Novel clinicopathological characteristics differentiate dementia with Lewy bodies from Parkinson's disease dementia

D. Hansen* (iD), H. Ling*† (iD), T. Lashley†‡ (iD), J. A. Foley§ (iD), C. Strand†, T. M. Eid†¶, J. L. Holton† (iD) and T. T. Warner*†§ (iD)

*Reta Lila Weston Institute, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, †Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, London, ‡Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, §National Hospital for Neurology and Neurosurgery, Queen Square, London, UK and ¶Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

---

D. Hansen, H. Ling, T. Lashley, J. A. Foley, C. Strand, T. M. Eid, J. L. Holton and T. T. Warner (2020) *Neuropathology and Applied Neurobiology*
Novel clinicopathological characteristics differentiate dementia with Lewy bodies from Parkinson's disease dementia

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) known as Lewy body dementias have overlapping clinical and neuropathological features. Neuropathology in both includes combination of Lewy body and Alzheimer's disease (AD) pathology. Cerebral amyloid angiopathy (CAA), often seen in AD, is increasingly recognized for its association with dementia. **Aims**: This study investigated clinical and neuropathological differences between DLB and PDD. **Methods**: 52 PDD and 16 DLB cases from the Queen Square Brain Bank (QSBB) for Neurological disorders were included. Comprehensive clinical data of motor and cognitive features were obtained from medical records. Neuropathological assessment included examination of CAA, Lewy body and AD pathology. **Results**: CAA was more common in DLB than in PDD ($P = 0.003$). The severity of CAA was greater in DLB than in PDD ($P = 0.009$), with significantly higher CAA scores in the parietal lobe ($P = 0.043$), and the occipital lobe ($P = 0.008$), in DLB than in PDD. The highest CAA scores were observed in cases with *APOE* ε4/4 and ε2/4. Survival analysis showed worse prognosis in DLB, as DLB reached each clinical milestone sooner than PDD. Absence of dyskinesia in DLB is linked to the significantly lower lifetime cumulative dose of levodopa in comparison with PDD. **Conclusions**: This is the first study which identified prominent concurrent CAA pathology as a pathological substrate of DLB. More prominent CAA and rapid disease progression as measured by clinical milestones distinguish DLB from PDD.

Keywords: cerebral amyloid angiopathy, Lewy body dementias, *APOE*

Introduction

PDD and DLB, currently characterized as a clinical spectrum of disorders and referred to as Lewy body dementia, share many clinical and neuropathological features [1,2]. The one year rule describing temporal onset of parkinsonism and dementia is used as the main criterion for their differentiation in clinical and research settings [1,3,4]. Several other differences in motor and cognitive features have been described [2,5]. More profound cognitive deficits occur in DLB [6–8] with DLB having more severe deficits in attention,

Correspondence: Thomas T. Warner, Reta Lila Weston Institute for Neurological Studies, UCL Queen Square Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, UK, Tel: +44 207 6794246; Fax: +44 207 2784993; E-mail: t.warner@ucl.ac.uk

executive functions, constructional tasks [6–8] and episodic verbal memory [7,8]. More severe parkinsonism was found in PDD than in DLB [6,9] with rest tremor being less frequent in DLB [7,9,10] and also milder and symmetrical in DLB [11].

Cortical Lewy bodies are the main neuropathological hallmark of Lewy body dementias [1]. Previous studies demonstrated that cortical Lewy bodies correlate with dementia in PD [12–14], with Lewy bodies in the frontal and cingulate gyrus correlating with the severity of cognitive impairment in PD and PDD [15]. Others found that the combination of Lewy body and Alzheimer's disease (AD) pathology correlates with dementia in PDD [16]. Neuropathological differences are relatively minor [17], and the main differentiating features are that DLB has less severe neuronal loss in the substantia nigra [18] and more severe AD pathology [19,20].

CAA is a condition defined by the presence of amyloid-β in the walls of small or medium cerebral blood vessels, mainly arteries and capillaries in leptomeninges and brain parenchyma [21–23]. There is increasing evidence that CAA is more frequently observed in demented rather than in nondemented individuals [24–27]. CAA is very common in AD with the prevalence of up to 97% [28]. However, CAA also occurs in Lewy body dementias and an association between CAA and cognitive decline in PDD and DLB has been demonstrated [29].

CAA is characterized as an age-related small vessel disease with increasing prevalence in older individuals [28,30]. It was found that CAA occurs in 36% of individuals over 60 years of age and 46% of those over 70 years [30]. Another study found a wider range of age-related CAA prevalence (2.3% in those aged 65-74 years and 100% in those older than 80 years) [28].

The primary objective of this study was to identify clinical and neuropathological differences that can distinguish PDD from DLB more clearly. CAA, as a concomitant neuropathology, was investigated with its frequency and topographical distribution in addition to Lewy body and AD neuropathology. *APOE* genotype was determined and its relationship to CAA was examined.

Materials and methods

Eight hundred brain donors with the clinical diagnosis of PDD, PD or DLB were identified in the database of Queen Square Brain Bank for Neurological disorders (QSBB) between 1990 and 2018. The clinical records were reviewed and only cases with sufficient clinical information for the clinical diagnosis of PDD according to Movement Disorders Task force criteria [3] and DLB according to McKeith's criteria [4,31] were selected. 95 clinically well-documented consecutive PDD and DLB cases were identified. Full clinical records of these cases were systematically reviewed by a neurologist (DH). 27 cases were excluded because they did not fulfil clinical diagnostic criteria for PDD, criteria for DLB (n = 13) or they had diagnosis of genetically confirmed PD/PDD (n = 6) or their neuropathological diagnosis was other than PDD or DLB (n = 8). The 1-year rule was used as the main criterion for the clinical differentiation between PDD and DLB. Overall, 68 (PDD 52, DLB 16) clinically well-documented and pathological confirmed PDD and DLB cases were included in this study. None of included cases had either a typical clinical course or typical clinical features for AD.

Clinical features

Demographic and clinical data were collected including gender, disease duration, age at first cognitive symptoms onset, age at first motor symptoms onset (defined as the year when clinical symptoms of parkinsonism occurred in clinical records for the first time), age at death, presence of visual hallucinations, age at visual hallucinations onset, presence of tremor and dyskinesia. Clinical data also included cumulative lifetime levodopa dose, calculated as follows: (daily amount of L-dopa [mg]) at 1 year after commencement × 365 + [1/2] [maximum daily amount L-dopa + daily amount L-dopa at 1 year after commencement] × [interval from 1 year after commencement to reaching maximum dose (years) × 365] + [1/2] [maximum daily amount L-dopa + daily amount L-dopa at death or discontinuation of L-dopa] × [interval from reaching maximum dose to death of L-dopa discontinuation (years) × 365] [32], and other medication use (dopamine agonists, monoamine oxidase inhibitors, amantadine, anticholinergics, antipsychotics, cholinesterase inhibitors and NMDA receptor antagonists). Cognitive data included last MMSE scores [33] and formal neuropsychometry assessments, where available. Severity of parkinsonism was evaluated retrospectively at the time of dementia and time at death by

using modified Hoehn–Yahr scale (retrospective assessment was performed by a neurologist (DH) and was based on the clinical description of motor symptoms in clinical records) [34,35]. Clinical milestones of the disease progression included: time to regular falls, time to wheelchair dependence, time to dysphagia, time to residential care placement and time to cognitive disability [36].

Neuropathology

All cases had been formally examined by a neuropathologist according to the standard protocols. Immunohistochemistry included the following antibodies: α-synuclein (Vector Laboratories; KM51; 1:50), phosphorylated tau (AT8; BioScience Life Sciences; 1:600), amyloid-β peptide (Dako; 6F/3D; 1:100). A standard immunohistochemistry avidin-biotin complex (ABC) method was used. Paraffin sections were blocked in methanol with 0.3% H_2O_2, followed by the treatment in citrate buffer (pH 6) in the pressure cooker and blocking in 10% dried milk. Incubation with the primary antibody was followed by the incubation with the secondary antibody and incubation with the ABC complex (Dako). Finally, sections were blocked in diaminobenzidine activated by 0.3% H_2O_2 to visualize the pathology of interest.

Neuropathological data such as brain weight and post-mortem delay were acquired from reports. Neuropathological assessment of Lewy pathology to provide Braak staging and McKeith typing was performed according to the current and established criteria [4,37]. AD neuropathology with Thal phases for amyloid-β [38], Braak and Braak stages for neurofibrillary tangles [39], CERAD criteria for neuritic plaques [40] were performed. 'ABC' scores for AD neuropathology were also determined [41]. CAA was assessed for all included cases by a neuropathologist (JH) from five brain regions (frontal lobe, parietal lobe, temporal lobe, occipital lobe and the cerebellum) according to the consensus protocol for the assessment of CAA in post-mortem brain tissue [21]. Scores (0-3) were used for the assessment of parenchymal and meningeal CAA. Scores (0-1) were used for the assessment of capillary CAA and scores (0-2) for vasculopathic changes associated with CAA separately in the neocortex and leptomeninges. The maximum CAA score per brain region was 11 (represented by the sum of maximum scores from: brain parenchyma (maximum score of 3), leptomeninges (maximum score of 3), capillaries (maximum score of 1), vasculopathic changes were evaluated separately in neocortex (maximum score of 2), and in leptomeninges (maximum score of 2). An overall CAA score for each case was then calculated as the sum of all scores from all brain regions (maximum possible overall score was: 11×5 brain regions = 55). Three cases (2 PDD and 1 DLB) had missing data where suitable tissue was not available for the assessment of CAA. One DLB case had missing data in the temporal lobe and two PDD cases had missing data in the parietal lobe, occipital lobe and in the cerebellum. To account for missing data, the total CAA scores were expressed as the percentage of the total score available for each case (Total CAA percentage score). We have also compared the severity of CAA in a subgroup of PDD and DLB cases with lower severity of AD neuropathology (Braak and Braak neurofibrillary tangles stage up to 4 and Thal amyloid-β phases up to 3).

A sample of 10% of the cases were randomly selected and analysed for the second time for the intra-rater reliability or level agreement to assess the consistency of the CAA neuropathological assessment.

APOE genotype

APOE genotype was determined in 58 cases (PDD 46, DLB 12) using DNA extracted from frozen cerebellar tissue using polymerase chain reaction (PCR) followed by restriction enzyme digestion [42]. *APOE* genotyping was not possible for 10 cases where DNA was not available.

Statistical analysis

Statistical software IBM SPSS version 26 was used for the statistical analysis. Nonparametric Mann–Whitney *U* test was used for the assessment of continuous variables as they did not have normal data distribution. Categorical variables were assessed according to chi-squared test or Fisher's exact test depending on the data distribution. Kaplan–Meier survival curves and Log Rank (Mantel–Cox) were used for the assessment of clinical milestones. Assessment of CAA also included multiple logistic regression and assessment for intra-rater reliability (level of agreement, assessment performed for the second time by the same examiner (JH)

Table 1. Demographic, clinical and neuropathological characteristics

	PDD n = 52 Median (IQR) or %	DLB n = 16 Median (IQR) or %	P value
Gender (male) %	37 (71.2%)	11 (68.8%)	1.000[‡]
Disease duration yrs	20 (14, 25)	9 (6, 10.75)	<0.001*,[†]
Age at 1st cognitive symptoms onset yrs	70 (60, 76)	65 (57.5, 70.5)	0.110[†]
Age at 1st motor symptoms onset yrs	58 (49, 66)	66 (62.7, 70.5)	0.012*,[†]
Age at death yrs	77.5 (72, 82)	71.5 (67, 78.5)	0.048*,[†]
Visual hallucinations %	46 (88.5%)	14 (87.5%)	1.000[‡]
Visual hallucinations age at onset yrs	n = 4671 (63, 76)	n = 1167 (64, 70)	0.209[a]
Last MMSE	n = 25 20 (17, 23)	n = 11 17 (8.5, 19.5)	0.035*,[†]
Last MMSE to death yrs	2 (1, 6)	2 (2, 4)	0.589[†]
Tremor %	44 (84.6%)	9 (56.3%)	0.034*,[‡]
Dyskinesia %	37 (71.2%)	0 (0%)	<0.001*,[§]
Cumulative lifetime dose of levodopa kg	n = 47 2.01 (1.21, 3.17)	n = 8 0.31 (0, 0.47)	<0.001*,[†]
Dopamine agonists %	39 (75%)	2 (12.5%)	<0.001*,[§]
MAOi %	34 (65.4%)	1 (6.3%)	<0.001*,[§]
Amantadine %	19 (36.5%)	0 (0%)	0.003*,[‡]
Anticholinergics %	44 (84.6%)	7 (43.8%)	0.002*,[‡]
Antipsychotics %	24 (46.2%)	7 (43.8%)	0.866[§]
Cholinesterase inhibitors %	39 (75%)	12 (75%)	1.000[‡]
NMDA antagonists %	5 (9.6%)	1 (6.3%)	1.000[‡]
Braak and Braak neurofibrillary tangles stages			
0	3 (5.8%)	0 (0%)	0.034[‡]
1	7 (13.5%)	1 (6.3%)	
2	25 (48.1%)	5 (31.3%)	
3	9 (17.3%)	2 (12.5%)	
4	5 (9.6%)	1 (6.3%)	
5	2 (3.8%)	4 (25%)	
6	1 (1.9%)	3 (18.8%)	
Thal amyloid-β phases			
0	7 (13.5%)	0 (0%)	0.083[†]
1	7 (13.5%)	0 (0%)	
2	2 (3.8%)	1 (6.3%)	
3	11 (21.2%)	1 (6.3%)	
4	14 (26.9%)	7 (43.8%)	
5	11 (21.2%)	7 (43.8%)	

*Statistically significant P values < 0.05.
[†]represents Mann–Whitney U test.
[‡]Fisher's exact test.
[§]chi[2] test.

blinded to the initial result) with Cohen's κ coefficient. P value of < 0.05 was considered as statistically significant.

Results

Clinical findings

68 (52 PDD, 16 DLB) neuropathologically confirmed cases were included in this study (demographic data summarized in Table 1). All cases fulfilled clinical diagnostic criteria for PDD [3] or DLB [4,31]. Males were more frequent in both groups (71.2% PDD, 68.8% DLB). Disease duration differed between the two groups; DLB had significantly shorter disease duration (P < 0.001) and were younger at death (P = 0.048) compared with the PDD group. DLB patients were significantly older at the time of their first motor symptoms onset (P = 0.012) compared with PDD. No significant differences were found in the age at onset of the first cognitive symptoms (P = 0.110). Visual hallucinations had a similar frequency in both groups (88.5% PDD, 87.5% DLB, P = 1.000) and a similar age at onset (P = 0.209). Last (closest to death) MMSE

score was significantly lower in DLB compared to PDD ($P = 0.035$), where the median of the interval between the last MMSE and death was the same in both groups ($P = 0.589$). Tremor was less frequent in the DLB group (56.3%) than in the PDD group (84.6%) ($P = 0.034$). Dyskinesia was absent in DLB cases compared to 71.2% of PDD, ($P < 0.001$) which is likely to relate to significantly lower lifetime cumulative dose of levodopa in DLB ($P < 0.001$). Similarly, DLB patients were treated with less dopamine agonists ($P < 0.001$), monoamine oxidase inhibitors ($P < 0.001$), amantadine ($P < 0.003$) and anticholinergics ($P = 0.002$). No significant differences were found in the frequency of use of antipsychotics ($P = 0.866$), cholinesterase inhibitors ($P = 1.000$) and NMDA antagonists ($P = 1.000$).
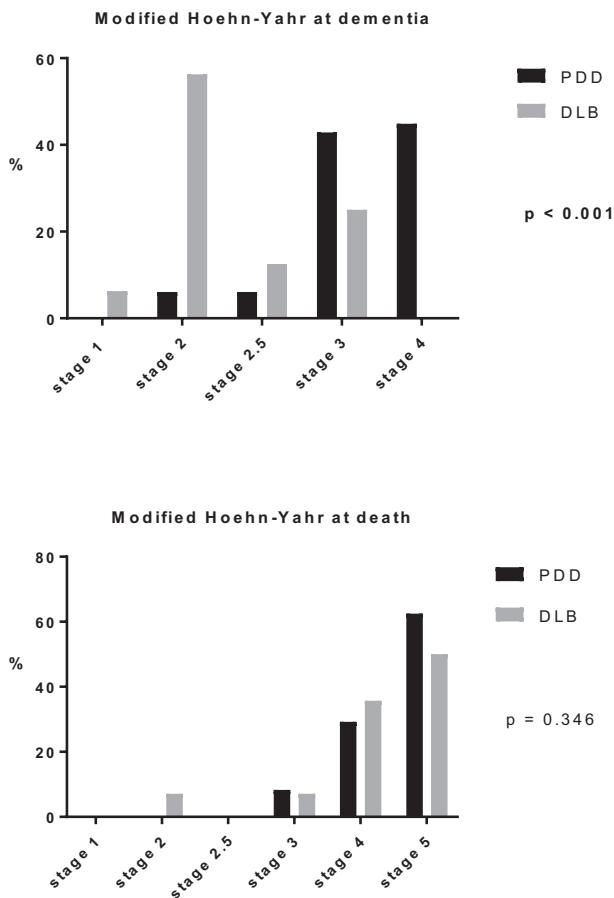

Figure 1. Modified Hoehn–Yahr stages at the time of dementia and time at death. Stage 1 – mild unilateral symptoms, stage 2 - bilateral involvement, stage 2.5 - mild bilateral involvement with recovery on pull test, stage 3 - mild to moderate symptoms with postural instability, stage 4 – severe disability, stage 5 - wheelchair or bed bound.

Severity of parkinsonism was assessed at the time of the diagnosis of dementia and time of death according to the modified Hoehn–Yahr scale and is illustrated in Figure 1, Table S1. Parkinsonism at the time of dementia was significantly less severe in DLB compared to PDD ($P < 0.001$) as the majority of DLB patients (56.3%) had bilateral symmetrical symptoms at the time of dementia diagnosis while PDD (44.9%) had severe disability. No significant differences in the severity of motor symptoms were found at the time of death ($P = 0.346$).

Clinical milestones of disease progression (time to regular falls, time to wheelchair dependence, time to dysphagia, time to cognitive disability and time to residential care placement) were assessed in both groups (Figure 2). Survival analysis showed that DLB patients reached each clinical milestone of the disease progression sooner than PDD (time to regular falls Log Rank $P < 0.001$, time to wheelchair dependence Log Rank $P < 0.001$, time to dysphagia Log Rank $P < 0.001$, time to cognitive disability Log Rank $P < 0.001$, time to residential care placement Log Rank $P < 0.001$).

Scores from specific tests of cognitive domains in the neuropsychometry assessment were included for those cases where available (6 PDD, 4 DLB). No significant differences were found between PDD and DLB in any cognitive domain, this is most likely due to the small number of cases for which data were available; Table S2.

Neuropathological results

Neuropathological assessment demonstrated similar brain weight in both groups ($P = 0.452$) and similar post-mortem delay ($P = 0.129$). Lewy body pathology did not show any statistically significant difference between PDD and DLB ($P = 1.000$). The majority of PDD cases (94.2%) and all DLB cases (100%) had neocortical stage of LB pathology. Only three cases (5.8%) in the PDD group had limbic type Lewy body pathology, Table S3.

AD neuropathology according to National Institute on Ageing – Alzheimer's association guidelines (NIA-AA) was more severe in DLB compared with PDD for Braak and Braak neurofibrillary tangles stages ($P = 0.034$) and B score (NIA-AA criterion reflecting Braak and Braak neurofibrillary stages) ($P = 0.004$), and in neuritic plaques according to C score (NIA-AA
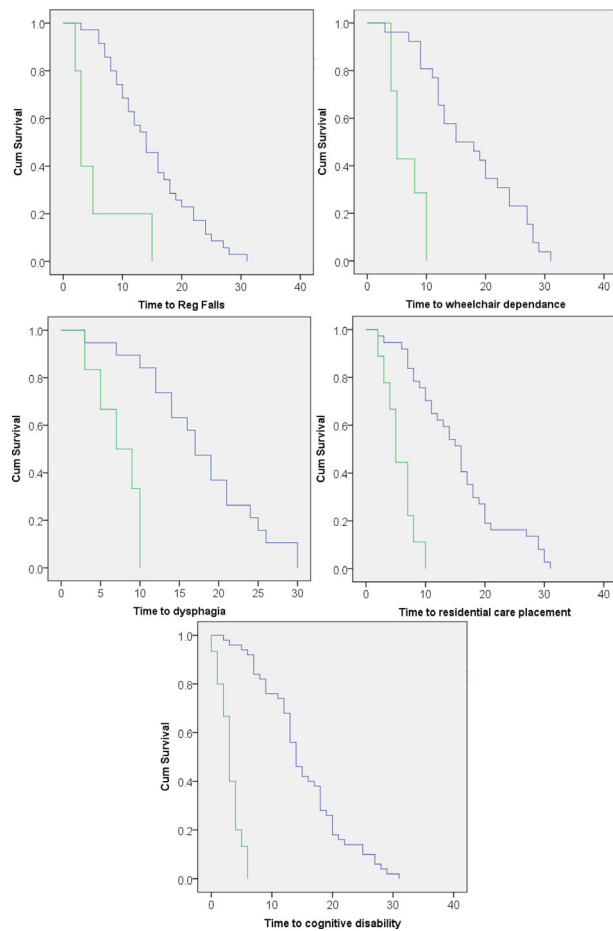
Figure 2. Kaplan-Meier survival curves of clinical milestones of PDD and DLB. Time to regular falls is the interval between disease onset and time of reaching regular falls, Log Rank (Mantel–Cox) P < 0.001. Time to wheelchair dependence is the interval between disease onset and time of wheelchair dependence, Log Rank (Mantel–Cox) P < 0.001. Time to dysphagia is the interval between disease onset and time of severe dysphagia, Log Rank (Mantel–Cox) P < 0.001. Time to residential care placement is the interval between disease onset and time of residential care placement, Log Rank (Mantel–Cox) P < 0.001. Time to cognitive disability is the interval between the disease onset and time of cognitive disability, Log Rank (Mantel–Cox) P < 0.001. PDD blue dotted line, DLB green dotted line. PDD – Parkinson's disease dementia, DLB, dementia with Lewy bodies.

CERAD neuritic plaque score) (P = 0.006) [41]. The distribution of amyloid-β neuropathology did not show any significant differences (Thal phases P = 0.083, A score (NIA-AA amyloid-β deposits) P = 0.059) [38], Figures 3 and 4, Table 1, Tables S4 and S5.

CAA frequency in both groups was significantly different (P = 0.003). CAA pathology was observed in 63.5% (33/52) of PDD cases and 100% (16/16) of DLB
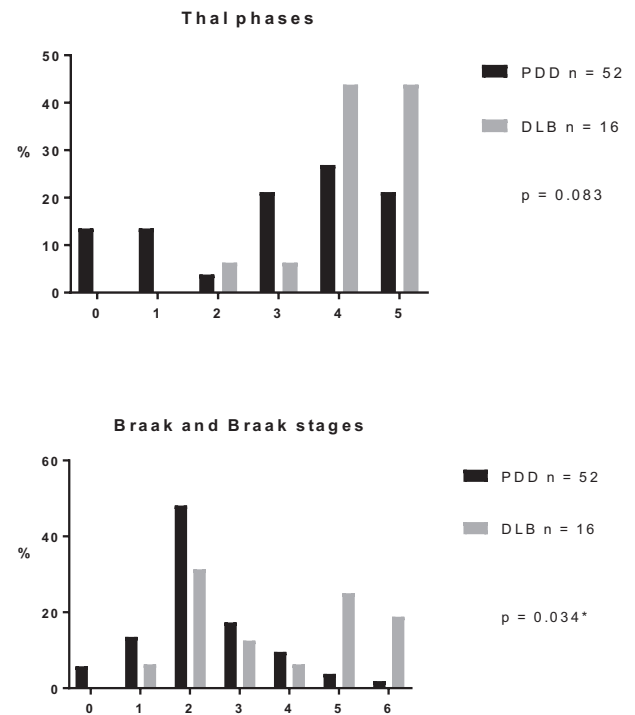

Figure 3. Thal phases for amyloid-β and Braak and Braak stages for neurofibrillary tangles in PDD and DLB. Significant *P* value < 0.05 is marked *.

cases. Multivariable logistic regression showed that the risk of CAA decreased with the diagnosis of PDD after adjusting for age at death (the odds are 0.039 times (96%) lower in PDD than in DLB; OR 0.039; 95% CI 0.004 – 0.355; P = 0.004; Hosmer Lemeshow test P = 0.292). The severity of CAA was evaluated using the CAA score in each brain region and for each case the total score was expressed as the percentage of the possible available score from all brain regions (Total CAA percentage score) and compared between the two disease groups (Figure 5 and Table S6). Our results showed significant differences in CAA scores between DLB and PDD with higher CAA load in posterior brain areas (occipital lobe P = 0.008, parietal lobe P = 0.043) and also an increased total CAA percentage score (P = 0.009). Anterior brain regions showed similar CAA scores in both groups (frontal lobe P = 0.152, temporal lobe P = 0.061).

Most variables (CAA assessment of meninges, cortex and capillaries in the frontal, temporal lobe and the cerebellum, and meninges in parietal lobe and occipital lobe) had Cohen's κ 1.000, P = 0.0008 and SE 0.000 which is consistent with 'almost perfect' level of intra-
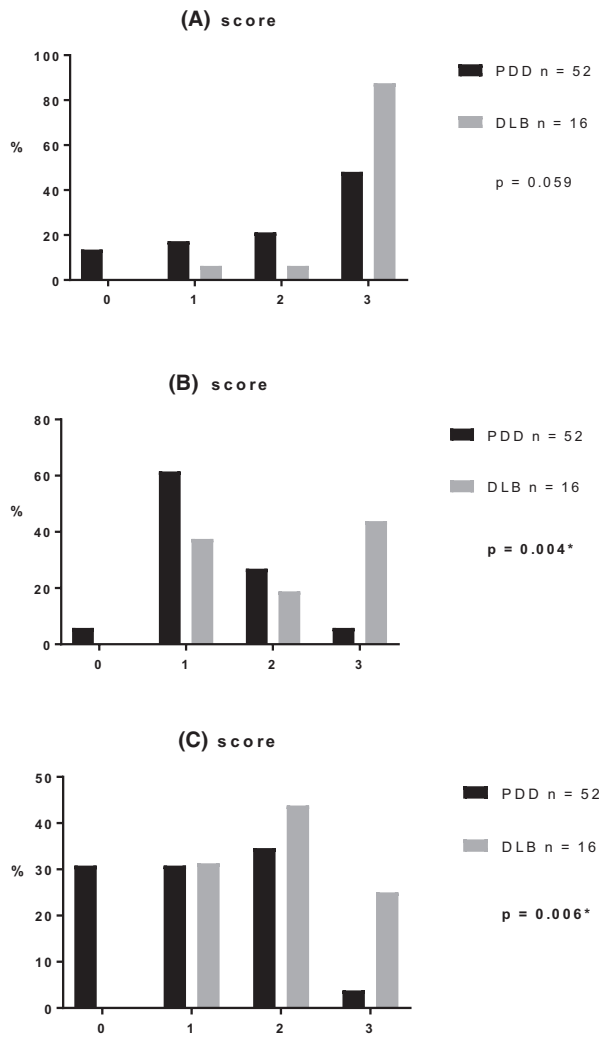
Figure 4. Alzheimer's disease neuropathology assessed via ABC score. A score reflects amyloid-β pathology (Thal phases), B score neurofibrillary tangles (Braak and Braak stages) and C score neuritic plaques (CERAD criteria). Significant *P* value < 0.05 is marked *.
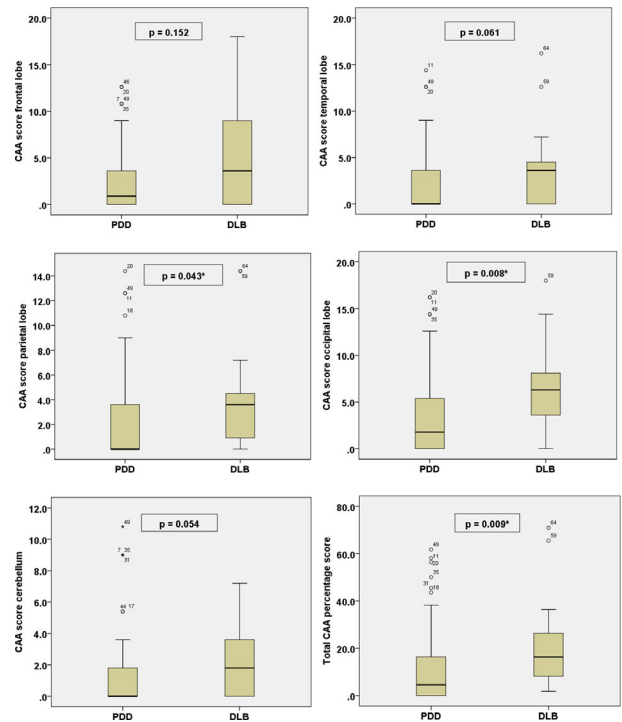

Figure 5. CAA scores in different brain regions and total CAA percentage scores for PDD and DLB. Boxplots demonstrate CAA scores in the frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellum and the total CAA percentage scores. There was a statistically significant increase in CAA in the parietal and occipital lobes and also in the overall CAA load in DLB compared with PDD. Boxplots show median CAA scores, interquartile range, full range (minimum – maximum score is represented by whiskers) and outliers in each brain region. *P* value < 0.05 was considered as statistically significant and is marked with *. CAA – cerebral amyloid angiopathy, PDD, Parkinson's disease dementia, DLB, dementia with Lewy bodies.

rater agreement. Two CAA variables: CAA of cortex in the occipital lobe (Cohen's κ 0.741, *P* = 0.013, SE 0.198 had 'moderate' level of agreement) and in the parietal lobe (Cohen's κ 0.588, *P* = 0.088, SE 0.347 had 'weak' level of agreement).

Results from the analysis of CAA severity in a subgroup of 26 PDD and 2 DLB cases with a low degree of AD neuropathology (Braak and Braak neurofibrillary stage less than 4 and Thal phases for amyloid-β up to 3) also showed significant differences in the severity of CAA in the temporal lobe (*P* = 0.032), parietal lobe (*P* = 0.032), occipital lobe (*P* = 0.023), in the

cerebellum (*P* = 0.011) and in the total CAA percentages score (*P* = 0.032), Table S9.

APOE genotype was determined in 58 cases (46 PDD, 12 DLB). The most frequent genotype was ε3/3 (47.8% PDD, 41.7% DLB) and followed by the genotype ε3/4 (41.3% PDD, 33.3% DLB). No significant differences were found between PDD and DLB in six different *APOE* genotypes (Figure 6 and Table S7). The relationship between *APOE* genotype and CAA was investigated. No significant differences between CAA scores in the combined PDD and DLB cohort were found across all six *APOE* genotypes but the highest CAA scores were observed in cases with *APOE* ε4/4 (median 19.5; 35.45%) and ε2/4 (median 24; 43.25%) (Figure 7, Table S8).
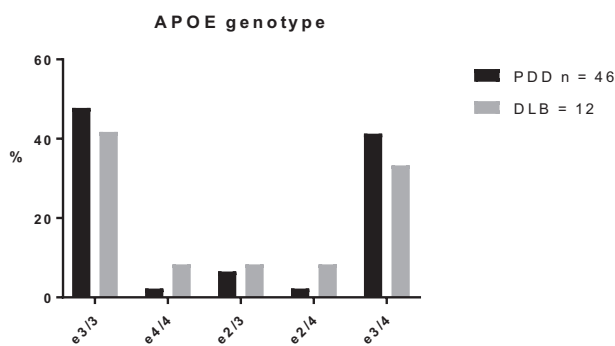
APOE genotype

Figure 6. APOE genotypes in PDD and DLB. Bar charts represent prevalence of individual homozygous and heterozygous APOE genotypes. APOE genotype ε2/2 was not represented in this cohort. PDD, Parkinson's disease dementia, DLB, dementia with Lewy bodies.
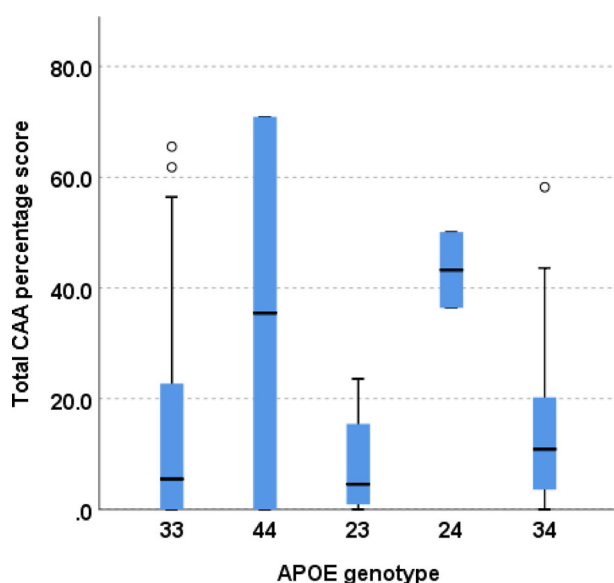

Figure 7. The relationship between APOE genotype and total CAA percentage score. Boxplots demonstrating the median and interquartile range illustrate the total CAA percentage scores in the combined DLB and PDD cohort. The highest CAA scores were observed in the group with APOE ε2/ε4 and ε4/ε4 but there was no statistical significance between the genotypes, $P = 0.313$. P value < 0.05 was considered as statistically significant in the Kruskal–Wallis test.

Discussion

This retrospective clinico-pathological study of neuropathologically confirmed PDD and DLB cases identified three novel differences.

The novel neuropathological finding is the higher frequency of CAA in DLB compared to PDD (100% vs.

63.5%, respectively) with lower risk for CAA in PDD after adjusting for age at death. Our results showed that DLB patients have more severe overall CAA scores, and higher CAA scores especially in the occipital lobe. CAA is most commonly seen in AD, again with the occipital lobe being most frequently involved [28]. The co-occurrence of CAA and AD neuropathology is already well-known [43]. Our CAA findings would be in keeping with previous studies showing more severe AD neuropathology in DLB than PDD [19,20]. CAA, as a part of the 'AD profile' on the neuropathological assessment is therefore more typical for DLB than for PDD. Nevertheless, interesting observation of more severe CAA neuropathology in DLB compared to PDD in a subgroup of cases with low degree of AD neuropathology might suggest a different mechanism of CAA pathogenesis in DLB.

CAA is more common in individuals with dementia compared to those without dementia [24–27] and previous research showed that cognitive decline is also associated with CAA in PDD and DLB [29]. CAA occurs in patients with cognitive impairment and cognitive profile of CAA has been characterized [44–46]. Boyle *et al.* found that CAA is an independent contributor to dementia in AD with an increased rate of global cognitive decline, perceptual speed, episodic and semantic memory after adjusting for AD neuropathology [44]. CAA also plays a role in multiple cognitive impairment in nondemented individuals who performed worse in nonamnestic domains including processing speed, executive functions, episodic memory, semantic fluency and attention [45]. This cognitive profile resembles that which is seen in cerebrovascular disease rather than in AD as individuals with CAA performed well on episodic memory tasks [46]. Further evidence that CAA is an independent contributor to cognitive decline was shown in a large multicentre study, CROMIS-2, in patients prior to the development of spontaneous intracerebral haemorrhage [47]. Therefore, CAA pathology may also have an effect on cognition in DLB, independent from AD neuropathological changes.

Currently, assessment of CAA is not included in the neuropathological criteria for DLB [4], which include only assessment of Lewy body and AD neuropathology with amyloid-β plaques, neurofibrillary tangles and neuritic plaques, with semi-quantitative assessment of neuronal loss in the substantia nigra [4]. Given our CAA findings and a strong link between CAA and AD

neuropathology, we propose adding CAA into McKeith's neuropathological assessment scheme.

CAA findings in the occipital lobe might have important clinical implications for neuroimaging in DLB. Functional imaging (SPECT and PET) studies of DLB patients have shown reduced metabolism and reduced perfusion in the occipital lobe [1,4]. Relative preservation of FDG-PET uptake in posterior or mid-cingulate metabolism, is known as the 'cingulate island sign', a useful marker when differentiating DLB from AD [48]. It has also been found that nigrostriatal abnormalities appear to be preceded by occipital hypometabolism in mild DLB [49]. Functional imaging in PDD shows reduced metabolism in the frontal, parietal and occipital regions [1,50]. One study correlated the reduced glucose metabolism in DLB with white matter spongiform changes and gliosis in the occipital lobe [51]. In the present study, CAA pathology is most prominent in the occipital lobe in DLB, suggesting that this may also contribute to the reduced occipital metabolism and perfusion on functional imaging.

CAA can be demonstrated on MRI blood-sensitive sequences, such as T2 – weighted gradient echo sequences and susceptibility-weighted images [47] as cerebral micro-bleeds or cortical superficial siderosis [45]. Boston criteria are commonly used for the clinical diagnosis of probable or possible CAA [52]. There is a strong association between cortical superficial siderosis and cognitive impairment prior to developing intracerebral haemorrhage [47], suggesting that leptomeningeal haemorrhages play a more important role in cognitive deficits than parenchymal haemorrhages [47]. Cortical superficial siderosis was shown to be the most important MRI marker of severe leptomeningeal CAA [53].

CAA often presents with cerebral microbleeds on the MRI imaging [54,55]. One study found that clinically diagnosed cases of DLB, demonstrated more frequent cerebral micro-bleeds compared to AD in the occipital and frontal lobe followed by the temporal and parietal lobe [54]. Furthermore, greater burden of cerebral microbleeds with lobar predominance was found in DLB compared to PDD [55]. These findings suggest that DLB patients have more cerebral microbleeds than PDD with prominent occipital lobe involvement. These imaging studies are consistent with our neuropathological findings with more severe CAA in DLB compared with PDD, particularly in the occipital lobe.

CAA pathology is important as it can be diagnosed in life on MRI (Boston criteria) [53]. CAA most frequently presents with spontaneous intracerebral haemorrhage, cognitive impairment and dementia, acute convexity subarachnoid haemorrhage and transient neurological symptoms [53]. Transient focal neurological episodes, known as 'amyloid spells' commonly manifest as short, recurrent and stereotyped focal episodes (often paraesthesia) with gradual spread of symptoms lasting for minutes [53,56,57].

The recurrent and transient nature of 'amyloid spells' may overlap with cognitive fluctuations in DLB or fluctuations in attention in PDD which to date do not have a neuropathological correlate. Cognitive fluctuations are described as spontaneous alterations of cognition which are often accompanied by changes in alertness or arousal [58]. Diagnostic criteria for DLB [4] define cognitive fluctuations as deficits in cognitive performance alternating with normal cognitive functioning. Cognitive fluctuations, with their character of transient and unpredictable events, can be, for example, staring spells, or episodes of blank or vague episodes [58]. It is known that the duration of cognitive fluctuations can range from seconds to minutes lasting episodes or even longer episodes lasting days or weeks [58]. We hypothesize that CAA may contribute as a pathological correlate of cognitive fluctuations in DLB which warrants further studies to validate.

Previous studies estimated genetic component of DLB to be approximately 36% [59]. DLB has been associated mainly with *APOE* genotype, mutations in the *SNCA*, *GBA* [59] and *SCARB2* [60]. *APOE* is a cholesterol transporter protein and regulator of amyloid-β metabolism and *APOE* ε4 is an important genetic risk factor for both Alzheimer's disease [61,62] and DLB [59]. However, information on the role of *APOE* in PDD remains contradictory [63]; both *APOE* ε2 and ε4 allele are associated with increased risk for dementia in PD with *APOE* ε2 showing a stronger association [64].

Our data showed no differences between the six different *APOE* genotypes in PDD and DLB, although there were increased CAA scores in those with *APOE* ε2/4 and ε4/4 genotypes. The ε4 allele is associated with increased frequency of CAA [65–67]. However, one large clinico-pathological study demonstrated that the severity of CAA was associated with lower cognition in those without *APOE* ε4 allele which suggests that there might be different CAA subtypes (i.e. with or

without AD neuropathology, and with or without *APOE* ε4 allele) [68].

CAA has different amyloid-β composition compared to amyloid-β plaques in the brain parenchyma with different amyloid-β_{40}/ amyloid-β_{42} ratio in vessels and plaques [69]. Shams *et al.* showed an association between low amyloid-β_{42} levels in CSF and increasing number of cerebral microbleeds in cognitively impaired patients [70]. In AD, low CSF levels of amyloid-β_{40} and amyloid-β_{42} were found in patients with CAA related cortical microbleeds [71]. One study with hereditary cerebral haemorrhage with amyloidosis-Dutch type as a model for sporadic cerebral amyloid angiopathy, demonstrated decreased CSF levels of amyloid-β_{40} and amyloid-β_{42} before these subjects developed clinical symptoms which suggests that their decreased levels might represent a biomarker for preclinical CAA [72]. Amyloid-β_{40}, amyloid-β_{42} and their ratio might therefore represent a potential CSF biomarker for CAA positive Lewy body dementia cases.

CAA, a vascular dementia subtype [27] seems to be of great importance for future research in Lewy body dementias. This idea is further supported by the fact that currently there is no specific treatment for CAA [56] and also our clinical abilities to diagnose CAA are limited [67].

AD neuropathology is well-described in Lewy body dementias [19]. Increasing levels of AD neuropathology contributes to shorter survival, interval to motor symptoms, and onset to dementia [19]. Our study is in keeping with previous research showing that AD neuropathology is more severe in DLB than in PDD [19,20]. Nevertheless, in our study, we did not find any significant difference in amyloid-β plaques, although our data show a trend for increased severity in DLB than in PDD. This variation from the results from previous studies is most likely caused by smaller number of DLB cases compared to PDD.

The strength of our study was use of pathologically confirmed cases and detailed clinical characterization of PDD and DLB. We recognize that one limitation of this project is the smaller number of DLB cases.

Two novel clinical findings from this study include differences in clinical milestones between DLB and PDD and the absence of dyskinesia in DLB.

We believe that this is the first study comparing clinical milestones of disease progression (residential care placement, dysphagia, regular falls, wheelchair dependence and cognitive disability) between DLB and PDD cases. DLB patients reached each clinical milestone sooner than those with PDD. DLB is the second most common neurodegenerative dementia after AD, but only a few studies have compared the two conditions [73,74]. These studies concluded that the prognosis in DLB is poorer than in AD, most likely due to increased frequency of neuropsychiatric features and faster cognitive decline [73].

There has been little research comparing prognosis and a long-term cognitive decline between DLB and PDD. Kramberger *et al.* showed that the mean annual decline in MMSE is greater in DLB (2 points) compared to PDD (1.8 points) and AD (1.6 points) [75]. Our findings contribute substantially to the description of disease progression in terms of functional disability with worse prognosis in DLB compared with PDD.

Absence of dyskinesia in DLB represents an absolute difference between PDD and DLB (present in PDD and completely absent in DLB). Previous research has identified differences in cognitive, motor and neuropathological features. However, they represent only relative differences as they describe mainly different severity levels in certain specific features. Dyskinesia is linked to the levodopa dose and the reason for their presence is clear in PDD, higher dose of levodopa due to more severe motor features, and longer disease duration. The most obvious reason for the absence of dyskinesia in DLB relates to the overall lower cumulative dose of levodopa therapy. This is due to less severe motor symptoms in DLB but may also relate to the more prominent psychiatric features. DLB patients are very sensitive to antipsychotics medication [4], and the same is likely to be the case for dopaminergic drugs. Therefore, levodopa doses may be deliberately kept low in DLB patients to avoid deterioration of neuropsychiatric features such as visual hallucinations or psychosis.

Other significant differences between PDD and DLB identified in the present study are in keeping with results in the literature. We have shown that the frequency of tremor is higher in PDD than in DLB as previously documented [7,9,10], as is the severity of motor features or parkinsonism [6,9]. Our results also confirmed that DLB patients had worse cognitive deficits than PDD [6–8]. We did not demonstrate any significant differesnces in cognitive domains according to the neuropsychometry assessments, which may reflect

the small sample size in which such data were available. Other studies have shown worse performance in a number of cognitive domains in DLB than in PDD [6–8].

In summary, the role of CAA pathology in Lewy body dementias, particularly DLB, is an important new finding warranting further study of its contribution to the disease pathogenesis, influence on the characteristic clinical features (cognitive fluctuations) and imaging findings, as well as disease progression and prognosis. The role of different *APOE* genotypes and subtypes of CAA also requires further exploration. DLB is known for its specific genetic background and given the fact, that CAA occurs in two main forms, hereditary and sporadic [23], it would be of interest to investigate for other genetic risk factors associated with CAA, particularly in DLB cases. Amyloid-β_{40} is the main component of CAA and might represent a good target for future treatment strategies or in studies focusing on biomarkers. Furthermore, CAA with its 'vascular' cognitive profile requires further investigation to understand the contribution of cerebral blood vessel pathology in DLB and other dementias.

Conclusion

This study identified three important findings: 1) CAA as an important neuropathological feature, which may help distinguish DLB from PDD, 2) study of clinical milestones shows more rapid progression and worse prognosis of DLB compared with PDD, 3) absence of dyskinesia in DLB reflects lower doses of levodopa treatment in DLB.

Acknowledgement

Ethical Approval

Material Transfer Agreement (MTA) was obtained according to the UCL standards and policies for neuropathological research studies. All brain donors included in this study signed a written consent for the participation in research projects prior to their death.

Funding

Conflict of Interest

The authors report no competing interests.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author, upon reasonable request.

References

1 Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. *Lancet* 2015; **386**: 1683–97

2 Jellinger KA. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna)* 2018; **125**: 615–50

3 Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 2007; **22**(12): 1689–707. quiz 1837

4 McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017; **89**(1): 88–100

5 Hansen D, Ling H, Lashley T, Holton Jl, Warner T. Review: Clinical, neuropathological and genetic features of Lewy body dementias. *Neuropathol Appl Neurobiol* 2019; **45**: 635–54

6 Petrova M, Mehrabian-Spasova S, Aarsland D, Raycheva M, Traykov L. Clinical and Neuropsychological Differences between Mild Parkinson's Disease Dementia and Dementia with Lewy Bodies. *Dement Geriatr Cogn Dis Extra* 2015; **5**: 212–20

7 Takemoto M, Sato K, Hatanaka N, Yamashita T, Ohta Y, Hishikawa N, et al. Different Clinical and Neuroimaging Characteristics in Early Stage Parkinson's Disease with Dementia and Dementia with Lewy Bodies. *J Alzheimers Dis* 2016; **52**: 205–11

8 Park KW, Kim HS, Cheon S-M, Cha J-K, Kim S-H, Kim JW. Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's Disease Dementia: A Comparison of Cognitive Profiles. *J Clin Neurol* 2011; **7**: 19–24

9 Burn DJ, Rowan EN, Minett T, Sanders J, Myint P, Richardson J, et al. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: A cross-sectional comparative study. *Mov Disord* 2003; **18**: 884–9

10 Fritz NE, Kegelmeyer DA, Kloos AD, Linder S, Park A, Kataki M, et al. Motor performance differentiates individuals with Lewy body dementia, Parkinson's and Alzheimer's disease. *Gait Posture* 2016; **50**: 1–7

11 Del Ser T, McKeith I, Anand R, Cicin-Sain A, Ferrara R, Spiegel R. Dementia with lewy bodies: findings from an international multicentre study. *Int J Geriatr Psychiatry* 2000; **15**: 1034–45

12 Irwin DJ, White MT, Toledo JB, Xie SX, Robinson JL, Van Deerlin V, et al. Neuropathologic substrates of Parkinson disease dementia. *Ann Neurol* 2012; **72**(4): 587–98

13 Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt Ml, Lee V, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. *Neurology* 2000; **54**: 1916–21

14 Kempster PA, O'Sullivan SS, Holton Jl, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. *Brain* 2010; **133**: 1755–62

15 Mattila PM, Rinne JO, Helenius H, Dickson DW, Röyttä M, Mattila P, et al. Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. *Acta Neuropathol* 2000; **100**: 285–90

16 Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton Jl, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* 2011; **134**: 1493–505

17 Kovari E, Horvath J, Bouras C. Neuropathology of Lewy body disorders. *Brain Res Bull* 2009; **80**: 203–10

18 Tsuboi Y, Dickson DW. Dementia with Lewy bodies and Parkinson's disease with dementia: are they different? *Parkinsonism Relat Disord* 2005; **11**: S47–51

19 Irwin DJ, Grossman M, Weintraub D, Hurtig H, Duda JE, Xie SX, et al. Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol* 2017; **16**: 55–65

20 Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology* 2007; **68**: 812–9

21 Love S, Chalmers K, Ince P, Esiri M, Attems J, Jellinger K, et al. Development, appraisal, validation and implementation of a consensus protocol for the assessment of cerebral amyloid angiopathy in post-mortem brain tissue. *Am J Neurodegener Dis* 2014; **3**: 19–32

22 Thal DR, Griffin WST, de Vos RAI, Ghebremedhin E. Cerebral amyloid angiopathy and its relationship to Alzheimer's disease. *Acta Neuropathol* 2008; **115**: 599–609

23 Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, et al. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. *Acta Neuropathol* 2009; **118**: 115–30

24 Zekry D, Duyckaerts C, Belmin Jl, Geoffre C, Moulias R, Hauw J-J. Cerebral amyloid angiopathy in the elderly: vessel walls changes and relationship with dementia. *Acta Neuropathol* 2003; **106**: 367–73

25 Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. *Stroke* 2004; **35**: 2616–9

26 Neuropathology Group. Medical Research Council Cognitive, F. and S. Aging, Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* 2001. **357**: 169–75.

27 Attems J, Jellinger K, Thal D r, Van Nostrand W. Review: sporadic cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol* 2011; **37**: 75–93

28 Attems J. Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. *Acta Neuropathol* 2005; **110**: 345–59

29 Jellinger KA, Attems J. Cerebral amyloid angiopathy in Lewy body disease. *J Neural Transm (Vienna)* 2008; **115**: 473–82

30 Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. *Stroke* 1983; **14**: 924–8

31 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien J t, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; **65**: 1863–72

32 O'Sullivan SS, Johnson M, Williams DR, Revesz T, Holton JL, Lees AJ, et al. The effect of drug treatment on neurogenesis in Parkinson's disease. *Mov Disord* 2011; **26**: 45–50

33 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–98

34 Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; **17**: 427–42

35 Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord* 2004; **19**: 1020–8

36 O'Sullivan SS, Massey LA, Williams DR, Silveira-Moriyama L, Kempster PA, Holton JL, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain* 2008; **131**: 1362–72

37 Alafuzoff I, Ince PG, Arzberger T, Al-Sarraj S, Bell J, Bodi I, et al. Staging/typing of Lewy body related alpha-synuclein pathology: a study of the BrainNet Europe Consortium. *Acta Neuropathol* 2009; **117**: 635–52

38 Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 2002; **58**: 1791–800

39 Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol* 2006; **112**: 389–404

40 Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991; **41**: 479–86

41 Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol* 2012; **123**: 1–11

42 Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990; **31**: 545–8

43 Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA, et al. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. *Ann Neurol* 2011; **69**: 320–7

44 Boyle PA, Yu L, Nag S, Leurgans S, Wilson RS, Bennett DA, et al. Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons. *Neurology* 2015; **85**: 1930–6

45 Xiong L, Davidsdottir S, Reijmer YD, Shoamanesh A, Roongpiboonsopit D, Thanprasertsuk S, et al. Cognitive Profile and its Association with Neuroimaging Markers of Non-Demented Cerebral Amyloid Angiopathy Patients in a Stroke Unit. *J Alzheimers Dis* 2016; **52**: 171–8

46 Case NF, Charlton A, Zwiers A, Batool S, McCreary CR, Hogan DB, et al. Cerebral Amyloid Angiopathy Is Associated With Executive Dysfunction and Mild Cognitive Impairment. *Stroke* 2016; **47**: 2010–6

47 Banerjee G, Wilson D, Ambler G, Osei-Bonsu Appiah K, Shakeshaft C, et al. Cognitive Impairment Before Intracerebral Hemorrhage Is Associated With Cerebral Amyloid Angiopathy. *Stroke* 2018; **49**: 40–5

48 Lim SM, Katsifis A, Villemagne VL, Best R, Jones G, Saling M, et al. The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. *J Nucl Med* 2009; **50**: 1638–45

49 Huang SH, Chang C-C, Lui C-C, Chen N-C, Lee C-C, Wang P-W, et al. Cortical Metabolic and Nigrostriatal Abnormalities Associated With Clinical Stage-Specific Dementia With Lewy Bodies. *Clin Nucl Med* 2015; **40**: 26–31

50 Jokinen P, Scheinin NM, Aalto S, Någren K, Savisto N, Parkkola R, et al. [(11)C]PIB-, [(18)F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia. *Parkinsonism Relat Disord* 2010; **16**: 666–70

51 Higuchi M, Tashiro M, Arai H, Okamura N, Hara S, Higuchi S, et al. Glucose hypometabolism and neuropathological correlates in brains of dementia with Lewy bodies. *Exp Neurol* 2000; **162**: 247–56

52 Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology* 2001; **56**: 537–9

53 Charidimou A. Cerebral amyloid angiopathy-related transient focal neurological episodes (CAA-TFNEs): A well-defined clinical-radiological syndrome. *J Neurol Sci* 2019; **406**: 116496

54 Gungor I, Sarro L, Graff-Radford J, Zuk SM, Tosakulwong N, Przybelski SA, et al. Frequency and topography of cerebral microbleeds in dementia with Lewy bodies compared to Alzheimer's disease. *Parkinsonism Relat Disord* 2015; **21**: 1101–4

55 Kim SW, Chung SJ, Oh Y-S, Yoon JH, Sunwoo MK, Hong JY, et al. Cerebral Microbleeds in Patients with Dementia with Lewy Bodies and Parkinson Disease Dementia. *AJNR Am J Neuroradiol* 2015; **36**: 1642–7

56 Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry* 2012; **83**: 124–37

57 Charidimou A, Peeters A, Fox Z, Gregoire SM, Vandermeeren Y, Laloux P, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. *Stroke* 2012; **43**: 2324–30

58 Matar E, Shine JM, Halliday GM, Lewis SJG. Cognitive fluctuations in Lewy body dementia: towards a pathophysiological framework. *Brain* 2020; **143**: 31–46

59 Guerreiro R, Ross OA, Kun-Rodrigues C, Hernandez DG, Orme T, Eicher JD, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *Lancet Neurol* 2018; **17**: 64–74

60 Bras J, Guerreiro R, Darwent L, Parkkinen L, Ansorge O, Escott-Price V, et al. Genetic analysis implicates

APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum Mol Genet* 2014; **23**: 6139–46

61 Corder EH, Saunders A, Strittmatter W, Schmechel D, Gaskell P, Small G, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; **261**: 921–3

62 Borroni B, Grassi M, Costanzi C, Archetti S, Caimi L, Padovani A. APOE genotype and cholesterol levels in lewy body dementia and Alzheimer disease: investigating genotype-phenotype effect on disease risk. *Am J Geriatr Psychiatry* 2006; **14**: 1022–31

63 Garcia-Ptacek S, Kramberger MG. Parkinson Disease and Dementia. *J Geriatr Psychiatry Neurol* 2016; **29**: 261–70

64 de Lau LM, Schipper CA, Hofman A, Koudstaal PJ, Breteler MMB. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. *Arch Neurol* 2005; **62**: 1265–9

65 Attems J, Lauda F, Jellinger KA. Unexpectedly low prevalence of intracerebral hemorrhages in sporadic cerebral amyloid angiopathy: an autopsy study. *J Neurol* 2008; **255**: 70–6

66 Nelson PT, Pious NM, Jicha GA, Wilcock DM, Fardo DW, Estus S,, et al. APOE-epsilon2 and APOE-epsilon4 correlate with increased amyloid accumulation in cerebral vasculature. *J Neuropathol Exp Neurol* 2013; **72**: 708–15

67 Ringman JM, Sachs MC, Zhou Y, Monsell SE, Saver JL, Vinters HV. linical predictors of severe cerebral amyloid angiopathy and influence of APOE genotype in persons with pathologically verified Alzheimer disease. *JAMA Neurol* 2014; **71**: 878–83

68 Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathologic changes. *Neurobiol Aging* 2015; **36**: 2702–8

69 Verbeek MM, Eikelenboom P, de Waal RM. Differences between the pathogenesis of senile plaques and congophilic angiopathy in Alzheimer disease. *J Neuropathol Exp Neurol* 1997; **56**: 751–61

70 Shams S, Granberg T, Martola J, Li X, Shams M, Fereshtehnejad S, et al. Cerebrospinal fluid profiles with increasing number of cerebral microbleeds in a continuum of cognitive impairment. *J Cereb Blood Flow Metab* 2016; **36**: 621–8

71 Noguchi-Shinohara M, Komatsu J, Samuraki M, Matsunari I, Ikeda T, Sakai K, et al. Cerebral Amyloid Angiopathy-Related Microbleeds and Cerebrospinal Fluid Biomarkers in Alzheimer's Disease. *J Alzheimers Dis* 2017; **55**: 905–913

72 van Etten ES, Verbeek MM, van der Grond J, Zielman R, van Rooden S, van Zwet EW, et al. beta-Amyloid in CSF: Biomarker for preclinical cerebral amyloid angiopathy. *Neurology* 2017; **88**: 169–76

73 Mueller C, Ballard C, Corbett A, Aarsland D. The prognosis of dementia with Lewy bodies. *Lancet Neurol* 2017; **16**: 390–8

74 Blanc F, Mahmoudi R, Jonveaux T, Galmiche J, Chopard G, Cretin B, et al. Long-term cognitive outcome of Alzheimer's disease and dementia with Lewy bodies: dual disease is worse. *Alzheimers Res Ther* 2017; **9**: 47

75 Kramberger MG, Auestad B, Garcia-Ptacek S, Abdelnour C, Olmo JG, Walker Z, et al. Long-Term Cognitive Decline in Dementia with Lewy Bodies in a Large Multicenter. *International Cohort. J Alzheimers Dis* 2017; **57**: 787–95

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Severity of parkinsonism according to modified Hoehn–Yahr scale at the time of dementia and time at death.
Table S2. Frequencies of impaired cognitive domains in PDD and DLB.
Table S3. Neuropathological data for brain weight, post-mortem delay and Lewy body pathology.
Table S4. Alzheimer's disease neuropathology assessed by Thal phase for amyloid-β and Braak and Braak stage for neurofibrillary tangle tau pathology.
Table S5. Alzheimer's disease neuropathology examined by ABC scores.
Table S6. The severity of CAA pathology assessed by regional scores and the total CAA percentage score in PDD and DLB.
Table S7. APOE genotypes in PDD and DLB.
Table S8. The severity of CAA estimated by total CAA percentage scores in different *APOE* genotypes in PDD and DLB combined.
Table S9. Analysis of CAA percentages scores in a subgroup of PDD and DLB cases with lower stage of AD neuropathology (Braak and Braak NFT stages and Thal amyloid-β phases up to 3).