Can early hyperphosphorylated tau depositions in mixed Alzheimer's disease and Lewy body disease give insights into disease progression?

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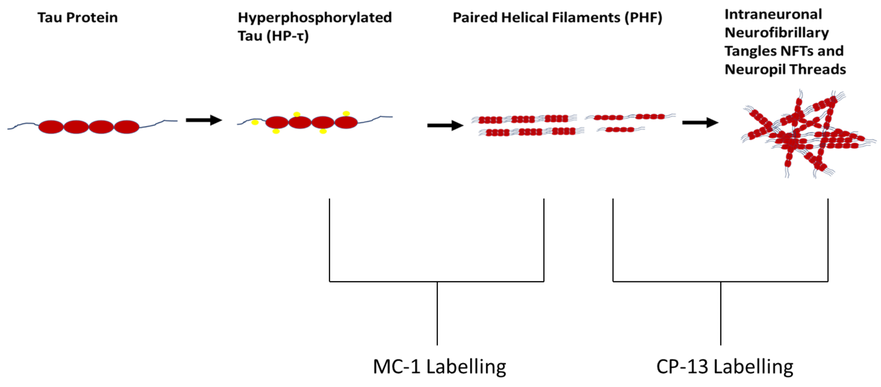
Introduction

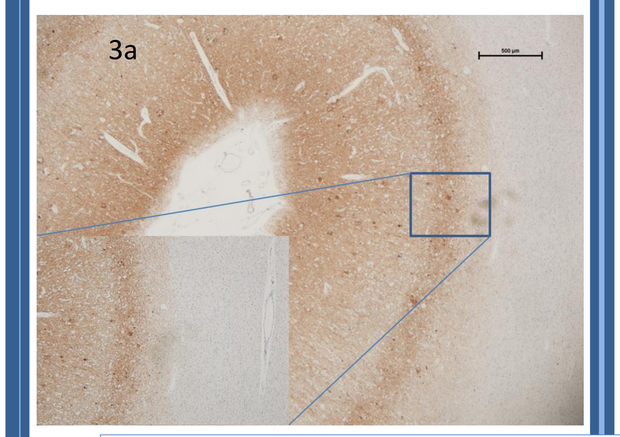
Dementia is a disease characterized by progressive memory loss and deterioration of behavior and mental function.
People with dementia are often affected by multiple pathologies like Alzheimer Disease (AD) and Lewy Body Disease (LBD), however in order to be considered mixed AD/LBD, the symptoms and neuropathological features need to fulfil the criteria of both AD and LBD. It is difficult to distinguish clinically between mixed AD/LBD and pure AD or LBD as the symptoms of one pathology are often masked by the symptoms of the other one. LBD is distinguished into cognitive (dementia with Lewy bodies, DLB) and motor (Parkinson's disease dementia, PDD) presentations(1).
The neuropathological features of AD are neurofibrillary tangles (NFTs), neuropil threads (NTs), neuritic plaques and extracellular depositions of amyloid. Whereas, LBD is characterized by Lewy Bodies which are abnormal depositions of the protein α-synuclein that disrupts the normal function of neurons.
In this study a set of cases that were neuropathologically classified as mixed AD/DLB because they fulfilled neuropathological criteria for both AD and DLB, were used to observe, with quantitative methods, the amount of HP- τ present in temporal cortex, which can give insight into the disease progression. Clinically, a proportion of these cases were diagnosed as AD (cAD), whereas others were diagnosed as DLB (cDLB) or PDD (cPDD).

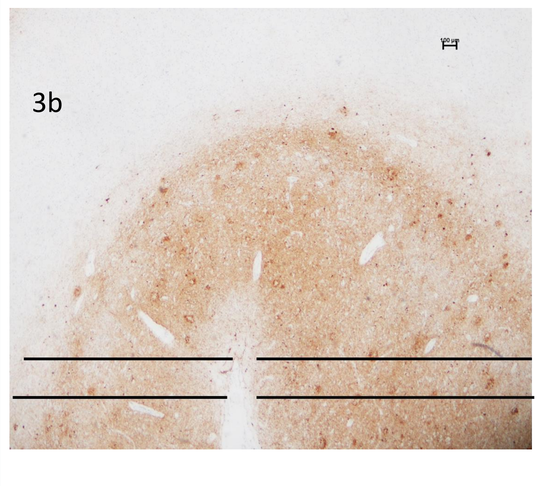


The figure 1: The pathological progression of the microtubule associated tau protein.
The tau protein becomes hyperphosphorylated forming hyperphosphorylated tau (HP-τ). The formation of insoluble paired helical filaments (PHF) is promoted by the self-aggregation of HP-τ. Whereas the self-aggregation of PHF leads to the formation of intracellular neurofibrillary tangles (NFT) and Neuropil threads (NTs). Pre-NFTs can be labelled using the antibody MC-1, detecting early conformational changes of HP-τ. MC1 is an early stage marker of the HP-τ pathology.
The antibody CP-13 labels HP-τ in pre-NFTs and intraneural NFTs. CP13 detects HP-τ conformations proceeding those detected by MC1. These two markers allow to illustrate the progression of tau-pathology present in cAD, cDLB and cPDD.

Methods and Materials

Post-mortem brain tissues from 31 donors (Mean age 78.64 SE: 7.2± years; female 14; mixed AD/DLB 21; AD 5; DLB 5) were collected from the Newcastle Brain Tissue Resource (NBTR). The neuropathological diagnoses of these donors were mixed AD/DLB, AD and DLB.
Fixed regions were taken from the temporal cortex and they were immunolabelled with antibodies MC1 and CP13.
Quantification of total immunopositivity for each MC1 and CP13 staining was calculated as a percentage area of each region of interest using standardized thresholds to include immunopositive structures using JVC 3-chip CCD true colour camera mounted on Zeiss Axioplan 2 bright field microscope and Infinity Capture Software (MediaCybernetics).





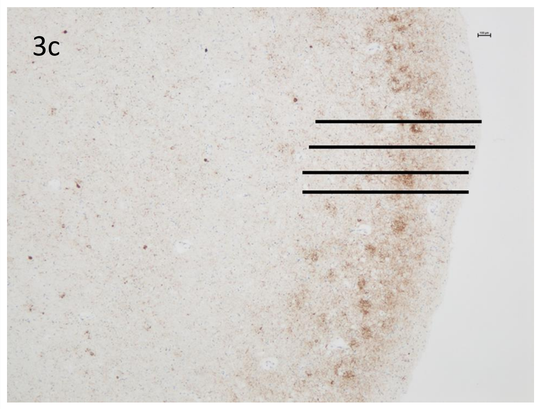


Figure 3:
For each case, between 4 – 8 pictures were taken from 3 regions indicating the gyrus (3c) and 3 regions showing the sulcus (3b). The region of interests is indicated, in the pictures, by the black lines. A section of the region of interest is highlighted in 3a.

Results

Study Number	Clinical Diagnosis	Neuropathological diagnosis	Age	Sex	Post Mortem Delay	Disease Duration (Years)
1	AD	Mixed AD/LBD	88	F	84	15
2	AD	Mixed AD/LBD	62	M	28	8
3	AD	Mixed AD/LBD	77	F	51	7
4	AD	Mixed AD/LBD	82	M	26	11
5	AD	Mixed AD/LBD	83	M	5	9
6	AD	Mixed AD/LBD	71	M	17	6
7	AD	Mixed AD/LBD	84	F	26	10
8	AD	Mixed AD/LBD	94	F	31	17
9	AD	Mixed AD/LBD	71	F	29	15
10	DLB	Mixed AD/LBD	75	F	78	5
11	DLB	Mixed AD/LBD	80	F	17	12
12	DLB	Mixed AD/LBD	83	M	-	15
13	DLB	Mixed AD/LBD	78	M	17	1
14	DLB	Mixed AD/LBD	67	M	46	6
15	DLB	Mixed AD/LBD	78	M	45	8
16	DLB	Mixed AD/LBD	79	F	36	5
17	DLB	Mixed AD/LBD	89	F	25	7
18	PDD	Mixed AD/LBD	68	M	11	6
19	PDD	Mixed AD/LBD	75	M	28	12
20	PDD	Mixed AD/LBD	77	M	6	4
21	PDD	Mixed AD/LBD	78	M	77	5
22	AD	AD	77	F	63	14
23	AD	AD	83	M	12	6
24	AD	AD	86	F	69	11
25	AD	AD	84	F	47	11
26	AD	AD	81	F	50	1
27	DLB	DLB	77	M	8	4
28	DLB	DLB	72	M	89	8
29	DLB	DLB	71	M	8	7
30	DLB	DLB	77	M	46	11
31	DLB	DLB	91	F	10	4

Table 1: Patient demographics, disease duration, clinical and neuropathological data, Post mortem Delays (years) and disease duration (years) for each of the 31 cases.

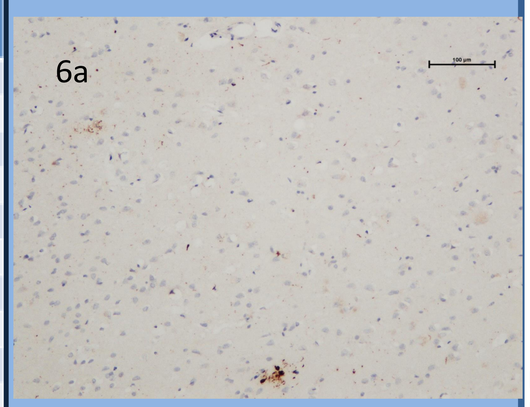
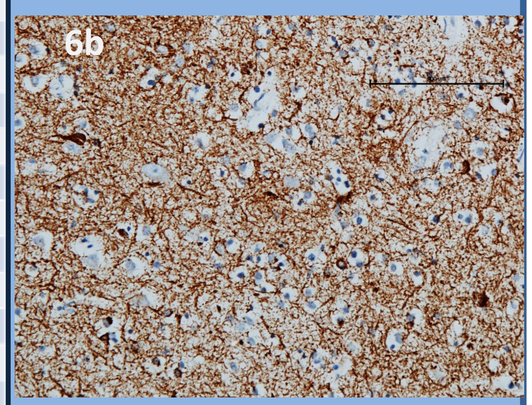
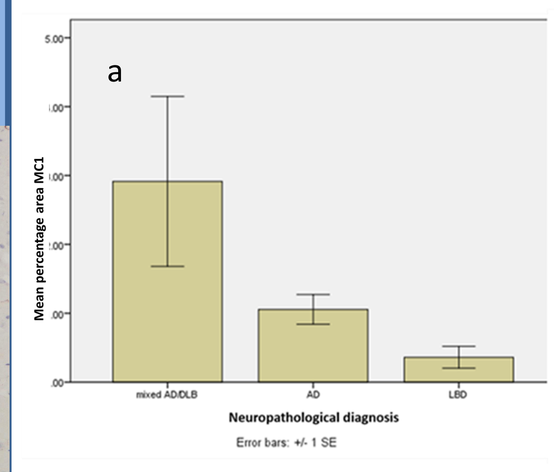


Figure 6:
The images 6a and 6b were captured throughout the temporal cortex respectively at 100X magnification and at 200X magnification, after MC1 IHC staining for 6a and CP13 IHC staining for 6b. There was more immunopositivity for CP13 staining than MC1 staining.





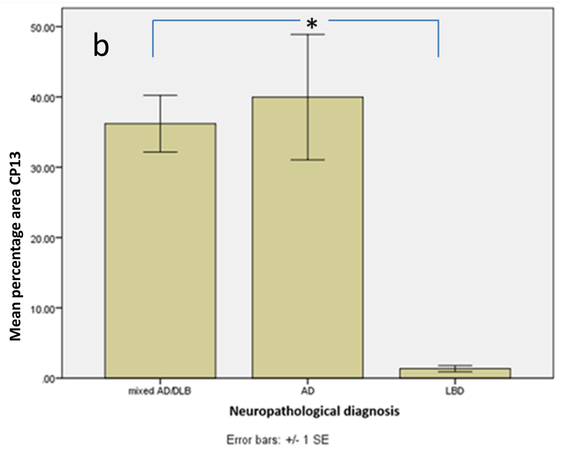
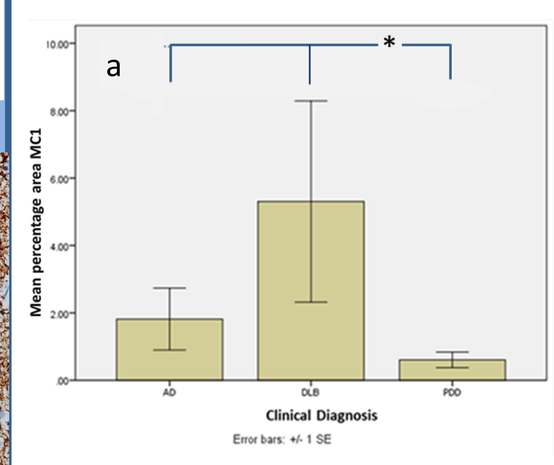


Figure 4: In the graphs all the 31 cases are grouped by neuropathological diagnosis; mixed AD/DLB, AD and LBD. The mean percentage area of immunopositivity across the whole temporal cortex was compared between each neuropathological group using the antibody MC1 (4a) and CP13 (4b). The greatest MC1 burden was seen in the mixed AD/DLB cases (4a). With respect to CP13 immunopositivity there was a higher percentage of coverage in the pure AD and mixed AD/LBD compared to pure DLB. $p<0.05$



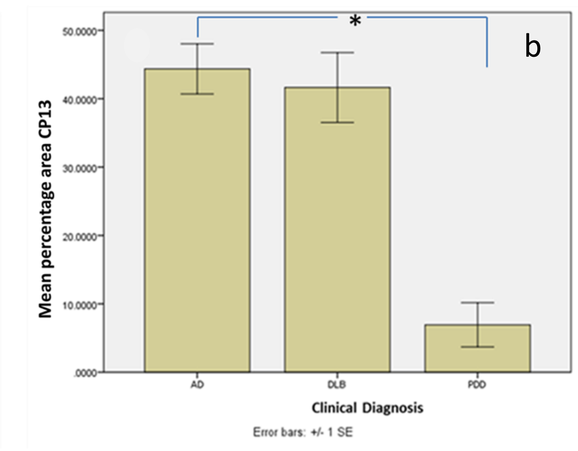


Figure 5:
Regarding MC1 immunopositivity, percentage coverage was greater in cDLB, followed by cAD and cPDD (5a). With respect to CP13 immunopositivity, very similar percentage coverage was revealed between cAD and cDLB, whereas less amount of CP13 immunopositivity percentage coverage was found in cPDD cases (5b). $P<0.05$.

Discussion

- Mixed AD/DLB group contain the highest amount of MC1 antibodies in comparison to the two pure disease groups (4a), this shows that at an early stage the presence of two neuropathological diseases have synergistic effect (the two pathologies influence the deterioration of each other's neuropathological and clinical features) and cause the presence of a higher amount of pathology. In fact, previous studies showed that AD patients who had also Lewy Body pathology, showed an accelerated decline in cognition and more aggressive course compared to patients who had AD only (2).
- In AD cases, there was the highest amount of CP13 antibodies present in comparison to the other groups (4b). These patterns can be explained by the fact that CP13 labels intermediate stage HP- τ pathology, detecting Pre-NFTs, intraneural NFT and NTs. Therefore, CP13 detects a nearly established HP-τ pathology in the brain which are seen more in people affected neuropathologically by AD rather than in patients in mixed AD/LBD.
- cDLB cases revealed a higher level of MC1 immunopositivity in comparison to the cAD and cPDD (5a), suggesting that in cDLB, the initial dementia was caused by DLB rather than AD pathology as there were detected a very high amount of MC1 antibody. This leads to the conclusion that AD occurred later in the patient and DLB was the main initial cause of dementia. Whereas in the cAD cases there were fewer MC1 antibody and more CP13 antibody, indicating that in cAD, dementia was caused by the AD as there were more established intraneural NFTs and NTs.

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References:

1. Walker L, McAleese KE, Thomas AJ, Johnson M, Martin-Ruiz C, Parker C, Colloby SJ, Jellinger K, Attems J. Neuropathologically mixed Alzheimer's and Lewy body disease: burden of pathological protein aggregates differs between clinical phenotypes. Acta neuropathologica. 2015 May 1;129(5):729-48.
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