CJD 2011 and the Ninth Annual CJD Foundation Family Conference

Summary of Day 1

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Florence Kranitz, CJD Foundation
Welcome

- Ninth CJD Foundation Family Conference (fourth joint with PrioNet Canada)
- Scientific update from world's leading prion researchers
- Input from family members
- Thanks to:
  - Board of Directors
  - Organizers
  - Sponsors
  - Speakers
  - Participants

Conference Co-Chairs

Pierluigi Gambetti and Neil Cashman

Keynote Address

Neil Cashman, University of British Columbia
Keynote Address I

- Protein misfolding disease: aggregates of misfolded proteins accumulate in cells of the nervous system
- Physical presence of misfolded prion protein triggers misfolding of normal prion protein
- Disease specific epitopes can be targeted for prion vaccine development
- Need to target misfolded prion protein, without impacting normal prion protein

- Misfolded SOD1 involved in ALS; cell to cell propagation of misfolded SOD1 demonstrated
- Antibodies can block the spread of misfolded SOD1 from cell to cell in vitro and in mice, providing a potential basis for human immunotherapy

Neil Cashman, University of British Columbia
Keynote Address II

- Aβ agglomerates involved in Alzheimer's disease
- Need to target disease specific epitope for Aβ in order to develop effective therapeutic treatments
- α-synuclein misfolding involved in Parkinson's disease
- Research underway to identify genes responsible for release and update of α-synuclein in the brain

- For the last seven years, PrioNet Canada has focused on classical prion diseases such as BSE,CWD and vCJD
- PrioNet is now exploring the role of protein misfolding in a broader class of neurodegenerative disease, particularly AD, PD, and ALS

Diagnostics

Richard Knight, University of Edinburgh
Difficulties in Making a CJD Diagnosis

- Four types of CJD: genetic, iatrogenic, **sporadic**, variant
- Rare disease with no simple, non-invasive test
- Early symptoms can be consistent with multiple diagnoses; later symptoms more clear cut
- Careful diagnosis is needed to rule out other possible conditions
- Median time from onset of symptoms to diagnosis is 3-4 months
- This is comparable to, or shorter than, other neurodegenerative diseases
- Because CJD progresses rapidly, diagnosis is often made just before death
- Diagnosis has improved in the UK because of awareness and diagnostics (fewer referrals of non-cases)

Ryuichiro Atarashi, Nagasaki University
Specificity of Human Prion Detection in CSF

- Main molecular event in prion disease is the conformational conversion of normal prion protein (PrP^{C}) to abnormal prion protein (PrP^{Sc})
- Sonication or **shaking** can stimulate prion conversion
- Real-time QuIC assay used to identify presence of PrP^{Sc}
- Safety ensured since prions sealed in 96 well plate throughout the test procedure
- Test can detect presence of minute amounts PrP^{Sc}

- Applicability of RT QuIC for clinical diagnosis confirmed using CSF samples from CJD, sCJD and other patients (87% sensitivity and 100% specificity)

Joel Watts, University of California at San Francisco
Spontaneous Prion Disease in Transgenic Mice

- Three pathways to disease: **spontaneous**, inherited, infectious
- Inoculation of brain homogenate from CJD patients results in infection in transgenic mice, but not normal mice (species barrier)
- Transgenic mouse model for sCJD developed (based on prion protein from Bank Voles found in Europe and Asia)
- Efficient transmission of prion diseases demonstrated in this new mouse model
- Pathological characteristics of neural tissue in mice remarkably similar to that of human sCJD cases
- Transmissibility to other mice (both predisposed and not predisposed to sCJD) demonstrated
- Transgenic mouse model will be a valuable tool for sCJD research

David Wishart, University of Alberta
The Future of Prion Disease Diagnostics

- Predictive, diagnostic, and prognostic biomarkers of interest
- Sensitivity and specific used to evaluate utility of biomarkers
- 14-3-3 (CSF) diagnostic test has sensitivity and specificity in the range of 80-90%
- RT-QuIC assay (CSF or serum) has high sensitivity and specificity approaching 100%
- Combinations of diagnostic biomarkers (biomarker profile) can improve both sensitivity and sensitivity

- Database (MarkerDB) includes information on interpretation of current and experimental biomarkers in relation to specific diseases
- Omics technologies provide a basis for developing non-invasive, inexpensive tests ($100 genome available in the foreseeable future)

Treatment

Neil Cashman, University of British Columbia
Risk of CJD from Urine Derived Pharmaceuticals

- Classical CJD can be sporadic (85%), familiar (15%), or **iatrogenic** (<1%)
- Iatrogenic CJD has occurred through corneal transplantation (3 cases), neurosurgical instruments (6), pituitary derived hormones from cadavers (150), dura mater transplantation (200)
- vCJD transmitted through blood transfusion (4 cases)
- Prion infectivity has been detected in cervid and hamster urine
- WHO labelled urine as a ‘low infectivity tissue’ in 2010

- Prion protein detected in human urine-derived injectable fertility products
- Recombinant fertility products contained no detectable prion protein

Gianluigi Forloni, Mario Negri Institute in Milano
Doxycycline Clinical Trial Results

- Tetracycline and other tetracycline derivatives shown to reduce prion infectivity
- Doxycycline used to treat CJD patients, resulting in a doubling of survival time in some observational studies
- MM and MV genotypes achieved greatest increase survival (no increase in VV genotype)

- Recent multicentre RCT in Italy suggests increased survival in patients treated with doxycycline, with females demonstrating longer survival than males
- Similar studies initiated in France and Germany

Surveillance

Pierluigi Gambetti, National Prion Disease Pathology Surveillance Centre

Prion Disease Surveillance in the United States

- Goal is to identify and characterize cases of prion disease in the U.S.
- Diagnoses bases on Western blot (detect PrP^{Sc}), Immunohistochemistry, and PrP gene sequencing
- 4,019 referrals have led to 2,360 diagnoses of prion disease (about 1 case per million population)
- 14-3-3 CSF analyses also done
- *In the absence of Congressional appropriations for FY 2012, the viability of program is in question*

Maurizio Pocchiari, Instituto Superiore de Sanita
Surveillance in Europe

- Surveillance in Europe initiated in 1993
- More than 11,000 cases indentified as of 2010 (majority are **sporadic**)
- Mortality rates in different countries range from 0.5 to 1.5 per million population
- Mortality rates in five main countries increased initially after 1993, but has now stabilized
- Revised diagnostic criteria has increased number of cases with MM2 genotype

- sCJD not strongly related to recognizable risk factors, although age, and surgery may be relevant

. . . our program continues after the break . . .