TDP-43 & Tau: From Molecule to Clinical Phenotype

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I do not have any disclosures

OUTLINE

- Video case presentation
- FTD clinical variants
- Pathological variants that underlie FTD
- Clinicopathological correlates
- Improving clinicopathological correlates
- Diagnosis of video case presented

- FTD = Clinical syndromes
- FTLD = Pathological diagnoses

Case Presentation

- 55 y.o. male physician presented in August 2003 with mixed extrapyramidal and behavioral impairment
- 3 years ago: personality change (got a tattoo)
- Last 1-2 years, trouble with balance, monotone speech, sweet cravings, disinhibited behaviors (flash his neighbors, grabbed a woman's breast)
- Blood transfusion from uncle who later died from CJD
- No family history of neurodegenerative disease
- On examination: impulsive & jocular
- Difficulties with AMT, go-no-go & Luria 3 step
- Video demonstrating progression over 1 year: August 2003, February 2004 & September 2004


AUG 6 2003

FTD Clinical Syndromes

- 3 well defined clinical variants subsumed under the term frontotemporal dementia (FTD)
  - Behavioral variant FTD (bvFTD)
  - Progressive non-fluent aphasia (PNFA)
  - Semantic dementia (SD)

Neary et al. 1998

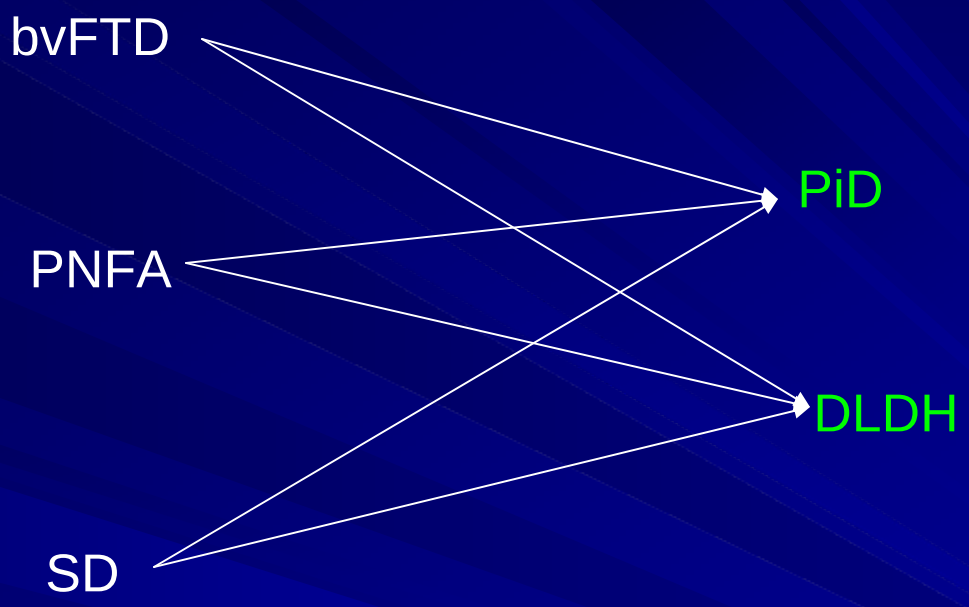
Characteristics of Clinical Syndromes

- bvFTD (56% of FTD; Johnson et al. 2005)
  - Personality change, behavioral dyscontrol, executive dysfunction
- PNFA (25%)
  - Non-fluent speech output with evidence of agrammatism and telegraphic speech
- SD (19%)
  - Loss of word, face and object meaning, and comprehension difficulties

FTLD Pathologies

- Two well defined non-Alzheimer's disease pathologies that underlie and accounted for FTD
  - Pick disease with Pick bodies (PiD)
    - Characterized by argyrophilic rounded inclusions and balloon neurons
  - Dementia lacking distinctive histology (DLDH)
    - Findings of neuronal loss and gliosis affecting the superficial cortical lamina of the frontal and temporal lobes, yet absent inclusions (Knopman et al. 1990)

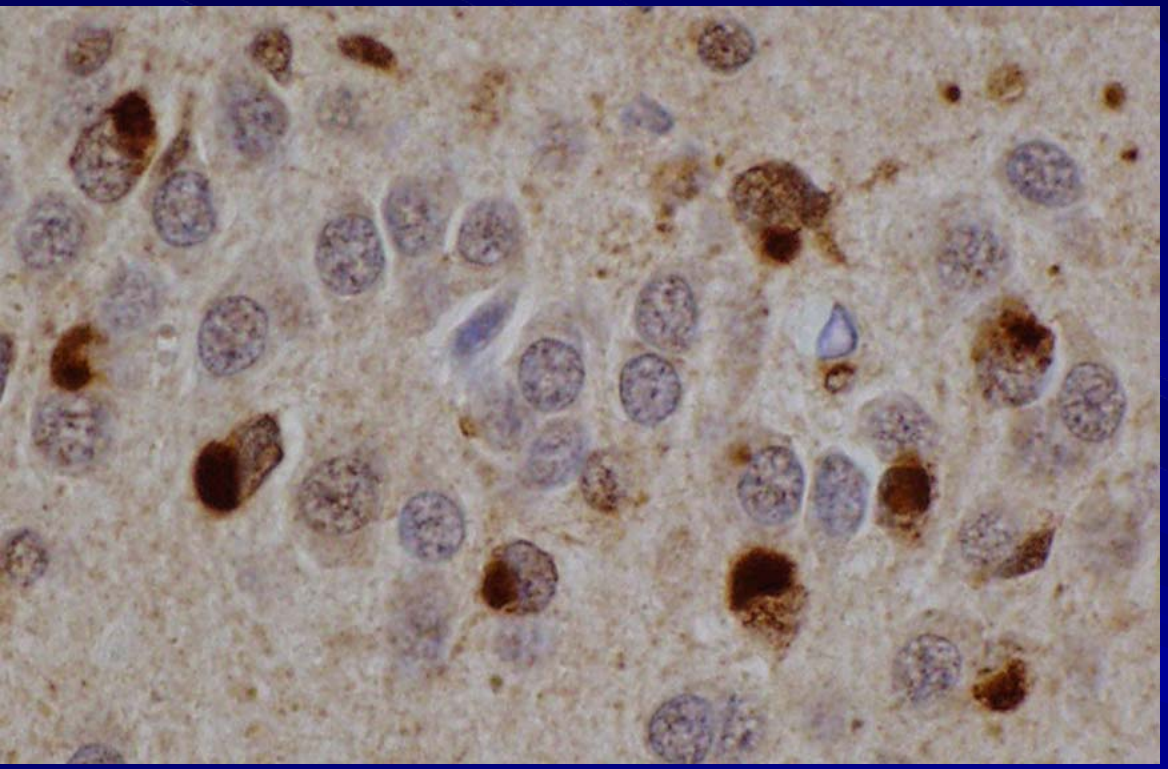
CLINICAL SYNDROMES PATHOLOGICAL DIAGNOSES



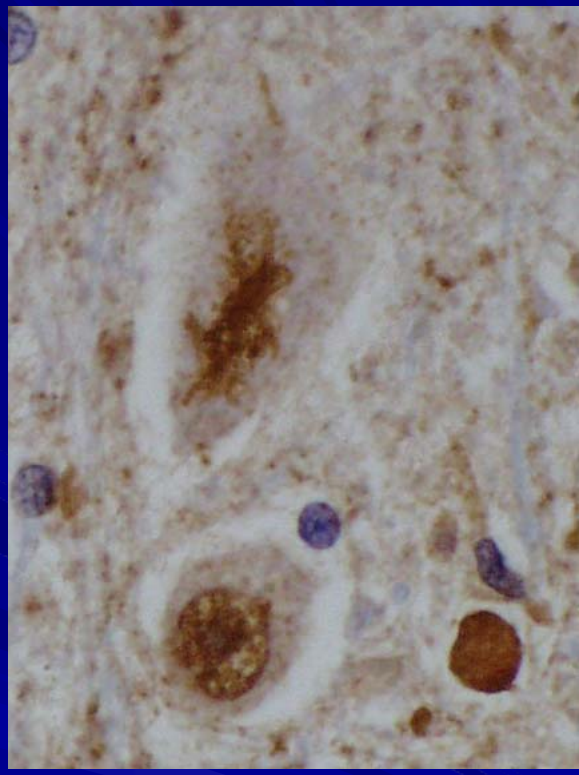
Advancements in FTD

1. Immunohistochemistry
   - PiD = tau immunoreactive (Tau+)
   - DLDH = not tau immunoreactive (Tau-) but ubiquitin immunoreactive (neurites and inclusions)
     - FTLD-U: Those with ubiquitinated inclusions/neurites without MND (Josephs et al., 2004; Lipton et al., 2004)
     - FTLD-MND: Those ubiquitinated inclusions/neurites with MND (Josephs et al., 2004)

FTLD-U



FTLD-MND



Advancements in FTD

2. 4 large clinicopathologic series with over 300 subjects (Hodges et al. 2003, Kertesz et al. 2004, Josephs et al., 2006, Forman et al 2006)
   - Identified other pathological disorders that account for FTD clinical syndromes
   - FTLD pathologies could account for other clinical syndromes

   - Disorders that are related to FTD
     - Progressive supranuclear palsy (PSP)
     - Corticobasal degeneration (CBD)
     - Motor neuron disease (MND)

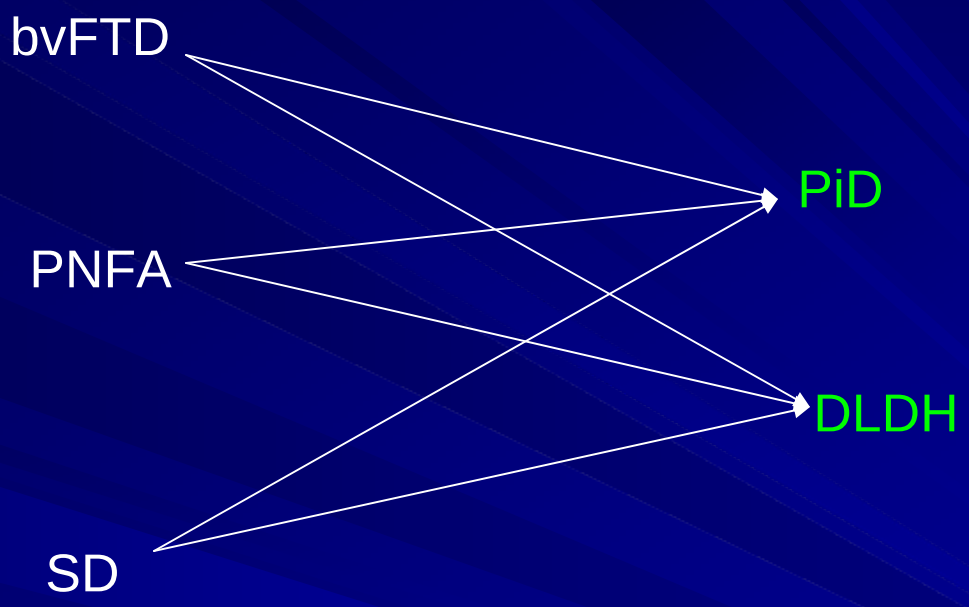
Related Disorders - Clinical

- c-PSP
  - Clinically characterized by the presence of vertical supranuclear gaze palsy, early falls, axial greater than appendicular rigidity, L-dopa unresponsive
- CBS
  - Asymmetric findings of cortical and basal ganglia dysfunction – ideomotor apraxia, cortical sensory loss, myoclonus, parkinsonism, L-dopa unresponsive
- FTD-MND
  - FTD signs + presence of bulbar signs, or signs of upper or lower motor neuron disease

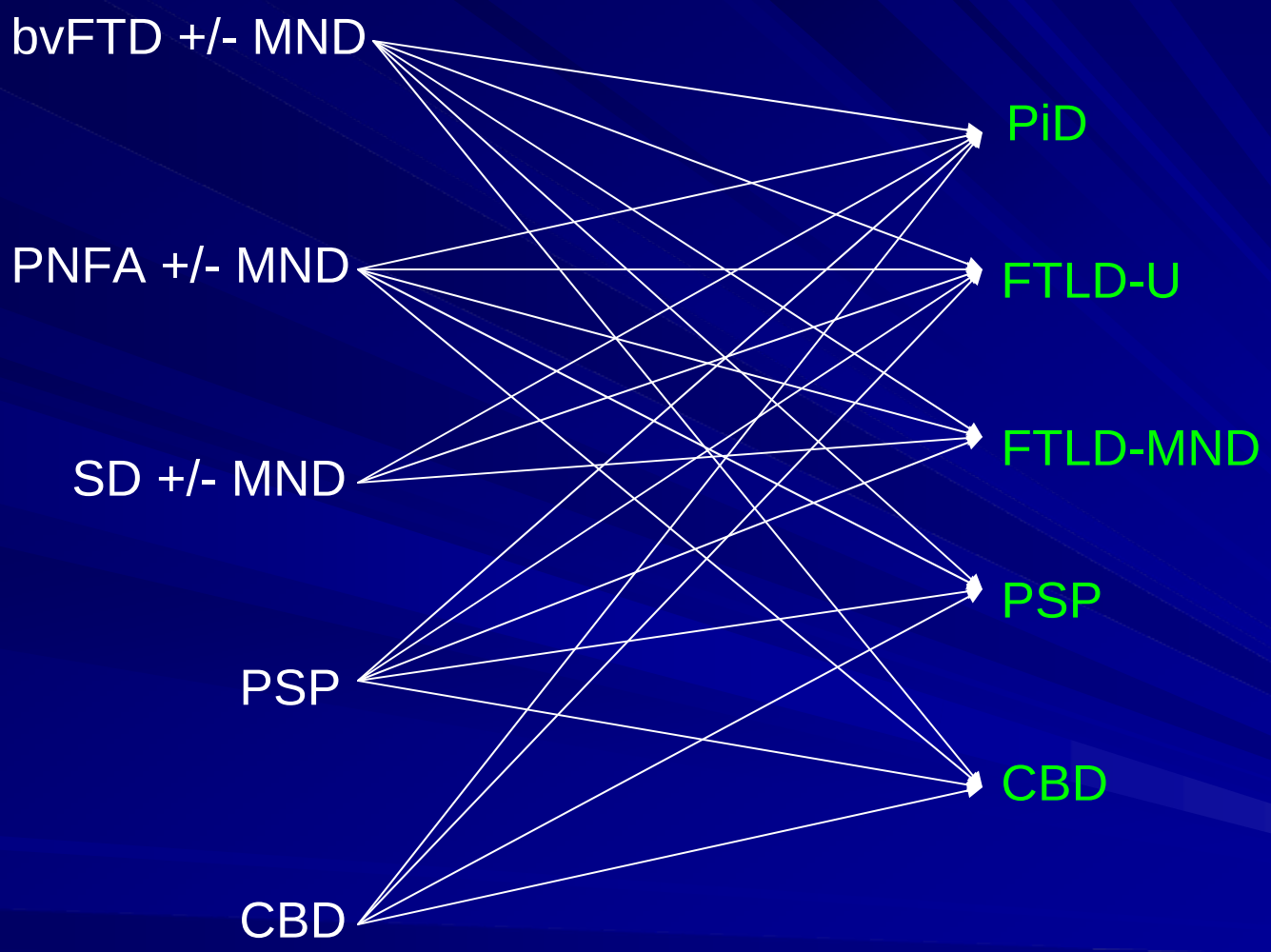
Related Disorders - Pathological

- PSP
  - Tau-positive lesions, e.g. globose NFT & tufted astrocytes found in cardinal nuclei especially basal ganglia and brainstem regions
- CBD
  - Tau-positive lesions, e.g. coiled bodies, threads, astrocytic plaques found in cardinal regions
- FTLD-MND
  - FTLD + MND (loss of brainstem motor neurons or anterior horn cells, Bunina bodies, evidence of corticospinal tract degeneration & TDP-43+ inclusions)

CLINICAL SYNDROMES PATHOLOGICAL DIAGNOSES



CLINICAL SYNDROMES PATHOLOGICAL DIAGNOSES

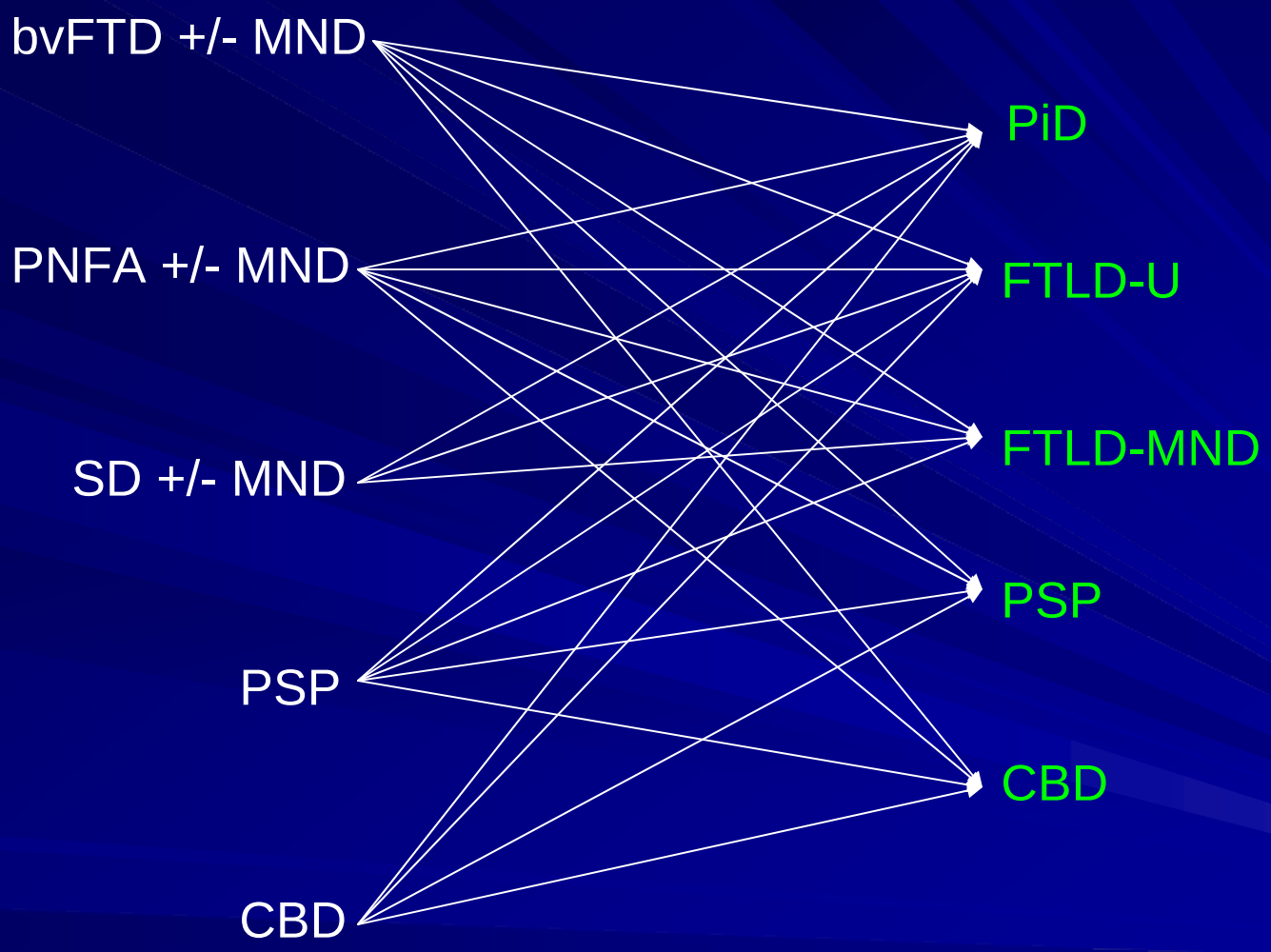


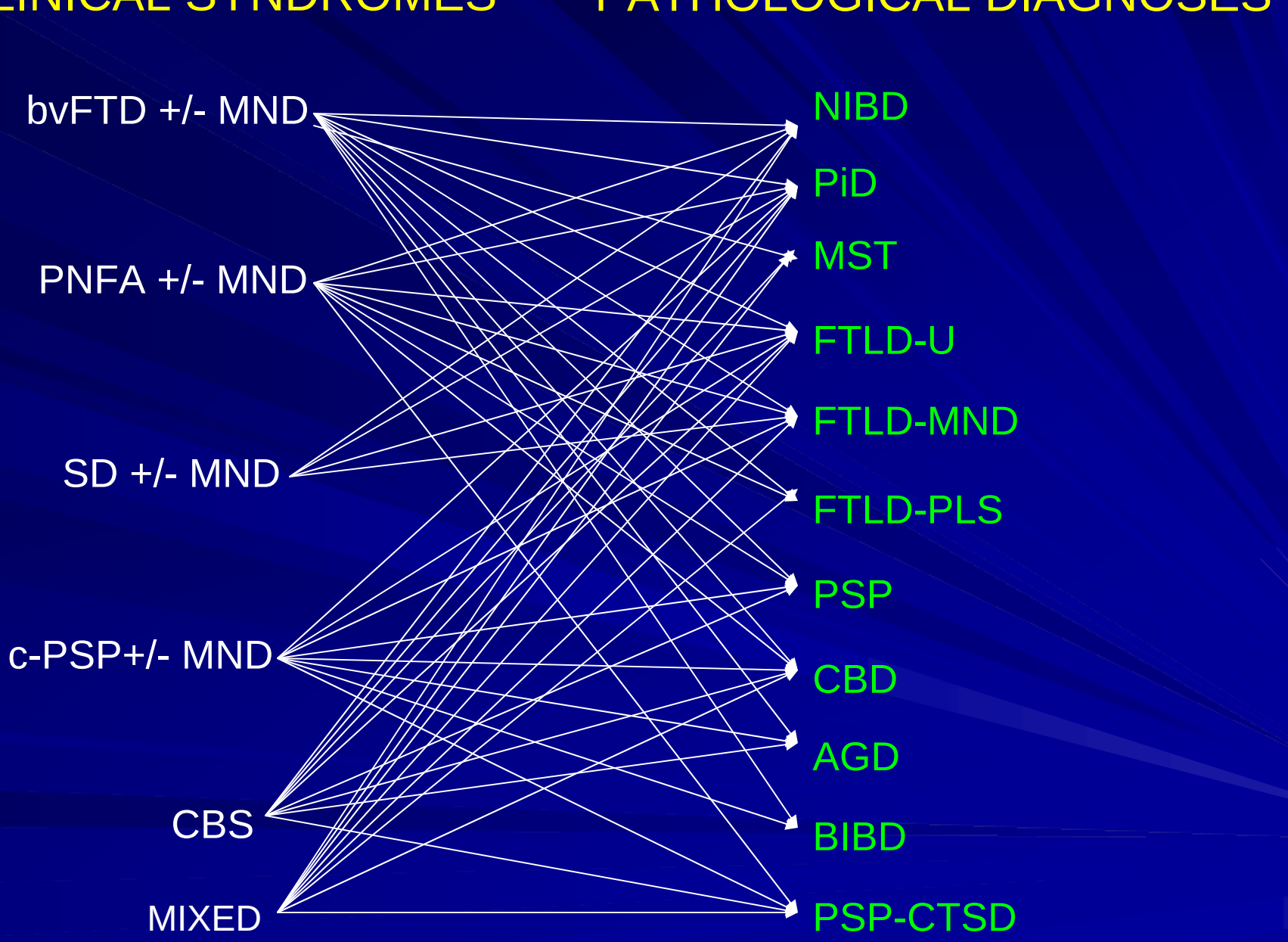
Additional appreciations

- Discovery that additional rare pathologies can underlie FTD
  - Basophilic inclusion body disease (BIBD)
  - Sporadic multisystem tauopathy (MST)
  - Neurofilament inclusion body disease (NIBD)
  - Argyrophilic grain disease (AGD)
  - PSP with corticospinal tract degeneration
  - FTLD-PLS

(Munoz et al., 1984; Braak & Braak 1987; Bigio et al., 2001; Josephs et al., 2003; Cairns et al., 2004; Josephs et al., 2006; Josephs & Dickson 2007)

CLINICAL SYNDROMES PATHOLOGICAL DIAGNOSES




CLINICAL SYNDROMES
PATHOLOGICAL DIAGNOSES
bvFTD +/- MND
PNFA +/- MND
SD +/- MND
c-PSP+/- MND
CBS
MIXED
NIBD
PiD
MST
FTLD-U
FTLD-MND
FTLD-PLS
PSP
CBD
AGD
BIBD
PSP-CTSD

Most recent advancements

- Discovery that mutations in the progranulin (PGRN) gene is associated with FTLD-U (Baker et al.,2006; Cruts et al., 2006)

- Discovery that one of the major proteins in FTLD-U and FTLD-MND is the TAR DNA binding protein 43 (TDP-43) (Neumann et al., 2006; Arai et al.,2006)

Simplify

- Although the pathology is heterogeneous lets divide the pathologies via a biochemical approach into Tau+ vs. Tau- FTLD
- Further refinement however was Tau+ vs. ubiquitin-only-immunoreactive
- With the recent discovery of TDP-43 lets go even further by dividing the pathology into Tau+ vs. TDP-43+ vs. Other
  - Can do this since FTLD-U = FTLD-TDP-43

Simplify

- Tau+ vs. TDP-43+ vs. others
  - Tau+ (PiD, CBD, PSP, PSP-CSTD, MST, AGD)
  - TDP-43+ (FTLD-U, FTLD-MND, FTLD-PLS)
  - TNT+ (NIBD, BIBD)
- Make sense for future treatment
- Creating the category TNT+ will account for <3% of FTLD

CLINICAL SYNDROMES		PATHOLOGICAL DIAGNOSES
FTD + MND	(100%) →	TDP-43+
c-PSP/CBS	(97%) →	TAU+
SD	(>80%) →	TDP-43+
PNFA	(76%) →	TAU+
bvFTD	(42%:58%) →	TAU+/TDP-43+

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Further refinement of PNFA

- PNFA
  - 70% Tau+
  - 30% TDP-43+ and AD
- Introduction of apraxia of speech & logopenic aphasia
  - Apraxia of speech (AOS) is a motor speech disorder characterized by slow speaking rate, abnormal prosody and distorted sound substitutions, additions, repetitions and prolongations, sometimes accompanied by groping, and trial and error articulatory movements
    - AOS ± PNFA = Tau+ (Josephs et al, 2006)
  - Logopenic aphasia characterized by non-fluent speech with word finding pauses and difficulty with repetition, with relatively preserved word comprehension and absence of agrammatism
    - Logopenic PNFA = AD? (Gorno-Tempini et al., 2004)

CLINICAL SYNDROMES		PATHOLOGICAL DIAGNOSES
FTD + MND	(100%) →	TDP-43+ FTLD-MND
c-PSP/CBS	(97%) →	TAU+
SD	(>80%) →	TDP-43+
AOS ± PNFA	(100%) →	TAU+
PNFA – LPA	(>90%) →	TDP-43+
bvFTD	(42%:58%) →	TAU+/TDP-43+

bvFTD

Characteristics	Cluster 1	Cluster 2	p value
Tau+ path	57%	29%	0.06
Poor planning/judgment	82%	25%	<0.001
Motor symptoms	42%	21%	0.15
Psychiatric symptoms	7%	25%	0.14
Decline in personal hygiene	4%	36%	<0.01
Impaired regulation in personal conduct	64%	100%	<0.001

Hu et al. 2007 in press

Cluster 1
PiD
PiD
FTLD-U
PGRN+ FTLD-U
PSP
FTDP
PGRN+ FTLD-U
PGRN+ FTLD-U
MND
MND
CBD
CBD
PiD
PiD
FTLD-U
CBD
PiD
FTLD-U
PSP
PiD
FTLD-U
PGRN+ FTLD-U
MND
PiD
FTLD-U
PiD
CBD
FTDP
Cluster 2
PiD
FTDP
FTLD-U
FTLD-U
FTLD-U
FTLD-U
FTLD-U
FTLD-U
PiD
FTLD-U
FTLD-U
FTDP
PSP
FTLD-U
FTLD-U
PSP
MND
FTLD-U
FTLD-U
FTLD-U
MND
MND
FTLD-U
CBD
FTLD-U
MST
FTLD-U
PGRN+ FTLD-U

Caveat

- There was a difference in TDP-43+ subjects in Cluster 1 that were progranulin positive compared to cluster 2 ($p<0.05$)
- Excluded PGRN subjects (TAU vs. TDP-43 clustered with $P<0.01$)
- The rules appear to differ for familial FTD
  - E.g. While the presence of prominent parkinsonism in sporadic FTD predicts Tau+ pathology
  - The presence of prominent parkinsonism in familial FTD does not necessarily suggest FTDP-17t; think FTDP-17p, i.e. TDP-43+ pathology (especially CBS)

Where are we now

- What is the significance of 3 variants of TDP-43 immunoreactivity?

PATHOLOGIC = CLINICAL

TDP-43 type 1 = FTD with PGRN
TDP-43 type 2 = SD
TDP-43 type 3 = FTD-MND

Sampathu et al., 2006; Mackenzie et al., 2006

Important questions

1. Which gene causes familial TDP-43 type 3?
2. How specific is TDP-43 to the diagnosis of FTLD when TDP-43 immunoreactivity occurs in 30% of AD cases?
3. What is the association of abnormal TDP-43 immunoreactivity and tau, ubiquitin and progranulin?

We are we going

- Identification of the perfect biomarker to predict protein biochemistry

  OR

- The closest approximation to a perfect biomarker
  - What we may need is an FTD probability model combining clinical diagnoses and good biomarkers (MRI, MRS, PET, CSF, others)
    - Correlations from this presentation do not take into account any biomarkers

Summary

- FTD is a complex (Pick- Complex suggested by Kertesz)
  - bvFTD, PNFA, AOS, SD, c-PSP, CBS, FTD-MND, PiD, PSP, CBD, FTLD-U, FTLD-MND
    - Must be careful in how we define this complex
      - Require clinicians, psychologists, genetics, pathologists
- It is important to recognize individual syndromes as they map well onto the simplified FTLD clinicopathologic scheme of Tau+ vs. TDP-43+

Summary

- Further refinement of the clinical syndrome of PNFA into those with a prominent motor speech disorder (AOS) vs. a linguistic disorders will improve diagnostic accuracy
- If we further separate PNFA into a logopenic variant we may even further improve accuracy
- bvFTD appears almost equally divided between Tau and TDP-43 but there may be clinical features that can help to improve diagnostic accuracy

Show of hands – case diagnosis?

1. PSP
2. CBD
3. PiD
4. FTLD-U
5. FTLD-MND
6. AD
7. NIBD

Show of hands – case diagnosis?

- Tau
- TDP-43
- Other

Diagnosis of Video Case

- Gross findings
  - Frontal > temporal > parietal lobe atrophy
  - Pale substantia nigra
- Histology
  - Tau-positive lesions characterized as coiled bodies, numerous threads in the white matter astrocytic plaques and balloon neurons.
- Pathological classification: Tau+
- Pathological diagnosis: CBD

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