Dementia: Who is at risk?
Identification of Aβ subtypes in DLB and PDD

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Aims

This pilot study investigated the pathological burden of amyloid beta plaques (Aβ) and amyloid beta plaquepyroglutamylated s (Aβ3(pE)-42) in cases of Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), to ascertain if a difference in levels of Aβ3(pE)-42 can be detected between DLB and PDD. I also investigated the relationship between α synuclein (α- syn) and Aβ3(pE)-42 pathology.

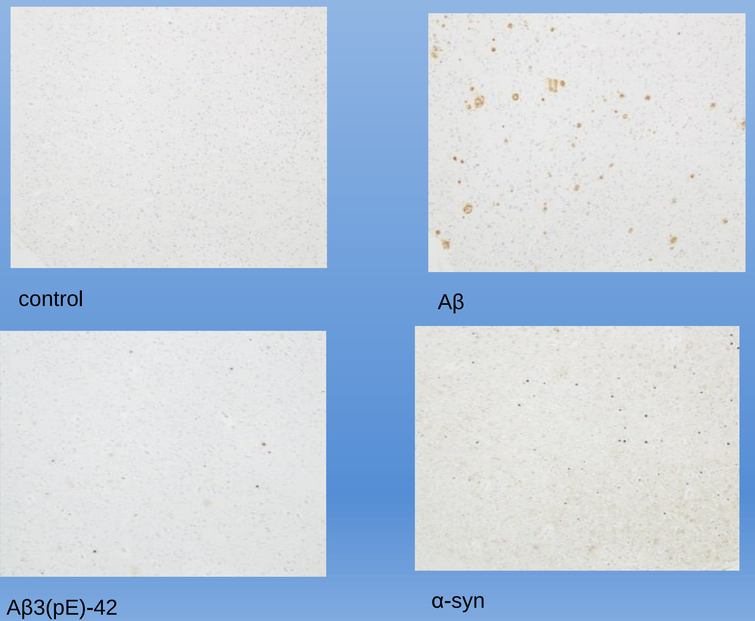

Fig 1: Showing screen shots of various protein aggregations in brain tissue at x40. Note that the plaques are much more in Aβ than in other samples, and plaques in the control are minimal.

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Introduction

DLB and PDD are classified as Lewy body diseases (LBD), and typically occur in older individuals. At present, the major difference between them is age of onset and temporal course of dementia. In DLB, dementia occurs concomitantly or before Parkinsonism, while in PDD, dementia occurs at least a year after. LBD's are clinically characterized by Parkinsonism, visual hallucinations, visuospatial and cognitive impairment, and the involvement of cortical neurons probably through secondary synapse dysfunction. Concomitant pathologies are often seen in LBD's, particularly Alzheimer-type pathologies. With increasing age, mostly over the age of 80, more people are presenting with multimorbidities, such that in post mortem brains, the presence of a single disease is rare. Aβ3(pE)-42, is a post-translational modification of Aβ, and is said to be more toxic than Aβ. It has been found that pyroglutamylaton increases aggregation of both Aβ3(pE)-42 and Aβ. Several clinicopathologic studies of PDD have found that increased levels of Aβ may lead to faster onset of dementia. Previous studies have also indicated that Aβ may be more common in DLB than in PDD, thus including an additional distinction between the two disease types.

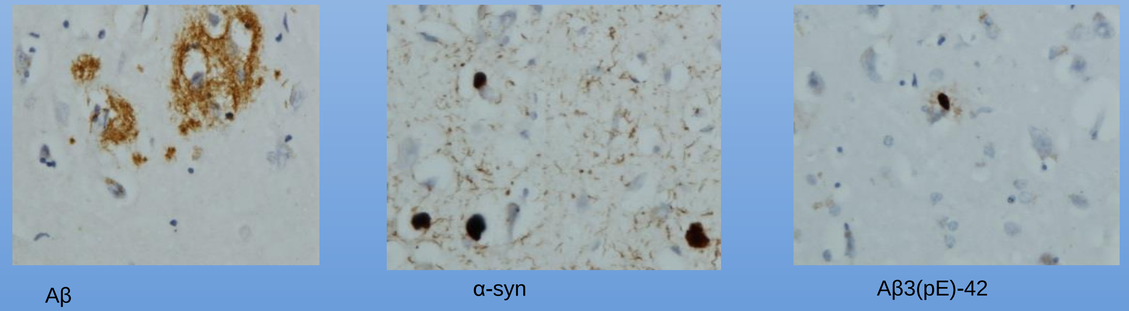
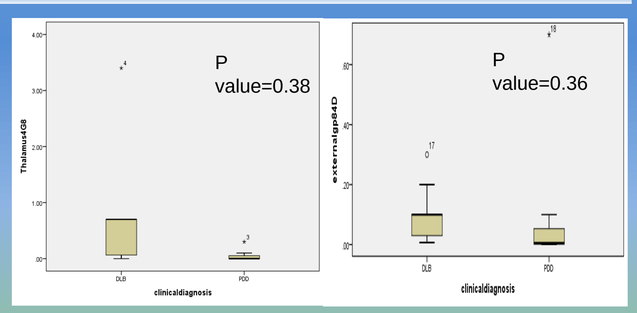


Fig 2: Showing extracellular Aβ plaques, neurofibrillary tangles in α-syn and intracellular plaques in Aβ3(pE)-42 .

Results

- There were more Aβ plaques in DLB than in PDD, as seen in the thalamus.
- In the external globus pallidus, there was a significantly higher amount of Aβ3(pE)-42 pathology in DLB than in PDD cases.
- Aβ3(pE)-42 significantly predicted αsyn in the entorhinal cortex, thalamus and external globus pallidus.
- No correlation between Aβ3(pE)-42 and αsyn in DLB cases.



Graph 1: Showing that in there is significantly more Aβ pathology in thalamus of DLB samples than in PDD samples, and there is more Aβ3(pE)-42 pathology in external gp of DLB samples than in PDD samples

Methods

- 20 post-mortem brains were used in this study
- Punches from 40 areas of the brain were collected, due to their importance in the diagnosis of the disease.
- These punches were then put together in a recipient Tissue microarray (TMA) block. Sections were then cut and immunohistochemistry was performed on the slides.
- Slides were viewed using a microscope and image acquisition and analysis was performed.

Conclusion

- ❖The effects of Aβ3(pE)-42 may be more severe in PDD than in DLB and may account for the difference in timing of presentation of motor dysfunction between the two cases.
- ❖This result, if verified with more cases, could lead to the development of an additional imaging technique, based on relative levels of Aβ3(pE)-42, to distinguish DLB from PDD, giving rise to more accurate clinical diagnosis.
- ❖Aβ3(pE)-42 could be an important protein to investigate clinical phenotypes of neurodegenerative diseases.
- ❖This is a pilot study, and further research needs to be carried out, to affirm the reasons and significance of the results obtained

References:
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Mandler, M., Walker, L., Santic, R., Hanson, P., Upadhaya, A. R., Colloby, S. J., Morris, C. M., Thal, D. R., Thomas, A. J., Schneeberger, A., and Attems, J. (2014) Pyroglutamylated amyloid-beta is associated with hyperphosphorylated tau and severity of Alzheimer's disease. *Acta Neuropathol* 128, 67-79