Cardiovascular Disease, Diabetes Mellitus, and Hypertension in Lewy Body Disease: A Comparison with Other Dementia Disorders

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Abstract
Background: Research concerning the potential roles of cardiovascular disease (CaVD) and diabetes mellitus (DM) as risk factors for Lewy body disease (LBD) is limited. These disorders are, however, established risk factors for vascular dementia (VaD) and have been proposed as risk factors for Alzheimer’s disease (AD).
Objective: The aim of this study was to investigate the prevalence of CaVD and DM in LBD and compare the results with previous findings in cases with AD, VaD, and mixed AD-VaD (MD).
Methods: Autopsy reports at the Clinical Department of Pathology in Lund from 2001–2018 were analyzed. All cases with a complete neuropathological diagnosis of LBD were selected, not distinguishing between subjects with clinical Parkinson disease dementia and dementia with Lewy bodies, on the condition of a clinical diagnosis of dementia. Clinical data were retrieved through the patients’ medical records and the Swedish National Diabetes Register (NDR) and compared with those of the AD, VaD, and MD cases.
Results: In LBD, there was less CaVD, significantly less DM (p = 0.002) and likewise significantly less hypertension (p < 0.001) than in VaD. The results of the LBD group were consistent with the results of the AD group.
Conclusion: Our findings of a low prevalence of CaVD and CaVD risk factors in LBD and in AD argue against the association between these risk factors and their contribution to the development of neurodegenerative diseases.

Keywords: Alzheimer’s disease, autopsy, cardiovascular disease, dementia, diabetes mellitus, hypertension, Lewy body disease, risk factors, vascular

INTRODUCTION

Major neurocognitive disorder (dementia [1]) is the seventh leading cause of death and approximately 50 million people worldwide suffer from it, a number that is rapidly increasing [2]. Alzheimer’s disease (AD) is considered the most prevalent of major neurocognitive disorders with vascular dementia (VaD) being second [3–6]. Dementia with Lewy bodies (DLB), or major neurocognitive disorder with Lewy bodies [1], is the second most common neurodegenerative disease after AD [7].

Within the group of Lewy body disease (LBD), DLB is one of the diseases while Parkinson disease dementia (PDD) is another. They present similar neuropathological appearance but differentiate in their clinical expression. In DLB, the cognitive symptoms precede the motor symptoms, whereas in PDD the non-cognitive symptoms are the first sign of the

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disease [8]. These two diseases associated with Lewy body pathology are considered to be under-diagnosed clinically [9].

It is known that cerebrovascular disease (CeVD) and cardiovascular disease (CaVD) contribute to cognitive impairment and dementia in general [8, 10, 11]. Hypertension (HT) and diabetes mellitus (DM), both considered risk factors for CeVD and CaVD [8, 12–14], are known risk factors for VaD [8] and they have been suggested as risk factors for AD [15–17]. However, research on these factors is limited when it comes to LBD. Chan et al. presented a lower association of HT and DM with DLB than with AD [18]. This study, however, was based on clinical diagnoses, and it has been shown that the clinicopathological concordance in dementia diagnostics for dementia in general, as for AD and DLB, is suboptimal [7, 19–21]. We hence believe that it is necessary to investigate the question in a study based on neuropathologically confirmed cases of LBD. LBD represents a group of neurodegenerative diseases, often accompanied by AD pathology [8]. This raises the question if the two diseases will have a similar association with the studied risk factors.

In this study we compared the prevalence of CaVD and CaVD risk factors in neuropathologically confirmed cases of LBD with findings from a previous article [22], in which the same risk factors in neuropathologically confirmed cases of AD, VaD, and mixed AD-VaD (MD) were studied. The aim of the study was to investigate the correlation of cardiovascular risk factors and their prevalence in LBD compared to their prevalence in AD, VaD, and MD, respectively. The results will help to clarify the question of CaVD and DM as potential risk factors in the different dementia subtypes.

**MATERIAL AND METHODS**

**Study design**

In this retrospective observational study, we analyzed findings of CaVD and CaVD risk factors in individuals with LBD, deceased and subject to brain autopsy in Lund, Sweden between 2001 and 2018, as reported in: 1) the autopsy reports from the Department of Genetics and Pathology in Lund, using the database systems SymPathy and LIMS, in which the referrals and all macro- and microscopical autopsy findings are assembled and stored; 2) the clinical records, as available at time of autopsy and afterwards, including patient charts and archived records; and 3) the Swedish National Diabetes Register (NDR) (Gothenburg Sweden).

An approval from the Regional Ethical Review Board, Lund University, now The Swedish Ethical Review Authority, was obtained for this study, nr 2019-00051.

The findings of this study were compared with a previous study in which the same study design was used [22], concerning subjects with AD, VaD, and MD from 1992–2017.

**Subjects**

All known cases of dementia neuropathologically diagnosed in Lund between 1992 and 2018 were searched (n > 1,200 individuals, averaging 50/year). All diagnoses without a significant LBD pathology were excluded (e.g., frontotemporal dementia, vascular dementia and cases with admixture of other brain pathology than the dominating/named disease), as were cases with irretrievable or insufficient clinical data.

A clinically diagnosed dementing disease (by a specialist in cognitive disorders or by a general practitioner) was a prerequisite for inclusion, as well as a performed comprehensive neuropathological examination. We thus excluded individuals with clinically unknown (not established diagnostically) dementing disorder and we excluded cases for which the neuropathological examination had been limited to a minor investigation of only a few brain regions.

The primary neuropathological investigations had resulted in confirmation, partial confirmation, or refusal of the clinical diagnosis and were performed by one pathologist prior to this study. The procedures of brain investigation have been thoroughly described in a previous publication [19] and is in brief an extensive examination of the entire brain, covering not only specified small sampling areas but entire lobar regions and whole-brain coronal sections. The stainings used were applied as described earlier [19], searching for tau, TDP-43, synuclein, and other protein pathologies as well.

**LBD subjects and pathology definitions**

The inclusion of subjects with LBD were solely based on the neuropathological examination and not on the clinical expression, thus including LBD as a group and not distinguishing between DLB and PDD.

The LBD pathology was defined as the presence of Lewy bodies and Lewy neurites in the cortex in
addition to pathology in the brain stem and limbic structures [8, 23]. Cases with a significant presence of cortical Lewy bodies and coincident AD pathology (Braak III-V) were also included, as these pathological findings are expected to appear in cases fulfilling the clinical criteria for probable DLB [20]. Cases with only the presence of limbic Lewy bodies were excluded.

Pathology definitions of AD, VaD, and MD

Cases with AD, VaD, and MD, from 1992–2017, were analyzed in the previous study (i.e., not studied here) and were defined as follows, according to established criteria referenced in that study [22] and more recent, expanded criteria [24]—in brief:

1) AD pathology was defined by brain tau neurofibrillary tangle pathology of Braak stage III or more and of amyloid deposition and neuritic plaques without any traits of vascular or other disease [25].

2) VaD patients were defined as having clear signs of vascular-ischemic pathology (several focal infarcts, ischemic white matter rarefaction, vasculopathy of arteriosclerotic or hypertensive type, or neurons regionally reduced in number and pycnotic, while having minimal and regionally restricted AD changes (at most Braak stage II) [26], or, as often: none.

3) The MD group was defined as having a significant vascular component as well as a significant component of AD pathology (Braak stage of III or more) [27, 28].

Pathological data

The severity of atherosclerosis in the coronary arteries and the aorta was assembled from the autopsy reports. It is general routine to dissect these blood vessels and to observe the presence and degree of atherosclerosis, as by a sum impression of number of plaques, degree of calcifications in these plaques, degree of vascular stenosis, or aneurysmal changes. The pathologists all used similar terms for reporting the severity degree of sclerosis and therefore each subject’s atherosclerosis degree was converted in to a scale between 0 and 3 (based on the described severity of the findings). The carotid arteries and the circle of Willis were not assessed with the same consistency in the primary reports and were hence not being subject to grading and specific comparisons.

We used the following grading system for atherosclerosis in the coronary arteries: 1 - No atherosclerosis; 2 - Mild atherosclerosis; 3 - Moderate atherosclerosis; 4 - Severe atherosclerosis, or mentioning of stenosis

We used the following grading system for atherosclerosis in the aorta: 1 - No atherosclerosis; 2- Mild atherosclerosis; 3 - Moderate atherosclerosis; 4 - Severe atherosclerosis, or mentioning of aneurysm.

In addition, information about presence of myocardial infarction, myocardial hypertrophy on autopsy, organ weights of the brain and heart, nephrosclerosis, and the presence of atherosclerosis in the brain vessels were also collected from the autopsy reports. The reported findings had been seen macroscopically, often also confirmed microscopically, the latter procedure being specifically essential in the assessment of myocardial lesions. Of these parameters, the myocardial hypertrophy, an increased heart weight (≥500 g), and nephrosclerosis more or less as a rule connote hypertension [29–33]. These factors were thus noted but did not count alone, without notion of clinical hypertension. Because of the wide range of what is considered normal heart weight among the general population [34–36], and to prevent an exaggerated interpretation of the findings, we decided that a weight ≥500 g would be interpreted as pathological.

Intracerebral hypertensive angiopathy (HTA) was noted, if present in the autopsy reports. HTA is highly associated with hypertension and exhibits specific microstructural details [37].

Clinical data

The information regarding presence of DM was assembled through 1) the database clinical records and 2) NDR and through archival medical records. Only presence or absence of DM diagnosis were taken into count and not type of DM nor choice of treatment or age at onset. The subjects were assumed to be free of (DM) disease if no documentation regarding DM was found through the NDR or in the medical records.

Concerning the presence of hypertension, information was accessed through medical records and from medical journals and the NDR. During the relevant period, the blood pressure cut off considered diagnostic for hypertension was 140/90 [38]. All subjects with either reported hypertension in the clinical records or being treated with anti-hypertensive medication were classified as having hypertension. Choice of anti-hypertensive treatment was not considered.
The subjects were also considered to have had hypertension if HTA was reported in the autopsy reports, even if the diagnosis was not mentioned in the medical records or in the NDR. If no documentation of hypertension was found nor presence of HTA on autopsy was described, the subjects were assumed to be free of this diagnosis.

Data analysis

The statistical analyses were done using IBM SPSS Statistics 25. Concerning HT, DM, myocardial hypertrophy, prevalence of myocardial infarction, heart weight, and nephrosclerosis, the four groups (LBD, AD, VaD, and MD) were compared using crosstabs and Pearson Chi-Square test was used to test for significance and to investigate the variance in prevalence between the groups. A p-value of 0.05 was considered statistically significant. If a difference was found to be significant when testing the four groups, the same analysis was made to compare LBD with each dementia group; LBD with AD, LBD with VaD, and LBD with MD. Because several statistical tests were being performed simultaneously, adjustment of the level of significance was done using the Bonferroni correction. As four consecutive tests were performed, the level of significance (0.05) was divided by 4 (0.05/4 = 0.013).

No statistical analysis was made regarding atherosclerosis of either the aorta or the coronary arteries as these findings were based on subjective interpretations from different pathologists, converted to a scale. A statistical test concerning these findings would mean a risk of a spurious conclusion of these results.

RESULTS

Subjects

The resulting sum of cases suitable for analyses with LBD was 61 individuals, including 52 cases of DLB, 3 cases of PDD, and 6 cases of DLB with significant presence of AD pathology (≥ Braak stage of III). Among the LBD cases with significant AD pathology, 3 had Braak stage of III, 1 had stage IV, and 2 had Braak stage of V. The cases with LBD were compared with a total of 268 cases from the previous study [22], comprising 81 cases of AD, 81 106 cases of VaD, and 81 cases of MD. For demographic data on the four groups, see Table 1.

CaVD Parameters from Autopsy: aortic sclerosis, coronary sclerosis, myocardial pathology, heart weight, nephrosclerosis, and intracerebral hypertensive angiopathy.

Data on the LBD cases regarding the CaVD parameters from autopsy were obtained in most of the cases (see Table 2), except from 8 (13%) cases which were only subjected to neuropathological examination of the brain and not a full autopsy.

The degree of atherosclerosis for both the coronary arteries and the aorta was compared as two categories, none to mild atherosclerosis and moderate to severe atherosclerosis.

Regarding the severity of coronary sclerosis, the LBD group was close to AD in having a high prevalence of severity grades 0 and 1 (none to mild atherosclerosis) and a low prevalence of severity grades 2 and 3 (moderate to severe atherosclerosis) (see Table 3). The MD and the VaD group presented with the opposite relation of sclerosis, a low preva-
Table 3
Prevalence of the studied cardiovascular pathologies and risk factors among the different dementia diagnoses. Confirmed data∗ compared to obtainable data∗∗. Macro- and microscopical findings (white background) and clinical data (grey background)

| Variables, n (%) | LBD | AD1 | MD1 | VaD1 | LBD | LBD | LBD |
|------------------|-----|-----|-----|------|-----|-----|-----|
|                  |     |     |     |      |     |     |     |
| Aortic sclerosis | n = 61 | n = 81 | n = 81 | n = 106 | AD | MD | VaD |
| None-Mild        | 21 (40) | 32 (41) | 18 (23) | 7 (7)   |
| Moderate-Severe  | 31 (60) | 46 (59) | 62 (77) | 95 (93) |
| Total**          | 52     | 78    | 80    | 102    |
| Coronary sclerosis | n = 52 | n = 80 | n = 81 | n = 104 |
| None-Mild        | 25 (48) | 48 (60) | 15 (19) | 21 (20) |
| Moderate-Severe  | 27 (52) | 32 (40) | 66 (81) | 83 (80) |
| Total**          | 52     | 80    | 81    | 102    |
| Myocardial Hypertrophy* | 14 (26) | 20 (25) | 27 (34) | 53 (52) |
| Total**          | 53     | 80    | 80    | 102    |
| Signs of Infarction* | 17 (33) | 22 (28) | 33 (41) | 77 (75) |
| Total**          | 53     | 80    | 80    | 102    |
| Nephrosclerosis* | 16 (31) | 25 (45) | 38 (60) | 66 (68) |
| Total**          | 51     | 55    | 63    | 97     |
| Pathological Heart Weight >500 g/Median* | 4/361 (11) | 5/337 (6) | 8/348 (11) | 29/433 (29) |
| Total**          | 50     | 77    | 75    | 101    |
| Diabetes*        | 5 (8) | 6 (12) | 11 (19) | 21 (31) |
| Total**          | 59     | 50    | 57    | 67     |
| Hypertension*    | 21 (36) | 21 (37) | 26 (44) | 60 (74) |
| Total**          | 59     | 57    | 59    | 81     |

LBD, Lewy body disease; AD, Alzheimer’s disease; MD, mixed dementia; VaD, vascular dementia. 1Presented in a previous publication [23]. a Count (percentage within each dementia group). b Chi-square value between each compared dementia group adjusted with Bonferroni correction: p = 0.05/4 = 0.013. c Significant results. X – No statistical analysis was made. ∗Confirmed cases among the obtainable data. **Obtainable data.

rence of none to mild atherosclerosis, and a high prevalence of moderate to severe atherosclerosis (see Table 3).

A similar pattern of results applied for atherosclerosis of the aorta. The cases with none to mild atherosclerosis were most prevalent among the AD and the LBD groups, whereas the cases with moderate to severe atherosclerosis were most frequently seen in the VaD group followed by the MD group (see Table 3).

Myocardial infarctions, including acute and subacute myocardial infarctions as well as older ischemic myocardial lesions were prevalent in 33% of the LBD group. This was a lower prevalence than seen in the MD group (41%) and the VaD group (75%) (p = 0.31 and p < 0.001, respectively) but a higher prevalence than in the AD group (28%) (p = 0.54) (See Table 3).

Cardiac and myocardial hypertrophy was found in 26% of the LBD cases, significantly lower than in the VaD group (52%) (p = 0.002), but not when compared with MD (34%) and AD (25%) (p = 0.35 and p = 0.85, respectively) (See Table 3).

The median heart weight in the LBD group was 361 g (interquartile range (IQR) = 295 – 426), 4 (11%) cases with a weight above 500 g. When comparing the LBD group with the other three groups regarding number of cases with a pathological heart weight (≥500 g), there was no significant difference after adjusting with Bonferroni correction (see Table 3).

Nephrosclerosis was seen in 68% of the VaD cases, 60% of the MD cases, 45% of the AD cases and 31% of the LBD cases (see Table 3). When comparing LBD with the three other groups, the comparison with the MD and the VaD group attained significant results (p = 0.008 and p < 0.001, respectively), but not when comparing with AD (p = 0.36).

HTA was found at neuropathological work-up in 6 cases with LBD, whereas 3 of these had no mentioning or diagnosis of HT in their medical records. The highest prevalence of HTA was found in the VaD group (n = 21), and the lowest in the AD group (n = 2).

CaVD associated diseases: Hypertension and diabetes

Data on HT in LBD, AD, MD, and VaD were obtained in 97%, 70%, 73%, and 76%, respectively, while data on DM in LBD, AD, MD, and VaD were obtained in 97%, 62%, 70%, and 63%, respectively (see Table 2).
Regarding HT and DM, both diseases were most prevalent in the VaD group, 74% and 31% respectively, and the least prevalent in the LBD group, 36% and 8%, respectively \( (p < 0.001 \) and \( p = 0.002 \), respectively). The AD group had a similar prevalence of HT and DM as the LBD group (37% and 12%), whereas the MD group was in-between that of the AD and the VaD group, 44% and 19%, respectively \( (p < 0.001 \) and \( p = 0.002 \), respectively). The findings in the LBD group regarding both HT and DM did not attain significant results when compared with the AD group and the MD group.

The LBD cases with significant presence of AD pathology \( (n = 6) \) (Braak stage of III or more), had similar prevalence of HT and DM as well as CaVD parameters from autopsy as the rest of the LBD group.

**DISCUSSION**

In this study, we presented the prevalence of CaVD and CaVD risk factors; DM and HT, as stated in the autopsy reports, clinical and national register in neuropathologically diagnosed cases with LBD. The findings were compared with prevalences in a previous article \[22\], in which the same risk factors in neuropathologically confirmed cases of AD, VaD, and mixed AD-VaD (MD) were studied. Since LBD is considered a neurodegenerative disease often accompanied with AD pathology \[8\], it seemed possible to assume, as our results also indicate, that the presence of CaVD, HT, and DM in the cases with LBD would be consistent with, or close to the findings in the AD group. Also, it seemed likely to assume that the findings would be inconsistent with the findings in the VaD group as the diseases exhibit dissimilar pathologies.

A reason for the different prevalences of CaVD and DM in the neurodegenerative diseases compared to VaD could be that factors that are associated with increased age and neurodegenerative disease, such as weight loss, decline in blood pressure, and sympathetic denervation, reverse the effect of the mid-life risk factors \[39, 40\]. Hence, CaVD and diabetes at mid-life could still not be ruled out as risk factors for AD and LBD even though they are clearly less prevalent in these dementia subtypes \[41\].

**Atherosclerosis of the aorta and coronary arteries**

Among our cases with LBD we found a low severity degree of atherosclerosis in the aorta and the coronary arteries when comparing with the other groups, of which only the AD group had an even lower severity degree. These results are also interesting as they display a strong difference with the atherosclerosis in the VaD group, where 80% and 93% of the cases presented with moderate to severe atherosclerosis in the coronary arteries and the aorta, respectively.

The prevalence of atherosclerosis in the LBD group was corroborated by the findings of myocardial infarction on autopsy, a marker that we interpret as a general vascular pathology condition, which was second lowest in the LBD group and with a significant difference in prevalence only when compared with the VaD group. These results are supported by Ghebremedin et al. who presented an inverse correlation of Lewy body pathology and the severity of atherosclerosis \[42\] and in the Honolulu-Asia Aging study which presented an association between low values of ankle-to-brachial index (atherosclerosis) and VaD \[43\].

Studies suggest that CeVD and atherosclerosis contribute to cognitive impairment, dementia, and to AD \[10, 11\]. Our findings clearly support the contribution of CeVD and atherosclerosis to VaD \[6, 8\]. However, when looking at the prevalence of atherosclerosis and general vascular pathology (myocardial infarction) in the LBD and AD groups, our results suggest that the relationships are more complex.

**Diabetes**

Diabetes is accepted as a risk factor for cognitive impairment and cognitive decline \[44\]. Studies regarding DM as a risk factor for LBD; however, are both few and inconsistent, where some studies support the claim \[45\], others do not \[46\]. The prevalence of DM in our cases with LBD (8%) was lower than in all the other three dementia groups, even AD (12%). As mentioned above, this was presented in a previous study, where Chan et al. showed a lower association of DM with LBD (both DLB and PDD) than with AD \[18\]. The prevalence of DM in our LBD group was also lower compared to the normal Swedish population (15.6%), at a similar age (>65 years). Our findings, of a low prevalence of DM, both among the cases with LBD as well as AD, should be considered a strong support against the claims of DM as a risk factor for these diseases \[45\].
Hypertension

Hypertension is an established risk factor for CeVD and CaVD and therefore known to contribute to the development of dementia and mostly to VaD [8, 12, 14]. However, studies are not in agreement when it comes to the connection and contribution of HT as a risk factor for AD and LBD [16, 18, 47, 48]. Chan et al. showed that the vascular risk factors (systolic blood pressure included) are significantly fewer in PDD and DLB compared to AD [18]. The prevalence of HT in our cases with LBD mimicked the findings in the AD group (36% compared to 37%) and were significantly lower than in the VaD group (74%). Both AD and LBD are associated with orthostatic hypotension (OH) and autonomic dysfunction (mostly LBD) [49]. OH is also found to be more prevalent in LBD than in VaD [49]. Perhaps this association is what contributes to the low prevalence of HT in the two neurodegenerative diseases. However, the possible effect and connection between mid-life HT and late-life OH is unclear.

The prevalence of myocardial hypertrophy, increased heart weight and nephrosclerosis, changes highly associated with hypertension [29–32], were also low in the cases with LBD and thus corroborated the findings of low prevalence of HT in the LBD group. The same was found regarding HTA in the brain, a disorder highly associated with HT [37].

Strengths and weaknesses

A strength of this study, as with the previous article [22], was that the confirmation of diagnosis was made by the same pathologist throughout the observation period and that the diagnostic procedures had the similar format.

The autopsies were carried out by different pathologists which could in some cases lead to different interpretations of the severity degree of cardiovascular and cerebrovascular disease, even though the pathologists were trained to follow the same general routine and template regarding performance and reporting of autopsies. Further, this was a retrospective study and as such, possibly providing both a limitation and an advantage that the autopsies were carried out without the current study in mind. However, a strength of this study design is that the clinical diagnoses DM and HT, were obtained by clinicians not affiliated with the current study, hence “blinded” to the objectives of the present study.

Since the cases with LBD were from 2001–2018, it was easier to access clinical data and the medical records (97%) compared to the previous study which had cases from 1992–2017. However, the cases with LBD had a lower amount of obtainable data regarding CaVD and organ/tissue findings since 8 (13%) cases were subjected to neuropathological examination of the brain only and not a full autopsy. These cases were omitted in the respective statistical analysis which hence somewhat weakened the calculations.

In summary, the present and our previous study together showed a similar and low prevalence of CaVD and CaVD risk factors in cases with LBD and AD, differing from cases with VaD which exhibited the highest prevalence of all studied disease manifestations and of both DM and HT. The MD group exhibited a lower prevalence than the VaD group, but a higher prevalence than the LBD group and the AD group.

Conclusion

We showed that LBD exhibits a low prevalence of CaVD, a relatively low prevalence of hypertension and a low prevalence of diabetes and thus this lends support against the association between LBD and CaVD and CaVD risk factors. Together with similar findings in AD, this study brings strong evidence against CaVD disease, DM, and HT and their contribution to the development of neurodegenerative diseases.

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