PART: part or not part of Alzheimer Disease?

Dr. med. Dimitrios Kanakis
Pathologist & Neuropathologist
Senior Lecturer
Democritus University of Thrace
When and How all began?

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CONSENSUS PAPER

Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff ·
Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson ·
Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha ·
Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah ·
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Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer ·
Masahito Yamada · Peter T. Nelson

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PART: A new term proposed for a previously known disease-entity?

PART: Primary Age-Related Tauopathy

Tangle-Predominant Senile Dementia (TPSD)
Tangle-Only Dementia (TOD)
Preferential Development of NFT without Senile Plaques
Senile Dementia of the NeuroFibrillary Tangle type (SD-NFT)
PART: Neuropathologic Changes

Macroscopic Findings:

“Normal for age”

or

Mild-to-moderate diffuse atrophy of the neocortex, and medial temporal lobe atrophy (individuals with dementia)

Crary et al., Acta Neuropathologica, 2014
PART vs. AD-Histopathology

PART:
- Braak stages I-IV (entorhinal, limbic)
- Minimal or no immunostaining for Aβ-amyloid (Thal Aβ Phase 0-2)

AD:
- Braak stages I-VI
- Always present, Aβ-amyloid positivity

Crary et al., Acta Neuropathologica, 2014
PART vs. AD Histopathology

Different types of Aβ-amyloid plaques in Alzheimer Disease

Thal & Braak, Der Pathologe, 2005
"ABC" Score for Alzheimer Disease

Montine et al., Acta Neuropathologica, 2011
Distribution pattern of Aβ-amyloid deposits

Thal & Braak, Der Pathologe, 2005
Distribution pattern of Neurofibrillary Changes

**TRANSENTORHINAL**
(Clinically asymptomatic)

**Stage I:** NFTs and NTs in small density, confined to transentorhinal cortex in pre-α cells.

**Stage II:** Tangles present in moderate density in pre-α cells of entorhinal cortex. Small numbers develop in CA1 region of hippocampus.

- **Mild**
- **Moderate**
- **Severe**
- **Very severe**

**Stages of maturation of NFTs**

- **Early stage:** There is accumulation of tau protein in neurons but in a dispersed form detectable only by immunohistochemistry for tau protein. There may be nuclear accumulation of immunoreactivity. Silver staining does not reveal any abnormality.

- **Established stage:** The tau protein is aggregated into paired helical filaments as well as a smaller number of straight filaments. There is hyperphosphorylation of some of the tau protein in tangles rendering them immunoreactive for ubiquitin. Silver staining reveals classical tangles.

- **Late stage:** There is death of the neuron and removal of cell debris by local phagocytes. The tangle structure remains as an amorphous extracellular "nematode" or ghost tangle. With time there is progressive loss of tau protein immunoreactivity. Amyloid peptide is later deposited around these structures as amyloid, and there is infiltration by astroglial processes making these NFTs apparently immunoreactive for GFAP.

**Thal & Braak, Der Pathologe, 2005**
CERAD Criteria

CERAD-Kriterien zur semiquantitativen Schätzung der Plaquezahl [38]

<table>
<thead>
<tr>
<th>CERAD-Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Keine neuritischen Plaques</td>
</tr>
<tr>
<td>1</td>
<td>Wenige neuritische Plaques</td>
</tr>
<tr>
<td>2</td>
<td>Moderate Anzahl neuritischer Plaques</td>
</tr>
<tr>
<td>3</td>
<td>Zahlreiche neuritische Plaques</td>
</tr>
</tbody>
</table>

Thal & Braak, Der Pathologe, 2005

Ellison & Love: Neuropathology 2e © 2004 Elsevier Ltd.
Να βάλω από τη δηθή σύνεση του Thal για το πώς γίνεται η διάγνωση της Alzheimer.
PART vs. AD-Histopathology

- **PART** pathology spares the neocortex
- **AD** involves neocortical areas

Crary et al., Acta Neuropathologica, 2014
PART vs. AD-Histopathology

NFTs in PART resemble those of AD

Crary et al., Acta Neuropathologica, 2014
PART vs. AD-Histopathology

NFTs in PART resemble those of AD

Crary et al., Acta Neuropathologica, 2014
PART vs. AD-Genetic

- Association between PART and the microtubule-associated protein tau gene \((MAPT)\) H1 haplotype

- No relation between PART and \(APOE\) ε4 allele; the later is the strongest risk factor for AD
Proposed PART Classification

Table 2 Primary age-related tauopathy (PART): working classification

1. Requires
   NFTs present with Braak stage ≤IV (usually III or lower)
2. Then subclassify as follows
   Category | Thal Aβ Phase | Other disease associated with NFT
   --- | --- | ---
   Definite | 0 | Absent
   Possible | 1–2 | Absent

Table 1 Hypothetical correlation between PART and AD

<table>
<thead>
<tr>
<th>Factor</th>
<th>No AD/no PART PART</th>
<th>Asymptomatic PART</th>
<th>p-preAD</th>
<th>NFT-predominant Dementia (symptomatic PART)</th>
<th>Symptomatic AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ phase</td>
<td>0</td>
<td>0–2</td>
<td>1–5</td>
<td>0–2</td>
<td>3–5</td>
</tr>
<tr>
<td>Braak-NFT-stage</td>
<td>0</td>
<td>1–IV</td>
<td>0–VI</td>
<td>III, IV</td>
<td>III–VI</td>
</tr>
<tr>
<td>Degree of AD pathology</td>
<td>No AD</td>
<td>No or low AD</td>
<td>Low–high AD</td>
<td>No AD or low</td>
<td>Intermediate–high AD</td>
</tr>
<tr>
<td>Clinical signs of dementia or cognitive decline</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PART vs. AD: symptomatic PART and symptomatic AD can be distinguished by Aβ pathology. Asymptomatic PART and p-preAD overlap in those cases with initial Aβ pathology (Aβ phases 1, 2)
PART & SNAP

SNAP: Suspected Non-Alzheimer Pathophysiology

Parallels between PART and SNAP:

✓ Atrophy of medial temporal lobe structures (MRI) and abnormally elevated CSF tau ⇔ Pathology of PART

✓ PART: Common in middle-aged and elderly persons

⇔ SNAP: Common in individuals over age 65

✓ Low frequency of APOE ε4 carriergship in PART & SNAP
PART & SNAP

Caveats:

- Medial temporal lobe atrophy (MRI) $\Leftrightarrow$ Hippocampal sclerosis, FTLD-TDP43, Argyrophilic grain disease
- Elevated CSF tau $\Leftrightarrow$ Ischemic cerebrovascular disease, traumatic brain injury, CJD
PART is part of Alzheimer disease

Charles Duyckaerts · Heiko Braak · Jean-Pierre Brion · Luc Buée · Kelly Del Tredici ·
Michel Goedert · Glenda Halliday · Manuela Neumann · Maria Grazia Spillantini ·
Markus Tolnay · Toshiki Uchihara

“We contend first that there is no way, neuropathologically, genetically, or clinically to differentiate PART from early AD”
The arguments against PART hypothesis

1. **PART**: Association of tau pathology with aging, and Aβ deposition with AD

1. Aβ accumulation observed also in centenarians (Delaere et al., Neurobiol Aging, 1993)

2. **PART**: Use of the tau/Aβ index

2. No further information is added; PART is used synonymously with tau/Aβ index

3. **PART**: The new term prevents the use of word dementia in neuropathological diagnosis

3. The current practice of NFT stages and Aβ-phases, separates pathology from clinical diagnosis
4. **PART:** Presence of Aβ-deposits speaks for an AD-related process rather than a pure tauopathy

4. Presence of Aβ-aggregates in isocortex at low NFT stages [found by biochemistry but not immunohistochemistry] (Delacourte et al., Neurology, 2002)

5. **PART:** Low Aβ-plaque score, compatible with possible PART

5. Is the separation between low plaque score (PART) and high plaque score (AD) justified?
Questions need to be answered

i. Why are Aβ and tau pathologies intermingled?

ii. What is their causal relationship?

iii. Why do they progress?

iv. Why the tangles of PART remain confined to ECH, whereas these of AD are capable of inducing the spread in other brain regions?

v. ……. 
Origins of Alzheimer's Disease: Reconciling CSF biomarker and neuropathology data regarding the temporal sequence of Aβ and tau involvement

Erik S. Musiek and David M. Holtzman
Department of Neurology, Hope Center for Neurologic Diseases, and Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA.

Key Points

1. Neurofibrillary tangles accumulate in a confined manner in limbic regions including the entorhinal cortex and hippocampal CA1 as part of normal aging.

2. Aβ aggregation and accumulation represents the initial pathogenic trigger of AD, and interacts with tau to exacerbate neurofibrillary pathology and induce its spread to the neocortex.

3. Decreases in CSF Aβ42 are the first hallmark of AD and precede an increase in CSF tau, which serves as later biomarker of neurodegeneration.

4. Animal models suggest that Aβ induces tau pathology, and that tau is required for some aspects of Aβ toxicity.
Does the difference between PART and Alzheimer’s disease lie in the age-related changes in cerebral arteries that trigger the accumulation of Aβ and propagation of tau?

Roy O. Weller¹ • Cheryl A. Hawkes² • Roxana O. Carare¹ • John Hardy³
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Thank you for your attention!