

Autopsy consent, brain collection, and standardized neuropathologic assessment of ADNI participants: The essential role of the Neuropathology Core

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Abstract

Background: Our objectives are to facilitate autopsy consent, brain collection, and perform standardized neuropathologic assessments of all Alzheimer's Disease Neuroimaging Initiative (ADNI) participants who come to autopsy at the 58 ADNI sites in the USA and Canada.

Methods: Building on the expertise and resources of the existing Alzheimer's Disease Research Center (ADRC) at Washington University School of Medicine, St. Louis, MO, a Neuropathology Core (NPC) to serve ADNI was established with one new highly motivated research coordinator. The ADNI-NPC coordinator provides training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants. Secondly, the ADNI-NPC maintains a central laboratory to provide uniform neuropathologic assessments using the operational criteria for the classification of AD and other pathologies defined by the National Alzheimer Coordinating Center (NACC). Thirdly, the ADNI-NPC maintains a state-of-the-art brain bank of ADNI-derived brain tissue to promote biomarker and multi-disciplinary clinicopathologic studies.

Results: During the initial year of funding of the ADNI Neuropathology Core, there was notable improvement in the autopsy rate to 44.4%. In the most recent year of funding (September 1st, 2008 to August 31st 2009), our autopsy rate improved to 71.5%. Although the overall numbers to date are small, these data demonstrate that the Neuropathology Core has established the administrative organization with the participating sites to harvest brains from ADNI participants who come to autopsy.

Conclusions: Within two years of operation, the Neuropathology Core has: (1) implemented a protocol to solicit permission for brain autopsy in ADNI participants at all 58 sites who die and (2) to send appropriate brain tissue from the decedents to the Neuropathology Core for a standardized, uniform, and state-of-the-art neuropathologic assessment. The benefit to ADNI of the implementation of the NPC is very clear. Prior to the establishment of the NPC in September 2007, there were 6 deaths but no autopsies in ADNI participants. Subsequent to the establishment of the Core there have been 17 deaths of ADNI participants and 10 autopsies. Hence, the autopsy rate has gone from 0% to 59%. The third major accomplishment is the detection of co-existent pathologies with AD in the autopsied cases. It is possible that these co-morbidities may contribute to any variance in ADNI data.

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Keywords: Alzheimer's disease; Alzheimer's Disease Neuroimaging Initiative; autopsy consent; brain bank; neuropathologic diagnostic criteria

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1. Introduction

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was established to determine the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of the entire spectrum of Alzheimer's disease (AD) as the pathology evolves from normal aging to dementia. ADNI will inform the neuroscience of AD, identify diagnostic and prognostic markers, identify outcome measures which can be used in clinical trials, and will help develop the most effective clinical trial scenarios. The project continues as a public-private collaboration between academia and industry to study biomarkers of AD.

To achieve the goals of ADNI, the Neuropathology Core is essential to validate the clinical classifications and diagnoses; otherwise, the data generated by the different clinical assessments, imaging modalities, and biomarkers obtained from ADNI participants believed to have AD may be contaminated by individuals who, in fact, do not have AD. As an example, in the A β vaccine trial AN1792 in persons with a clinical diagnosis of AD, 1 of 9 participants who came to autopsy had progressive supranuclear palsy rather than AD [1]. If there is no neuropathologic validation, ADNI data are likely to be contaminated by individuals who do not have AD, or, more commonly, co-morbidities such as vascular disease and non-AD neurodegenerative disorders [1]. Also, a single Neuropathology Core site is necessary because different neuropathologists use different processing and staining methods, as well as different antibodies and interpret diagnostic criteria differently. Even for the neuropathologic diagnosis of AD, not all sites use the same sets of criteria. The literature has extensive data showing variability between different neuropathologists, sites, and countries [2, 3]. A single Neuropathology Core ensures uniformity and fidelity of staining and application of diagnostic criteria to all ADNI participants who come to autopsy [2, 3].

The ADNI-NPC capitalizes on the existing infrastructure of the Washington University Alzheimer Disease Research Center (WU ADRC; P50-AG05681, JC Morris, PI), funded continuously by the National Institute on Aging since 1985. The ADRC's Administrative (Dr Morris) and Neuropathology (Dr Cairns) Cores provide the framework for the ADNI-NPC, and will continue to do so during the period of renewed funding. Fidelity of data between ADNI and the National Alzheimer Coordinating Center (NACC; U01AG016976, W. Kukull, PI) is maintained by using the same NACC Neuropathology Data Form as is used by all Alzheimer Disease Centers (ADCs) to report neuropathological findings from autopsied cases, and will remain the primary data collection instrument. In this way, the ADNI-NPC uses standard criteria for neuropathologic diagnoses of dementing illness and existing protocols and procedures to achieve these diagnoses. Importantly, the ADNI-NPC does not interfere with or supersede neuropathologic activities at any ADNI site. The ADNI-NPC uses brain tissue obtained at the participating ADNI sites to provide a uniform

neuropathologic assessment to support the clinical classifications and research aims of ADNI and the proposed ADNI.

Funding of the Neuropathology Core started on September 1, 2007, and since that time the ADNI-NPC has become fully operational and serves all ADNI sites. During the initial period of funding (September 1st 2007 to August 31st 2009), the ADNI-NPC has achieved its stated goals. It has: (1) provided and implemented training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants; (2) established a central laboratory to provide uniform neuropathologic assessments in all autopsied ADNI participants in accordance with standard criteria [4-18], and promotes clinical-neuroimaging-neuropathologic correlations; (3) it established and maintains a state-of-the-art resource for fixed (10 of 10 cases) and frozen brain tissue (9 of 10 cases) obtained from autopsied ADNI participants to support ADNI's biomarker studies), and it developed a process wherein investigators may have access to the tissue and data for research purposes; and (4) the ADNI-NPC interacts with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into ADNI's database, promotes data sharing and collaborative research, and integrate the ADNI-NPC with all ADNI components to support its administration, operations, and progress toward goals.

2. Methods

2.1. Provision of training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants and to maintain a central laboratory to provide uniform neuropathologic assessment

As there may be personnel changes over time, there is a continuing need to monitor each site to ensure that training and protocols for obtaining autopsies are in place, so it is essential to maintain a dedicated Coordinator to ensure these functions are performed over the period of the grant. To obtain consent for an autopsy, the ADNI physician leads a discussion about the autopsy with all participants (demented and non-demented) at their initial assessment (study partners and families are welcomed in the discussion and required for AD participants). There are three objectives of the discussion: 1) to convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding MCI and AD; 2) to initiate consideration of the individual's wishes concerning an autopsy; and 3) to answer questions, misconceptions, or concerns about autopsy. The involvement of the physician in these discussions emphasizes the importance of the autopsy. The discussions are repeated on an annual basis if the individual has not decided about autopsy, but are terminated once a decision is reached. There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that

a decision not to have autopsy in no way jeopardizes their research participation or any other patient rights.

When voluntary consent is granted, more detailed information is provided about procedures to follow at time of death, including telephone numbers to call and other guidelines (sample forms are available in the printed appendix and online). Participants are strongly encouraged to share this information with their next-of-kin, a Durable Power of Attorney (DPOA), and private physicians. In many states, final legal authorization by the Legally Authorized Representative (LAR) or next-of-kin must be obtained at the time of death. Each ADNI site is encouraged to establish an autopsy coordinator (typically a research nurse or coordinator) who processes the autopsy consent, provides information as needed, and monitors the need to update any information (eg, change in residence) at the ADNI participant's longitudinal assessments. The coordinator also develops procedures for that site to facilitate autopsies outside of usual hours (eg, evenings and weekends). The actual procedures vary in accordance with local needs and resources (one model used by many ADCs is to provide 24-hour telephone access).

At the time of death, the autopsy coordinator (or a suitable representative) facilitates arrangements to ensure the completion of the autopsy. The coordinator will notify the ADNI-NPC, which in turn verifies that the site neuropathologist has the dissection protocol and necessary materials to send the requisite tissue to the ADNI-NPC in St. Louis, MO. The ADNI-NPC, in addition to instructing site personnel at each ADNI Steering Committee Meeting in these procedures, will be available at any time to answer questions. Contact information, including a 24-hour pager, is available. At ADNI sites that already have ADRC/ADC neuropathology services, these continue to follow their own existing protocols. For ADNI sites that do not have established neuropathology services, transportation costs from point of death to the autopsy suite, costs of the autopsy procedure, and shipment of materials are covered by the ADNI-NPC so that the decedent's family and the individual ADNI site do not incur extra expense. Once the participant has given consent (provisional or otherwise), the Acknowledgement of Autopsy Authorization letter and supporting documentation will be sent to the following: participant and/or family and/or applicable other (eg, Power of Attorney), nursing home, funeral home/transport service (as requested), and the participant's private physician (as requested).

2.2. Maintain a central laboratory to provide uniform neuropathologic assessments

Where possible, each center has been encouraged to undertake its own brain assessment and forward a standard set of fixed-tissue blocks or sections and frozen tissue to the ADNI-NPC (see below). For sites that do not routinely undertake neuropathologic studies, a separate brain removal protocol is available. When requested, the Neuropathology Core makes available financial assistance with the autopsy, block

sampling, preservation, and shipping costs. The Neuropathology Core funds all costs in shipping frozen and fixed tissue samples to St. Louis, MO. To assist participating centers and neuropathologists with the costs of obtaining frozen tissue blocks and/or formalin-fixed paraffin wax-embedded tissue costs are reimbursed, if requested. To minimize the burden on participating centers, formalin-fixed paraffin wax-embedded tissue blocks from the following 16 areas from the left cerebrum are forwarded to the ADNI-NPC: middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobe (angular gyrus), occipital lobe to include the calcarine sulcus and peristriate cortex, anterior cingulate gyrus at the level of the genu of the corpus callosum, posterior cingulate gyrus and precuneus at the level of the splenium, amygdala and entorhinal cortex, hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus, striatum (caudate nucleus and putamen) at the level of the anterior commissure, lentiform nucleus (globus pallidus and putamen), thalamus and subthalamic nucleus, midbrain, pons, medulla oblongata, cerebellum with dentate nucleus, and spinal cord. In the unusual situation where it is impractical to forward a tissue block (eg, if the block is used for stereology), 10 paraffin wax sections (4–8 μ m) from each block may be sent to the ADNI-NPC for systematic neuropathology and diagnosis.

To provide tissue for biochemical studies and to advance the aims of the Biomarkers Study, snap frozen tissue is dissected, snap frozen, and sent to the ADNI-NPC. The following coronal hemibrain slices (0.5 to 1cm thick), where possible, are taken: (1) frontal lobe to include striatum; (2) frontal and temporal lobe at the level of the mamillary body; (3) temporal and parietal lobes at the level of the lateral geniculate nucleus; and (4) occipital lobe to include the calcarine sulcus.

2.3. Histology

In all cases, the following stains are performed at the ADNI-NPC lab on the blocks indicated above, and/or as requested by the neuropathologist: hematoxylin and eosin and modified Bielschowsky silver impregnation. Routine immunohistochemistry is performed using the following antibodies: ubiquitin (Dako); tau (PHF1 and/or AT8); β -amyloid (4G8 and/or 10D5); and α -synuclein (LB509). In cases with ubiquitin-positive inclusions, the following additional IHC is performed: TDP-43 and FUS [19–21].

2.4. Neuropathologic assessment

The operational criteria for the classification of AD and other pathologies defined by NACC is applied to all ADNI-NPC cases [4–18]. The neuropathologic diagnosis is determined by Dr Cairns and Dr Robert Schmidt (Division of Neuropathology, Washington University School of Medicine, St. Louis, MO) using consensus neuropathologic criteria for AD and for non-AD disorders. The NACC Neuropathology Form includes an entry for the diagnosis of AD by each of the three sets of

criteria: CERAD, NIA-Reagan Institute, and Khachaturian. ADNI-NPC cases are thus diagnosed in accordance with each of these criteria, as no consensus currently exists in favor of one set in relation to the others (particularly for the incipient stages of AD addressed by the ADNI study). This will allow investigators maximal utility in applying the neuropathologic diagnoses most appropriate to their research aims [22]. The neuropathologic data are entered into the NACC Neuropathology Data Form and transmitted to the Biostatistics and Informatics Cores at the ADNI Coordinating Center. The final neuropathologic diagnosis and neuropathologic report are forwarded to ADNI for entry into the central database and to the center that made available the tissue.

3. Results

Progress since September 1st 2007: The ADNI-NPC Research Coordinator, Mrs Lisa Taylor-Reinwald, has contacted all participating ADNI sites to implement the protocols established for obtaining autopsy consent and performing neuropathology services. Mrs Taylor-Reinwald continuously monitors the sites to encourage and facilitate autopsy consent in ADNI participants. In addition, all ADNI-NPC documentation is available at the ADNI website: <http://www.adcs.org/Resource/studyResources.aspx>. Where autopsy procedures do not exist locally, arrangements have been put in place with the site PI and local hospital to harvest brain tissue and forward to the ADNI-NPC in St Louis, MO. To promote the goals of the ADNI-NPC and to inform participating ADNI sites, meetings were held concurrently in April 2008, at the American Association of Neuropathologists Annual Meeting, Washington, D.C., and at the American Academy of Neurology Meeting in Boston, MA. Interestingly, the first ADNI participant to come to autopsy had neuropathologic diagnoses of dementia with Lewy bodies (DLB) and coexisting AD. Of the nine autopsies, three have combined DLB and AD (see Table 1 for all neuropathologic diagnoses encountered in ADNI cases).

3.1. Autopsy rate

During the period of funding of ADNI, there have been 22 participant deaths (Table 2). In the initial phase of ADNI (September 1st, 2005 to August 31st, 2007), when no resources were available for neuropathology, there were six participant deaths and no autopsies (autopsy rate = 0%). During the initial year of funding of the ADNI Neuropathology Core (September 1st, 2007 to August 31st, 2008), there was notable improvement in the autopsy rate to 44.4%. In the most recent year of funding (September 1st, 2008 to August 31st 2009), our autopsy rate improved to 71.5% (Table 2). Although the overall numbers to date are small, these data demonstrate that the Neuropathology Core has established the administrative organization with the participating sites (Washington University School of Medicine) to harvest brains from ADNI participants who come to autopsy. As ex-

Table 1
Clinical and neuropathologic diagnoses at expiration

Clinical diagnosis	Neuropathologic diagnosis [N (%)]				TOTAL (%)
	AD	AD + DLB	AD + AGD	AD + TDP-43	
DAT	2 (22)	3 (33)	1(11)	1 (11)	7 (78)
MCI	2 (22)	0 (0)	0(11)	0 (0)	2 (22)
Normal	0 (0)	0 (0)	0(11)	0 (0)	0 (0)
TOTAL (%)	4 (44)	3 (33)	1(11)	1 (11)	9 (100)

Abbreviations: N, number of ADNI cases. AD, Alzheimer's disease; AGD, argyrophilic grain disease; DAT, dementia of the Alzheimer type; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; TDP-43, TDP-43 proteinopathy in the medial temporal lobe.

NOTE. Mild small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases but none had infarcts.

pected, the numbers of ADNI participants who come to autopsy is increasing as the period of the study lengthens and participants age.

3.2. Neuropathologic assessment of ADNI participants at autopsy

Brain tissue from 10 ADNI participants has been received and all brains samples have been neuropathologically assessed by the ADNI-NPC (Table 1). Seven men and two women have come to autopsy. The mean age at expiration of the men was 82 years (range: 65 to 89) and the women were aged 79 and 85 years old at expiration. One participant was an African American; the remainder were white. The mean postmortem interval (time from death to snap freezing of brain tissue) was 6.7 hours (range: 2.8 to 16.0). Of the nine autopsied cases, the clinical diagnoses at the time of expiration were DAT in six and MCI in three. All nine cases had AD according to the neuropathologic diagnostic criteria of Khachaturian, CERAD, and the NIA-Reagan Institute. In addition, three of the nine cases (33%) had sufficient alpha-synuclein pathology (Lewy bodies and Lewy neurites) to fulfill McKeith et al criteria for the neuropathologic diagnosis of DLB (neocortical stage) [10,11]. Other co-morbid pathologies were argyrophilic grain disease (4R tauopathy) (n=1) [17] and TDP-43 proteinopathy in the medial temporal lobe (n=1) [23]. The identification of cases with co-morbid molecular pathology is important for determining the potential contribution of other molecular pathologies to the clinical

Table 2
Autopsy rates: September 1st 2005 to August 31st 2009

Funding Period	ADNI-NPC	Deaths	Autopsies	Autopsy Rate (%)
09-01-2005 to 08-31-2007	NO	6	0	0
09-01-2007 to 08-31-2008	YES	9	4	44.4
09-01-2008 to 08-31-2009	YES	7	5	71.5
Total (2005-2009)	-	22	9	40.9

NOTE. During the initial stage of ADNI, the NPC had not been established and no autopsies were performed on the six ADNI participants who expired during 2007 and the first half of 2008. Autopsy rate = number of brain autopsies/total number of ADNI participants who died.

phenotype. The presence of cases with an additional molecular pathology in this sample, although representative of other larger series, indicates that the contribution of tauopathy, alpha-synucleinopathy, and TDP-43 proteinopathy, and possibly other proteinopathies, will need to be assessed in the ADNI series as more cases come to autopsy. If the neuropathologic sample is representative of the total ADNI cohort of dementia patients, these preliminary data indicate widespread co-morbidity which may contribute to variance in the data obtained by the different Cores.

4. Discussion

ADNI-NPC has become an extension of the ADNI specific aims in that it provides the gold standard validation of the clinical diagnoses and imaging surrogates through neuropathologic examination of ADNI participants who come to autopsy. If there were no neuropathologic assessment, the data generated by the different clinical assessments, imaging modalities, and biomarkers obtained from ADNI participants believed to have AD may be contaminated by individuals who in fact do not have AD. For example, of the ADNI participants who have come to autopsy, in addition to AD, other co-morbidities have been detected including dementia with Lewy bodies, argyrophilic grain disease, and a recently described molecular pathology called TDP-43 proteinopathy [1]. The contribution of these additional pathologies to the clinical, neuroimaging, and biomarker phenotypes will be the subject of future studies.

Previous studies indicate that a single Neuropathology Core site is necessary because different neuropathologists use different processing and staining methods, as well as different antibodies, and interpret diagnostic criteria differently. Even for the neuropathologic diagnosis of AD, not all sites use the same sets of criteria. The literature has extensive data showing variability between different neuropathologists, sites, and countries [2,3]. A single Neuropathology Core ensures uniformity and fidelity of staining and application of diagnostic criteria to all ADNI participants' brain tissue [2, 3]. A single Neuropathology Core ensures uniformity and fidelity of staining and application of diagnostic criteria to all ADNI participants who come to autopsy.

The initial success of the ADNI-NPC is built on the already established infrastructure of the Washington University Alzheimer Disease Research Center, funded continuously by the National Institute on Aging since 1985. The ADRC's Administrative (Dr Morris) and Neuropathology (Dr Cairns) Cores provide the framework for the ADNI-NPC and continue to do so during the period of ADNI funding. Fidelity of data between ADNI and the NACC has been maintained by using the same NACC Neuropathology Data Form as is used by all ADCs to report neuropathologic findings from autopsied cases. In this way, the ADNI-NPC uses standard criteria for neuropathologic diagnoses of dementing illness and existing protocols and procedures to achieve these diagnoses.

Importantly, the ADNI-NPC does not interfere with or supersede neuropathologic activities at any ADNI site. The ADNI-NPC uses brain tissue obtained at the participating ADNI sites to provide a uniform neuropathologic assessment to support the clinical classifications and research aims of ADNI and the proposed ADNI2.

Funding of the Neuropathology Core started on September 1st, 2007 and since that time the ADNI-NPC has become fully operational and serves all 58 ADNI sites. During the initial period of funding (September 1st 2007 to August 31st 2009), the ADNI-NPC has achieved its stated goals. It has: (1) provided and implemented training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants; (2) established a central laboratory to provide uniform neuropathologic assessments in all autopsied ADNI participants in accordance with standard criteria [4-18] and promotes clinical-neuroimaging-neuropathologic correlations; (3) established and maintains a state-of-the-art resource for fixed (10 of 10 cases) and frozen brain tissue (nine of 10 cases) obtained from autopsied ADNI participants to support ADNI's biomarker studies) and it developed a process wherein investigators may have access to the tissue and data for research purposes; and (4) the ADNI-NPC interacts with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into ADNI's database, promotes data sharing and collaborative research, and integrate the ADNI-NPC with all ADNI components to support its administration, operations, and progress toward goals.

Acknowledgments

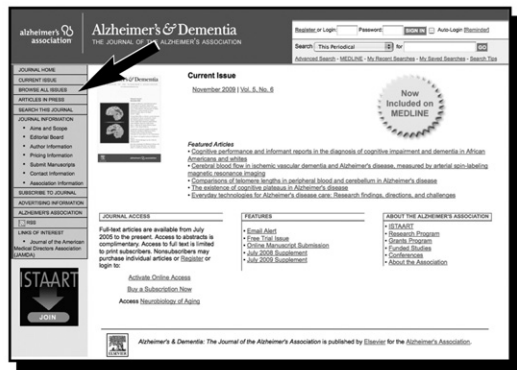
This work was supported by grants P50-AG05681, P01-AG03991, and P01-AG26276 from the National Institute on Aging, and P30-NS048056 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, and by the Charles and Joanne Knight Alzheimer's Research Initiative of the Washington University Alzheimer's Disease Research Center. The ADNI (National Institute of Health Grant U01 AG024904) is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Pfizer Inc, Wyeth Research, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Merck and Co. Inc, AstraZeneca AB, Novartis Pharmaceuticals Corporation, Alzheimer's Association, Eisai Global Clinical Development, Elan Corporation plc, Forest Laboratories, and the Institute for the Study of Aging, with participation from the U.S. Food and Drug Administration. Industry partnerships are coordinated through the Foundation for the National Institutes of Health.

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