New Goals and Organizational Structure of the National Prion Disease Pathology Surveillance Center (NPDPSC)

Presented by Jiri G. Safar
CJD Fdn Family Conference
July 10-13, 2015
Human prion diseases are invariably fatal brain disorders

<table>
<thead>
<tr>
<th>Manifestation (Frequency)</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sporadic (90%)</td>
<td>Creutzfeldt-Jakob disease (CJD); age-adjusted incidence is 4-6 cases/million in age 65-79 worldwide; prevalence ~200-300/million</td>
</tr>
<tr>
<td>2. Inherited (10%)</td>
<td>Familial CJD, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia</td>
</tr>
<tr>
<td>3. Infectious (&lt;1%)</td>
<td>Kuru among New Guinea natives transmitted by cannibalism Iatrogenic CJD caused by growth hormone derived from human pituitaries, dura mater and cornea transplants New variant CJD caused by BSE prions from contaminated beef</td>
</tr>
</tbody>
</table>
Reservoirs of zoonotic and iatrogenic prion pathogens

- Variant Creutzfeldt-Jakob Disease (CJD)
- iatrogenic CJD
- Creutzfeldt-Jakob Disease (CJD)
- zoonotic BSE ("Mad Cow Disease")
- iatrogenic (hospital)
- Chronic Wasting Disease (CWD)
- scrapie
Imperative goals of National Prion Disease Pathology Surveillance Center (NPDPSC)

• Detection and characterization of vCJD and other human prion diseases caused by zoonotic or hospital transmissions, or new prion types (strains)

• Monitoring changes in the incidence and prevalence of human prion disease and identification of epidemiological foci

• Monitoring spectrum of human prions

• Development and validation of rapid presymptomatic tests for human prions

• NPDPSC is the only reference laboratory for human prion diseases in the US providing training and consultation

• Genetic screening, counseling for hereditary forms of prion diseases

• Public education and outreach in partnership with CJD Foundation
Clinical and laboratory diagnostics – CSF, blood, urine

Surveillance of human prion diseases

Epidemiology of human prion diseases

Autopsy & diagnostic neuropathology

Detection of genetic prion diseases

Molecular typing of human prions

Case reports and publications

Development and validation of new methods for prion diagnostics and differentiation

NATIONAL PRION DISEASE PATHOLOGY SURVEILLANCE CENTER

MANDATES AND PROGRAMS

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
IN PARTNERSHIP WITH
CASE WESTERN RESERVE UNIVERSITY
NEW STRUCTURE OF NATIONAL PRION DISEASE PATHOLOGY SURVEILLANCE CENTER

Director: Jiri G. Safar, Scientific Leadership and General Oversight
Co-Directors: Mark Cohen, Clinical Neuropathology
Brian Appleby, Clinical Diagnostics
Clive Hamlin, Laboratory Diagnostics
Associate Director: Wenquan Zou, Prion Strain Typing
Other Program Faculty: Marta Couce, Neuropathology
Shulin Zhang, Genetics
Pierluigi Gambetti, Neuropathology

Advisory Board:
Chair - Cliff Harding, Chair of Pathology
Anthony Furlan, Chair of Neurology
Jonathan Haines, Chair of Epidemiology & Biostatistics
Mark Chance, Vice Dean for Research
Debbie Yobs, President, Florence Kranitz, Past President of Creutzfeldt-Jakob Disease Fdn
Bernardino Ghetti, Distinguished Professor, Indiana University School of Medicine
James Ironside, UK CJD Surveillance Unit, University of Edinburgh, United Kingdom

REPOSITORIES AND DATABASE

- Frozen tissues, CSF, & Urine
- Fixed tissues
- Blood & Olphactatory epithelium
- Database
National Prion Disease Pathology Surveillance Center Cases Examined\(^1\)
(April 10, 2015)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Referrals(^2)</th>
<th>Prion Disease</th>
<th>Sporadic</th>
<th>Familial</th>
<th>Iatrogenic</th>
<th>vCJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 &amp; earlier</td>
<td>54</td>
<td>35</td>
<td>31</td>
<td>4</td>
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<td>1997</td>
<td>111</td>
<td>66</td>
<td>57</td>
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<tr>
<td>1998</td>
<td>87</td>
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<td>43</td>
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<td>121</td>
<td>73</td>
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<td>99</td>
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<tr>
<td>2004</td>
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<td>164</td>
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<tr>
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<td>179</td>
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<tr>
<td>2006</td>
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<td>183</td>
<td>164</td>
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<tr>
<td>2007</td>
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<td>203</td>
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<tr>
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<td>241</td>
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<td>23</td>
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<tr>
<td>2014</td>
<td>353</td>
<td>209</td>
<td>185</td>
<td>22</td>
<td>0</td>
<td>1(^5)</td>
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<tr>
<td>2015</td>
<td>92</td>
<td>59</td>
<td>42</td>
<td>4</td>
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<tr>
<td>TOTAL</td>
<td>5459(^6)</td>
<td>3202(^7)</td>
<td>2847</td>
<td>330(^8)</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^1\) Listed based on the year of death or, if not available, on year of referral; \(^2\) Cases with suspected prion disease for which brain tissue was submitted; \(^3\) Disease acquired in the United Kingdom; \(^4\) Disease acquired in the United Kingdom in one case and in Saudi Arabia in the other; \(^5\) Disease possibly acquired in a Middle Eastern or Eastern European country; \(^6\) Includes 14 (13 from 2015) cases with type determination pending in which the diagnosis of vCJD has been excluded. The sporadic cases include 3127 cases of sporadic Creutzfeldt-Jakob disease (sCJD), 54 cases of Variably Prionase-Sensitive Prionopathy (VPSPr) and 21 cases of sporadic Fatal Insomnia (sFl). \(^7\) Excludes positive blood tests for pathogenic PRNP mutations on 191 persons for whom no brain tissue was submitted, including primarily the living family members of prion disease patients.

Rev 5/19/2015
Analytical sensitivity of second generation RT QuIC

Thioflavin Fluorescence (arbitrary units x 1,000)

Time (hours)

- $10^{-6}$ 4/4
- $10^{-7}$ 4/4
- $10^{-8}$ 4/4
- $10^{-9}$ 4/4

- 53 fg sCJD PrP$^{Sc}$
- 5.3 fg
- 0.53 fg
- 0.053 fg

No seeds
Diagnosis of sCJD using cerebrospinal fluid (CSF) and second generation RT QuIC
Future plans and goals

• Optimization and validation of next generation – ultrasensitive tests for human prions (RT QuIC diagnostics)

• Development of new strategies for rapid postmortem and early antemortem diagnostics of human prion diseases to prevent iatrogenic (hospital) transmissions

• Development of new approaches for rapid antemortem and postmortem differentiation of human prions to identify their origin – iatrogenic, zoonotic, or genetic

• Upgrading operating structure and standards of National Prion Center – biobank, database, clinical data collection

• Improving and updating the outreach program techniques in partnership with CJD Foundation and medical associations