alzheimer's research&therapy

COMMENTARY

From model system to clinical medicine: pathophysiologic links of common proteinopathies

Pamela J McMillan[1,2] and James B Leverenz*[1-4]

Abstract

Recent clinical evidence suggests that Alzheimer disease (AD), Parkinson disease (PD), and dementia with Lewy bodies (DLB), though distinct neurological disorders, have some common pathological features that may have an impact on the clinical characteristics of these diseases. However, the question of whether these disorders have a common pathophysiology remains. Clinton and colleagues recently reported a mouse model that exhibits the combined pathologies of AD, PD, and DLB, a finding that may shed some light on this issue. Using this mouse model, the authors demonstrate that the pathogenic proteins amyloid beta, tau, and alpha-synuclein interact synergistically to enhance the accumulation of one another and accelerate cognitive decline. These data indicate shared pathogenic mechanisms and suggest the possibility that therapeutic interventions successfully targeting one of these pathogenic proteins have implications for a number of related neurodegenerative disorders.

Alzheimer disease (AD), the most common neurodegenerative disorder, is characterized by the accumulation of amyloid beta (Aβ) and tau into plaques and tangles, respectively. Other neurodegenerative disorders such as Parkinson disease (PD) and dementia with Lewy bodies (DLB) are broadly characterized as synucleinopathies because of the accumulation of alpha-synuclein (SNCA) into Lewy bodies. Although these disorders are not the same, there is overlap with respect to the pathogenic proteins Aβ, SNCA, and tau. A large subset of patients with AD (Lewy body variant, AD-LBV) exhibit Lewy body pathology in addition to plaques and tangles [1]. Lewy body pathology is also common in patients with early-onset familial AD [2,3]. Conversely, dementia in PD (PDD) may involve AD-related pathological changes. Increased Aβ plaque burden and low cerebrospinal fluid (CSF) Aβ levels have been demonstrated in PDD and are highly correlated with increased Lewy body pathology [4-7]. Evidence linking tau pathology to PDD is less evident, although one study has demonstrated increased phospho-tau in post-mortem PDD brain [8]. Recent evidence suggests that this pathological overlap may predict the clinical course of the disease. Patients with AD-LBV exhibit a more aggressive disease course, a more severe memory impairment, and a more rapid rate of cognitive decline compared with AD patients without Lewy body pathology [9]. Reductions in CSF Aβ levels have been reported in PDD subjects and are associated with memory impairment [6], and there is a strong association between declines in CSF Aβ and longitudinal declines in cognition over time in patients with PDD [10]. Low CSF Aβ levels are considered a reflection of increased Aβ deposition in brain [11] and, along with high CSF tau levels, act as a biomarker to predict the presence of AD neuropathology [12] and a more rapid rate of cognitive decline during the course of the disease [13,14]. Thus, although there does not appear to be an association between CSF tau, PDD, and cognitive decline, at least one AD biomarker, CSF Aβ, reflects cognitive impairment in PD. From a clinical perspective, these studies are important because they link PD, a classic SNCA-associated disease, with AD, suggesting interplay between some of the pathophysiological mechanisms underlying these diseases.

The human clinical studies discussed above suggest that, in the etiology of these diseases, there may be a common thread involving the synergistic interaction of the pathogenic proteins Aβ, SNCA, and tau. However, understanding the mechanism of a disease process in humans is inherently difficult through clinical studies. Thus, animal models are needed to provide an experimentally accessible system in which to study the molecular pathogenesis of a disease. To this end, an important recent study by Clinton and colleagues [15] describes a mouse model that exhibits the combined

*Correspondence: leverenz@u.washington.edu
[1]Mental Illness Research Education and Clinical Center, Veterans Administration Puget Sound Health Care System, 1660 South Columbian Way, Seattle, WA, 98108, USA
Full list of author information is available at the end of the article

pathologies of Aβ, tau, and SNCA. This animal was generated by introducing a mutant human *SNCA* transgene ($SNCA_{A53T}$) into the 3xTg-AD triple-transgenic mouse ($hAPP_{SW}$/$hTau_{P301L}$/$hPS1_{M146V}$). The authors report that the resulting 4xTg mice exhibit increased insoluble Aβ and thioflavin-S-positive plaque pathology and increased insoluble tau and AT8 phosphorylated tau immunoreactivity compared with the 3xTg-AD mouse model, suggesting that the addition of SNCA promotes the accumulation of these pathogenic proteins. Additionally, the 4xTg mice exhibit increased insoluble SNCA, increased phosphorylated SNCA, and accelerated deposition of Lewy body inclusions compared with single-transgenic SNCA mice, suggesting an effect of Aβ and tau on SNCA pathology. Importantly, the 4xTg mice exhibit accelerated cognitive decline compared with 3xTg-AD mice and single-transgenic SNCA mice, suggesting that the exacerbated pathology is clinically relevant. The authors conclude that Aβ, tau, and SNCA can synergistically promote the aggregation and deposition of each other and thereby accelerate cognitive decline.

There are many animal models of neurodegenerative diseases, yet none fully reproduces the full neuropathological or clinical features of the human disease. The mouse model described above is unique because it exhibits all three proteinopathies clinically associated with AD, DLB, and PD. But what disease does this animal model represent? One might argue that it represents a composite of several distinct diseases – AD, DLB, PD, and tauopathies – that do not naturally occur together. The resulting pathologies may be driven separately by the different transgenes: plaque pathology by the AD-associated APP and PS1 mutations; tau pathology by the frontotemporal dementia with Parkinsonism-chromosome 17 (FTDP-17) mutation in tau; and Lewy body pathology by the familial PD-associated mutation in SNCA. However, this mouse model strongly suggests that an interaction among these proteins results in a behavioral manifestation that models the clinical characteristics of these diseases to some extent. Importantly, clinical research in humans indicates that these diseases may be linked by common pathological changes involving these proteins and that these changes have clear clinical effects.

The molecular mechanisms that promote the synergistic aggregation of Aβ, tau, and SNCA remain to be elucidated. These proteins, and their aggregated pathological forms, often do not reside in the same neurons or cellular compartments, making physical interactions problematic. Thus, one can hypothesize that there may be a common underlying pathogenic mechanism that independently promotes the aggregation of multiple proteins in susceptible cells. However, the data from Clinton and colleagues suggest a more direct cooperative interaction in which the aggregating proteins themselves may seed each other. Under pathological conditions, there may be aberrant co-localization of these proteins, as either oligomers or fibrils. These proteins may then act as seeds to promote the fibrillization of one another in a synergistic manner. The amyloidogenic nature of these proteins may play a role in this interaction. Such a seeding mechanism has been proposed to explain how tau and SNCA inclusions can co-localize in the same cells in several neurodegenerative diseases, including AD and DLB [16]. The authors propose a mechanism by which amyloidogenic SNCA forms a seed that then primes tau to acquire a conformational change allowing its polymerization. In support of this seeding mechanism is a finding by Yagi and colleagues [17] that the amyloid fibril formation of SNCA is enhanced by the preformed amyloid seeds of other proteins. Additional support comes from data demonstrating the co-localization of epitopes of tau and SNCA in Lewy bodies in some neurons [18] as well as the co-localization of Aβ and tau in neurofibrillary tangles and extracellular Aβ deposits (reviewed in [19]). Of particular clinical relevance is that interfering with this seeding process could impact the aggregation of multiple pathogenic proteins and, hopefully, impact the clinical progression of disease.

In summary, the study by Clinton and colleagues is a good example of how animal models studied in parallel with their human diseases can be complementary and provide novel information about the mechanisms of the disease process. In addition, such a model may provide opportunities for screening therapeutic interventions and validating diagnostic tests that could be useful for a number of closely related neurodegenerative diseases.

Abbreviations

Aβ, amyloid beta; AD, Alzheimer disease; AD-LBV, Alzheimer disease-Lewy body variant; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTDP-17, frontotemporal dementia with Parkinsonism-chromosome 17; PD, Parkinson disease; PDD, dementia in Parkinson disease; SNCA, alpha-synuclein.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

This work was supported in part by the US Department of Veterans Affairs, Office of Research and Development Clinical R&D Program, and National Institutes of Health grants 2P50AG005136-27 and 1P50NS062684-01A1.

Author details

[1]Mental Illness Research Education and Clinical Center, Veterans Administration Puget Sound Health Care System, 1660 South Columbian Way, Seattle, WA, 98108, USA. [2]Department of Psychiatry and Behavioral Sciences, University of Washington, 1959 N.E. Pacific Street, Seattle, WA, 98195, USA. [3]Parkinson Disease Research Education and Clinical Center, Veterans Administration Puget Sound Health Care System, 1660 South Columbian Way, Seattle, WA, 98108, USA. [4]Department of Neurology, University of Washington, 1959 N.E. Pacific Street, Seattle, WA, 98195, USA.

Published: 17 September 2010

References

1. Hamilton RL: **Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry.** *Brain Pathol* 2000, **10:**378-384.
2. Lippa CF, Fujiwara H, Mann DM, Giasson B, Baba M, Schmidt ML, Nee LE, O'Connell B, Pollen DA, St George-Hyslop P, Ghetti B, Nochlin D, Bird TD, Cairns NJ, Lee VM, Iwatsubo T, Trojanowski JQ: **Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes.** *Am J Pathol* 1998, **153:**1365-1370.
3. Leverenz JB, Fishel MA, Peskind ER, Montine TJ, Nochlin D, Steinbart E, Raskind MA, Schellenberg GD, Bird TD, Tsuang D: **Lewy body pathology in familial Alzheimer disease: evidence for disease- and mutation-specific pathologic phenotype.** *Arch Neurol* 2006, **63:**370-376.
4. Lashley T, Holton JL, Gray E, Kirkham K, O'Sullivan SS, Hilbig A, Wood NW, Lees AJ, Revesz T: **Cortical alpha-synuclein load is associated with amyloid-beta plaque burden in a subset of Parkinson's disease patients.** *Acta Neuropathol* 2008, **115:**417-425.
5. Pletnikova O, West N, Lee MK, Rudow GL, Skolasky RL, Dawson TM, Marsh L, Troncoso JC: **Abeta deposition is associated with enhanced cortical alpha-synuclein lesions in Lewy body diseases.** *Neurobiol Aging* 2005, **26:**1183-1192.
6. Alves G, Brønnick K, Aarsland D, Blennow K, Zetterberg H, Ballard C, Kurz MW, Andreasson U, Tysnes OB, Larsen JP, Mulugeta E: **CSF amyloid-{beta} and tau proteins, and cognitive performance, in early and untreated Parkinson's Disease: the Norwegian ParkWest study.** *J Neurol Neurosurg Psychiatry* 2010 Jun 14. [Epub ahead of print].
7. Montine TJ, Shi M, Quinn JF, Peskind ER, Craft S, Ginghina C, Chung KA, Kim H, Galasko DR, Jankovic J, Zabetian CP, Leverenz JB, Zhang J: **CSF Abeta(42) and tau in Parkinson's disease with cognitive impairment.** *Mov Disord* 2010 Sep 3 [Epub ahead of print].
8. Wills J, Jones J, Haggerty T, Duka V, Joyce JN, Sidhu A: **Elevated tauopathy and alpha synuclein pathology in postmortem Parkinson's disease brains with and without dementia.** *Exp Neurol* 2010, **225:**210-218.
9. Kraybill ML, Larson EB, Tsuang DW, Teri L, McCormick WC, Bowen JD, Kukull WA, Leverenz JB, Cherrier MM: **Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both.** *Neurology* 2005, **64:**2069-2073.
10. Siderowf A, Xie SX, Hurtig H, Weintraub D, Duda J, Chen-Plotkin A, Shaw LM, Van Deerlin V, Trojanowski JQ, Clark C: **CSF amyloid beta 1-42 predicts cognitive decline in Parkinson's disease.** *Neurology* 2010 Aug 18. [Epub ahead of print].
11. Motter R, Vigo-Pelfrey C, Kholodenko D, Barbour R, Johnson-Wood K, Galasko D, Chang L, Miller B, Clark C, Green R, Olson D, Southwick P, Wolfert R, Munroe B, Lieberburg I, Seubert P, Schenk D: **Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease.** *Ann Neurol* 1995, **38:**643-648.
12. Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H, Pirttila T: **Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain.** *Arch Neurol* 2009, **66:**382-389.
13. Kester MI, van der Vlies AE, Blankenstein MA, Pijnenburg YA, van Elk EJ, Scheltens P, van der Flier WM: **CSF biomarkers predict rate of cognitive decline in Alzheimer disease.** *Neurology* 2009, **73:**1353-1358.
14. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ, Alzheimer's Disease Neuroimaging Initiative: **Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects.** *Ann Neurol* 2009, **65:**403-413.
15. Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM: **Synergistic interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline.** *J Neurosci* 2010, **30:**7281-7289.
16. Lee VM, Giasson BI, Trojanowski JQ: **More than just two peas in a pod: common amyloidogenic properties of tau and alpha-synuclein in neurodegenerative diseases.** *Trends Neurosci* 2004, **27:**129-134.
17. Yagi H, Kusaka E, Hongo K, Mizobata T, Kawata Y: **Amyloid fibril formation of alpha-synuclein is accelerated by preformed amyloid seeds of other proteins: implications for the mechanism of transmissible conformational diseases.** *J Biol Chem* 2005, **280:**38609-38616.
18. Ishizawa T, Mattila P, Davies P, Wang D, Dickson DW: **Colocalization of tau and alpha-synuclein epitopes in Lewy bodies.** *J Neuropathol Exp Neurol* 2003, **62:**389-397.
19. Armstrong RA, Lantos PL, Cairns NJ: **What determines the molecular composition of abnormal protein aggregates in neurodegenerative disease?** *Neuropathology* 2008, **28:**351-365.

doi:10.1186/alzrt50
Cite this article as: McMillan PJ, Leverenz JB: **From model system to clinical medicine: pathophysiologic links of common proteinopathies.** *Alzheimer's Research & Therapy* 2010, **2:**26.