Neuropathology of Neurodegenerative Disease

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Objectives

♦ Introduce the major neuropathological classes of neurodegenerative disease

♦ Present exemplary clinical case studies

♦ Demonstrate complexities of clinicopathological correlations in neurodegenerative disease
  • Importance of “diagnostic splitting” for successful clinical trials
Protein aggregation in neurodegenerative disease

- Intraneuronal/glial inclusions composed of abnormally processed proteins
  - Correlation with neuronal loss and clinical symptoms
  - Diagnostic “gold standard”

- Pathogenic mutations in these proteins cause disease
  - Altered function
  - Increased fibrillization

- Toxicity in animal/cell models
  - Transmission studies

FTDP-17 (P301L MAPT) Cingulate Gyrus

Image courtesy of PENN CNDR
Disease-modifying therapy: Targeting protein aggregation

Classes of Proteinopathies

- α-synuclein
  - PD/DLB
  - MSA

- Tau
  - AD
  - PSP
  - CBD
  - PiD
  - FTDP-17

- TDP-43
  - ALS
  - FTLD-TDP
  - FUS
  - SOD-1
  - Ubl-2
  - Optineurin
α-synuclein: Function and Genetics

**Function:** Pre-synaptic soluble protein involved in synaptic plasticity

**Genetics:** Chromosome 4- SNCA (α-synuclein, PARK1)
- mutation/duplication, triplication leads to early onset PD/DLB

Synucleinopathies: PD/PDD, DLB

**Clinical:**
- Movement disorder
  - Bradykinesia
  - Postural instability
  - Tremor
- Dementia
  - Executive dysfunction
  - Hallucinations
  - Visuospatial dysfunction
  - 1-year rule – PDD vs DLB

**Pathology:**
- Lewy bodies/Neurites-substantia nigra, olfactory bulbs, brainstem also limbic/neocortical regions

Images courtesy of PENN CNDR
Synucleinopathies: Multiple System Atrophy

**Clinical:**
- autonomic symptoms (Shy-Drager)
- MSA-C (OPCA) cerebellar symptoms
- MSA-P (SND) extrapyramidal symptoms

**Pathology:**
- glial cytoplasmic inclusions in brainstem, cerebellum, cortical white matter

Image courtesy of PENN CNDR
Classes of Proteinopathies

α-synuclein
PD/DLB
MSA

Tau
AD
PSP
CBD
PiD
FTDP-17

TDP-43
ALS
FTLD-TDP

FUS
SOD-1
Ubl-2
Optineurin
**Tau: Function and Genetics**

- **Function:** MT stability
- **Genetics:** Chromosome 17 - MAPT
  - FTDP17
- 6 isoforms (3-4 MTBDs)

Adapted from: Brunden, et al. *Nat Rev.* 2009
**Clinical**: AD Amnestic symptoms
- Later progress to include language, visuospatial and executive dysfunction

**Pathology**: Medial temporal lobe, limbic and neocortical Grey Matter.

**Genetics**: APP and APP processing enzymes (i.e. PSN-1,2)

From: Irwin et al, *Brain* 2012
AD: Atypical presentations

- Posterior Cortical Atrophy
- Corticobasal Syndrome
- Logopenic Progressive Aphasia
- Frontal Variant AD
Tauopathies: Pick’s disease

- **Clinical:** bvFTD- social comportment disorder, executive difficulties. Visuospatial and memory relatively spared. Also **PNFA**

- **Pathology:** Ventromedial and dorsolateral frontal, anterior temporal. *Knife-edge atrophy.*

Images courtesy of PENN CNDR
Tauopathies: Corticobasal Degeneration

- **Clinical**: CBS  
  Asymmetric akinetic-rigid syndrome. Apraxia, cortical sensory loss, myoclonus. Also bv-FTLD & PNFA.

- **Pathology**: brainstem, basal ganglia, peri-sylvian cortex. **White matter** glial inclusions

From: Irwin et al, *Brain* 2012
Tauopathies: Progressive supranuclear palsy

- **Clinical**: PSP akinetic-rigid syndrome, supranuclear gaze palsy, axial rigidity, gait imbalance. Also CBS, bvFTD, PNFA.

- **Pathology**: Midbrain, pons, dentate nucleus (cerebellum) Variable cortical involvement.

From: Irwin et al, Brain 2012.
Classes of Proteinopathies

α-synuclein
- PD/DLB
- MSA

Tau
- AD
- PSP
- CBD
- PiD
- FTDP-17

TDP-43
- ALS
- FTLD-TDP

FUS
- SOD-1
- Ubl-2
- Optineurin
**Function:** RNA binding protein

**Genetics:**
- Chromosome 1 TARDPB (TDP-43)
  - *ALS >> FTLD*
- Chromosome 17 *PGRN*
  - FTLD-TDP (Type A)
- Chromosome 9 *C9orf72*
  - FTLD-TDP/ALS (Type B)


**Clinical:** upper and lower motor neuron +/- bvFTD/PNFA

**Pathology:**
- TDP-43 inclusions
  - Skeins
  - Lewy-like
  - Glial inclusion
- Variable non-motor involvement

Images courtesy of PENN CNDR

TDP-43 proteinopathies: FTLD-TDP

**Clinical:**
- bvFTD
- Primary progressive aphasia: **SD** > PNFA
- CBS
- +/- ALS

**Pathology:**
- Neuronal Cytoplasmic/Nuclear Inclusions, Dystrophic neurites
- Glial inclusions
- Subtypes = Genetics

Images courtesy of PENN CNDR

Stereotypical progression of neuropathology in human disease

Alzheimer’s Disease  Parkinson’s Disease

From Goedert et al. *Trends Neurosci* 2010
Animal transmission models mirror disease staging in humans

From Iba et al. *J Neurosci* 2013

From Luk et al. *Science* 2013
**Transmission: The Google Experience**

**HUFFPOST HEALTHY**

*About Alzheimer's Treatment*

*Living with Alzheimer's Ask an Expert*

**AHAF Statement Clarifying “Infection” and Alzheimer's Disease**

*May 27, 2012*

*Source: American Health Assistance Foundation*

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**Los Angeles Times**

*Alzheimer’s, Parkinson’s, more -- due to infectious proteins?*

*June 20, 2012 | By Rosie Miel, Los Angeles Times / For the Booster Shots blog*

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**Fox News**

*Can You 'Catch' Alzheimer's Disease?*

*Published October 04, 2011 / FoxNews.com*

*Alzheimer's disease transmission may be similar to infectious prion diseases*

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**NBCNEWS.com**

*Alzheimer's may be transmissible, study suggests*
Beyond Google: PubMed


“Recent developments in our understanding of the pathogenesis of neurodegenerative diseases suggest that there may be risks to the recipients of organs from such patients due to prion-like propagation of protein misfolding from affected donor to unaffected host.”

CELL BIOLOGY

A Unifying Role for Prions in Neurodegenerative Diseases

Stanley B. Prusiner

“A profound change in thinking about the etiologies of many neurodegenerative diseases has far-reaching implications for developing therapeutics.

“… alternative unifying explanation is that a diverse group of proteins can form prions. Although small numbers of prions could be cleared by protein degradation pathways, accumulation above a certain threshold over time would enable the prions to self-propagate resulting in central nervous system dysfunction”
Transmissibility of ND: The Human Experience

- Fetal dopaminergic grafts in human PD patients
  - LB-like α-synuclein inclusions
    - 7 cases >10 years after grafting
  - Accompanied by decreased TH, DAT, microglial invasion in some cases
  - Host factors vs. transmission?

From Li et al. Nat Med 2008
Transmissibility of ND: The Human Experience in hGH Recipients

From Irwin et al. JAMA Neurol, 2013
Objectives

- Introduce the major neuropathological classes of neurodegenerative disease
- Present exemplary clinical case studies
- Demonstrate complexities of clinicopathological correlations in neurodegenerative disease
  - Importance of “diagnostic splitting”
Case # 1 : “Positive Outlook”

- 59 year old female CC: “I feel funny”
  - Self informant at first visit
  - Claims paradoxical episodes of tingling sensation over body, treated for seizures and doctors found “thyroid test- I felt better after steroid treatment in the hospital.”
  - Mentions interpersonal problems at work, during a road-side assistance to a stranger in a MVA she was arrested for unclear reasons. Tattoo= “Stay positive”
  - **Exam: Mild Dysexecutive Syndrome** (preservation of memory)
    - MMSE= 27 lost items in orientation
    - Poor verbal fluency
    - Delayed recall 2/6 with intact recognition
Case #1: “Positive Outlook”

- Visit #2: bvFTD
  - Daughter present states:
    - No improvement with steroids
    - Approaching strangers
    - Hoarding Candy
    - Obsessive about trips to the dollar store
    - Spent large sums of money with a publisher
    - Less initiative to do things
    - Multi-tasking difficulties led to job termination
Case # 2 : “I’m all over the place”

♦ 57 year old male CC :
♦ “I’m all over the place”

- Son claims over past seven years progressive mood/emotional disturbance- diagnosed with bipolar disorder initially. Developed word-finding difficulty and repetitive speech. Multi-tasking difficulty forced him to retire early. Ritualistic about running, daily schedule. **Exam: Severe loss of object knowledge with dysexecutive syndrome and memory loss.**
  - MMSE= 23 lost items in orientation, recall, world
  - Could name 1 of six objects and could not categorize
  - Stereotypic speech- repetitive phrases largely empty of content.
  - Surface dyslexia
Case # 2: “I’m all over the place”

- Visit 2+
  - Patient develops rage episodes, crying fits.
  - Explosive anger when driver’s license revoked
  - Increasing apathetic and ritualistic behavior.
  - Increasing comprehension deficits - cannot follow multi-step commands
  
  • Diagnosis = svPPA
Case # 3: “Moving Target”

- 66 year old female CC: “Memory loss”
  - Claims one-year history of confusion with dates/appointments, anxiety, disorganization. Nocturnal hallucinations.
  - **Exam: Dysexecutive Syndrome + Episodic Memory Impairment**
    - MMSE=26
    - 2/6 word recall- inconsistent recognition
    - Mild visuo-spatial difficulty
    - Subtle word-finding difficulty
  - **Diagnosis- Mild Cognitive Impairment (multi-domain)**
Case # 3: “Moving Target”

Visit #2:

- Develops rigidity/clumsiness in right hand. Sudden jerking movements.
- New Exam findings
  - Worse cognitive performance in visuospatial and executive domains
  - Apraxia right hand
  - Asymmetric Parkinsonism on right side
- Diagnosis= CBS
Case # 3: “Moving Target”

Visit #3:

- Expressive language problems leading to social isolation. Improvement of limb rigidity with carbidopa-leavdopa treatment,
- **New Exam findings:**
  - Expressive language deficit with motor speech impairment and orobuccal apraxia.
- **Diagnosis: CBS + naPPA**
Clinicopathological Complexity

From Irwin et al. Front Neurosci, 2013
Key Features of FTLD

♦ Young Onset
  • Significant loss of independence

♦ Cognitive/Behavioral symptoms often vague
  • Rely on reliable caregiver

♦ Lack of FTLD-specific biomarkers

♦ Clinical Diagnosis encompasses a large heterogeneous group of underlying neuropathologies

♦ No prognostic indicators

♦ Improving diagnostics is critical for clinical trials targeting these proteinopathies
Objectives

- Introduce the major neuropathological classes of neurodegenerative disease
- Introduce the methodology of neuropathological diagnosis
- Demonstrate complexities of clinicopathological correlations in neurodegenerative disease
  - Importance of “diagnostic splitting”
### The Old Dogma of Neurodegenerative Disease

#### Movement Disorders
- Parkinson’s Disease
- Multiple System Atrophy
- Corticobasal Degeneration
- Progressive Supranuclear Palsy

#### Cognitive Disorders
- Alzheimer’s Disease
- Frontotemporal Dementia
- Primary Progressive Aphasia

#### Neuromuscular Disorders
- Amyotrophic Lateral Sclerosis
- Progressive Muscular Atrophy
- Primary Lateral Sclerosis
The New “Dogma” of Neurodegenerative Disease: Clinicopathological Entities

Neurodegenerative Disease

- Parkinson’s Disease/
  Dementia with Lewy Bodies
- Corticobasal syndrome
- Progressive Supranuclear Palsy
- Alzheimer’s disease
- Frontotemporal Dementia/
  Primary Progressive Aphasia
- Amyotrophic lateral Sclerosis
Complexity of clinicopathological correlations in FTLD

Irwin et al. Front Aging Nerosci 2013
Relevance of diagnostic splitting

Can these neuropathological subtypes of bvFTD accurately be differentiated during life?
Untangling the clinicopathological overlap in FTLD: AD vs FTLD

- CSF biomarkers of t-tau and Aβ_{1-42} can distinguish AD from FTLD with >90% sensitivity and specificity
  - Training (30 AD, 10 FTLD)
  - Test (11 AD, 10 FTLD)
  - Diagnostic Cutoff = Ratio 0.34

Irwin et al. Arch Neurol 2012
Diagnostic Splitting of FTLD

TAU

AD

TDP

bvFTD
Untangling the clinicopathological overlap in FTLD: FTLD-tau vs FTLD-TDP

- White matter imaging (DTI) may accurately distinguish (>90% sensitivity, specificity) FTLD-Tau (n=10) from FTLD-TDP (n=25)
  - Differences observed in DTI confirmed by neuropathological assessment of WM inclusion burden

McMillan et al. JNNP 2013
Diagnostic Splitting of FTLD
Untangling the clinicopathological overlap in FTLD: C9orf72 expansion

- Comparative study of C9orf72 expansion positive (C9P) ALS (n=31) and FTLD (n=33) vs expansion negative ALS (n=36) and FTLD-TDP (n=43)
  - C9P ALS
    - Shorter survival (2.6 vs 3.8 y, \( p=0.04 \))
  - C9P FTLD
    - More rapid decline in cognitive performance (VF, MMSE)
    - more extensive cortical atrophy corresponding to more severe neurodegeneration at autopsy

Irwin et al. JNNP 2013
Diagnostic Splitting of FTLD

bvFTD

TDP

C9orf72

Sporadic

GRN

Modifying SNPs?
Clinical sub-phenotypes?
Biofluid biomarkers?
Neuroimaging features?
Genetic Modifier in bvFTD

- Cohort of 80 sporadic clinical bvFTD (mixed neuropathology)
  - Carriers of ≥ 1 risk allele in MOBP gene
    - Shorter survival (~ 3 years)
    - Increased WM degeneration in midbrain and SLF
  - Effect is independent of underlying tauopathy

Irwin et al, under review.
Untangling the clinicopathological overlap in PDD

- Multivariate analysis to predict PDD from large autopsy cohort (92 PDD, 48 PD)
  - **cortical Lewy pathology** strongest correlate of dementia
  - APOE ε4 carrier status significant
  - PDD+AD (28.6%)
    - *Older age of onset*
    - *Higher burden of Lewy pathology*
    - *Shorter time to dementia*

**TABLE 3: Stepwise Selection Logistic Regression Model to Predict Parkinson Disease with Dementia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>z</th>
<th>p</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>-1.37</td>
<td>0.50</td>
<td>-2.73</td>
<td>0.0063</td>
<td>0.25</td>
<td>0.10–0.63</td>
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<tr>
<td>Global cortical LB/LN score</td>
<td>1.40</td>
<td>0.40</td>
<td>3.53</td>
<td>0.0004</td>
<td>4.06</td>
<td>1.87–8.81</td>
</tr>
<tr>
<td>APOE4 carrier</td>
<td>1.43</td>
<td>0.61</td>
<td>2.44</td>
<td>0.0182</td>
<td>4.19</td>
<td>1.28–13.75</td>
</tr>
</tbody>
</table>

Based on 116 observations.
LB = Lewy body; LN = Lewy neurite; SE = standard error.

Clinicopathological correlations across the Lewy body spectrum

Clinical Phenotype

Postural-gait instability phenotype
Non-tremor-dominant phenotype
Older-onset

Hallucinations
Fluctuations
Executive Deficits

Tremor-dominant phenotype
Younger-onset

DLB
DLB + AD
PDD+AD
PDD
PD

GBA
SCNA
APOE ε4
H1/H1 MAPT

Genetic Factors
Improving Diagnostic Accuracy

Refine Diagnostics

Detailed Clinical Exam

Prospective Multi-modal Biomarker Study
- Clinical
- Genetic
- Biofluid
- Neuroimaging

Detailed Neuropathologic Assessment

Homogeneous Patient Groups for Clinical Trials

Refine Diagnostics
Potential pathway for treatments

**Diagnosis**
- PDD + AD
- bvFTD (FTLD-TDP)
- lvPPA (AD)
- CBS (FTLD-Tau)
- ALS-D+ AD

**Treatment Target**
- $\alpha$-synuclein
- $A\beta$
- Tau
- TDP-43

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