Imaging of Prion Diseases & Related Disorders

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Acknowledgements:
D. Collie, Edinburgh, UK
Prions & Prion Diseases

• Definition and History
• Genetics
• Pathogenesis
• Classification
• Diagnosis and Differential Diagnosis
• Imaging
  – Standard
  – Advanced
• Summary
Prions & Prion Diseases

- **Definition:** a *proteinaceous infectious* particle that lacks nucleic acid (Stanley Prusiner, ~1982)

- **“The Prion Hypothesis”:**
  - prions multiply in an incredible way – they convert normal proteins into dangerous ones by simply inducing the benign molecules to change their shape or “conformation”
  - Conformationally altered proteins can cause a variety of communicable AND inherited disorders

- Most common human prion disease is Creutzfeld-Jacob Disease (CJD): Sporadic, Familial, Iatrogenic and Variant forms.

- Other recognized human prion diseases include:
  - Fatal Insomnia (FI)
  - Gerstmann-Straussler-Scheinker Syndrome
  - Kuru
Prions & Prion Diseases

• Definition: a **proteinaceous infectious** particle that lacks nucleic acid (Stanley Prusiner, ~1982)

Stanley Prusiner
1997 Nobel Prize Winner for Prion Hypothesis
Prions & Prion Diseases

- Definition: a *proteinaceous infectious* particle that lacks nucleic acid 
  *(Stanley Prusiner, ~1982)*

Stanley Prusiner
1997 Nobel Prize Winner for Prion Hypothesis
Brief History of Prion Diseases

• 1920: Creuztfeld, Jacob describe first cases of CJD
• 1929: Heidenhain describes 3 similar cases in patients with prominent visual findings
• 1936: Gerstmann describes case with severe ataxia w family history of similar illness going back 6 generations
• 1950’s: Gaduszek & Zigas find high incidence of fatal dementing illness in Fore tribe in New Guinea where ritualistic cannibalism practiced – “Kuru”. Infectious agent suspected but cannot be identified; idea of “slow viruses”
• 1982 - Stanley Prusiner (UCSF) proposes the “prion hypothesis”
• 1997 – Stanley Prusiner awarded Nobel Prize
• 1982 – 2014: Possible prion relationship with other neurodegenerative diseases explored
Prions: The Prion Protein
Genetics & Propagation

- The normal prion protein “PrPc” is present in everyone
- Cell membrane glycoprotein > 200 amino acids long
- Possible physiologic functions:
  - protection against apoptotic and oxidative stress
  - cellular uptake or binding of copper ions
  - transmembrane signaling
  - formation and maintenance of synapses
  - adhesion to the extracellular matrix.
- The gene responsible for encoding this protein is on chromosome 20
- In CJD the abnormal prion protein has exactly the same amino acid sequence as the normal prion protein, but it has a different shape (“conformation”) – PrPsc
**PrPc**
- ~42% alpha-helix
- ~3% beta-sheet
- detergent soluble
- protease sensitive

**PrPsc**
- ~30% alpha-helix
- ~43% beta-sheet
- detergent insoluble
- protease resistance

*From Scientific American*
Prions – Genetics & Propagation

• In CJD, very high homozygosity rate on chromosome 20 at codon 129:
  – sCJD: 70% Met/Met, 16% Val/Val.
  – vCJD: all known cases have been Met/Met
CJD by Molecular Subtypes
Incidence, and Clinical, Lab & Imaging Features

• Molecular subtypes based on Codon 129 genotype (methionine or valine) and PrP<sup>sc</sup> type (1 or 2)
  – Clinical features differ between each (w substantial overlap):
    age of onset, average disease duration, clinical symptoms and signs
  – Frequency of PSWC on EEG, and frequency of +ve CSF for 14-3-3 differ

• Molecular subtypes: (*very high % homozygous 80%+: MM or VV)
  – MM1 46-68%
  – MM2 ~10%
  – MV1 <10%
  – MV2 ~10%
  – VV1 ~2%
  – VV2 ~15%

• MM2 genotype has 2 phenotypes
  • Cortical <10%
  • Thalamic 2% (usually negative MRI, neg EEG, neg CSF 14-3-3)
    Insomnia, hyperactivity, ataxia, cognitive impairment
Areas of visible involvement on MRI (DWI or FLAIR) by molecular subtype

MRI lesion profiles in sporadic sCJD
Meissner B et al

211 sCJD patients
Multi-center pooled data
Propagation & Pathogenesis

Infection

Inheritance

Spontaneous Mutation

PrP\textsuperscript{sc}

If large amount prions →
- Protein deposits
- Neuronal death
- Spongiform lesions
- Disease Expressed

If small numbers of prions →
- Cleared via regular protein degradation pathways
- No disease results

PrP\textsuperscript{sc}

PrP\textsuperscript{c}

PrP\textsuperscript{sc}
Classification: Human Prion Diseases

- **Sporadic Forms**
  - sporadic Creutzfeld-Jacob Disease (sCJD)
  - sporadic Fatal Insomnia (sFI)

- **Inherited Forms**
  - familial Creutzfeld-Jacob Disease (fCJD)
  - familial Fatal Insomnia (fFI)
  - Gerstmann-Straussler-Scheinker Syndrome (GSS)

- **Acquired Forms**
  - iatrogenic Creutzfeld-Jacob Disease (iCJD)
    - Dura grafts, corneal transplants, deep brain stimulators
cadaveric pituitary hormone extracts
  - variant Creutzfeld-Jacob Disease (vCJD)
    - “Mad Cow” disease
  - Kuru
Total Incidence: ~1 case / million population / year

• Sporadic Forms (~ 90% or slightly less)
  – sporadic Creutzfeld-Jacob Disease (sCJD) – ~85-90%
  – sporadic Fatal Insomnia (sFI) – extremely rare

• Inherited Forms (~ 10% or slightly more)
  – familial Creutzfeld-Jacob Disease (fCJD) - ~3-5-10%
  – familial Fatal Insomnia (fFI) - extremely rare
  – Gerstmann-Straussler-Scheinker Syndrome (GSS) - ~3-4%

• Acquired Forms – all are now extremely rare

Source:
USA Surveillance Center, Case Western University, Cleveland
UK CJD Surveillance Center, Edinburgh
Incidence of Acquired Forms: all are now extremely rare

- Iatrogenic Creutzfeld-Jacob Disease (iCJD) –
  - ~700 cases in world
  - Dura grafts, corneal transplants, surgery instruments, cadaveric pituitary hormone extracts

- Variant Creutzfeld-Jacob Disease (vCJD) –
  - < 200 cases in world, almost all in the U.K.
  - “Mad Cow” disease; no new human cases in a decade; none alive today

- Kuru –
  - “ritual cannibalism banned…disease is eliminated”
  - ~2700 cases, Fore tribe, New Guinea highlands
Prion Diseases

Are there more?

• “Many neurodegenerative diseases including CJD, Alzheimer’s, Parkinson’s, and amyotrophic lateral sclerosis (ALS) share two remarkable characteristics:
  – more than 80% of cases are sporadic*
  – although many of the disease-specific mutant proteins are expressed in embryogenesis, the inherited forms of these neurodegenerative diseases are late-onset. This suggests that some event occurs with aging that renders a disease-specific protein pathogenic*.”

• In the past decade, there has been renewed interest in the possibility that the proteins causing neuro-degeneration in all the above diseases are prions

• Apart from sharing the two above characteristics with CJD, do the proteins in these other diseases have the other characteristics of prion diseases: prion forms? protein deposits? and transmissability?

*Prusiner SB. Science 2012
Prion forms, protein deposits & transmissability in these other diseases?

Evidence for prions causing many different neurodegenerative diseases

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<th>Prion diseases</th>
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<th>Prion forms</th>
<th>Protein deposits</th>
<th>Self-propagation in mammals</th>
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<td>CJD/scrapie</td>
<td>PrP^C</td>
<td>PrP^Sc</td>
<td>PrP plaques</td>
<td>inoc apes, monkeys, wt mice &amp; Tg mice</td>
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<td>APP</td>
<td>Aβ</td>
<td>Aβ plaques</td>
<td>inoc mammosets &amp; Tg(ΔAPP) mice</td>
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<td>Tauopathies (FTD, PSP, Pick’s, CTE)</td>
<td>tau</td>
<td>tau aggregates</td>
<td>NFTs, Pick bodies</td>
<td>inoc Tg(HuTau), inoc Tg(HuTau,P301S) &amp; inducible Tg(HuTau, ΔK280) mice</td>
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<td>Parkinson’s</td>
<td>α-synuclein</td>
<td>α-synuclein aggregates</td>
<td>Lewy bodies</td>
<td>Lewy bodies in grafts &amp; inoc Tg(HuSNCA,H53T) mice</td>
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<td>fALS</td>
<td>ΔSOD1, ΔTDP43</td>
<td>ΔSOD1 aggregates</td>
<td>Bunina bodies</td>
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<td>Huntington’s</td>
<td>ΔHtt</td>
<td>ΔHtt aggregates</td>
<td>Nuclear inclusions</td>
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Prusiner SB. Science 2012

Prion Forms: YES
Protein Deposits: YES
Transmissability: YES

“A Unifying Role for Prions in Neurodegenerative Diseases”
Stanley B. Prusiner, MD; ASNR 2014 Keynote Lecture
CJD: Diagnosis
Clinical features, Imaging, EEG, CSF

A. Rapid cognitive decline
B. Specific neurological manifestations
C. Laboratory tests
D. Routine investigations do not suggest an alternative diagnosis

- Cognitive decline is a major feature, but may not be the first feature
- Imaging is important but by itself cannot make a definite diagnosis
- Small numbers of cases have normal imaging, EEG, and CSF
- Definite diagnosis: Biopsy with immunocytohistochemistry
- Imaging: MRI is the only imaging method that is used in formal diagnostic criteria (DWI/ADC, FLAIR)
Probable sCJD = A + at least 2 of B + at least 1 of C + D

A. Rapid cognitive decline

B. Specific neurological manifestations
   1. Myoclonus
   2. Pyramidal or extrapyramidal
   3. Visual
   4. Cerebellar
   5. Akinetic mutism
   6. Other focal higher cortical sign (e.g., neglect, aphasia, apraxia, acalculia)

C. Laboratory tests
   1. Positive EEG: periodic epileptiform discharges
   2. Positive MRI: subcortical or cortical gyral hyperintensity (cortical ribboning) on DWI and preferably restricted diffusion on ADC map

D. Routine investigations do not suggest an alternative diagnosis
CJD: Diagnostic Criteria
MRI-CJD Consortium (2009)

Probable sCJD = at least 2 of A + at least 1 of B
Possible sCJD = at least 2 of A + duration < 2 yrs

A. Clinical signs
   1. Dementia
   2. Cerebellar or visual
   3. Pyramidal or extrapyramidal
   4. Akinetic mutism

B. Laboratory tests
   1. Positive EEG: periodic sharp wave complexes
   2. Positive CSF: 14-3-3 protein in patients with a disease duration of less than 2 years
   3. Positive MRI: high signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal-parietal-occipital) either on DWI or FLAIR
Sporadic CJD – sCJD: Clinical & Lab

- By far the commonest type of CJD
- Mean age – 65 years
- Sporadic – no known cause
- Mean survival from diagnosis – 6 months
- Dementia, ataxia, involuntary movements, myoclonus, cortical blindness
- EEG
  - generalised periodic triphasic sharp wave complexes
  - 65% of patients late in the disease
- CSF electrophoresis for 14-3-3 protein
  - sensitivity 80%, specificity 90%
Familial CJD (fCJD)

- ~ 10% of all CJD cases
- Mean age – slightly younger than sCJD (~55-60 yrs)
- Caused by mutations in the gene that codes for prion protein on chromosome 20
- Most common pathogenic mutation is “E200K”
- Inheritance: Autosomal dominant w nearly 100% penetration by age 80 yrs
- Clinical features similar to sCJD (esp. MM1 subtype)
- MRI features similar to sCJD w ~10% false neg rate

Fulbright RK et al. AJNR 2008
Variant CJD (vCJD)

- Via BSE contaminated beef; major public health concern
- Peak incidence 1998-2001 with almost all cases in UK
- No new cases in over a decade and no cases alive today
- Age of onset much younger and duration of disease much longer than sCJD (Mean age of onset – 26 years; Mean survival from diagnosis – 14 months)
- Sensory (sensation of cold, paraesthesia or pain), neuropsychiatric (withdrawal, depression, fleeting delusions), involuntary movements, cerebellar signs, abnormal eye movements & involuntary movements
- EEG – does not show “typical abnormality”
- CSF electrophoresis - 14-3-3 protein ~50% +ve
- MRI was very important for diagnosis: “pulvinar sign”
## Spongiform Encephalopathies

- Spongiform changes
- No inflammatory reaction

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<thead>
<tr>
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<th>CJD - human</th>
<th>Kuru - human</th>
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<th>BSE - (cow)</th>
<th>Scrapie - (sheep)</th>
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Florid Plaque = amyloid-like protein aggregate surrounded by a halo

Positive Staining for PrP\textsuperscript{SC}
Imaging - sCJD

- MRI – standard technique
  - DWI, FLAIR, Gd-T1W (Gd-T1W is done to “r/o” other pathology)
  - DWI and FLAIR: 90-95% sensitive; 90-95% specific; 90-95% accurate **

- Findings:
  - high signal (FLAIR, DWI), no mass effect, never enhance
  - DWI hyperintensity occurs early*, progressive appearance of new lesions over days/months, stay +ve for months, may normalize late; ADC low in affected areas
  - usually bilateral, but unilateral and asymmetric cases not rare
  - Areas most frequently affected: deep grey nuclei only; cortex only; both **
  - Caudate head, putamen, (globus pallidus less common), cerebral cortex
  - also thalamus, cerebellar cortex, periaqueductal GM
  - “pseudo-sparing” of sensorimotor cortex: not bright on DWI but low ADC
  - Findings in fCJD, iCJD, GSS, FI are similar to sCJD (few reports)
  - Co-morbid disease: CJD usually occurs in the elderly so often also have chronic microangiopathic white matter changes


* Shiga Y et al. DWI abnormalities as an early diagnostic marker for CJD. Neurology. 2004;63:443-449.
sCJD: “Classic” MRI Appearance
Basal Ganglia and Cortex (diff dx very limited)
“Cortical ribbons”, Basal ganglia w relative sparing of GP, postero-medical thalamus, low ADC

Relative sparing of sensorimotor (Rolandic) cortex on DWI but on ADC is same as other cortex: “pseudo-sparing”
sCJD: Cortex only, Basal Ganglia normal

DWI

ADC

FLAIR
**sCJD** – Basal Ganglia only; broader diff dx

**some cortical disease may be missed unless DWI included**

**note:**
co- incidental
NSWM changes
Pulvinar Involvement in sCJD

Pulvinar can be involved in sCJD but pulvinar lesion < striatum lesion
** compared with vCJD where pulvinar lesion > striatum lesion
Note: sparing of globus pallidus
“Pseudo-sparing” of sensorimotor (Rolandic) cortex
The SM cortex is darker on DWI and SWI than adjacent cortex in normals
Sensorimotor Cortex
(Rolandic Cortex: pre- & post-central gyri)

CONCLUSION: Quantitative ADC measurements in patients with early sCJD demonstrate a similar degree of reduced water diffusivity in the primary somatosensory cortex as in other neocortical areas, despite the normal appearance of these areas on visual inspection of epi-DWI.
Progression: 45 y/o with myoclonic jerks: Day 1
First findings were cortical ribbons on DWI. Note: Normal caudate
The Heidenhain type of sCJD

- Initially described in 1929; term adapted 1954
- Visual signs/symptoms occur first and continue to be prominent throughout the illness (clinical diagnosis)
- 5-20% of all sCJD cases
- Most patients first present to ophthalmologists before CJD diagnosis established and could be a risk of procedural cross-contamination to other patients (e.g., if cataract or corneal surgery done)
- More rapid progression (5 month survival vs 7 month survival)
- MRI findings similar to other CJD cases (striatum and/or cortex)
  - High % of cortical lesions are in the occipital/visual cortex
- Other clinical types:
  - Brownell-Oppenheimer – cerebellar predominance
  - ? Panencephalitic (East Asia) – white and gray matter involvement


Heidenhain type
Pseudohypertrophic Cortex

At admission:
hyper-intensity in the head of caudate nuclei, left lentiform nucleus, medial frontal lobe cortex bilaterally.

MRI 1 year later:
marked gyral atrophy and thickening of cerebral cortex with CSF-like signal and enlargement of lateral ventricles (pseudohypertrophic cortex).

Gasparini S et al. Neurology 2013;80:e21
**MM2-type sCJD**

- Thalamic form of MM2-type sCJD has high incidence of normal MRI and no PSWCs on EEG. Dx difficult.
- SPECT CBF shows abnormal thalamic CBF in some cases
- For the clinical diagnosis of MM2-type sCJD, cortical hyperintensity signals on DWI are useful for cortical form and thalamic hypoperfusion or hypometabolism on CBF SPECT or FDG-PET for the thalamic form.

*From Hamaguchi T et al. Neurology 2005*
Variant CJD – Clinical & Lab

- 1995-2005, < 200 cases worldwide, almost all in the UK, peak annual number of deaths = 28 in 2000
- No new cases in over a decade; 0 cases still alive today
- Via BSE contaminated beef
- Mean age of onset 26 yrs, mean survival from dx 14 months
- Sensory (sensation of cold, paraesthesia or pain), neuropsychiatric (withdrawal, depression, fleeting delusions), involuntary movements, cerebellar signs, abnormal eye movements & involuntary movements
- EEG – “does not show “typical abnormality”
- CSF electrophoresis - 14-3-3 protein ~50% +ve
- Genetics: all proven cases homozygous MM at codon 129
- MRI very useful for diagnosis
Imaging - vCJD

• Findings:
  – high signal (FLAIR and DWI)
  – no mass effect or enhancement
  – usually bilaterally symmetric
  – **Pulvinar sign (78% sensitivity, 100% specificity)**
  – also globus pallidus, thalamus, cerebellar cortex, periaqueductal GM

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<th>Location</th>
<th>vCJD</th>
<th>Controls</th>
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<td>Pulvinar</td>
<td>28/36</td>
<td>0/57</td>
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Imaging - vCJD

Case 1

Case 2

Images courtesy of D. Collie
Prion Diseases: Differential Diagnosis

• In the clinical setting of a non-acute illness with prominent dementia, ataxia, myoclonus or visual disturbances, the MRI findings of CJD of:
  – Striatal and/or cortical location
  – +ve on DWI and low ADC that persists for months
  – Highly accurate in establishing the correct diagnosis with a very limited differential diagnosis

• Ddx:
  – Viral encephalitis
  – Paraneoplastic syndromes & “Auto-Immune” disorders / encephalitidies (eg. Voltage-Gated Potassium channellopathy, anti-NMDA encephalitis)
  – Multi-focal subacute infarcts
Autoimmune Encephalitis & Paraneoplastic Syndromes

• especially… Voltage-Gated Potassium Channel (VGKC) autoimmunity - an increasingly recognized disease that can closely mimic CJD (clinically and on MRI)
• Rapidly progressive dementia, myoclonus, extrapyramidal dysfunction, visual hallucinations, psychiatric disturbance, and seizures (seizures not common in CJD)
• Hyponatremia common (>50% of cases).
• CSF 14-3-3 protein or neuron-specific enolase levels elevated in > 50% patients.
• Neoplasia in many patients (~50%)
• Most VGKC patients improved with immune modulation therapy (usually steroids).
Voltage-Gated Potassium Channel Disease (VGKC) – Potential False +ve for CJD

- No PSWC on EEG
- Hyperintense on DWI but ADC not restricted
- Dx: High VGKC autoantibody levels in CSF

Differential Points vs CJD:
- Hyponatremia
- Seizures
- Neoplasia elsewhere
- ADC not restricted

Image from Geschwind MD et al. Arch Neurol. 2008
Why is DWI Positive in CJD?

- Hyperintensity on DWI / restricted diffusion is an early, helpful and consistent finding in CJD
- MRI regions of restricted diffusion co-localize well with histopathology of spongiform change and prion protein deposition
- Theories to explain restricted diffusion in diseased areas:
  - Spongiform holes of 20 – 50 micron size are of appropriate size to cause restricted diffusion
  - Neuronal loss and gliosis
  - Prion protein deposition restricts diffusion
  - All of the above usually occur together – which is the cause?

Geschwind MD et al. Correlating DWI MRI With Pathologic … AlzDis Assoc Disord, 2009
Manners DN et al. Pathologic correlates of DWI in CJD. Neurology 2009
Pathologic Correlates of DWI in CJD
(left frontal lobe showed abnormal DWI, right side did not)
(patient had clinical deficit of left cerebral cortex)

FIGURE 2. Photomicrographs from right and left cortex. A and D show H&E stains. B and E show CD68 immunostaining for glia (astrocytic gliosis), and C and F show a synaptic pattern of staining for PrPSc using 3F4 antibody after hydrolytic autoclaving. H&E indicates hematoxylin and eosin.

Geschwind MD et al. Correlating DWI MRI With Pathologic … Alz Dis Assoc Disord, 2009
Pathologic correlates of DWI in CJD – Manners DN et al - Neurology 2009

ADC values vs spongiosis score in the Creutzfeldt-Jakob disease brains

Graph of regression for ADC against spongiosis for (A) deep gray matter and (B) cortical gray matter. Mean control values for deep gray (0.713 103 mm2s1) and cortical gray matter (0.871 103 mm2s1) are shown as red bars crossing the y-axis.
Diffusion reductions precede clinical disease onset in fCJD

- MRI scans of:
  - 14 patients with the E200K genetic form of Creutzfeldt–Jakob Disease,
  - 20 healthy carriers of this mutation that causes the disease and
  - 20 controls without the mutation from the same families.

- Compared to the mutation-negative controls, ADC was significantly reduced in a thalamic-striatal network, comprising the putamen and thalamic nuclei, in both the patients and the healthy mutation carriers.

- With disease onset, these diffusion reductions intensified, but did not spread to other areas. The caudate nucleus was reduced only after symptomatic onset.

- These findings indicate that cerebral diffusion reductions can be detected early in the course of CJD, and years before symptomatic onset in mutation carriers, in a distinct subcortical network.

Lee H et al. Brain 2009
fCJD: Diffusion reductions precede clinical disease onset

**DIFFERENCE IMAGES**

A. Symptomatic fCJD vs E200K -ve controls

B. E200K +ve carriers vs E200K –ve controls

C. Symptomatic fCJD vs E200K +ve carriers

Lee H et al. Brain 2009
White Matter in CJD (fCJD)

21 patients w fCJD (E200K) c/w 19 controls from same families

Found significant reductions in FA in white matter pathways

MRI 2.8 months from symptom onset
Not yet demented
WM impaired prior to dementia

FA deficits increased w disease duration (FA deficit: 8% → 20%)
mainly due to increase in RD

Could not determine whether WM changes primary or secondary to GM degeneration

Lee H et al. AJNR 2012
White Matter in CJD (fCJD)

21 patients w fCJD (E200K) c/w 19 controls from same families

Found significant reductions in FA in white matter pathways

Lee H et al. AJNR 2012
MR Spectroscopy

- Very limited number of studies
- Variability of results
- Not sufficiently robust to be a useful clinical tool
- Results:
  - Low NAA
  - High Myoinisitol
- Subject of further investigation
Propagation & Progression of Disease

The Prion Hypothesis: “prions convert normal proteins into dangerous ones by simply inducing the benign molecules to change their shape or “conformation”. It is a reasonable assumption that the prion must be physically close to the normal proteins that it affects.

Why do anatomically non-contiguous areas of the brain get affected as the disease progresses?

Direct evidence supports disease propagation along trans-synaptic connections (Scott et al., 1992).

What’s the connection?
Prion proteins aggregate in selectively vulnerable neuron populations in specific brain regions. Often, later-affected regions bear known anatomical connections with the sites of earlier injury.

Pathology, imaging, & transgenic animal models suggest that neuro-degeneration may relate to neural network dysfunction.

In human spongiform encephalopathies, direct evidence supports disease propagation along trans-synaptic connections (although this may not be the exclusive method of propagation).

**Network Degeneration Hypothesis**

**Disease Propagation along trans-synaptic connections**

**Use of Resting State fMRI**

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<td>Seeley et al.</td>
<td>Neurodegenerative diseases target large-scale human brain networks Neuron 2009</td>
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resting state fMRI

During task-free conditions, correlated spontaneous activity occurs within spatially distinct, functionally related groups of cortical and subcortical regions with synchronous baseline activity feature direct or indirect anatomical connections. BOLD signal fluctuations occur within these intrinsic connectivity networks (ICNs).

Two 6-minute task-free fMRI scans after being instructed only to remain awake with their eyes closed.

Detailed network mapping of the right frontal insula, a focus of neuro-degeneration in FTD

(A) Reduced gray matter volume in FTD vs. controls occurs within regions showing (B) intrinsically correlated BOLD signals in controls and (C) structural covariance. These distributed spatial maps overlap (D) within a “network” that reflects known primate neuroanatomical connections.

Seeley et al. Neuron 2009
Neural Networks and Connectivity

• DWI / ADC / DTI together with fMRI

• Exciting potential for new insights into CJD and other neurodegenerative disorders
Amyloid PET for Aβ deposits in AD
Can an analogous CJD PET agent for PrP<sup>sc</sup> be developed?

• The in-vivo visualization of brain Aβ deposition with amyloid PET is virtually equivalent to demonstration of the pathology at autopsy (but a positive amyloid PET does not by itself establish any clinical diagnosis, including that of AD dementia).

• If an analogous agent for PrP<sup>sc</sup> was developed, it would allow:
  • studies of PrP<sup>sc</sup> in normals, and pre-symptomatic fCJD populations
  • quantitation of PrP<sup>sc</sup> disease burden
  • definite diagnosis of CJD without biopsy, in possible and probable CJD cases
Summary: Imaging Prion Diseases

- Prion diseases are rare
- Sporadic CJD is by far the commonest
- Imaging plays an extremely important role in diagnosis
- Imaging helps avoid biopsy
- MRI (DWI/ADC & FLAIR) findings are the only imaging findings used in any formal diagnostic criteria
  - High signal in basal ganglia and/or cortex on DWI or FLAIR; low ADC; no mass effect, never enhance
  - Abnormal signal in cerebellum and brainstem rare
  - Caution: Even classic MRI pattern is not 100% specific for CJD
  - Main Ddx: Autoimmune Encephalitis & Paraneoplastic Syndromes
- Normal MRI does not exclude dx of CJD
Summary: Imaging Prion Diseases

- Quantitative diffusion measures show abnormalities that are not visible on conventional images in GM and WM including non-symptomatic carriers of the E200K mutation in familial CJD and are promising areas for further research.
- Resting state networks on fMRI correlate with anatomic distribution of lesions in some neurodegenerative diseases.
- Alzheimer’s, tauopathies, ALS, and Parkinson’s share many clinical, histologic, and transmissability features with the “proven” prion diseases.
- The concept of prion disease is expanding to possibly include these other neurodegenerative diseases.
Imaging of Prion Related Diseases

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THE END