Prions Diseases: Current and Future Challenges

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Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

Transmissible Spongiform Encephalopathies (TSEs) of Humans

- Kuru
- Gertsmann-Straussler-Scheinker (GSS)
- Fatal Familial Insomnia (FFI)
- Creutzfeldt-Jakob Disease (CJD)
- Variant CJD (vCJD), 1995 (221 cases, August 2011): 172 UK, 25 France, 4 Ireland, 2 Italy, 3 USA, 2 Canada, 1 Saudi Arabia, 1 Japan, 3 Netherlands, 2 Portugal, 5 Spain, 1 Taiwan

Prion Diseases

- Etiology
  - Prions (proteinaceous infectious agent)
    - No agent-specific nucleic acid
    - Host protein (PrP\textsuperscript{C}) converts to pathologic isoform (PrP\textsuperscript{Sc}); PrP gene resides on chromosome 20
    - The function of the normal prion protein is unknown
    - Mutation in this gene may trigger transformation
    - Accumulates in neural cells, disrupts function
    - Resistant to conventional D/S procedures

Disclosure

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Epidemiology of CJD in the US
- Degenerative neurologic disorder with progressive dementia
- Incidence
  - One death/million population
  - No seasonal distribution, no geographic aggregation
  - Both genders equally affected
  - Age range 50-80+ years, average 67
  - Long incubation disease (months-years)
  - Rapid disease progression after onset (death within 6 mo)

Clinical Features of CJD
- Degenerative neurological disorder with progressive dementia (memory, intellect, personality)
- Progressive motor deterioration
  - Unsteadiness and clumsiness
  - Visual deterioration
  - Muscle twitching
  - Severe dementia, mute, immobile
- Death (< 1 year)

Diagnosis of CJD
- Clinical syndrome
  - Progressive intellectual and neurological deterioration
- EEG-classic periodic triphasic wave
- MRI-hyperlucency in the putamen
- CSF testing (surrogate markers-14-3-3 [sensitivity/specificity >90% in the presence of typical clinical picture], tau protein)
- Neuropathology
  - Brain biopsy (dx in 95% of cases confirmed by autopsy)
  - Autopsy, neuropathology confirmation

Transmissibility of Prions
- Transmission
  - Not spread by contact (direct, indirect, droplet) or airborne
  - Not spread by the environment
  - Experimentally-all TSEs are transmissible to animals, including the inherited forms
  - Epidemiology of CJD: sporadic-85%, familial-15%; iatrogenic-1% (majority after implant of contaminated grafts [dura mater] or receive hormone therapy. ~400 cases worldwide; contaminated medical equipment [6 cases])

General Infection Prevention Precautions
- Standard Precautions should be used for patients with CJD.
  - Gloves worn for handling blood and body fluids.
  - Masks, gowns, and eyewear if exposure is anticipated.
  - No additional precautions for laundry or handling food utensils.
  - Patients with prion diseases should not serve as organ donors
  - No special precautions for disposal of body fluids or regulated medical waste.
  - No excess precautions needed for burial.
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Iatrogenic Transmission of CJD

- Contaminated medical instruments
  - Electrodes in brain (2)
  - Neurosurgical instruments in brain (4 suspected cases)
  - Implantation of contaminated grafts
    - Dura mater grafts (>190)
    - Corneal grafts (3)
  - After patients received hormone therapy
    - Use of human growth hormone and gonadotropin (>190 cases)

CJD and Medical Devices

- Six cases of CJD associated with medical devices
  - 2 confirmed cases-depth electrodes; reprocessed by benzene, 70% alcohol and formaldehyde vapor
  - 4 unconfirmed cases-CJD following brain surgery, suspect neurosurgical instruments; index CJD identified-1
- Cases occurred from 1953-1980 in UK, France and Switzerland
- No cases since 1980 and no known failure of steam sterilization

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Risk of CJD Transmission

- Epidemiologic evidence (eye, brain) linking specific body tissue or fluids to CJD transmission
  - Experimental evidence in animals demonstrating that body tissues or fluids transmit CJD
  - Infectivity assays a function of the relative concentration of CJD tissue or fluid

Risk of CJD Transmission

<table>
<thead>
<tr>
<th>Risk of Infection</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Brain (including dura mater), spinal cord, pituitary tissue and posterior eye</td>
</tr>
<tr>
<td>Low</td>
<td>CSF, liver, lymph node, kidney, lung, spleen, placenta, olfactory epithelium</td>
</tr>
<tr>
<td>No</td>
<td>Peripheral nerve, intestine, bone marrow, whole blood, leukocytes, serum, thyroid gland, adrenal gland, heart, skeletal muscle, adipose tissue, gingiva, prostate, testis, tears, nasal mucus, saliva, sputum, urine, feces, semen, vaginal secretions, sweat and milk</td>
</tr>
</tbody>
</table>

High-transmission to inoc animals >100%, Low-transmission to inoc animals 10-20% but no epidemiological evidence of human inf
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CJD: DISINFECTION AND STERILIZATION

- Effectiveness must consider both removal by cleaning and disinfection/sterilization
  - Probability of a device remaining capable of transmitting disease depends on the initial contamination and effectiveness of cleaning and disinfection/sterilization.
  - Device with 100µg of protein (median protein contamination from 8-91µg per instrument) and CJD brain tissue has a titer of 5 log10 LD50IC/g (mean infectivity calculated from group of 27), an instrument would have 10 potentially infectious units without considering prionicidal activity of process.

CJD: DISINFECTION AND STERILIZATION

- Cleaning
  - Cleaning results in a 4 to 6 log10 reduction of microbes and ~2 log10 reduction in protein contamination (prions ?)
  - Some alkaline detergents reduce 5 log10 prions; some enzymatic detergents reduce 5 log10 prions
- Sterilization
  - Steam sterilization (121°C or 132°C) results in a 4 to 7 log10 reduction

Decreasing Order of Resistance of Microorganisms to Disinfectants/Sterilants

- Prions
- Spores
- Mycobacteria
- Non-Enveloped Viruses
- Fungi
- Bacteria
- Enveloped Viruses

Prion Inactivation Studies

- Problems
  - Studies do not reflect reprocessing procedures in a clinical setting (e.g., no cleaning)
  - Factors that affect results include: brain tissue macerates vs. intact tissue (smearing, drying), weights of tissue (50mg-375mg), strain of prion (22A), prion concentration in brain tissue, animal used, exposure conditions, validation and cycle parameters of sterilizers, resistant subpopulation, different test tissues, different duration of observations, screw cap tubes with tissue (air), etc

Ineffective or Partially-Effective Disinfectants: CJD

- Alcohol
- Ammonia
- Chlorine dioxide
- Formaldehyde
- Glutaraldehyde
- Hydrogen peroxide
- Iodophors/iodine
- Peracetic acid
- Phenolics
Ineffective or Partially Effective Processes: CJD

- Gases
  - Ethylene oxide
  - Formaldehyde
- Physical
  - Dry heat
  - UV
  - Microwave
  - Ionizing radiation
  - Autoclave at 121°C, 15m

Effective Processes: CJD

- Autoclave
  - 134°C for 18m (prevacuum)
  - 132°C for 60m (gravity)
- Combination (chemical exposure then steam autoclave, potentially deleterious to staff, instruments, sterilizer)
  - Soak in 1N NaOH for 1 hour, remove and rinse in water, then autoclave 121°C for 60m

Effective Disinfectants (\(>4 \log_{10}\) decrease in LD\(_{50}\) within 1 hour)

- Sodium hydroxide
  - 1 N for 1h (variable results)
- Sodium hypochlorite
  - 5000 ppm for 15m
- Guanidine thiocyanate
  - >3M
- Phenolic (LpH)
  - 0.9% for 30m
- Some alkaline and enzymatic detergents

Disinfection and Sterilization

- EH Spaulding believed how an object will be D/S depended on the objects intended use
  - CRITICAL-objects that enter normally sterile tissue or the vascular system should be sterile
  - SEMICRITICAL-objects that touch mucous membranes or skin that is not intact requires a disinfection process (high level disinfection) that kills all but bacterial spores (prions?)
  - NONCRITICAL-objects that touch only intact skin require low-level disinfection

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CJD: potential for secondary spread through contaminated surgical instruments
**CJD: Disinfection and Sterilization**

**Conclusions**
- Critical/Semicritical-devices contaminated with high-risk tissue from high-risk patients require special prion reprocessing
  - 134°C for 18m (prevacuum)
  - 132°C for 60m (gravity)
  - NaOH and steam sterilization (e.g., 1N NaOH 1h, then 121°C 1h)
- Discard instruments that are impossible to clean
- No low temperature sterilization technology currently recommended*
- Noncritical-four disinfectants (e.g., chlorine, Environ LpH) effective (4 log decrease in LD50 within 1h)

*R and HP gas plasma (Sterrad NX) reduced prion infectivity but not cleared by FDA.

**Examples: CJD D/S**
- High risk patient, high risk tissue, critical/semicritical device-special prion reprocessing
- High risk patient, low risk tissue (defined as CSF, kidney, liver, spleen, lung, etc) critical/semicritical device-no recommendation, use either conventional D/S or special prion reprocessing
- High risk patient, no risk tissue, CISC device-conventional D/S
- Low risk patient, high risk tissue, critical/semicritical device-conventional D/S
- High risk patient, high risk tissue, noncritical device-conventional disinfection
**Prevent Patient Exposure to CJD Contaminated Instruments**

How do you prevent patient exposure to neurosurgical instruments from a patient who is later given a diagnosis of CJD?

Hospitals should use the special prion reprocessing precautions for instruments from patients undergoing brain biopsy when a specific lesion has not been demonstrated (e.g., CT, MRI). Alternatively, neurosurgical instruments used in such cases could be disposable.

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  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges and changes

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**Inactivation of Prions**

**Recent Studies**

- Lemmer et al. J Gen Virol 2004;85:3805. SDS/NaOH, AC, 0.2% PA, 5% SDS-effective (in vitro)
- Fichet et al. JHI 2007;67:278. Gaseous HP-effective
- Yan et al. Zentr Steril 2008;16:26-34. HP Gas Plasma effective (Sterrad NX)
- Rogez-Kreuz C. ICHE 2009;30:769. HP Gas Plasma effective (Sterrad NX)

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**Variant CJD**

- Strongly associated with epidemiology of BSE (1983) in UK
- BSE amplified by feeding cattle meat and bone meal infected with BSE (bovine spongiform encephalopathy)
- August 2011, 221 cases: 172 UK, 25 France, 4 Ireland, 2 Italy, 3 USA, 2 Canada, 1 Saudi Arabia, 1 Japan, 3 Netherlands, 2 Portugal, 5 Spain, 1 Taiwan)
- Affects young persons (range 13-48y, median 28y)
- Clinical course is longer (14 mo vs <6 mo)
- BSE not reported in the United States
- vCJD and BSE are believed caused by the same prion agent
vCJD: Disinfection and Sterilization

- To date no reports of human-to-human transmission of vCJD by tissue but 4 possible cases by blood transfusion reported
- Unlike CJD, vCJD detectable in lymphoid tissues (e.g., spleen, tonsils, thymus, appendix) and prior to onset of clinical illness
- Special prion reprocessing (or single use instruments) proposed in the UK in dental, eye, or tonsillar surgery on high risk patients for CJD or vCJD
- If epidemiological and infectivity data show these tissues represent a transmission risk then special prion reprocessing could be extended to these procedures

Conclusions

- Epidemiologic evidence suggests nosocomial CJD transmission via medical devices is very rare
- Guidelines based on epidemiologic evidence, tissue infectivity, risk of disease via medical devices, and inactivation data
- Risk assessment based on patient, tissue and device
- Only critical/semicritical devices contacting high risk tissue from high risk patients require special prion reprocessing

CJD: Disinfection and Sterilization

Conclusions

- Critical/Semicritical-devices contaminated with high-risk tissue from high-risk patients requires special prion reprocessing
  - 134°C for 18m (prevacuum)
  - 132°C for 60m (gravity)
  - NaOH and steam sterilization (e.g., 1N NaOH 1h, then 121°C 1h)

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Thank you
Disinfection and Sterilization for Prion Diseases

References


CJD and Medical Devices

- World Health Organization, 2000
  - When instruments contact high infectivity tissue, single-use instruments recommended.
  - If single-use instruments not available, maximum safety attained by destruction of re-useable instruments.
  - Where destruction is not practical, reusable instruments must be decontaminated by immerse in 1N NaOH and autoclaved (121°C/30m), cleaned, rinsed and steam sterilized.
  - After decontamination by steam and NaOH, instruments can be cleaned in automated mechanical reprocessor.

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Table 1: Comparative Frequency of Infection in Organs, Tissues, and Body Fluids of Humans with Transmissible Spongiform Encephalopathies (Creutzfeldt-Jakob Disease)

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