[Frontiers in Bioscience 8, s223-227, May 1, 2003]

FROM LEWY BODY DISEASE TO ALZHEIMER'S DISEASE: HYPOTHESIS AND EVIDENCE

Deng-Shun Wang

Department of Neuropathology, Mayo Clinic Jacksonville, Jacksonville, FL 32224

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. General Hypothesis
3.1. Hypothesis 1 and supporting arguments: NFT-like structure should have some kind of morphologically visible pre-lesion(s)
3.2. Hypothesis 2 and supporting evidence: there should be substantial overlapping between LB and NFT in terms of major biochemical compositions
3.3. Hypothesis 3 and supporting evidence: α-synuclein is the earlier aggregated component than tau for the formation of LB
3.4. Hypothesis 4 and supporting evidence and arguments: NP may be the outcome resulted from the process of clearing dead neurons with LB/NFT by glial cells
3.5. One more argument to support the current hypothesis
4. Discussion and conclusion
5. Acknowledgement
6. References

1. ABSTRACT

The mechanisms underlying Alzheimer's disease and Lewy body disease have long been a controversial subject among neurologists and neuropathologists. Here, we hypothesize that three most common histopathological structures, Lewy body (LB), neurofibrillary tangle (NFT) and neuritic senile plaque (NP) found in neurodegenerative diseases are different stages of the same lesion. Lewy body disease (LBD) and Alzheimer's disease (AD) are based on a similar or the same pathogenic mechanism. Different clinical manifestations and pathological features found in postmortem brains between LBD and AD is due to the different intensities of initial insults, rate of the disease progression and temporal involvement of different brain regions during the AD development.

2. INTRODUCTION

Alzheimer's disease (AD) and Lewy body disease (LBD) are two major categories of neurodegenerative diseases and together account for more than 95% of dementia. Although enormous efforts have been made to investigate these two diseases and several theories about AD pathogenesis have been proposed in the last several decades, the relationship between AD and LBD as well as the pathogenic mechanisms underlying these two diseases have remained unclear (1).

Under the current diagnostic criteria, AD and LBD share significant pathological and clinical features (2) (3) (4) (5). At the same time, as many as 70% of AD cases have LB (6) (7). These facts imply that AD and LBD may share substantial pathogenic mechanisms, or that they may represent different stages of AD.

3. GENERAL HYPOTHESIS

Diagnostic morphological features of LBD (Lewy bodies) and AD (NFT and NP) indicate different developmental stages of the same structure beginning with Lewy body and ending with NP. NFT is the transitional stage between LB and NP.

LBD and AD are based on similar or the same pathogenic mechanisms and are the different subtypes of the disease determined by the intensity of the initial insult and the heterogeneity of individual reactions. The different clinical symptoms of LBD and AD might be due to the insult and the rate of progression of the disease. LBD is a more progressive type or malignant AD compared to typical AD.

3.1. Hypothesis 1 and supporting arguments: NFT-like structure should have some kind of morphologically visible pre-lesion(s)

Morphologically, LB is a very well organized structure that has a "younger" looking appearance. In chronic state, these structures ultimately lose their organization and order. On the other hand, NFT has an "older" looking appearance compared to LB. Considering the lengthy process of AD, formation of NFT must take some time and should have some kind of pre-lesional attribute before reaching the typical NFT stage. So far,

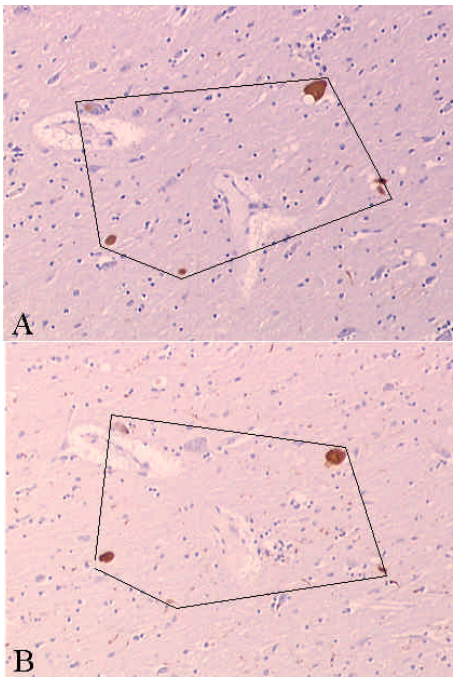

Figure 1. Both α-synuclein and tau are the components of LB. Serial sections of paraffin-embedded LBD brain tissue were immunostained with NACP98 polyclonal antibody to α-synuclein (A) and CP13 monoclonal antibody against tau (B). In this field, there are five LB were stained by both antibodies and imply that LB containing both α-synuclein and tau is a common feature for LB structure.

there is no identified pre-lesional attribute for NFT. Because LB is the most common pathological structure that co-exists with NFT, it is plausible that LB represents an earlier stage or pre-lesional form of NFT.

3.2. Hypothesis 2 and Supporting Evidence: There should be substantial overlapping between LB and NFT in terms of major biochemical compositions

If hypothesis 1 holds up, it can be expected to see overlapping and transitional pictures at the molecular levels. Because α-synuclein and tau have been widely accepted as the immunohistochemical marker to identify LB and NFT respectively in neuropathology, the immediate hypothesized picture will be that there should be co-existing α-synuclein and tau in at least some LBs. To prove it, serial sections from paraffin-embedded brain tissues were immunostained with polyclonal anti-α-synuclein antibody NACP98 and monoclonal anti-tau antibody CP-13. The results proved that α-synuclein and tau do co-exist in LBs (Figure 1).

3.3. Hypothesis 3 and Supporting Evidence: a -synuclein is an earlier aggregated component for the formation of LB rather than tau

If LB is the pre-lesion of NFT, then the major component of LB, α-synuclein should be one of the major components to form the "core" of LB followed by the aggregation of tau around it. Findings from α-synuclein and tau immunostaining with NACP98 and CP-13 antibodies on the serial sections of brain with LBD seems easily prove to this concept. Figures 2 and 3 showed that α-synuclein stained by NACP98 antibody located in the center of the Lewy body and the ring-like structure formed by tau detected with CP-13 antibody wrapping around the α-synuclein positive core. Later double staining with different anti-tau and α-synuclein antibodies performed in our group also confirmed this kind of distributions of tau and α-synuclein in the Lewy body/NFT like structures (unpublished data). It strongly supports the premise that aggregation of α-synuclein may be a prelude to tau aggregation during the formation of LB/NFT-like structures, although the possibility that other biological molecules may be seeding for the initiation of α-synuclein aggregation cannot be excluded at this time.

3.4. Hypothesis 4 and Supporting Evidence and arguments: NP may be the outcome resulting from the process of clearing dead neurons with LB/NFT by glial cells and proteases

Tau-positive neuritic components in NP largely come from glial cells. Amyloid components in NP may come from intraneuronal, glial cells and sera. Non-neuritic plaques can be non-specific deposits of β-amyloid that can result from various stimulations to human brains. If NP indeed come from the evolution of LB and NFT, it will be possible to detect residual α-synuclein in NP although the chances are relative low because the volume of each individual NP is much larger than the α-synuclein-rich core that has been "absorbed" and condensed during the LB-NFT morphogenesis. To prove this hypothesis, paraffin-embedded AD brain sections were stained with NACP98 and CP-13 antibody. As expected, a residual core-like α-synuclein positive staining can been seen in an apparently NP-like structure (Figure 4A), and tau showed a more extensive, neuritic-like staining pattern (Figure 4B). This hypothesis will also help to explain the contradictory results about the existence of α-synuclein in NP from different research groups (8, 9).

3.5. One more argument to support the current hypothesis

One question need to be answered is how to explain different clinical manifestations between LBD and AD based on this proposed hypothesis, i.e. LBD and AD are the different stages/forms of the same disease. Typically, LBD and AD have some "characteristic" clinical symptoms to help the clinical differential diagnosis. For example, patients with LBD but not AD usually show hallucination. To explain this phenomenon, it should be realized that the human brain actually is comprised of functionally multiple organs instead of a single organ as it is materially. Pathogenic processes of AD can initiate from any locations of brain at different progressive rates depending upon the initial impact locations, intensities of causative impact or agents and the individual difference of patients, etc. At the certain stage, patients can present various clinical symptoms due to the different temporal and geographic combinations of involved brain regions and the intensities. Hallucinations occurring usually in LBD patients may result from the more progressive disease

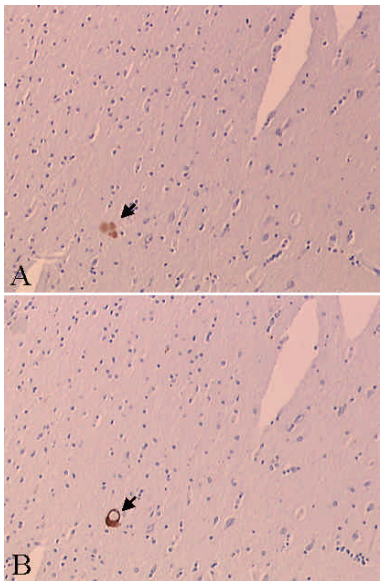

Figure 2. α-synuclein is the core of LB and tau forms a ring-like structure to wrap around α-synuclein-positive core. Serial sections from paraffin-embedded LBD brains were stained with NACP98 polyclonal anti-α-synuclein antibody (A) and CP13 monoclonal anti-tau antibody (B). One of three α-synuclein-positive structures (↓) in figure 2A was clearly wrapped around by a tau-positive ring-like structure (↓) in figure 2B. It suggests that α-synuclein may form aggregates before abnormal tau does for the formation of LB.

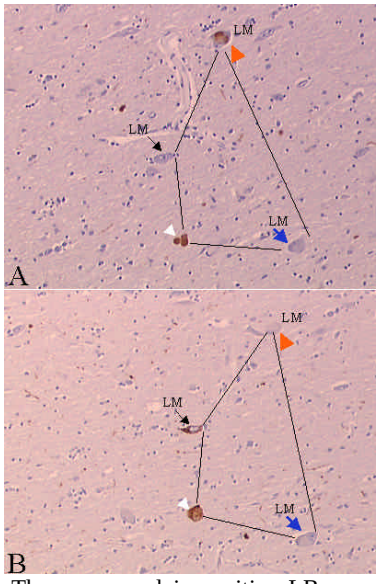

Figure 3. Three α-synuclein positive LBs were wrapped around by tau-positive nets. Serial sections from paraffin-embedded human LBD brains were immunostained with NACP98 anti-α-synuclein polyclonal antibody (A) and CP13 anti-tau monoclonal antibody (B). Three landmarks (LM) were labeled with three paired arrows or arrowheads. White arrowhead in (A) and (B) indicate three α-synuclein positive LBs and tau-positive regions around them respectively.

process and more extensive involvement of multiple brain regions within a shorter time frame. Patients with classical AD progress at a slower speed that may not result in some symptoms that are generated from certain multiple affected regions in that same time frame.

4. DISCUSSION AND CONCLUSION

It is very important for us to notice that most published data on AD from human subjects so far are obtained from postmortem brains. This is particularly true for biochemical and morphological data. Most material, if not all used in those studies, were from subjects with end or very late stage AD in terms of pathogenesis, even for brains with lower Braak stages (10). From the molecular pathogenic point of view, AD has been implanted into the brain once there are any NFT or NP formed in it. Higher Braak stages can only represent that the same or similar pathogenic processes have been undertaken or repeated in more areas of brain that will eventually lead to the clinical end stage of AD.

Based on the hypothesis and supporting data presented in this paper, it can be argued that the formation of α-synuclein-rich aqueous boundless structure (pale body?) may be an earlier stage of LB. After the initial deposition of aggregated tau around α-synuclein-rich aqueous structure, typical LB is gradually formed. With the further deposition of abnormally aggregated tau around LB and the gradual degradation of α-synuclein, tangle is gradually formed (Figure 5). With the morphological development, intracellular tangles are transforming into extracellular tangles while neuronal membrane is breaking down. At the final stage of the morphogenesis, PHF tau and other aggregated protein filaments are gradually broken down by proteases followed by the deposition of β-amyloid from microglia and possibly serum to form a no-organized structure, i.e. neuritic plaques, although there is a possibility that some amyloid deposition may occur earlier parallel to the morphogenesis from LBs to tangles.

Based on the hypothesis of the morphological evolution for LB, NFT and NP, the next natural hypothesis will be that patients who died of "LBD" are due to the more extensive and more aggressive reactions to the initial causative insulting to the brain compared to AD mixed with LBD or classical AD (Figure 6). Lewy body-like changes are spread over multiple brain regions within a relative shorter period of time. Because LBD patients usually die within 2-3 years, there is no enough time for Lewy bodies to go through the morphological changes into tangles or neuritic plaques and large portion of Lewy-bodies are still in the early stage of morphogenesis and manifested as "Lewy body disease" brain at the time of the death. Patients who die of classical AD have slower and less extensive reactions to the initial causative insulting to the brain and can survive as long as 20 years from the time of initial clinical AD diagnosis. In these patients, Lewy body formation happens at a much slower rate and in a much smaller population of neurons over a certain time frame. These Lewy bodies usually go through a lengthy process to evolve into NFT and finally NP. Because only a very small

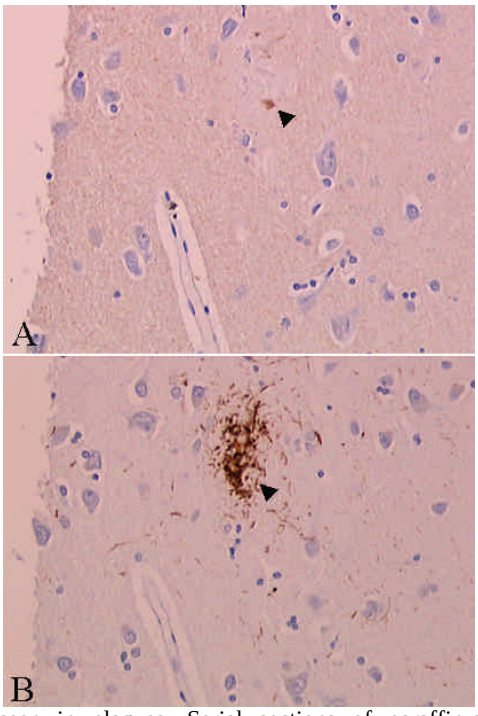

Figure 4. Residual α-synuclein can be seen in plaques. Serial sections of paraffin-embedded LB brain tissue were immunostained with NACP98 anti-α-synuclein antibody (A) and CP13 anti-tau antibody (B). Positive α-synuclein staining (arrowhead in figure 4A) co-localized with plaque labeled with anti-tau antibody (figure 4B).

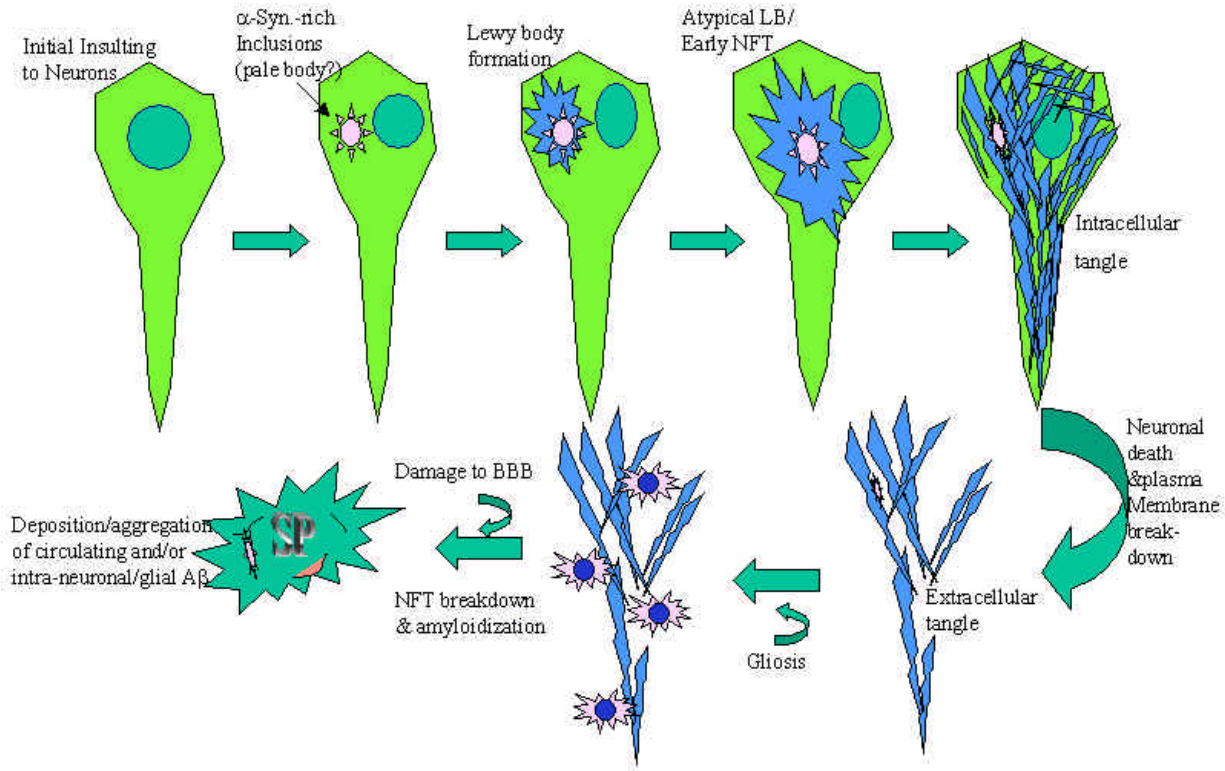

Figure 5. Proposed sequential events for the morphogenesis from Lewy Body (LB), neurofibrillary tangle (NFT) and neuritic plaques (NP). See text for details.

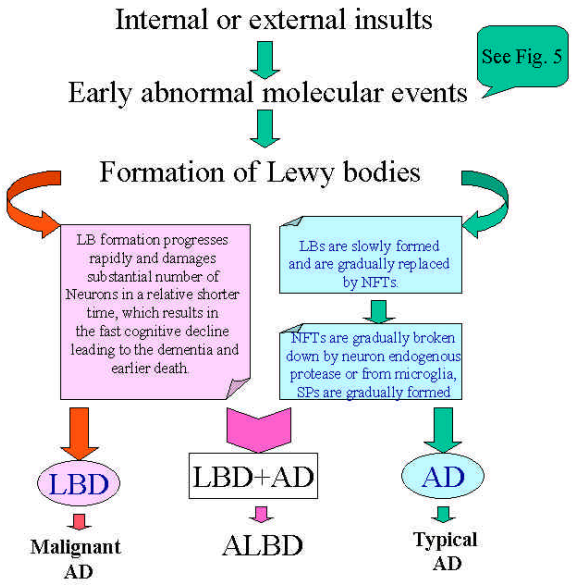

Figure 6. Proposed different clinical pictures of AD. See text for details.

number of neurons are involved in the disease process at the certain temporal time, the majority of Lewy bodies had undergone the morphological changes and become NFT and NP. So the diagnosis established on the findings in these postmortem brains will be “classical” AD. For those cases fallen between “classical LBD” and “classical AD”, more complicated histopathological pictures such as significant number of co-existed LB, NFT and NP will be found in postmortem brains and usually are diagnosed as AD mixed with LBD by neuropathologist.

5. ACKNOWLEDGEMENT

My sincere thanks go to Dr. Dennis W. Dickson for his critical reading and suggestions during the writing of this manuscript and his generous support for those experiments done in his laboratory. My thanks also go to Ms. Natalie Cookson, Virginia Phillips, Linda Rousseau for their wonderful technical help and Ms. Marten, Beth A. and Mr. Michael De Lucia for their proof reading of the final version of this manuscript.

6. REFERENCE

1. Hansen L. A. & W. Samuel: Criteria for Alzheimer's disease and the oncology of dementia with Lewy bodies. Neurology 48(1): 126-32 (1997)

2. Dickson D.W, P. Davies, R. Mayeux, H. Crystal, D.S. Horoupian, A. Thompson & J.E. Goldman: Diffuse Lewy body disease. Neuropathological and biochemical studies of six patients. Acta Neuropathol 75(1): 8-15 (1987)

3. Ditter, S. M. & S. S. Mirra: Neuropathologic and clinical features of Parkinson's disease in Alzheimer's disease patients. Neurology 37(5): 754-60 (1987)

4. Hansen L, D. Salmon, D. Galasko, E. Masliah, R. Katzman, R. DeTeresa, L. Thal, M.M. Pay, R. Hofstetter & M. Klauber: The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. Neurology 40(1): 1-8 (1990)

5. Revesz T, J.L. McLaughlin, M.N. Rossor & P.L. Lantos: Pathology of familial Alzheimer's disease with Lewy bodies. J Neural Transm Suppl 51: 121-35 (1997)

6. Kazee, A. M. & L. Y. Han: Cortical Lewy bodies in Alzheimer's disease. Arch Pathol Lab Med 119(5): 448-53 (1995)

7. Lippa C.F, D. Pulaski-Salo, D.W. Dickson & T.W. Smith: Alzheimer's disease, Lewy body disease and aging: a comparative study of the perforant pathway. J Neurol Sci 147(2): 161-6 (1997)

8. Ueda K, H. Fukushima, E. Masliah, Y. Xia, A. Iwai, M. Yoshimoto, D.A. Otero, J. Kondo, Y. Ihara & T. Saitoh. Molecular cloning of cDNA encoding an unrecognized component of amyloid in Alzheimer disease. Proc Natl Acad Sci U S A 90(23): 11282-6 (1993)

9. Culvenor J.G, C.A. McLean, S. Cutt, B.C. Campbell, F. Maher, P. Jakala, T. Hartmann, K. Beyreuther, C.L. Masters & Q.X. Li: Non-Abeta component of Alzheimer's disease amyloid (NAC) revisited. NAC and alpha-synuclein are not associated with Abeta amyloid. Am J Pathol 155(4): 1173-81 (1999)

10. Braak, H. & E. Braak: Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. Neurobiol Aging 18(4 Suppl): S85-8 (1997)

Key Words: Alzheimer’s disease, Lewy Body, Amyloid, α-Synuclein, Tau

Send correspondence to: Dr Deng-shun Wang, Department of Neuropathology, Mayo Clinic Jacksonville, Jacksonville, FL 32224, Tel: 904-953-2231, Fax: 904-953-7117, E-mail: Wang.Dengshun@mayo.edu