The Spectrum of Age-Associated Astroglial Tauopathies

Dennis W. Dickson MD
Department of Neuroscience
Mayo Clinic, Jacksonville, FL
Thorn-shaped astrocytes

- TSA were first reported by Ikeda (1995), as tau-positive astrocytes in various neurodegenerative disorders.
- TSA are found most often in subpial and perivascular spaces of the medial temporal lobe, as well as in the subependymal region.
- Recent studies have shown that TSA increase in frequency with age.
- Frequency with age (Schulz 2004).
  - 40-74 y/o = 10/48 (21%)
  - 75-100 y/o = 24/52 (46%)


Thorn-shaped astrocytes (TSA)

Basal forebrain

Temporal white matter

Temporal cortex
TSA are composed of 4R tau

Frequency of TSA and AGD in AD

- Investigate frequency and relationship of AGD and TSA in Mayo Clinic brain bank.
- Medial temporal lobe sections from 239 cases of pathologically-confirmed AD (109 men, 130 women; 55-102 years of age)
- Immunohistochemistry with antibodies to phospho-tau (CP13) and 4R-tau (ET3) (from Petr Davies, PhD)
- Double immunostaining & immuno-EM

**Basal forebrain section**

- Lentiform nucleus
- Substantia innominata (basal nucleus of Meynert)
- Hypothalamus (infundibulum)
- Optic tract
- Amygdala
 Thorn-shaped astrocytes

4R tau (ET3) immunostain

Gallyas silver stain
Double immunostain for 4R tau and GFAP

ET3 (BCIP-blue) / GFAP (DAB-brown)
EM of thorn-shaped astrocytes

- tau filaments
- glial filaments
TSA scores as none (0), mild (1+), moderate (2+) and marked (3+).
AGD increases with age

![Bar chart showing the frequency of AGD (%) at different age groups: <70, 70-79, 80-89, >89. The frequency increases with age.]
4R tauopathy in AD

• AGD & TSA were found in ~30% of AD.
• AGD & TSA both increased with age.
• Neither not correlate with AD pathology.
• AGD & TSA are distinctive and independent medial temporal 4R tauopathies.
Age-associated astrogliopathy in non-demented elderly from Einstein Aging Study

- Prospective cohort (P01 AG003949-30)
- Minimal or no Alzheimer type pathology
  - Median Braak stage: III
  - Median Thal phase: 1
- Old age (range: 74 to 105 years)
- Median age: 88 years (25%-tile 84 y, 75%-tile 97 y)
- Sex: 13 men & 31 women
- Racially mixed: 40 White & 4 Black
- Screening section – basal forebrain
Thorn-shaped astrocytes

Mediobasal forebrain

Anterior commissure
Thorn-shaped astrocytes

Mammillary body

Less common sites for TSA in aging

Optic tract
Ramified or bushy astrocytes (gray matter)
# Spearman Correlations

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Brain weight</th>
<th>Braak NFT stage</th>
<th>Thal Amyloid Phase</th>
<th>AGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorn shaped astrocytes</td>
<td>$r = 0.28$</td>
<td>$r = -0.04$</td>
<td>$r = 0.43$</td>
<td>$r = 0.14$</td>
<td>$r = 0.07$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.06$</td>
<td>ns</td>
<td>$p &lt; 0.01$</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Bushy astrocytes</td>
<td>$r = 0.07$</td>
<td>$r &lt; -0.01$</td>
<td>$r &lt; 0.01$</td>
<td>$r = 0.22$</td>
<td>$r = 0.43$</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>$p &lt; 0.01$</td>
</tr>
</tbody>
</table>
• TSA score increases with age.
• Ramified (bushy) astrocyte more frequent in AGD.

Age Quartiles vs. TSA score
Average TSA Score

Ramified astrocyte score vs. AGD
Average Bushy Astrocyte Score
TSA score increases with Braak stage

Average TSA Score

Braak NFT Stage

0-II (n=14)  III (n=19)  IV (n=11)
Astrocytic tauopathy in aging

Preclinical PSP in prospectively studied elderly

- 87 subjects clinically normal at death
- 33 had extensive AD pathology (preclinical AD)
- 17 had incidental Lewy bodies (preclinical PD)
- 4 had pathology consistent with PSP (preclinical PSP); one with parkinsonism

<table>
<thead>
<tr>
<th>Case #</th>
<th>9</th>
<th>30</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Features</strong></td>
<td><strong>Pathologic Features</strong></td>
<td><strong>Pathologic Features</strong></td>
<td><strong>Pathologic Features</strong></td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT, Tft, Thm, CB</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT, Tft, Thm, CB</td>
<td>—</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT, Tft, Thm, CB</td>
<td>—</td>
</tr>
<tr>
<td>Putamen</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT, Tft, Thm, CB</td>
<td>—</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>NFT</td>
<td>NFT, Tft, Thm, CB</td>
<td>—</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT, Tft, Thm, CB</td>
<td>—</td>
</tr>
<tr>
<td>Thalamus</td>
<td>—</td>
<td>NFT, Tft, Thm, CB</td>
<td>—</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>NFT</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT</td>
</tr>
<tr>
<td>Substantia nigra pigment loss</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Pons</td>
<td>NFT</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT</td>
</tr>
<tr>
<td>Dentate nucleus</td>
<td>NFT, Tft</td>
<td>NFT, Tft, Thm, CB</td>
<td>NFT</td>
</tr>
</tbody>
</table>

Gallyas silver stain

Tufted astrocyte in basal ganglia

Globose NFT in S. nigra

Preclinical CBD

- Neurologically normal woman.
- Morphology and distribution of tau pathology consistent with CBD.


• Subtype of ARTAG
  • Subpial type (most often mediobasal)
    • Note if pronounced at sulcal depths of convexity cortices (CTE)
  • Subependymal type (most often temporal horn, third ventricle)
  • Gray matter type - fine granular tau immunoreactivity in cytoplasmic processes (most often medial temporal lobe)
  • White matter type – thorn-shaped astrocytes in subcortical white matter

• Anatomical regions affected by ARTAG
  • Mediobasal
  • Lobar
  • Subcortical
  • Brainstem
Summary

• With advancing age, the brain is susceptible to glial, as well as neuronal tauopathies.

• Glial tauopathies affect oligodendroglia and astrocytes

• Oligodendroglial “coiled bodies” - most often seen in association with AGD

• Astrocytic lesions
  • Thorn-shaped (tauopathy of “fibrous astrocytes” – glia limitans, subpial, perivascular subependymal; white matter)
  • Ramified or bushy astrocytes (tauopathy of protoplasmic astrocytes – gray matter, especially amygdala)

• As antemortem biomarkers are developed to detect tau, non-Alzheimer age-associated pathologies need to be taken into consideration.
Acknowledgements

• Brain bank coordinators
  • Deann Gibson and Beth Marten
• Neuropathology – histology & immunohistochemistry
  • Monica Casey-Castanedes, Virginia Phillips, Linda Rousseau
• Database management & image analysis
  • Melissa E. Murray, PhD
• Electron microscopy
  • Wenlang Lin, PhD
• Funding
  • P50 AG 016574 – Mayo Clinic ADRC
  • P50 NS072187 – Udall Center for Excellence in Parkinson’s Disease Research
  • P01 AG003949 – Einstein Aging Study
  • Florida DOEA – Alzheimer Disease Initiative Brain Bank