Neuropathology in Dementia with Lewy Bodies

Marima Kauser, 160722169,
School of Biomedical Sciences,
m.kauser@Newcastle.ac.uk

Newcastle University

NHS National Institute for Health Research

Introduction

The Lewy body disease (LBD) spectrum consists of Parkinson's disease (PD), Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB).

LBD is the second most common form of neurodegenerative dementia[1].

LBDs are characterised by the accumulation of a protein called alpha-synuclein (α-syn).

The amount of α-syn detected in post-mortem brain tissue does not correlate to the severity or distinction of the LBD.

There are different types of α-syn, which possess different properties and vary in toxicity[2].

Truncated forms of α-syn are associated with accelerated disease progression[2].

The presence of tau pathology is believed to influence α-syn aggregation. LBDs are often investigated by stains that show all α-syn present and therefore do not differentiate between individual types[2].

Aims

❖ The use of a new technique to investigate different types of α-syn in post-mortem brain tissue.

❖ Relate the forms of α-syn detected with symptoms experienced by patients.

❖ Identify particular strains of α-syn as potential biomarkers for diagnosis or future therapies.

Staining Patterns

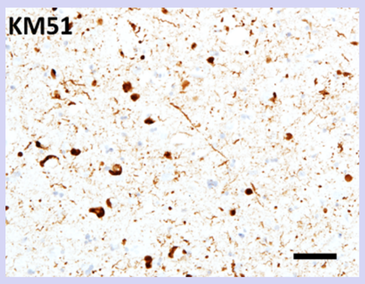

Figure 1a. Image of KM51* stained section taken on 20x magnification.

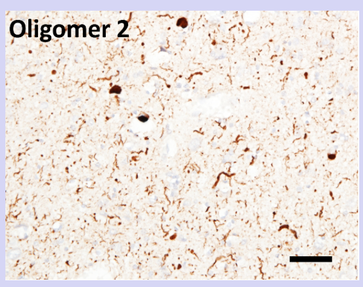

Figure 1b. Image of α-syn oligomer 2 stained section taken on 20x magnification. α-syn oligomer 2 was detected more than any other a-syn including KM51*.

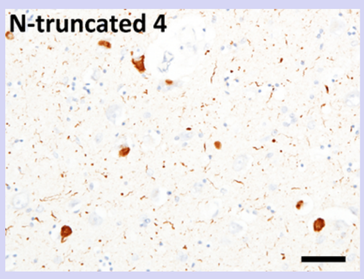

Figure 1c. Image of N-truncated α-syn 4 stained section taken on 20x magnification.

Figures 1a-c. depict the different patterns of staining observed against the antibodies for oligomeric and truncated α-syn species across the LBD cases. The scale bar on each image is 50μm.
Antibodies were visualised with the use of histological techniques and then quantitatively analysed for immunoreactivity.
*KM51 is the typical diagnostic antibody used for all α-syn.
Quantitative hierarchy of α-syn detected (α-syn oligomer 2>KM51>N-truncated α-syn 4).

Immunoreactivity

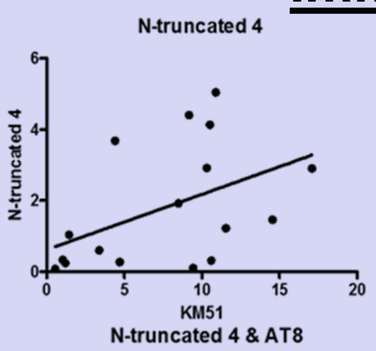

Figure 2a. Graph to model the significant positive correlation between N-truncated α-syn 4 and KM51 (rs=0.493, p=0.045). KM51 is the current diagnostic antibody used which detects all α-syn.

Figure 2b. Graph expressing the significant positive correlation between N-truncated α-syn 4 and AT8 (rs=0.581. p=0.014). AT8 is the current tau diagnostic antibody used. Tau proteins form tangles and are a hallmark of Alzheimer's disease.

The graphs in *figures 2a-b* evaluate the relationship between truncated a-syn antibodies and diagnostic α-syn antibody KM51, and tau expression with diagnostic antibody AT8. The relationships shown indicate that N-truncated α-syn 4 interacts with both tau and a-syn and may be involved in their putative relationship.

Phenotypic importance

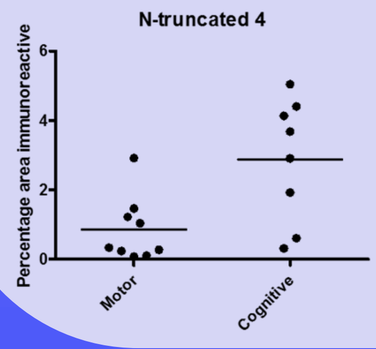

Figure 3. Graph expressing the significant phenotypic difference in N-truncated α-syn 4 levels (U=11, p=0.016). The cohort was split into cases with a motor presentation (PD/PDD) and cases with a cognitive presentation (DLB and mixed DLB/AD). N-truncated α-syn 4 levels were 337.89% higher in cases with a cognitive presentation.

Discussion

The greater burden of pathology detected by α-syn oligomer 2 in comparison to KM51 may be attributed to antibody conformation as α-syn aggregation can alter the recognition sites, preventing it from being as readily detected.

N-truncated α-syn 4 was the only antibody which correlated with both KM51 and tau, indicating it may be a mediator in the relationship between a-syn and tau. This is further supported by increased N-truncated α-syn 4 levels in DLB/mixed DLB in which tau is present.

The sample size used was 17, this is too small for the results to be generalised onto the population, warranting a further more comprehensive study with at least 100 cases.

Conclusion

❖ The results are a positive indicator towards the use of N-truncated α-syn 4 being used as a future diagnostic marker for DLB/ mixed DLB.

❖ Further research into N-truncated α-syn 4's interaction between tau and α-syn is required in order to determine it's use for future therapies.

❖ A larger, more comprehensive study is required with at least 100 cases including different sections of the brain along with clinical data in order to correlate the quantity of truncated α-syn pathology with specific clinical symptoms.

References

1. Attems J, Jellinger KA. Neuropathology. Oxford textbook of old age psychiatry. 2013; 2:87-105.
2. Vaikath, N., et al. Heterogeneity in a-syn sub types and their expression in cortical brain tissue lysates from Lewy body diseases and Alzheimers disease. Under review for Neuropathology and Applied Neurobiology.