

Lateral spread within humans?

CJD and blood donation: no association

vCJD:
impressive lympho-reticular tropism (not in cattle!)

Problem:
Eventually transmission within humans (blood products, surgeries…)

Protection means:
removal PBLs, donor selections, testsings, prophylaxis...

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion.
Llewelyn CA et al. Lancet. 2004 Feb 7;363(9407):417-21
48 rec/15 donors; 1 vCJD 6.5 a; donor -3.5 a
2004 2. case?? (M/V)
2006 3. (ev. 4.) case; 5. case?; 2009: factor 8/haemophilia
Risk assessment: tonsil/appendix biopsies: 1:13,000 to 1:25,000
Genetic susceptibility (human)

Polymorphism in codon 129 (Met/Val) in PrP gene (PRNP)
- Normal distribution (cascadians):
  50% Met/Val, 40% Met/Met, 10% Val/Val
- Acquired and sporadic CJD: > 90% homozygous
- hGH/France or Kuru: almost no Met/Val
  much longer incubation time
- vCJD: 100% Met/Met of clinical ill patients

Heterozygous „protected” against BSE/vCJD???

Mutations (human): disease associated (100% penetrance)

Polymorphisms (human/mouse/sheep): modulating

Polymorphisms in deer/elk PrP

Deer: 132 M/L
MD: 225 S/F
WTD: 96 S/G
<table>
<thead>
<tr>
<th>Type of Transmission</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Sporadic/spontaneous generation (co-factors)</td>
<td>e.g. sporadic BSE</td>
</tr>
<tr>
<td>Intraspecies transmission (+/-humans)</td>
<td>e.g. epidemic BSE</td>
</tr>
<tr>
<td>Transspecies infection (‘zoonosis’)</td>
<td>e.g. vCJD</td>
</tr>
<tr>
<td>Intraspecies transmission (e.g. iatrogenic)</td>
<td>e.g. iatrogenic vCJD</td>
</tr>
</tbody>
</table>

Summary: inherent/not evitable/always…