The Diagnosis of CTE

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Pathognomonic lesion of CTE

- First NINDS/NIBIB consensus panel (1): “an accumulation of abnormal hyperphosphorylated tau (p-tau) in neurons and astroglia distributed around blood vessels at the depths of the cortical sulci and in an irregular pattern”

- Second NINDS/NIBIB panel (2): a single pathognomonic lesion in the cortex is the minimum threshold for a diagnosis of CTE

- The following features of the pathognomonic lesion are necessary:
  - $p$-tau aggregates in neurons
  - with or without $p$-tau in astrocytes
  - at the depth of the sulcus
  - around blood vessels
  - deep in the parenchyma, not in the subpial and superficial region

(1) McKee et al, Acta NP 2015   (2) Bieniek et al, in prep, 2020
Supportive features of CTE

1) superficial NFTs

2) p–tau in CA2 and CA4 hippocampus

3) p-tau in: mammillary bodies, hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus.

4) p-tau thorn-shaped astrocytes (TSA) in the subpial region

5) p-tau dot-like neurites

McKee et al, Acta NP, 2020
Proposed Working Protocol

The panel also proposed an operational workflow for the diagnosis and binary classification of CTE as “Low CTE” or “High CTE”

Pathognomonic CTE Lesion:
- p-tau aggregates in neurons around small blood vessels at the depth of the sulcus, deep in parenchyma and not restricted to subpial and superficial region

**Dx = CTE**

- Present
  - Neuronal p-tau pathology (select all that apply):
    - NFT in gyral crest adjacent to CTE focus
    - NFT in gyral crest adjacent to CTE focus
    - NFT in superficial cortical laminae
    - CA4 hippocampus NFT, pretangles or dendritic swellings
    - CAL hippocampus NFT
    - NFT in entorhinal cortex
    - NFT in amygdala
    - NFT in thalamus
    - NFT or glial p-tau pathology in mammillary body
    - NFT in cerebellar dentate nucleus

- Absent
  - If there is:
    - Clinical concern
    - P-tau pathology at sulcal depth NOS
    - Superficial cortical NFT

  - None
    - Not diagnostic of CTE
      - Recommend re-sample of 4-8 bilateral cortical sulci including dorsolateral frontal gyri, orbital frontal gyri, superior middle temporal gyri, and inferior temporal gyri

- CTE focus?
  - Present
    - Low CTE
    - High CTE
  - Absent
    - Not diagnostic of CTE

Bieniek et al, in prep, 2020
Distinction from ARTAG

- The consensus panel also confirmed that purely astrocytic perivascular p-tau lesions, including subpial ARTAG, did not meet criteria for CTE.

- Clusters of p-tau astrocytes in the white matter of the frontal and temporal cortex, basal ganglia, and brainstem are considered ARTAG and are not specific features of CTE.

Bieniek et al, in prep, 2020
Case 1

- Played football for 19 years: 4 years youth, 4 years high school, 4 years college, 7 years NFL.
- Long-standing attention difficulties. Occasional temper outbursts.
- Late 40s: Mild memory complaints
- Early 50s: Forgetful, misplaced objects, word-finding difficulty
  MicroCog assessment: Average to above average
- Late 50s: Repeating himself, getting lost driving
- Age 61: Metastatic cancer diagnosis
  Neurological evaluation: Dx: Traumatic Encephalopathy Syndrome (TES), possible
- Age 61: Death
Brain weight: 1453 grams
Sulcal depth of superior frontal cortex

AT8: Pathognomonic lesions of CTE
Sulcal depth of dorsolateral frontal cortex

AT8: Pathognomonic lesions of CTE
Subpial thorn-shaped astrocytes
Diagnoses:

1. Chronic traumatic encephalopathy, High, (Stage III)

2. Subpial ARTAG
Case 2

- Boxing career: 18 years, amateur and professional, retired at 33 years old
- Stably “irritable”, quick temper, gambling addiction
- Age 66: Left MCA embolic stroke with little residual
- Age 71: accused grandchildren of stealing his keys and money, got lost while driving, retired
- Age 73: diagnosed with: AD, VCID
- Age 74: increasingly impaired orientation, memory, verbal fluency, visuospatial function, judgment, reasoning and problem solving
  - MOCA: 10/30; started on Aricept and Namenda
- Age 76: Unable to remember children’s names, urinary and fecal incontinence; MOCA: 3/30
- Age 78: Death from congestive heart failure
Brain weight: 991 grams
Severe neuronal loss and gliosis:
frontal and temporal lobes, medial temporal lobe,
nucleus accumbens, severe white matter rarefaction
Inferior parietal

Superior temporal

AT8: pathognomonic lesions
Superior temporal

AT8: pathognomonic lesions
Severe neuronal loss and gliosis: MTL

CA1 hippocampus

Amygdala
Aβ plaques: mostly diffuse
Diagnoses:

1. CTE, High (Stage IV)
2. Alzheimer’s disease neuropathological change:
   (Thal 4) A3, (Braak 5) B3, CERAD sparse, C1
   NIA Reagan: Intermediate likelihood
3. LATE
4. Vascular disease:
   Atherosclerosis
   Left insular-inferior parietal infarct
5. Cerebellar degeneration
6. ARTAG
References


Introduction of new ARTAG data entry elements for NACC
18. Aging Related Tau Astroglioniopathy (ARTAG)

18 a. Based on review of all slides, not restricted to frontal cortex or amygdala
Not assessed: ARTAG pathology was not evaluated
Missing/unknown: If ARTAG pathology was examined but the data cannot be found

18. AGING-RELATED TAU ASTROGLIOPATHY (ARTAG)
Evaluation should follow published guidelines. See the Coding Guidebook for the NACC Neuropathology Data Form.

a. Is ARTAG pathology present?

- 0 No (SKIP TO QUESTION 19)
- 1 Yes (CONTINUE)
- 8 Not assessed (SKIP TO QUESTION 19)
- 9 Missing/unknown (SKIP TO QUESTION 19)

b. Overall severity of ARTAG pathology

- 1 Mild
- 2 Moderate
- 3 Severe
- 8 Not assessed
- 9 Missing/unknown
18 b. Provide a semi-quantitative assessment of overall ARTAG pathology as identified using p-tau immunohistochemistry.

The tau pathology in the frontal cortex and amygdala are the foci of this semi-quantitative measure.

1- Mild: minimal or sporadically distributed ARTAG pathology
2- Moderate: intermediate level of ARTAG pathology
3- Severe: Numerous and widespread ARTAG pathology
18.c. ARTAG in the amygdala

Is ARTAG pathology present in the **AMYGDALA**?

- No (SKIP TO QUESTION 18e)
- Yes (CONTINUE)
- Not assessed (SKIP TO QUESTION 18e)
- Missing/unknown (SKIP TO QUESTION 18e)

**Localization of ARTAG pathology in the amygdala:**

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18.d. Amygdala gray matter and perivascular ARTAG

Images Courtesy of Gabor Kovacs, MD, PhD
Amygdala white matter and perivascular ARTAG

Image Courtesy of Gabor Kovacs, MD, PhD
Amygdala subpial and subependymal

Images Courtesy of Russ Huber, MD, PhD
18.e. Is ARTAG present in the frontal cortex?

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18.e. ARTAG in the frontal cortex

- Is ARTAG pathology present in the **FRONTAL NEOCORTEX**?  
  - No (SKIP TO QUESTION 19)
  - Yes (CONTINUE)
  - Not assessed (SKIP TO QUESTION 19)
  - Missing/unknown (SKIP TO QUESTION 19)

18.e. Localization of ARTAG pathology in the frontal neocortex:

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</table>
Frontal cortex gray matter and perivascular

Image Courtesy of Gabor Kovacs, MD, PhD
GFA frontal cortex

Image Courtesy of Gabor Kovacs, MD, PhD
Frontal lobe white matter and perivascular ARTAG

Images Courtesy of Gabor Kovacs, MD, PhD
Frontal lobe subpial TSA

Image Courtesy of Russ Huber, MD, PhD
References


- Forrest S, Kril J, Wagner S, et al. CTE is absent from a European community-based aging cohort while ARTAG is highly prevalent. JNEN. 2019 May 1;78(5):398-405.