CJD 2011 and the Ninth Annual CJD Foundation Family Conference

Summary of Day 1

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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
• 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)
Main molecular event in prion disease is the conformational conversion of normal prion protein (PrPC) to abnormal prion protein (PrPSc).

Sonication or shaking can stimulate prion conversion.

Real-time QuIC assay used to identify presence of PrPSc.

Safety ensured since prions sealed in 96 well plate throughout the test procedure.

Test can detect presence of minute amounts PrPSc.

Applicability of RT QuIC for clinical diagnosis confirmed using CSF samples from CJD, sCJD and other patients (87% sensitivity and 100% specificity).
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
The Future of Prion Disease Diagnostics

- Predictive, diagnostic, and prognostic biomarkers of interest
- Sensitivity and specificity 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 specificity
- 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
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 PrPSc), 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*
• Surveillance in Europe initiated in 1993
• More than 11,000 cases identified 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 ...