Movement Disorders
CLINICAL PRACTICE
LETTERS: PUBLISHED ARTICLE

Is Pathology Always the Diagnostic Gold Standard in Neurodegeneration?

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I read with interest Galit Kleiner and colleagues' report of a 79-year-old man suffering from progressive hemichorea, spasticity, and a frontal behavioral syndrome, with thrombocytopenia and positive antiphospholipid antibodies.[1] Rationally, antiphospholipid antibody syndrome (aPS) was the antemortem diagnosis. However, brain autopsy revealed a pattern of tau aggregation diagnostic of the pallidonigroluysian atrophy (PNLA) variant of progressive supranuclear palsy (PSP). The authors concluded that aPS must have been a red herring.

Is neuropathology always the final diagnosis? If so, was chorea also a red herring? Will any entity ever cease to expand if held to a pathology gold standard? Will the differential between hyper- and hypokinetic movement disorders remain negotiable pending a pathology report?

As a clinician, I struggle with these questions. We recently evaluated a 60-year-old woman with a 7-year history of a progressive ataxic-dystonia syndrome, an unusual jerky head tremor, and supranuclear vertical gaze palsy we suspected to be Niemann-Pick C.[2] There were no mutations in *NPC1* or *NPC2*. To our surprise, the neuropathological evaluation revealed tau deposition in a pattern diagnostic of PSP. As we considered reporting this case as an "expansion of PSP phenotype," genetic studies demonstrated a pathogenic mutation in *TGM6*, which codes for transglutaminase 6 (TG6). TG6 has a role in polyaminating proteins and fostering isopeptide bonds between them, supporting microtubular stability.[3] With low TG6, tau crosslinking is affected and axon microtubules become compromised. Plausibly, this enzymatic deficiency affecting the structure of tau could have caused this patient's disease; the 4-repeat tau deposition was its consequence.

A similar dilemma is at play in Kleiner et al.'s case. As anticardiolipin antibodies can be elevated among healthy elderly and microangiopathy was absent on autopsy, aCL may have been a red herring. On the other hand, aCL was associated with thrombocytopenia, raising the odds for an underlying autoimmune disorder.[4] Advances in immunology have revealed disorders never before considered antibody-mediated, such as "atypical PSP" due to anti-immunoglobulin-like cell adhesion molecule 5 (IgLON5) disease. Anti-IgLON5 antibodies disrupt the neuronal cytoskeleton and induce neurodegeneration. The authors argue that IgLON5 antibodies were unlikely because of insufficiently supportive pathology. Even then, would it not be reasonable to speculate that an autoantibody could have caused (or contributed to) the tau deposition in a man with aPS and thrombocytopenia?

Toward supporting the notion that pathology is a secondary expression of many diseases, Kleiner et al.'s case exhibited nigral pathology without parkinsonism. The authors helpfully referenced a previously reported case (Wong et al.[5]) reminiscent of theirs: progressive hemichorea and gait difficulties with autopsy-diagnosed PNLA, although with TDP-43 instead of tau pathology. Hemichorea, then, could be thought of as a nonspecific manifestation of a PNLA pattern of degeneration, regardless of the associated proteinopathy.

The value of clinicopathologic correlations notwithstanding, the weight of human observations suggests that protein aggregation is not the epicenter of neurotoxicity but a reactive phenomenon to a broad range of cellular pathobiologies.[5] If we continue to enshrine pathology as the final diagnosis, would not we continue to find paradoxes, red herrings, and "expansions of the phenotype"?

Author Roles

1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

AJE: 1A, 1A, 2B, 2C, 3A, 3B.

Disclosures

Funding Sources and Conflicts of Interest: There are no competing interests for the subject matter in this letter. There was no funding for this manuscript.

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Received 21 May 2022; accepted 6 June 2022.
Published online 3 October 2022 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13570

Financial Disclosures for the Previous 12 Months: Dr. Espay has received grant support from the NIH and the Michael J. Fox Foundation; personal compensation as a consultant/scientific advisory board member for Neuroderm, Neurocrine, Amneal, Acadia, Acorda, Bexion, Kyowa Kirin, Sunovion, Supernus (formerly, USWorldMeds), Avion Pharmaceuticals, and Herantis Pharma; personal compensation as honoraria for speakership for Avion; and publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer. He cofounded REGAIN Therapeutics (a biotech start-up developing nonaggregating peptide analogues as replacement therapies for neurodegenerative diseases) and is co-owner of a patent that covers synthetic soluble nonaggregating peptide analogues as replacement treatments in proteinopathies.

Ethical Compliance Statement: The author confirms that approval of an institutional review board and/or patient consent was not required for this letter. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. ■

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