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The Impact of Cerebral Amyloid Angiopathy in Lewy Body Dementia: A Neuropathological Study with Magnetic Resonance Imaging Correlations

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Abstract

Background and Purpose: Cerebral amyloid angiopathy (CAA) is frequently associated to Alzheimer's disease (AD) but can also occur in Lewy body dementia (LBD). The present post-mortem study compares the incidence and the topographic distribution of small cerebrovascular lesions in LBD brains without and with severe CAA (LBD-CAA).

Materials and Methods: The incidence of these lesions was compared between fourteen LBD brains without CAA and seven with CAA on neuropathological examination of a large coronal section of a cerebral hemisphere at the level of the mamillary body and on 7.0-tesla magnetic resonance imaging (MRI) of a frontal, a central and a parieto-occipital section.

Results: only cortical micro-infarcts (CoMIs) were significantly increased in the LBD-CAA group, while the severity of the white matter changes and the number of cortical micro-bleeds were not different. On MRI the CoMIs were only increased in the frontal sections of the LBD-CAA brains. Cortical lobar haematomas were absent in both groups and isolated superficial siderosis was rare.

Discussion: Surprisingly CAA has not the same severe cerebrovascular impact in LBD compared to AD. Possibly some protective effect or the epsilon 2 allele could reduce the amyloid inducing effect of the epsilon 4allele. The frontal predominance of CoMIs in the LBD-CAA patients can be explained by the higher cerebrovascular vulnerability of this region in neurodegenerative diseases.

Keywords: Lewy Body Disease; Cerebral Amyloid Angiopathy; Neuropathology; Post-Mortem 7.0 Tesla Magnetic Resonance Imaging; White Matter Changes; Cortical Micro-Bleeds; Cortical Micro-Infarcts

List of Abbreviations: LBD: Lewy body disease or dementia; AD: Alzheimer disease or dementia; CAA: cerebral amyloid angiopathy; CoMIs: cortical micro-infarcts; CoMBs: cortical micro-bleeds; WMCs: white matter changes; CoSS: cortical superficial siderosis; MRI: magnetic resonance imaging; SD: standard deviation

Introduction

CAA is frequently associated to AD and is also a main cause of spontaneous lobar cerebral haematomas [1]. The occurrence of cerebrovascular lesions is different in CAA brains with severe and with mild AD features [2]. However, CAA with or without associated neurofibrillary tangles, can also occur in LBD [3]. Overall CoMIs are significantly prevalent in brains with LBD [4]. This is mainly considered to be due to associated arteriosclerotic cerebrovascular pathology [5]. CoMBs also prevail in LBD independently from AD pathology and CAA [6]. Arterial hypertension and older age are considered to be the main risk factors for cerebrovascular lesions in LBD. In mixed dementia diseases LBD pathology and CAA are frequently associated to AD [7-9]. So it is interesting to investigate whether CAA has the same impact on LBD as on AD, in particular concerning the frequency of associated cerebrovascular lesions.The present post-mortem study compares the incidence and the topographic distribution of these lesions in LBD brains without and with severe CAA on neuropathological examination and on 7.0-tesla MRI.

Material and Methods

Twenty-one patients with post-mortem confirmed LBD, who had been followed up at the Lille University Hospital, underwent an autopsy. The brain tissue samples were acquired from the Neuro-Bank of the Lille University federated to the 'Centre des Resources

Biologiques' that acted as an institutional review board. The incidence of cerebrovascular lesions was compared between fourteen LBD brains without CAA and seven with CAA on neuropathological examination and on 7.0-tesla MRI. The neuropathological diagnosis of LBD was made according to the report of the consortium on DLB international workshop [10]. The severity of CAA was evaluated according to a recent consensus protocol in 4 cortical samples and graded from 0 to 3 [11]. Only brains with grade 2-3 in all samples were selected for this study. Additional AD features, grade I to IV, were determined according to the Braak and Braak criteria [12]. The standard diagnostic procedure consisted of examining samples from the primary motor cortex, the associated frontal, temporal and parietal cortex, the primary and secondary visual cortex, the cingulate gyrus, the basal nucleus of Meynert, the amygdaloid body, the hippocampus, basal ganglia, mesencephalon, pons, medulla and cerebellum. Slides from paraffin-embedded sections were stained with haematoxylin–eosin, luxol fast blue and Perl. Immune-staining for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin was performed.

In addition to the detection of the macroscopic visible lesions such as haematomas, territorial and lacunar infarcts, a whole coronal section of a cerebral hemisphere at the level of the mamillary body was taken for the semi-quantitative microscopic evaluation of the small cerebrovascular lesions: WMCs, CoMBs and CoMIs. The mean values of WMCs were the average of the ranking scores: no change (R0), a few isolated (R1), frequent scattered in the corona radiata (R2) and forming confluent lesions (R3) of myelin and axonal loss. For the other cerebrovascular lesions their mean values corresponded to their average numbers in the individual brains. A 7.0-tesla MRI Bruker BioSpin SA was used with an issuer-receiver cylinder coil of 72 mm inner diameter (Ettlingen, Germany), according to a previously described method [13]. Three coronal sections of a cerebral hemisphere were submitted to SPIN ECHO T2 and T2* MRI sequences: frontal, central and parieto-occipital ones. The ranking scores of severity of the WMCs were evaluated separately on the different brain sections in the same way as done on the neuropathological section. The number of the small cerebrovascular lesions was also determined by consensus evaluation. The incidence of isolated focal CoSSs, not associated to a visible underlying lesion, was evaluated on the T2* sequence [14]. The inter-rater reliability resulted in an interclass correlation coefficient of 0.80. Statistical analysis consisted in univariate comparisons of unpaired groups, performed with the Fisher's exact test for categorical data. The non-parametric Mann-Whitney U–test was used to compare continuous variables. The significance level, two-tailed, was set at ≤ 0.05 for moderately significant, at ≤ 0.01 for significant and at ≤ 0.001 for highly significant.

Results

The average age of the LBD patients without and with CAA was similar: 80 (SD: 9) years in the former and 78 (SD: 12) years. Also the gender distribution was not statistically different with 57% male gender in those without and 71% in those with CAA. AD stage I-IV was observed in 52% of the LBD brains without and in 71% of those with CAA. Also the vascular risk factors were not statistically different between both groups (Table 1). 0n neuropathological examination only CoMIs were significantly increased in the LBD-CAA group compared to the LBD one without CAA (p = 0.01). Although more or less similar in both groups only the severity of WMCs and the frequency of CoMBs were elevated. Lobar haematomas were absent in those with and without CAA (Table 2). On MRI the CoMIs were only significantly increased in the frontal section (p = 0.01), while comparable in the central

Items LBD LBD-CAA p value
(n = 14) (n = 7)
Arterial hypertension 44 47 1.0
Diabetes 0 0 1.0.
Hypercholesterolemia 19 20 1.0
Smoking 7 7 1.0
Antithrombotic use 37 40 1.0

Table 1: Percentage comparison of the vascular risk factors in Lewy body dementia patients without (LBD) and those with cerebral amyloid angiopathy (LBD-CAA)

Items LBD LBD-CAA p value
(n = 14) (n = 7)
Cerebral lobar haematoma 0.0 (0.0) 0.0 (0.0) 1.0
Isolated superficial siderosis 0.0 (0.0) 0.0 (0.0) 1.0
Territorial infarct 0.1 (0.3) 0.0 (0.0) 1.0
Lacunar infarct 0.1 (0.3) 0.3 (0.5) 0.60
White matter changes 0.9 (0.9) 0.9 (0.9) 1.0
Cortical micro-infarct 0.8 (0.7) 1.9 (0.7) 0.01
Cortical micro-bleed 0.9 (0.8) 1.0 (0.8) 0.85

Table 2: Comparison of the severity of the cerebrovascular lesions (standard deviation) in Lewy body dementia patients without (LBD) and those with cerebral amyloid angiopathy (LBD-CAA)

and the parieto-occipital sections. WMCs and CoMiBs were equally present in the three sections of both groups. CoSSs were rare and equally distributed in all sections of LBD-CAA and LBD patients without CAA (Table 3) (Figure 1).

Items LBD LBD-CAA p value
n=14 n=7
White matter change
Frontal 1.0 (1.8) 1.3 (1.5) 0.73
Central 1.1 (0.8) 1.5 (0.5) 0.22.
Patieto-occipital 1.1 (0.6) 1.5 (1.0) 0.22
Cortical micro-infarcts
Frontal 0.7 (0.9) 2.3 (0.8) 0.01
Central 1.8 (1.0) 2.0 (0.9) 0.79
Parieto-occipital 1.7 (0.9) 1.5 (0.5) 0.40
Cortical micro-bleeds
Frontal 0.1 (0.4) 0.0 (0.0) 1.0.
Central 0.2 (0.6) 0.2 (0.4) 1.0
Parieto-occipital 0.0 (0.0) 0.0 (0.0) 1.0

Table 3: Magnetic resonance imaging comparison of the distribution and the severity of the small cerebrovascular lesions (standard deviation) in Lewy body disease (LBD) without and with cerebral amyloid angiopathy (LBD-CAA)

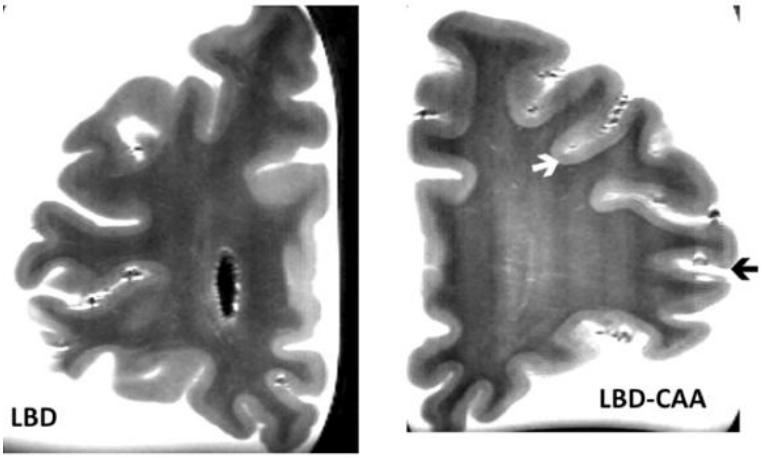

Figure 1: Spin-Echo T2 MRI of frontal sections of Lewy body (LBD) dementia without and with associated cerebral amyloid angiopathy (CAA). The arrows indicate cortical micro-infarcts in the LBD-CAA brains

Discussion

As we have previously compared the occurrence of cerebrovascular lesions in LBD to normal controls, the present study is restricted to the comparison of LBD brains with and without CAA [4-6]. The present study indicates that CAA contributes only to an increase of CoMIs in LBD. Surprisingly the other lesions included in the Boston criteria for CAA are missing: no cortical lobar haematomas, a similar incidence of CoMBs and WMCs, and the rare occurrence of CoSSs in the LBD groups with and without CAA [15,16]. The frequent additional mild AD features did not influence their occurrence [2]. The epsilon 4 allele is associated with an increase of neuritic plaques and frequency of CAA [17]. The APOE e4 is also a strong risk factor for LBD and can contribute to neurodegeneration through mechanisms unrelated to the amyloid processing [18,19]. Both LBD and AD post-mortem brains share a similar reduction of APOE DNA methylation as a possible aberrant epigenetic change [20]. A lower incidence of cerebrovascular lesions has been demonstrated in AD-CAA brains compared to CAA without AD [21]. This difference has been attributed to the interaction between APOE e4 and APOE e2 [22]. A protective effect of the epsilon 2 allele, in addition to the dose effect of the epsilon 4 allele, has been demonstrated in sporadic AD. Perhaps a similar protective effect of the epsilon 2 allele can explain the low incidence and the mild differences of cerebrovascular lesions between LDB brains with and without CAA [23]. Why CoMIs in LBD-CAA brains are more frequent in the frontal regions cannot clearly be explained. However, a previous study has demonstrated a higher incidence of CoMBs in the frontal sections of LBD brains, indicating the higher cerebrovascular susceptibility of these regions [24]. Increased and angiogenesis and microglial activation could be responsible [25]. They could lead to an increased permeability at the level of the blood-brain barrier [26,27].

Conclusion

CAA has less impact in LBD compared to AD.

Conflicts of interest

The authors have no conflicts of interest to declare.

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