Movement Disorders
CLINICAL PRACTICE
LETTERS: PUBLISHED ARTICLE

Comment on "Is it Useful to Classify PSP and CBD as Different Disorders?"

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In reply,

I enjoyed reading the two commentaries on this topic in MDCP and feel that both Drs. Ling and Hoglinger outlined very cogent arguments in favor of their opinions.[1,2] The clear differences between PSP and CBD definitely justify continuing to study them individually. However, I feel that the similarities, particularly the importance of 4R tau and the striking predisposition for astrocytic pathology (admittedly different in the two), argue more strongly for "lumping" them together, especially when it comes to developing novel therapeutic strategies. Certainly there are biological differences in the presumed strains of 4R tau involved in the different disorders. In fact, there is even experimental evidence for inter-patient differences within the same pathological disorder.[3] Differences in selected neural networks predisposed to initial involvement and pathological spread clearly account for clinical differences, but there is considerable overlap as well. The role of important host factors (genetic, other) in influencing anatomic and pathologic characteristics is also not understood at all.

From my perspective, the most important factor that weighs on how we should consider these disorders is whether they will respond to the same approaches to disease modification therapy. At this time, there is considerable interest in tau therapeutics, particularly anti-tau monoclonal antibodies. Numerous other approaches are also being explored.[4] Given the relative rarity of CBD and the considerable clinical phenotypic overlap with PSP, there is a strong argument for combining the two 4R tauopathies for the purposes of clinical trials of putative disease modifying therapy (after carefully excluding Alzheimer's disease in patients presenting with corticobasal syndrome and accepting that there will be a small number of false positive diagnoses in the remainder; [e.g., TDP-43opthies]).

These are both inexorably progressive disorders that result in profound disability and premature death. We need to do everything we can to alter this miserable state of affairs. I believe that combining the two for the purposes of therapeutics is the only way that we can move forward in our current state of knowledge (or, if you prefer, ignorance). My hope is that the pathogenic commonalities between the two distinct pathologic disorders will outweigh their differences with respect to response to treatments. One important concern and caveat comes from the interesting recent work of Woerman and colleagues in Prusiner's laboratory[5] that showed that tau prion propagation in HEK cells requires isoform pairing between the infecting prion and the recipient substrate, suggesting that developing successful anti-tau therapies will actually require inhibiting the propagation of specific tau prion strains. If successful therapy will require targeting selected strains of pathogenic proteins in neurodegenerative diseases we are probably a very long way away from effective disease modification. For the time being I would support concentrating on the commonalities, but not ignoring the differences.

Author Roles

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

A.E.L.: 3A, 3B

Disclosures

Ethical Compliance Statement: The author confirms that neither the approval of an institutional review board nor patient consent was required for this work. The author has read the Journal's position on issues involved in ethical publication and affirms that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: No specific funding was received for this work and the author declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months: The author declares that there are no additional financial disclosures to report.

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Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 8 June 2018; accepted 9 June 2018.
Published online 3 October 2018 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mdc3.12676

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