Alzheimer's Disease Neuroimaging Initiative

Steering Committee Meeting

April 18, 2016

Neuropathology Core

John C. Morris, MD

Nigel J. Cairns, PhD, FRCPath

Erin Franklin, MS

KnightADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Table 1. Participants Autopsied per Funding Period

ADNI Funding Period	ADNI-NPC	Deaths	Autopsies	Annual Autopsy Rate (%)
9-1-05 to 8-31-07	NO	6	0	0
9-1-07 to 8-31-08	YES	7	2	28
9-1-08 to 8-31-09	YES	8	8	100
9-1-09 to 8-31-10	YES	4	1	25
9-1-10 to 8-31-11	YES	13	6	46
9-1-11 to 8-31-12	YES	4	3	75
9-1-12 to 8-31-13	YES	15	8	53
9-1-13 to 8-31-14	YES	20	13	65
9-1-14 to 8-31-15	YES	17	11	65
9-1-15 to 2-1-16	YES	8	4	50
Total (2005-2016)	-	102	56	55
Total since NPC established	-	96	56	58

Note: The ADNI-NPC was established on 9/1/2007. Figures based upon ADNI participants that passed away while enrolled as well as those no longer actively seen due to protocol changes or advanced dementia.

Table 2. Clinical and Neuropathologic Diagnoses at Expiration

Clinical Diagnosis	Neuropathologic Diagnosis [N (%)]										
	AD	AD +DLB	AD +TDP	AD +DLB +TDP	AD+DLB +TDP +AGD	AD +ALB	AD + AGD	AD +HS	AD+TDP +Infarcts	AGD +PART	TOTAL (%)
ADD	18*	12**	3§	2	2§	2	1	3†	1	2	46 (92)
ADD +DLB				1	1	2‡					4 (8)
TOTAL (%)	18 (36)	12 (24)	3 (6)	3 (6)	3 (6)	4 (8)	1 (2)	3 (6)	1 (2)	2 (4)	50 (100)

ADD, Alzheimer disease dementia; AD (NIA-AA score: A1, B0, C0 or greater); ALB, AD with amygdala Lewy bodies; DLB, dementia with Lewy bodies; AGD, argyrophilic grain disease; TDP, AD with TDP-43 proteinopathy in medial temporal lobe; HS, hippocampal sclerosis.

Notes:*One case had additional infarcts; **One case had additional AGD and one case had additional age-related tau astrogliopathy; §One case had additional age-related tau astrogliopathy; †One case had additional AGD and one case had additional TDP-43 proteinopathy; ‡One case had additional TDP-43 proteinopathy. Small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases.

Six additional cases are pending shipment and/or review.

Average age at death = 81.9 y (range: 59-97)

Of 42 ADNI cases with expiration CDRs, 5 were CDR 0.5, 3 were CDR 1, 8 were CDR 2, and 26 were CDR 3.

Major Accomplishments/Knowledge Gained during the lifetime of the ADNI NPC

- The Neuropathology Core has successfully developed protocols for the notification and administration of an autopsy and procurement of donated tissue from participating ADNI sites.
- The Neuropathology Core has coordinated with ADNI sites to obtain 56 autopsies; uniform neuropathology is now available on 50 participants.
- Neuropathology has helped to validate clinical and neuropsychological data, MRI, PET, and CSF biomarkers.
- Neuropathology provides a very rich data set for validation of biomarkers in AD clinical trials.
- The presence of significant comorbidity in LOAD indicates that the pathology in this cohort is heterogeneous and likely influences biomarker outcomes and the design of clinical studies.

ADNI-3: Neuropathology Core Aims

- **Aim 1:** Provide training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants.
- **Aim 2:** Maintain a central laboratory to provide uniform neuro-pathological assessments in all autopsied ADNI participants in accordance with standard criteria and to promote clinical-neuroimaging-genetic-neuropathologic correlations.
- **Aim 3A:** Maintain a state-of-the-art resource for fixed and frozen brain tissue obtained from autopsied ADNI participants to support ADNI's biomarker studies and make available to ADNI-approved investigators access to the tissue and data for research purposes.
- **Aim 3B:** Interact with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into ADNI's database, promote data sharing and collaborative research, and integrate the ADNI3-NPC with all ADNI3 components to support its administration, operations, and progress toward goals.

ADNI-3: Neuropathology Core Aims (cont.)

- **Aim 4:** To test the hypothesis that comorbidities including Lewy bodies (synucleinopathy) and TDP-43 proteinopathy contribute to the variance in clinical, CSF biomarker, and neuroimaging data we will correlate molecular pathologic heat maps with neuroimaging and CSF biomarker data using the methods previously developed by Dr. Toledo and colleagues (Biomarkers Core).
- **Aim 5:** Using the methods developed to correlate PET-PiB Aβ data with neuropathologic Aβ burden observed at autopsy, we will undertake correlation analyses using PET-tau (AV-1451) SUVR data with regional tau burden measured in postmortem brain tissue.
- **Aim 6:** In collaboration with the Genetics Core we aim to undertake comprehensive integrative genomics and bioinformatics analyses using ADNI genome sequencing data and neuropathology variables including synucleinopathy and other comorbidities.

Problems faced during ADNI-Why ADNI 3 is important to overcome problems and advance the field….

- The NPC was only established in the third year of ADNI 1 and the value of an autopsy at non-ADCs/ADRCs was not fully appreciated.
- In ADNI-3 all site PIs and site coordinators will be regularly encouraged to participate in the autopsy program.
- Sustained coordination with all sites is essential to ensure that autopsy consent is promoted and achieved and that protocols are in place for the administration of autopsy and shipment of tissue to NPC.
- In ADNI-3 regular webinars are proposed to ensure optimal participation and adherence to protocols.

Reminders about Autopsy Consent/Brain Donation

- Neuropathology remains the gold standard for diagnosing dementing diseases. Neuropathologic data permit multimodal and genetic studies of these comorbidities to improve diagnosis and provide etiologic insights.
- All ADNI participants should be asked to consider brain donation. The ADNI Neuropathology Core Coordinator, Erin Franklin (efranklin@path.wustl.edu), will assist in establishing the protocol and/or finding autopsy services for all sites.
- Physical location of a participant at time of death does not prevent an ADNI autopsy. **We can find autopsy services almost anywhere!**
- If a participant wishes to donate his or her brain to another program (e.g. an ADC Neuropatholgy Core), the ADNI NPC can still arrange tissue sharing with that program with the participants consent. Just let Erin know and she is happy to make the appropriate contacts.

Reminders –II.

- Please follow up with participants who are undecided about autopsy consent. Frequently update the participant's and next-of-kin's contact information and let the NPC know if any change in autopsy services is required.
- Notify the ADNI Neuropathology Core (available 24/7: 314-362-8079; after hours pager 314-841-4738) as soon as the participant dies. This information is needed for our records regardless of whether an autopsy is being performed.
- Please communicate with the Neuropathology Core Coordinator prior to shipping the brain tissue. We need certain information to receive tissue in our Neuropathology Division at Washington University School of Medicine. We also require additional information regarding the participant's cause of death and estimated CDR at the time of death that is not available in ADNI participant records.

Reminders –III.

- Please do not have a participant believe that their wishes regarding brain donation will be carried out unless **prior arrangements have been made**.
- If you have ANY questions related to brain donation, autopsy, or reimbursable autopsy expenses, please ask. We are only an e-mail or phone call away (314-362-8079; after hours pager 314-841-4738; efranklin@path.wustl.edu)

Looking forward to ADNI 3….

- ADNI 3 is an excellent time to incorporate brain donation into your site's study protocol. Erin can help with consent issues and logistical planning of any kind.
- It is easier than you might think and will contribute greatly to the valuable data being obtained as part of the ongoing ADNI project!