전두측두엽변성 타우형의 분류와 병리

이 경 화
전남의대 병리학교실

Fronto Temporal Lobar Degeneration-tau (FTLD-tau) Classification and Pathology

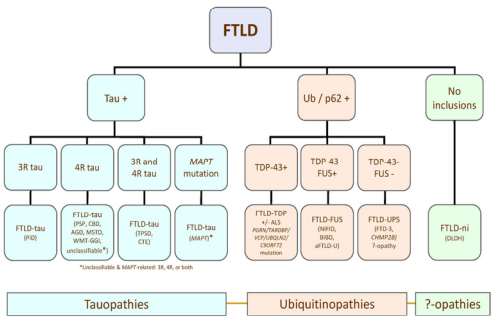
Kyung-Hwa Lee
Department of Pathology, Chonnam National University Medical School

FrontoTemporal Lobar Degeneration

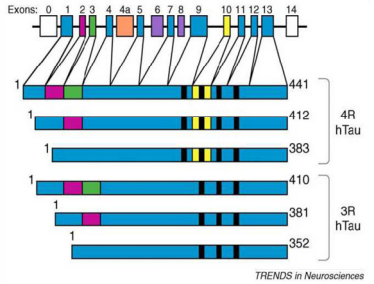
- Characteristic features
  - Neurodegeneration in frontal and temporal lobes
    - Relative sparing of the parietal and occipital lobes
  - Behavioral disturbances d/t loss of frontal-lobe function
    - Memory defects, later
- Clinical FTD
  - 10-15% of dementia
    - 2nd most common cause under 65 yrs
  - FTLD-TDP
    - m/c pathology asso/w clinical FTD
    - Approximately 50% of cases

- 3 main clinical syndromes asso/w FTLD
  - **[bvFTD]** behavioral variant of FTD
    - Changes in social and personal conduct with difficulty in regulating behavior
  - **[PNFA]** Progressive non-fluent aphasia
    - Disorder of expressive language – word retrieval
    - Atrophy of perisylvian regions in the dominant hemisphere
  - **[SD]** Semantic dementia
    - Profound impairment of semantic memory
      - Related to verbal and visual input
    - Preservation of episodic memory
    - Anterior temporal atrophy, in the dominant hemisphere

FTLD Classification

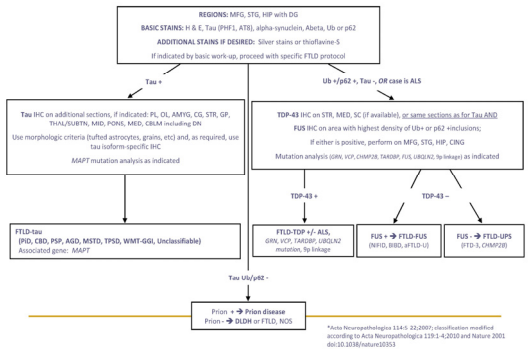


Schematic representation of the human tau gene and the six tau isoforms expressed in adult brain.



Goedert et al. Trends Neurosci. 2010 ;33(7):317-25.

FTLD Flowchart*



Classification

- **FTLD** = *pathologic* frontotemporal lobar degeneration, encompasses:
  - 1. **FTLD-tau** (inclusions immunolabeled with antibodies to tau; includes:
    - **More Common Primary Diagnoses**
      - **FTLD-tau (PiD)** – Pick disease
      - **FTLD-tau (CBD)** – corticobasal degeneration
      - **FTLD-tau (PSP)** – progressive supranuclear palsy
    - **Less Common Primary Diagnoses**
      - **FTLD-tau (AGD)** – argyrophilic grain disease
      - **FTLD-tau (MSTD)** – multiple system tauopathy with dementia
      - **FTLD-tau (NFT-dementia)** – tangle predominant senile dementia
      - **FTLD-tau (WMT-GGI)** – white matter tauopathy with globular glial inclusions
      - **FTLD-tau (unclassifiable)** – unclassifiable tauopathies

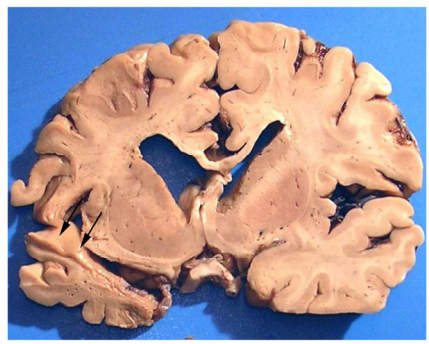
  - 2. **FTLD-U** (inclusions labeled by antibodies to ubiquitin and p62); includes:
    - **FTLD-TDP (most common FTLD-U**; inclusions labeled by antibodies to ubiquitin, p62, and TDP-43; TDP is TAR DNA-binding protein of 43 kD mw)
    - **FTLD-FUS** (rare; inclusions immunopositive for FUS, +/- for ubiquitin and p62, and negative for TDP-43; FUS is fused in sarcoma protein)
      - **FTLD-FUS (aFTLD-U)** – atypical FTLD-U
      - **FTLD-FUS (NIFID)** – neuronal intermediate filament inclusion disease
      - **FTLD-FUS (BIBD)** – basophilic inclusion body disease
    - **FTLD-UPS** (very rare; inclusions labeled ubiquitin and p62 and negative for tau, TDP-43, and FUS; UPS is ubiquitin protease system) includes:
      - **FTLD-UPS (FTD-3)** – familial FTLD associated with *CHMP2B* mutations
      - **FTLD-UPS (sporadic)** – possibly some sporadic cases of TDP-43 and FUS negative FTLD-U
    - **FTLD-ni**, (very rare; no inclusions seen on immunostains with tau, ubiquitin, p62, TDP -43, or FUS)

FTLD-TAU

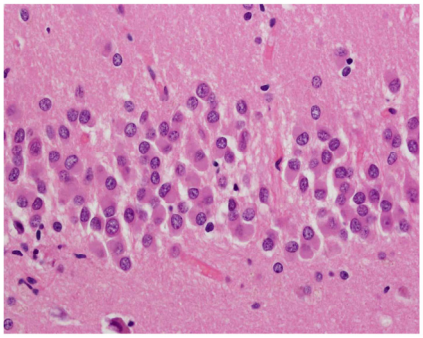
FTLD-tau (PiD)
FTLD-tau (CBD)
FTLD-tau (PSP)
FTLD-tau (AGD)

Case 1

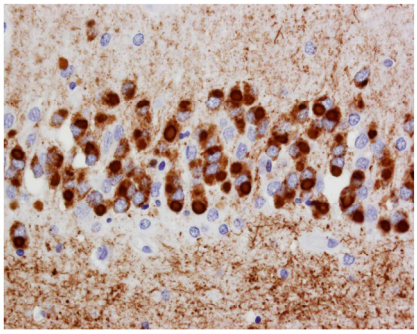
- 78/F, 12 yr Hx of FTD
- Gross findings
  - Brain wt.—1010 gms
  - Atherosclerosis—Moderate
  - Atrophy
    - Moderate – frontal & temporal (R>L) cortex
    - Mild – anterior temporal cortex, parietal cortex, hippocampus, brain stem
  - Ventricular dilatation – moderate
  - Pallor – locus mild, nigra severe



PiD – Gross



PiD – DG



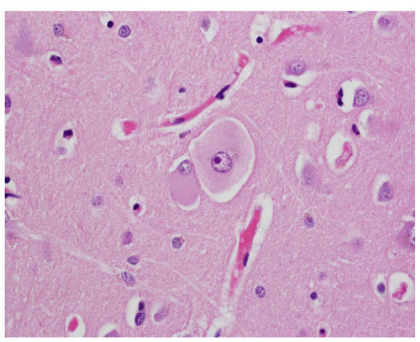
PiD – AT8

Pick Disease

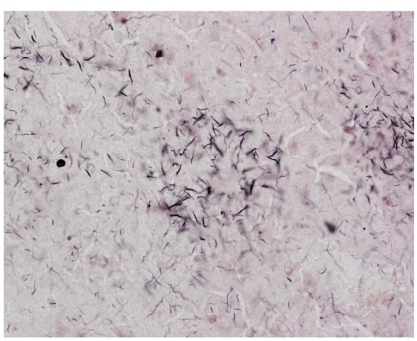
- Gross appearance
  - Frontotemporal atrophy
    - Relative sparing of the posterior 2/3 of the superior temporal gyrus
    - 'knife-blade' appearance
  - Asymmetry, common
  - Severe involvement of Ammon's horn & amygdala
    - Responsible for memory loss
- Microscopic appearance
  - Massive neuronal cell loss and dense astrocytic gliosis
  - Pick bodies - argyrophilic intraneuronal cytoplasmic inclusions
    - (+) for 3R tau
  - Pick cells – ballooned neurons; present in the cortex

Case 2

- 49/F (A12-51), 5 yr hx of PSP ?
  - Age at onset: 44 (2007)
    - Balance problems, "problems with vision"
  - Age at presentation to CNADC: 48 (2011)
    - Hoarse voice – weak bulbar muscles?
    - Vertical gaze palsy
    - MR: frontotemporal atrophy, tegmental atrophy?
  - Father's cousin had PSP, autopsy confirmed by Mayo in 2003
- Brain wt.—1200 gms
- Atrophy
  - Moderate – frontal cortex and caudate
  - Mild – temporal, parietal & occipital , hippocampus, midbrain, pons
- Pallor – nigra severe, locus moderate



CBD – Balloon



CBD – Astrocytic plaque

Corticobasal Degeneration

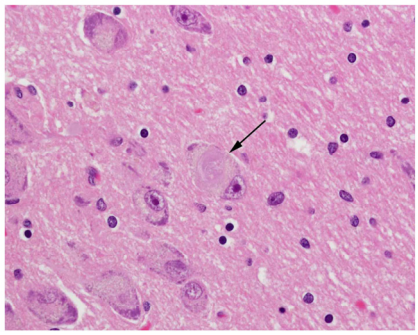
- Degeneration of Cerebral cortical areas, basal ganglia, substantia nigra
  - "Asymmetric" rigidity, clumsiness, stiffness or jerking
    - Progressive apraxia; "alien limb" phenomenon; difficulty with walking
  - Cognitive abnormalities with aphasia & dementia of frontotemporal type
- Gross
  - Asymmetric atrophy of the cerebral cortex
  - Substantia nigra: loss of pigment
  - (±) atrophy of the basal ganglia, and cerebellum
- Miscroscopic
  - Variable cortical neuronal loss and astrocytic gliosis
  - Ballooned "achromatic" neurons in the cortex
  - Tau staining: 4R tau
    - Abundant deposition in thread-like processes; Coiled bodies
    - "Asrocytic plaques" – accumulation of tau in astroglial cells

Argyrophilic Grain Disease

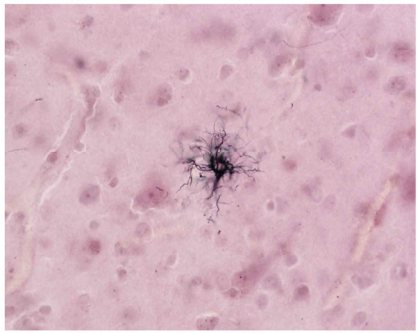
- Clinical features
  - Amnesic syndrome
  - Psychiatric features – agitation or apathy
- Neuropathology
  - Tau pathology: 4R tau
    - Argyrophilic spindle- or comma-shaped grains
    - Coiled bodies ~ m/c in temporal stem white matter
    - White matter threads
  - Ballooned neurons in limbic structures
  - Medial temporal lobe (± hypothalamus, Nu. Accumbens)
    - Entorhinal cortex, Ammon's horn, amygdala
    - Frequent involvement of **CA2 +dentate gyrus**

Case 3

- 81/F (A11-15), 6 yr Hx of PSP
- Gross findings
  - Brain wt.—1140 gms
  - Atherosclerosis—Mild
  - Atrophy
    - Mild – frontal & temporal cortex, caudate, subthalamus
    - Moderate – pons
    - Indistinct cerebellar dentate nucleus
  - Ventricular dilatation – moderate
  - Pallor – nigra moderate, locus mild



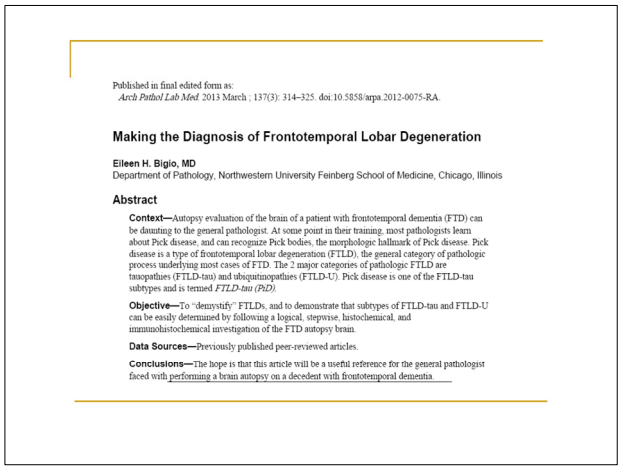
PSP – Globose NFT



PSP – Tufted astocytes

Progressive Supranuclear Palsy

- "Parkinsonism (w/o tremor)" + "Supranuclear ophthalmoplegia"
  - Pseudobulbar palsy and cognitive abnormality (→ dementia), common
- Gross
  - Loss of pigment from the subtantia nigra and locus ceruleus
  - Variable atrophy of the globus pallidus and subthalamic nucleus
  - Cerebellar dentate nucleus, locus ceruleus, oculomotor nuclei, pontine nuclei…
- Microscopic features
  - Neurons with globose neurofibrillary tangle – tau (+)
    - Pigment-containing phagocytes: in substantia nigra
  - Glial cells
    - Tufted astrocytes – tau (+), often binulceated



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Making the Diagnosis of Frontotemporal Lobar Degeneration

Eileen H. Bigio, MD
Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract

Context—Autopsy evaluation of the brain of a patient with frontotemporal dementia (FTD) can be daunting to the general pathologist. At some point in their training, most pathologists learn about Pick disease, and can recognize Pick bodies, the morphologic hallmark of Pick disease. Pick disease is a type of frontotemporal lobar degeneration (FTLD), the general category of pathologic process underlying most cases of FTD. The 2 major categories of pathologic FTLD are tauopathies (FTLD-tau) and ubiquitinopathies (FTLD-U). Pick disease is one of the FTLD-tau subtypes and is termed *FTLD-tau (PiD)*.

Objective—To "demystify" FTLDs, and to demonstrate that subtypes of FTLD-tau and FTLD-U can be easily determined by following a logical, stepwise, histochemical, and immunohistochemical investigation of the FTD autopsy brain.

Data Sources—Previously published peer-reviewed articles.

Conclusions—The hope is that this article will be a useful reference for the general pathologist faced with performing a brain autopsy on a decedent with frontotemporal dementia.