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Integrated Neurodegenerative Disease Autopsy Diagnosis

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Introduction

The classification of human neurodegenerative diseases, while heavily dependent on neuropathologic analyses, increasingly relies on a number of data sources. Advances in the classification of clinical phenotypes and the expansion of molecular genetic alterations associated with various neurodegenerative diseases provide neuropathologists with additional means to categorize neurodegenerative disease. In the face of increasing data complexity, neuropathologists are poised to serve the critical role of integrating numerous data streams into an integrated autopsy report. I propose here a transition towards an integrated neurodegenerative disease autopsy report where the role of the neuropathologist is to assimilate clinical, molecular and anatomic/morphologic data to provide a succinct, layered diagnosis.

Data-driven Evolution of Human Disease Nosology

Various neuropathologic criteria have been established for the morphologic post-mortem analysis of neurodegenerative diseases.[2–6, 11, 14–17, 19] Rather than being a static set of rules, neurodegenerative disease criteria are continuously updated and revised, driven by the identification of shortcomings associated with existing criteria, new knowledge regarding the human disease and the development of new disease concepts.

The impetus for establishing the National Institutes on Aging-Alzheimer's disease Association (NIA-AA) criteria for the neuropathologic diagnosis of Alzheimer's disease can serve as an exemplar. The prior NIA-Reagan criteria were implemented to include analysis of both neurofibrillary tangle stage and amyloid plaque burden with the goal of determining the likelihood that the observed neuropathologic change was associated with clinical dementia.[7] While the NIA-Reagan criteria were successful in incorporating tau pathology and predicting the likelihood of clinical dementia, implementation of the criteria revealed a few shortcomings. First, the NIA-Reagan criteria presumed that amyloid and tau pathology were both seen at similar levels. However, there are cases where the neuritic plaque burden does not match the neurofibrillary tangle stage.[20] Secondly, studies by Thal and colleagues demonstrated that amyloid plaques appear in a stereotyped neuroanatomic distribution pattern.[23] Finally, the concept of Alzheimer's disease had matured such that it was no longer considered a binary state but rather a continuum from pre-symptomatic disease to mild cognitive impairment to dementia.[9] This concept required the neuropathologic documentation of Alzheimer's disease to be dissociated from the clinical phenotype in order

to acknowledge that the underlying disease may be present in the absence of clinical dementia. Thus, the identification of shortcomings, new knowledge, and new concepts coordinately prompted the creation of the NIA-AA criteria.[6, 19]

This process whereby diagnostic criteria evolve is not unique to the study of neurodegenerative diseases. Indeed, the classification of tumors is continuously being updated as evidenced by the series of five World Health Organization Classification of Tumors of the Central Nervous System that have been published since 1979. The expectation is that the advancement of knowledge that impacts diagnosis should be integrated into the neuropathologic classification of disease. This was most evident in the 2016 WHO Classification of Tumors of the Central Nervous System which for the first time integrates molecular genetic data as a requirement for the classification of various gliomas. [13]

With knowledge driving the classification of human disease, there comes a point at which classic morphology-based diagnosis of disease is insufficient. While our understanding of human neurodegenerative diseases is far from complete, important advances have been made in terms of clinical phenotyping of affected individuals, molecular genetics, and morphologic analysis of post-mortem tissue. Here, I propose that our understanding of neurodegenerative diseases has matured such that a layered, integrated diagnosis should be considered by neuropathologists when issuing final neurodegenerative disease autopsy diagnoses.

Integrated Neurodegenerative Disease Diagnosis

I propose a layered and integrated approach to neurodegenerative disease autopsy reporting, modeled after the Haarlem guidelines for CNS tumor classification and grading.[12] A layered and integrated diagnosis may be considered for autopsy reporting for dementias (Alzheimer’s disease, frontotemporal degeneration, prion diseases), movement disorders (Parkinson’s disease and related Lewy body disorders), and other movement, motor and/or cognitive diseases (amyotrophic lateral sclerosis, tauopathies other than Alzheimer’s disease). The autopsy report should still include many of the components that already exist within a neuropathology autopsy report including sections that describe gross and microscopic findings. A clinicopathologic correlation section may also be considered where morphologic findings are related to clinical and molecular data, if available. The proposed change here is only with regards to formulating the final diagnosis where a layered format may be considered in which key diagnostic data are included in the various layers with the top diagnostic layer representing the final integrated diagnosis (Table 1).

An integrated diagnostic approach does not alter or supersede any of the existing or future neurodegenerative disease neuropathology criteria such as the NIA-AA or Brain Net Europe criteria for Alzheimer’s disease.[1, 6, 19] Rather, this approach integrates these existing criteria into a more global classification scheme, reported as one of several layered diagnoses (shown as the second layer in the provided examples in Table 2). Importantly, co-morbid pathologies are common in neurodegenerative diseases and so an additional layer may be considered in order to document the presence of co-morbid pathologies, with the

caveat that there may be instances in which it may be difficult to ascertain what represents the primary disease process versus a co-morbidity.[8, 10]

Another layer which may be included in the report is the clinical classification of disease based on the various diagnostic modalities available to the clinician.[9, 17, 18, 21] While clinical phenotypes and underlying pathology are often synonymous, there are instances of "phenotypic heterogeneity" where disparate clinical phenotypes are associated with a single histopathologic entity.[22] For example, Alzheimer's disease neuropathology may be associated with a variety of clinical syndromes including amnestic mild cognitive impairment, Alzheimer-type dementia, posterior cortical atrophy, logopenic variant frontotemporal degeneration, and others.[18] Similarly, clinical categories typically associated with frontotemporal lobar degeneration includes behavioral variant frontotemporal degeneration, semantic variant of primary progressive aphasia, nonfluent/agrammatic variant of primary progressive aphasia, and others.[21] There are also instances of "clinicopathologic convergence" where disparate pathologies cause the same clinical phenotype.[22] For example, nonfluent/agrammatic primary progressive aphasia may be associated with underlying Alzheimer's disease, frontotemporal lobar degeneration with tau inclusions, or frontotemporal lobar degeneration with TDP-43 inclusions. Incorporating the decedent's clinical phenotype as an additional layer will undoubtedly require a close collaboration between the neuropathologist and clinician, and reflect the reality of clinicopathologic heterogeneity within neurodegenerative diseases.

Genetic variants associated with disease or genetic mutations that cause disease provides another layer of diagnostic data which can be incorporated into the autopsy report. If genetic data are available, a molecular layer may include known genetic variants that have strong associations with disease such as *APOE* status in the setting of Alzheimer's disease, or pathogenic mutations such as *C9orf72* repeat expansion mutations in frontotemporal degeneration and/or amyotrophic lateral sclerosis. Interpretation of genetic results, in particular negative results, should be tempered by an understanding of technical issues associated with sequencing (sequencing methods/quality/depth/coverage, whether deletion or duplication analysis has been done, etc.). Moreover, the advent of relatively cheap sequencing methods allows for identification of many genetic variants for a given individual, many of which may have little to no bearing on disease classification. A balance should be sought where validated genetic variants that represent a strong risk factor for disease or known pathogenic mutations are reported. Of equal importance are ethical issues surrounding genetic testing, including whether consent was obtained at time of autopsy for genetic testing, whether genetic counseling is available for next-of-kin, and whether genetic results are obtained from clinical laboratories (as opposed to genetic results from a research laboratory). These deliberations should tailor whether such data is included within the diagnostic autopsy report.

Finally, additional layers may be considered if they help in the classification of disease. For example, protein biochemistry is important in terms of the classification of prion disease subtypes and should thus be included within the layered diagnosis.[24] Similarly, if immunoblot or immunohistochemical analysis reveals that tau inclusions in a given case are strictly comprised of 3- versus 4- repeat tau isoforms, this result may be included as a

biochemical layer as it bears relevance to the diagnosis of various tauopathies. In contrast, differences in the biochemical profile of aggregated proteins are not definitely known to be associated with different subtypes of Alzheimer's disease or Lewy body disease and thus should not be included within the layered diagnosis until such diagnostic signatures are better defined. Thus, in lieu of prescribing a defined set of diagnostic layers, the expertise of the neuropathologist is tantamount in deciding the components of the layered diagnosis.

In conclusion, a final autopsy report should represent the integration of all the diagnostic modalities available that assists in the classification of disease. As such, a succinct layered diagnosis provides a clear means to communicate effectively with clinicians and next-of-kin as to the complexity of the underlying disease, tempered by a single integrated diagnosis which conveys the synthesis of various data sources to arrive at a final diagnosis. As the autopsy remains the final and often most definitive diagnostic procedure, an integrated final diagnosis represents the final and comprehensive disease classification. Moreover, an integrated autopsy report reflects the expert role of the neuropathologist as both morphologist, being able to integrate and interpret complex histologic images, and consultant, being able to integrate and interpret increasingly complex and sometimes esoteric data as it relates to the classification of human disease.

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Table 1:

Proposed layered and integrated neurodegenerative disease autopsy diagnosis

Layer 1:	Integrated diagnosis *Incorporating clinical, molecular and morphologic data*
Layer 2:	Histologic classification *Based on existing neuropathologic criteria*
Layer 3:	Clinical classification *Based on existing clinical criteria*
Layer 4:	Molecular classification *Included if available and informative*
Layer 5:	Additional layers as needed *For example, prion biochemistry*

Table 2:

Examples of integrated neurodegenerative disease autopsy diagnosis

Final Diagnosis #1 (Example of frontotemporal degeneration):
Integrated diagnosis: *C9orf72*-associated frontotemporal degeneration
Histologic diagnosis: Frontotemporal lobar degeneration with TDP-43 inclusions, type B
Co-morbid pathology: Low level of Alzheimer's disease neuropathologic change (Al, B2, Cl)
Clinical classification: Behavioral variant frontotemporal degeneration (bvFTD)
Molecular data: *C9orf72* hexanucleotide repeat expansion present

Final Diagnosis #2 (Example of Alzheimer's disease):
Integrated diagnosis: Alzheimer's disease, posterior cortical atrophy variant
Histologic diagnosis: High level of Alzheimer's disease neuropathologic change (A3, B3, C3)
Clinical classification: Posterior cortical atrophy
Molecular data: *APOE* E3/E4

Final Diagnosis #3 (Example of Lewv hodv disease):
Integrated diagnosis: Parkinson's disease dementia
Histologic diagnosis: Lewy body disease, neocortical pattern with a high level of Alzheimer's disease neuropathologic change (A3, C3, B2)
Clinical classification: Parkinson's disease dementia
Molecular data: Not available

Final Diagnosis #4 (Example of motor neuron disease):
Integrated diagnosis: Amyotrophic lateral sclerosis
Histologic diagnosis: Motor neuron disease with TDP-43 inclusions
Clinical classification: Amyotrophic lateral sclerosis, bulbar onset
Molecular data: *SOD1* and *C9orf72* mutations not detected