Cerebral Age-Related TDP-43 with Sclerosis (CARTS): Random or Diagnostic?

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What is Alzheimer’s Disease?

**Clinical**
- Progressive deficits in memory, visuospatial skills, judgment, personality, and language
- 5 – 20 year progression
- ~1% are familial

**Pathological**
- Initiating event
- β-secretase cut instead of α-secretase → Aβ aggregates
- Phospho. Tau
- Hippocampus → cortex
- Cell loss and cognitive decline

- β-amyloid Plaques
- Neurofibrillary Tangles
Clinically Diagnosed Alzheimer’s Disease (AD)

- **Preclinical stage**: biological changes that have not yet manifested clinically

- **Mild cognitive impairment (MCI)**
  - Memory/thinking deficits greater than normal for person’s age and education, **NOT interfering with his/her independence**
  - May or may not progress

- **Alzheimer’s dementia**: Symptoms manifest with memory loss, word-finding difficulties, visual/spatial problems **limiting patient independence**
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→ BROAD Clinical Symptoms!!

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Potential Causes of AD: Pathological Diagnoses

Note: Most cases have overlapping diagnoses

1. True Alzheimer’s disease
   Suspected non-Alzheimer pathology (SNAP)
   - no amyloid deposition

2. Primary age-related tauopathy (PART)
   - no neurofibrillary tangle deposition

3. Cerebral Age-Related TDP-43 with Sclerosis (CARTS)/Hippocampal Sclerosis (HS)
   - HS less specific term when TDP-43 not present
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What is Hippocampal Sclerosis?

- Affects 25% of those ≥ 85 years old
- >10% of clinical Alzheimer’s actually HS due to similar memory manifestations
- Most specific biomarker: TDP-43 pathology
HS-Aging

Sclerosis

Neuron loss and gliosis in hippocampal sector CA1 and subiculum

Accumulates within inclusions (cytoplasm of neurons/glia)

TDP-43 cleaved/ubiquinated/phosphorylated

Associated with cerebral arteriolosclerosis, but not due to ischemia (no infarcts)

Genetics
TDP-43

- Normal: **Aggregates in stress granules** in response to stress stimuli
  - Strong **self-regulation**

- **Regulation malfunction** thought to cause pathologies (Amyotrophic Lateral Sclerosis)
CARTS Criteria

- More **specific to TDP-43** than HS-Aging
- Previous studies proposed this criteria to **expand HS-Aging**
  - Unknown prevalence

- **Diagnosis Criteria**
  - Age at death $\geq 85$ years
  - **TDP-43** in hippocampus and other areas
  - **Tau severity stage $\leq IV$**
  - **No clinical features of frontotemporal dementia**
Hypothesis

**Hypothesis**: Given the proposed Cerebral Age-Related TDP-43 with Sclerosis (CARTS) to expand the traditional Hippocampal Sclerosis diagnosis, we hypothesized that CARTS may *not properly reflect* sclerosis-related dementia.

**Project Goal**: Evaluate the application of CARTS on available brain samples.

- Diagnostic & Treatment Implications
Method: Sample Selection

**Inclusion Criteria** from brain bank at Alzheimer’s Disease Research Center (ADRC)

- Age at death ≥ 85 years
- Tau severity stages ≤ IV
- No frontotemporal dementia
- Hippocampus sample available for staining

→ Hippocampus sample was sectioned and fixed onto slide
Method: Staining for TDP-43

Day 1

- Rehydrate
- Eliminate blood vessels with $\text{H}_2\text{O}_2$ methanol
- Incubate in goat serum
- Incubate in primary antibody overnight (TDP-43 of rabbit in goat serum)

Day 2

- Incubate in secondary antibody (Anti-rabbit)
- Stain using DAB protocol
- Dehydrate
- Cover slip with Entellan
Results-General

- Total slides: 148
- HS-Aging Patients: 23 (18.9% of sample)
- TDP-43 cytoplasmic translocation in hippocampus: 12 (8.1%) = CARTS sample
  - 7 had HS (58% of 12)

https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(10)70195-2/fulltext
Results – CARTS Sample

- Average Age: 90.2 years old
- 9 had dementia
- Tau Severity Stage: 1 Stage O, 2 Stage I - III, 5 Stage IV
- 2 Europeans
- Average Brain Weight: 1099 grams
  - Estimate of older normal brain with 2.5g lost every year after adulthood until 90: 1495g
Discussion – Results

CARTS may not a good diagnosis related to HS-Aging

- All Tau Severity Stages represented and not all had dementia → not good expansion of HS
- Not all were HS → not specific to HS-Aging
- TDP-43 should not be focus? → treatment implications
Discussion

Limitations/Strengths

Limitations

- Subjective grading of TDP-43
- Overlapping pathologies
- Volunteer bias sample
- Staining 1 section of hippocampus

Strengths

- Accurate database managed by 1 neuropathologist
- Large brain bank sample (>1,000)
- 1 person reviewed/prepared all slides
- First CARTS sample study
Future projects

- **Less subjective** grading of TDP-43
- TDP-43 proposed to be found in hippocampus, amygdala and basal forebrain
- Staining method of **TDP-43 vs phospho-TDP-43**
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Mahalo!

Questions?
References


