Meeting report:

Toward a consensus-based nomenclature and classification scheme for common TDP-43 pathology associated with aging.

Meeting at Emory U., October 17 and 18th, 2018

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Outline

- What was the meeting about?
- Who was at the meeting?
- Why do we need this meeting?
- What is the new consensus-based nomenclature and classification scheme?
- Some specific topical questions
- What will the consensus paper look like?

Meeting goal(s)

- Produce a data-driven consensus-based paper laying out what is known about common (>1:100 lifetime risk) age-related TDP-43 proteinopathic conditions.
- Generate new guidelines for diagnosis and classification.
- Identify areas needing further work.

Aim for a broad target audience and major impact on multiple disciplines.

Participants

Planning committee

Pete Nelson (co-chair); Nina Silverberg (co-chair); Dennis Dickson, Julie Schneider, John Trojanowski, Helena Chui

Meeting participants

Rosa Rademakers, Clifford Jack, Patricia Boyle, Eliezer Masliah, Bud Kukull, Cerise Elliott, C. Dirk Keene, Gabor Kovacs, Charles White, Gregory Jicha, Irina Alafuzoff, Konstantinos Arfanakis, Linda Van Eldik, Tom Montine, William Seeley, Melissa Murray, Robert Rissman, Margaret Flanagan, Allan Levey

Off-site participants

Su Nag, Lei Yu, Dave Fardo, Reisa Sperling, Shigeo Murayama, Keith Josephs, Claudia Kawas

Prior "definition"

Hippocampal sclerosis and TAR DNA binding protein (TDP)-43 inclusions

Hippocampal sclerosis (HS) is defined by pyramidal cell loss and gliosis in CA1 and subiculum of the hippocampal formation that is out of proportion to AD neuropathologic change in the same structures [7]. HS can be observed in the context of AD neuropathologic change, frontotemporal lobar degeneration (FTLD), and VBI, likely reflecting a heterogeneous etiology. We recommend that HS be reported as present or absent.

TDP-43 immunoreactive inclusions are observed in the majority of cases of HS (Fig. 6) [8, 28, 40, 64], about one-

Acta Neuropathol (2012) 123:1–11
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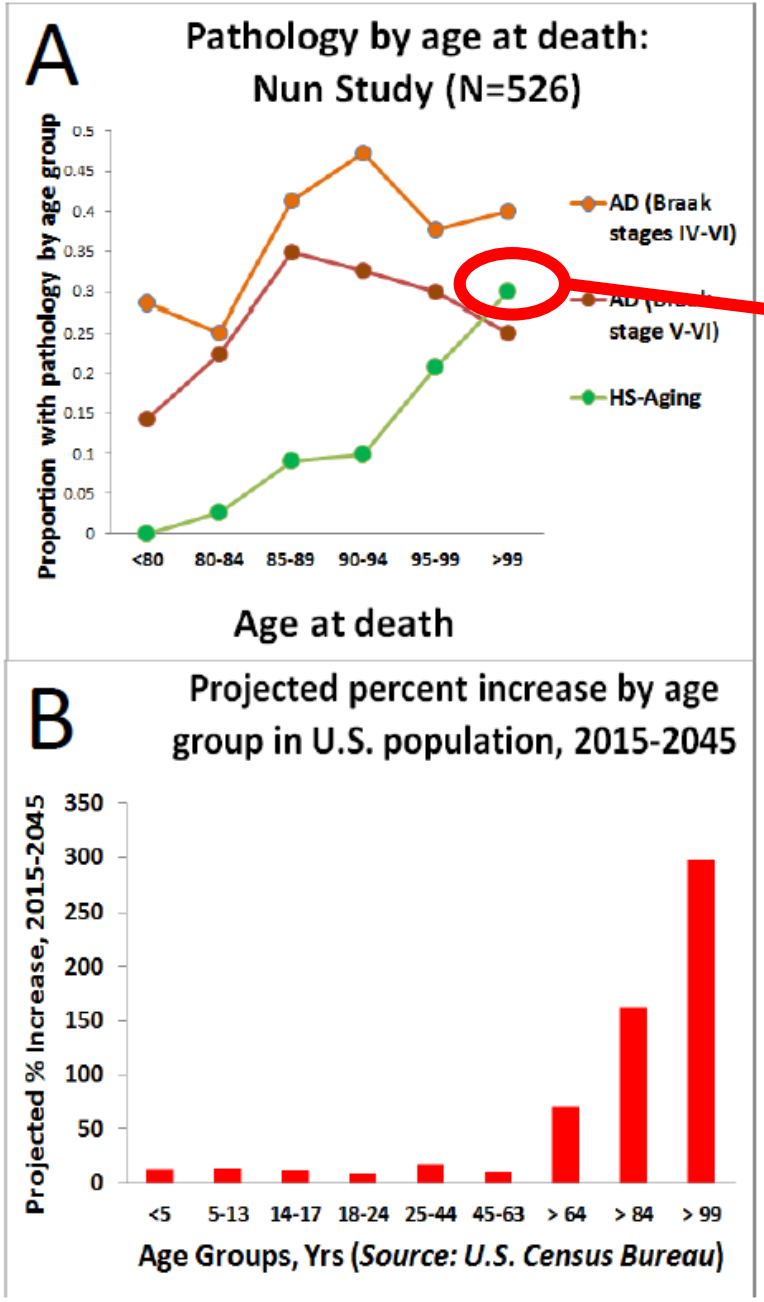
CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman



Nelson et al
Acta NP, 2013

Nun Study
100+ yr olds (n=34)

Rush U. TDP-43 Stage	Frequency	%
0	11	32.35
1	0	0.00
2	9	26.47
3	10	29.41
4	2	5.88
5	2	5.88
TOTAL	34	100.00

68% TDP-43 +

Thanks
Dr. Maggie Flanagan

TDP-43 pathology is common in advanced age and is associated with cognitive impairment (a prevalent Alzheimer's disease "mimic")

There was no widely accepted specific name(s)/term(s)/label(s) for common age-related TDP-43 pathology

(Challenges)

No prior consensus-based effort has tackled TDP+ in aging.

There was no universal terminology for this disease.

The term “hippocampal sclerosis” connotes other diseases.

This disease is not in fact hippocampus-specific.

(Opportunities)

<u>Good terminology is needed to help…</u>

- **Diagnose at autopsy ("standardize the gold standard")**
- **Increase public awareness of this condition**
- **Catalyze research**
  - **Diagnostic studies – specific biomarkers required**
  - **Important therapeutic target in its own right**
  - **Key consideration in AD clinical trials**
  - **Animal models and other experimental contexts**
  - **Genetics, risk factors, and many other correlates**
- **Enable a "common language" across disciplines**

A proposed nomenclature for this disease…

Limbic-predominant age-related TDP disease (LATE)

LATE Neuropathologic Change (LATE-NC):

Simplified stage-based classification:

0-no TDP-43 pathology detected

1-Amygdala

2-Hippocampus

3-Middle frontal gyrus

Definitive diagnosis can be obscured by other TDP-43 disease (FTLD-TDP, ALS, etc.)

- Is this effort worth the bother? Is this really a disease anyway?

Study of community-based autopsy cohorts indicate that the impact of LATE-NC among persons beyond age 80 is on the same order of magnitude as AD (plaques and tangles).

- Do clin-path studies indicate that TDP+HS- pathology is cognitively impactful?

Yes. There also is a pre-clinical state as is generally true with non-traumatic pathologies.

- Can we suggest specific methodology, TDP-43 antibodies, etc.?

Not presently; but common tools may be helpful in the future.

- If classification is by anatomy-based staging (any pathology in that area), how about pathologic subtyping/grading?

Subtyping/grading may be merited in the future,
and for research purposes, but more work is required to guide consensus-based recommendations.

- Is there expected LATE-NC TDP-43 pathology outside of the staging-based sampling areas (amygdala, hippocampus, mid-frontal gyrus)?

Yes, the sampling recommended for disease diagnosis is indeed a simplified staging scheme.

- Can we suggest specific histopathologic (H&E) features of LATE-NC hippocampal sclerosis?

No; for now, the NIA-AA recommendation (Montine et al, 2012) criteria are suggested but future work may show utility in this.

- How can a pathologist differentiate severe LATE-NC from FTLD-TDP (type A)?

This is an area that needs further study.

- If there is a comorbid non-TDP pathology (e.g., PSP), should one still diagnose LATE-NC if there is TDP-43 pathology there?

Yes although this may require refinement in the future.

- Is there a specific clinical syndrome associated with LATE-NC?

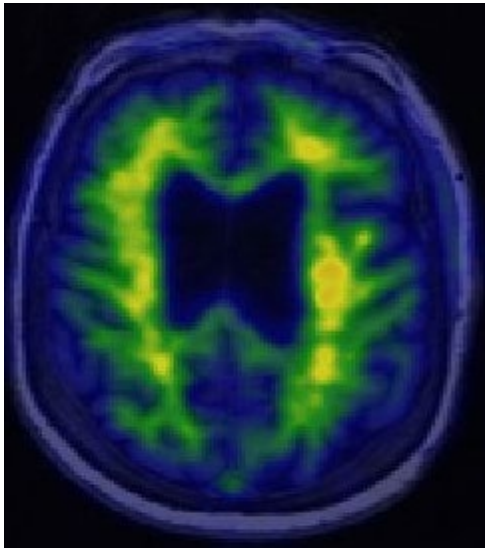
  Autopsied individuals with LATE-NC tend to have been diagnosed as AD in the clinical setting -- the disease preferentially affects episodic memory but may culminate in dementia.

- Is there a specific way to identify persons at high risk for LATE-NC in the clinical context?

  This disease is probably a large component of biomarker-defined “SNAP” (suspected non-amyloid pathology), and in particular cases with “T-N+” biomarker profile. We hope that future studies will develop specific biomarkers for LATE-NC.

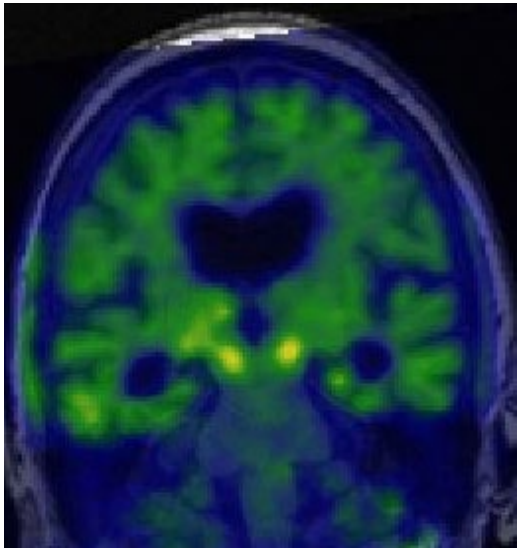
86 yo, F, progressive amnestic dementia. Clinic Dx “AD”. Biomarker profile: A-T-(N)+, suspected non Alzheimer’s pathologic change.

A-



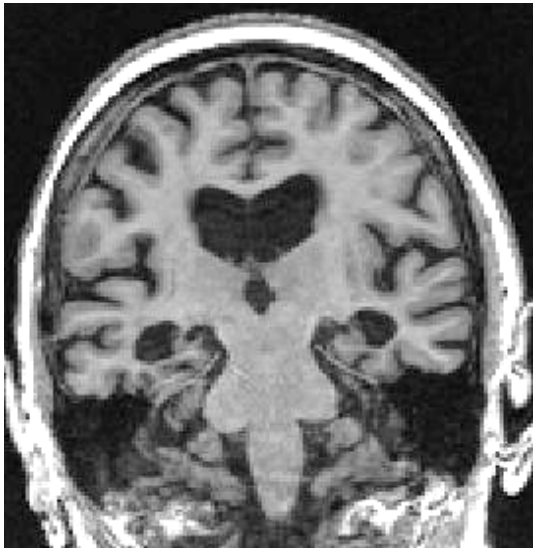
Amyloid PET

T-



Tau PET

(N)+



MRI

New correct autopsy diagnosis:

Autopsy result: Hippocampal sclerosis with LATE NC (Stage 3) with hippocampal sclerosis TDP-43 pathology

Thanks to Dr. Clifford Jack, Mayo

Limbic-predominant age-related TDP disease (LATE)

Forthcoming consensus paper

- **Background**
- **Neuropathology (Dennis Dickson)**
- **Clinical features (Patricia Boyle)**
- **Public health impact (Julie Schneider)**
- **Issues related to biomarkers and clinical trials (Cliff Jack standing in for Reisa Sperling)**
- **Genetics (Rosa Rademakers)**
- **Research challenges and future directions**