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The influence of vascular risk factors on the survival rate of patients with dementia with Lewy bodies and Alzheimer disease

Wpływ naczyniowych czynników ryzyka na przeżycie pacjentów z otępieniem z ciałami Lewy'ego i chorobą Alzheimera

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Abstract

Background and purpose: The aim of this study was to determine whether dementia with Lewy bodies (DLB) progresses more rapidly than Alzheimer disease (AD) and to compare survival after dementia onset and mortality in both dementia groups.

Material and methods: A medical records analysis of AD ($n = 183$) and DLB ($n = 51$) patients was performed to determine age at onset of symptoms, the date of first presentation to the psychiatric services, dementia severity at diagnosis (MMSE score), and mean disease duration before diagnosis. Categorical data regarding vascular risk factors were collected. Projected decline rate (MMSE/year), survival rate after the diagnosis of dementia, mean survival time after diagnosis and mortality rate were calculated and compared between DLB and AD groups.

Results: The comparison of clinical and demographic parameters revealed no significant differences between groups, apart from a more pronounced decline rate in the DLB group. Diabetes, and to a lesser extent hypertension, influenced survival in AD, but not in DLB subjects. Overall, however, the difference in mortality rates and survival time between DLB and AD subjects cannot be attributed to the presence of any vascular risk factor analysed. DLB, independently of the presence of vascular risk factors, seems to be a more aggressive disorder than AD, when mortality and survival time are taken into account.

Streszczenie

Wstęp i cel pracy: Celem pracy była ocena szybkości progresji otępienia oraz śmiertelności w otępieniu z ciałami Lewy'ego (DLB) i porównanie uzyskanych wartości do obserwowanych w chorobie Alzheimera (ChA).

Materiał i metody: Dokonano retrospektywnej analizy dokumentacji chorych na ChA ($n = 183$) i DLB ($n = 51$) i określono wiek zachorowania, wiek zgłoszenia do placówki psychiatrycznej, nasilenie otępienia w chwili rozpoznania (punktacja MMSE) oraz średni czas trwania choroby przed ustaleniem rozpoznania. Zebrano także dane dotyczące naczyniowych czynników ryzyka. Dla obu otępień dokonano porównania wyznaczonego tempa progresji otępienia (MMSE/rok), wskaźnika śmiertelności i czasu przeżycia po rozpoznaniu otępienia.

Wyniki: Obie badane grupy były porównywalne pod względem zmiennych demograficznych, z wyjątkiem oszacowanego tempa progresji otępienia, większego w DLB niż w ChA. Cukrzyca, i w mniejszym stopniu nadciśnienie, wpływały na długość przeżycia u chorych na ChA, ale nie w DLB. Obecność jakiegokolwiek z czynników ryzyka nie wyjaśniała jednak stwierdzonych różnic w śmiertelności i czasie przeżycia pomiędzy ChA a DLB. Biorąc pod uwagę wskaźnik śmiertelności i czas przeżycia, DLB, niezależnie od obecności naczyniowych czynników ryzyka, wydaje się być chorobą o bardziej agresywnym przebiegu niż ChA.

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Conclusions: More rapid progression of cognitive decline and shorter duration of dementia were found in DLB in this naturalistic study. The findings may have important implications for the management and treatment of DLB and should be confirmed in prospective studies.

Key words: dementia with Lewy bodies, Alzheimer disease, survival, mortality, risk factors.

Wnioski: W naturalistycznym badaniu wykazano szybszą progresję zespołu otępiennego i krótszy czas trwania choroby w DLB. Stwierdzone zależności, mogące mieć istotne implikacje dla diagnostyki i leczenia chorych na DLB, wymagają potwierdzenia w badaniach prospektywnych.

Słowa kluczowe: otępienie z ciałami Lewy'ego, choroba Alzheimera, czas przeżycia, śmiertelność, czynniki ryzyka.

Introduction

Following Alzheimer disease (AD), dementia with Lewy bodies (DLB) has been suggested to be the second most common type of degenerative dementia in older people [1]. Substantial variation in the prevalence of DLB has been reported, with estimates ranging from 0 to 26.3% of all dementia cases, accounting for approximately 20% of cases in autopsy series [2,3], 0 to 5% with regard to the general population [4], and about 10% in psychogeriatric outpatient unit cohorts [5].

The clinical progression of AD is well characterized, with disease duration from 2 to 20 years. The median survival times ranged from 8.3 years for persons diagnosed as having AD at age 65 to 3.4 years for persons diagnosed as having AD at age 90 [6]. Conflicting data have been published in the field of the progression rate of DLB compared to AD. In some studies it was suggested that the mean duration of illness (from diagnosis to death) is shorter in DLB patients [7,8]. More recent papers have not confirmed significant differences between DLB and AD in age at onset, rate of cognitive decline, age at death or survival [9], but a greater risk for the progression of non-cognitive symptoms for DLB compared to AD was reported [10,11].

The goal of this study was to determine whether DLB progresses more rapidly than AD and to compare the differences in mortality between dementia groups as related to diabetes and other vascular risk factors.

Material and methods

The study was naturalistic and retrospective. A total of 234 (AD, $n = 183$; DLB, $n = 51$) charts from the university-based AD outpatient unit were reviewed. Of those, prospective data for 103 AD and 47 DLB subjects were available for follow-up analyses. All patients were monitored and treated by the authors of the report, which allows for strict drug regimen monitoring during the study. The majority of subjects have been visiting the department regularly once in 4-6 weeks for clinical examination.

All DLB subjects fulfilled the Consortium on DLB International Workshop Criteria for probable DLB [12,13]. In the present study, the diagnosis of DLB was established based on the previous versions of the diagnostic criteria, since the current criteria were published after we had diagnosed the study participants [14]. All AD patients were diagnosed using the NINCDS-ADRDA criteria [15]. The medical records of all patients were reviewed to determine age at onset of symptoms, the date of first presentation to the psychiatric services, dementia severity (Mini-Mental State Examination, MMSE), and mean disease duration before diagnosis. Categorical (present or absent) data regarding vascular risk factors (diabetes, hypertension, stroke and/or transient ischaemic attack [TIA], atrial fibrillation [AF], hypercholesterolaemia and the presence of vascular lesions on neuroimaging) were collected. Diabetes, hypertension and hypercholesterolaemia were regarded as present if either a medical record confirming each diagnosis existed or a patient was on specific treatment; AF, stroke and/or TIA were regarded as present relying on medical records. Patient's clinical documentation was analysed regarding the use of standardized criteria for each vascular factor and their existence was counted only if there were enough data to acknowledge it.

Projected decline rate (MMSE/year), survival after diagnosis of dementia and mortality rate were calculated and compared between DLB and AD groups.

Systematic analysis of the presence and severity of parkinsonism, psychotic symptoms, depression and activities of daily living was performed for the representative and well-matched subgroups of AD and DLB subjects (AD, $n = 23$, DLB, $n = 20$). For those purposes the Geriatric Depression Scale (GDS), the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS), the Neuropsychiatric Inventory (NPI) and the Activities of Daily Living (ADL) were used. Data

Table 1. Clinical and demographic characteristics of the population studied at study entry

	Alzheimer disease group (n = 103)	Dementia with Lewy bodies group (n = 47)	P-value* for the difference between groups
Gender, fraction of women	70/103	33/47	0.8
Mean age at diagnosis, years (mean ± SD)	78.1 ± 4.9	76.6 ± 4.4	0.06
Mean age at symptom onset, years (mean ± SD)	74.1 ± 4.5	73.4 ± 4.4	0.4
Mean MMSE at diagnosis, pts. (mean ± SD)	20.3 ± 3.1	19.9 ± 4.0	0.5
Mean disease duration before diagnosis, years (mean ± SD)	4.0 ± 1.9	3.1 ± 1.5	0.004
Calculated disease progression, MMSE score/year (mean ± SD)	2.8 ± 1.1	4.0 ± 2.4	0.001

SD – standard deviation, MMSE – Mini-Mental State Examination

**Independent samples t-test except for gender (Pearson's χ^2)*

on antipsychotics and pro-cognitive drug use were also collected and analysed.

Statistical analyses were performed using SPSS for Windows, v.15.0. Progression to death was the primary outcome measure. Descriptive statistics were used to compare demographic data. Kaplan-Meier survival curves were constructed to estimate the survival distribution for all participants, and log-rank tests were used to compare survival distributions between groups.

Results

The initial population and the final study group were comparable in terms of mean age at onset, age at diagnosis, and MMSE-rated dementia severity at diagnosis. Both groups had a greater proportion of women. Mean disease duration before diagnosis was significantly shorter for the DLB group. Calculated disease progression (expressed as mean loss of MMSE points per year) was significantly different between groups (AD 2.8 ± 1.1, and DLB 4.0 ± 2.4; $p = 0.001$). Detailed characteristics of patients included in the follow-up analysis and calculated progression rates are provided in Table 1.

At follow-up (median follow-up time was 8 years, range 4-13 years) significantly more subjects with DLB than AD had died. Crude mortality rate was 53.2% for the DLB and 30.1% for the AD group (Pearson's ($\chi^2 = 17.4$; $p = 0.007$). Estimated survival time was about 2 years shorter for DLB (see Table 2 and Fig. 1 for details).

Table 2. Estimated survival time (years) for dementia with Lewy bodies (DLB) and Alzheimer disease (AD) patients ($p < 0.001$ for the difference between groups)

Diagnosis	Mean	
	Estimate	Standard deviation
Dementia with Lewy bodies	6.3	0.4
Alzheimer disease	8.3	0.4
Overall	7.4	0.3

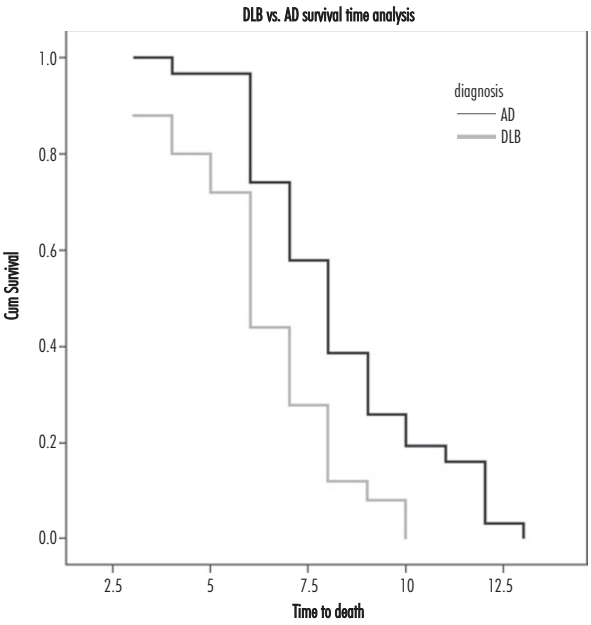

Fig. 1. Kaplan-Meier survival curves comparing the survival time analysis for dementia with Lewy bodies (DLB) vs. Alzheimer disease (AD). AD group is represented by black line and DLB group is represented by grey line

Table 3. Vascular risk factors load for both diagnostic groups

	Alzheimer disease group (fraction)	Dementia with Lewy bodies group (fraction)	*P*-value* for the difference between groups
Diabetes			
absent	70/103 (0.68)	36/45 (0.80)	
present	33/103 (0.32)	9/45 (0.20)	0.16
Stroke			
absent	89/103 (0.86)	43/45 (0.95)	
present	14/103 (0.13)	2/45 (0.04)	0.15
TIA			
absent	86/103 (0.83)	37/44 (0.84)	
present	17/103 (0.16)	7/44 (0.16)	1.0
Stroke or TIA in anamnesis			
absent	77/103 (0.74)	36/44 (0.81)	
present	26/103 (0.25)	8/44 (0.18)	0.4
Hypertension			
absent	57/103 (0.55)	26/45 (0.57)	
present	46/103 (0.44)	19/45 (0.42)	0.86
Atrial fibrillation			
absent	85/95 (0.89)	41/45 (0.91)	
present	10/95 (0.10)	4/45 (0.08)	1.0
Hypercholesterolaemia			
absent	78/103 (0.75)	32/45 (0.71)	
present	25/103 (0.24)	13/45 (0.28)	0.63
Vascular lesions on neuroimaging			
absent	76/97 (0.78)	40/45 (0.88)	0.16
present	21/97 (0.22)	5/45 (0.11)	

**Pearson's χ^2*

Factors potentially influencing survival time were isolated and analysed. We collected data on diabetes, stroke, TIA, hypertension, AF, hypercholesterolaemia and vascular changes on neuroimaging. Both groups were comparable in terms of the presence of vascular risk factors. Vascular risk factors load for both diagnostic groups is presented in Table 3.

An analysis of the influence of particular risk factors on survival time was performed, with the strongest correlations being found for diabetes. Mean survival time for DLB cases with diabetes was similar to the DLB group without diabetes (6.7 vs. 6.3 years). Mean survival time for AD cases with diabetes was significantly shorter when compared to the AD group without diabetes (6.3 vs. 9.1 years). When diabetes is present, the survival curve for AD cases overlaps the curve for DLB cases (data presented in Figs. 2A and 2B).

Similarly, the analysis of data revealed that hypertension shortens survival time for AD cases as well. Mean survival time for DLB cases with hypertension was similar to the DLB group without hypertension (6.3 vs. 6.5 years). Mean survival time for AD cases with hypertension was shorter when compared to the AD group without hypertension (7.9 vs. 8.6 years). When hypertension is present, the survival curve for AD cases tends to overlap the curve for DLB cases, but the observed effect is not statistically significant (data presented in Figs. 3A and 3B).

Other analysed factors did not differentiate the examined groups. History of stroke or TIA shortened

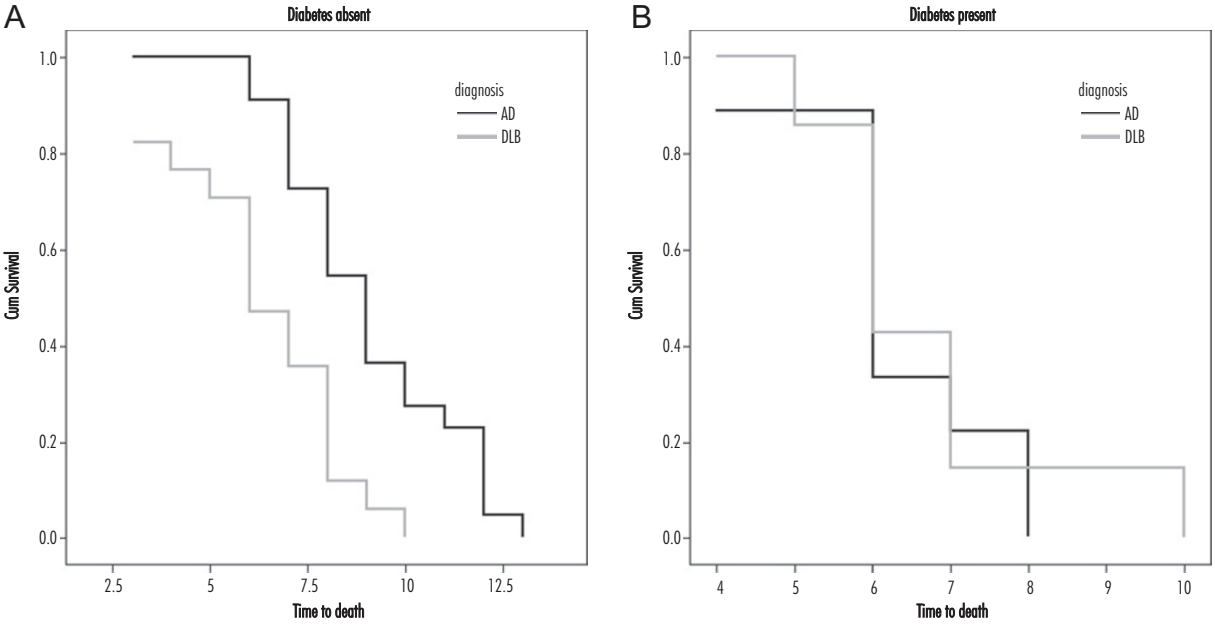

Fig. 2. Kaplan-Meier survival curves comparing dementia with Lewy bodies (DLB) vs. Alzheimer disease (AD) survival time for diabetes. (A) diabetes absent; (B) diabetes present. AD group is represented by black line and DLB group is represented by grey line

survival time. In the group without stroke/TIA survival time was 8.7 and 6.6 years (AD vs. DLB, respectively). For those with the presence of stroke/TIA, survival time was 7.4 and 5.5 years (AD vs. DLB, respectively). The observed effect was statistically significant, but did not allow for differentiating between the examined dementia groups.

Finally, a stratified Cox regression analysis was executed with backward conditional method of entering variables into the model employed. The final model

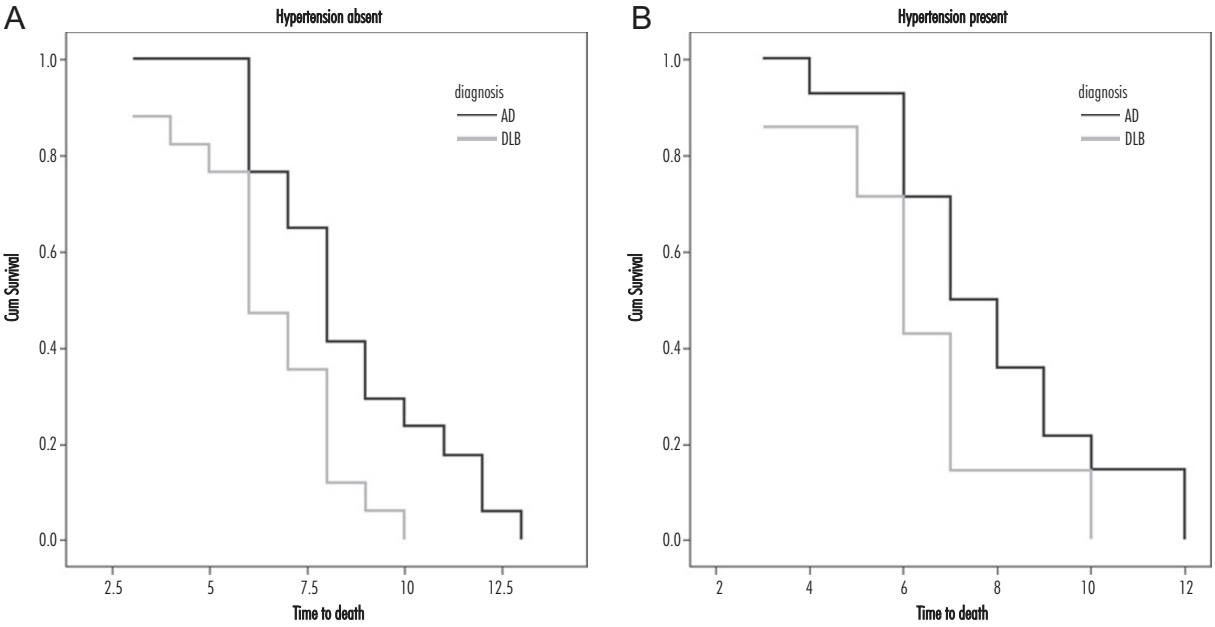

Fig. 3. Kaplan-Meier survival curves comparing dementia with Lewy bodies (DLB) vs. Alzheimer disease (AD) survival time for hypertension. (A) hypertension absent; (B) hypertension present. AD group is represented by black line and DLB group is represented by grey line

Table 4. Gender comparison of survival time in diagnostic groups

Gender	Study group	Estimated survival time, years (mean ± SD)	Within gender comparison of survival time in diagnostic groups
Female	AD ($n = 91$)	10.7 ± 0.6	$p < 0.0001$
	DLB ($n = 26$)	7.8 ± 0.5	
Male	AD ($n = 38$)	12.1 ± 0.5	$p < 0.0001$
	DLB ($n = 17$)	6.9 ± 0.5	

AD – Alzheimer disease, DLB – dementia with Lewy bodies

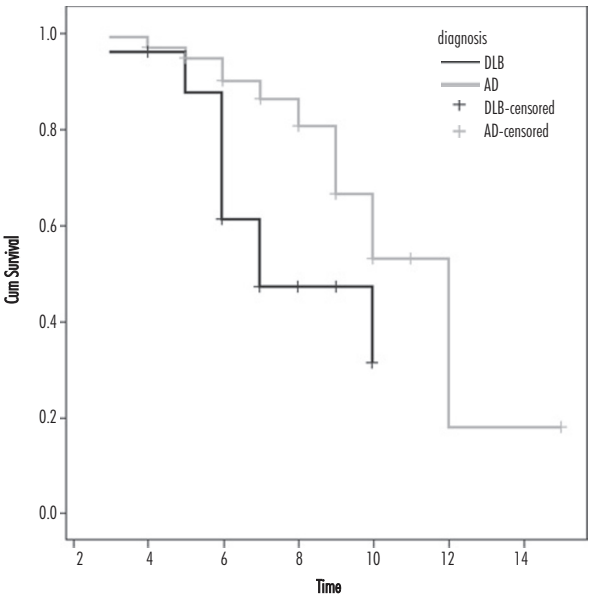

Fig. 4. Kaplan-Meier survival curves comparing dementia with Lewy bodies (DLB) vs. Alzheimer disease (AD) survival time for female gender. AD group is represented by grey line and DLB group is represented by black line

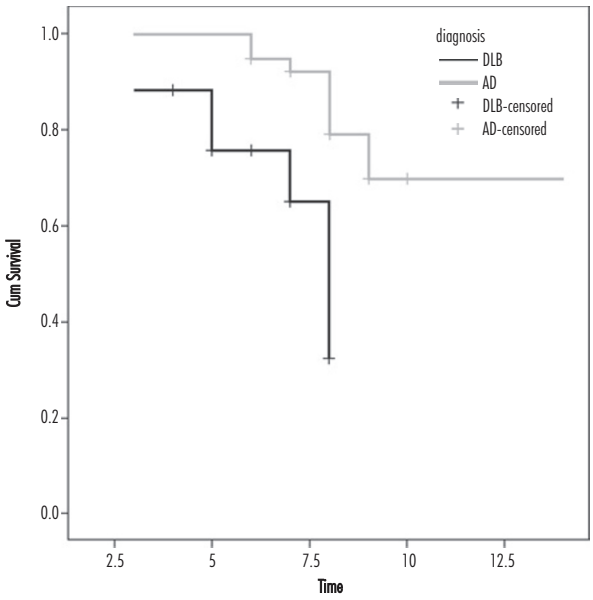

Fig. 5. Kaplan-Meier survival curves comparing dementia with Lewy bodies (DLB) vs. Alzheimer disease (AD) survival time for male gender. AD group is represented by grey line and DLB group is represented by black line

included age, progression rate and the presence of TIA (omnibus test of model coefficients; ($\chi^2 = 17.5$; $p = 0.001$). As this effect is difficult to understand, further analyses are needed to clarify the validity of this finding.

A sub-analysis of other risk factors was also performed. For this purpose we selected and matched AD and DLB cases ($n = 129$ and $n = 43$, respectively; ratio 3 : 1). The examined populations were comparable in terms of mean age, age at onset and MMSE-rated dementia severity (data not presented). Both groups had more women than men.

Significant differences in the survival time were revealed between the dementia groups when gender was taken into analysis. Survival time for women was longer when compared to men in the DLB group (7.8 vs. 6.9 years; mean difference 0.9; $t = -5.8$; $p < 0.001$); surprisingly, the opposite trend was observed in the AD group, with longer survival time for men (10.7 vs. 12.1 years; mean difference 1.4; $t = 12.7$; $p < 0.001$). The between-dementia difference in survival time (DLB vs. AD) is more pronounced in males compared to females (5.2 vs 2.9 years). Details of AD vs DLB comparison are presented in Table 4 as well as in Fig. 4 and Fig. 5.

Stratified Cox regression analysis was performed to find out whether baseline demographic variables other than gender influence estimated survival time in DLB

Table 5. Logistic regression coefficients analysis

	β	SE	Wald statistics	df	*p*-value	Exp(β) (hazard ratio)	95% CI for Exp(β)
Calculated rate of progression	0.26	0.08	9.4	1	0.002	1.3	1.1-1.6
Age at onset	0.02	0.03	0.3	1	0.6	1.0	0.9-1.1
MMSE	–0.04	0.05	0.8	1	0.4	0.9	0.9-1.1

vs. AD groups. Age at onset, MMSE at diagnosis and calculated progression rate were used as covariates and diagnostic groups as strata. The omnibus test of model coefficients revealed that the model as a whole was significant ($p = 0.006$). However, logistic regression analysis proved that the only variable influencing estimated survival time was the calculated rate of dementia progression (data presented in Table 5).

Discussion

Many studies present conflicting evidence as to whether DLB progresses more rapidly than AD. Limitations of many of them are small sample sizes, short follow-up periods, lack of autopsy verification of clinical diagnoses, or analysis of retrospective data from autopsy series. Most of them are focused on the analysis of survival time, mortality rates, and disease progression without assessment of risk factors.

Some studies revealed that the rate of decline and mortality in DLB is similar to that of AD [9,10,16], while others indicate shorter survival for patients suffering from DLB [8]. Data on clinical or non-neuropathological risk factors are limited.

The goal of this study was to determine whether DLB progresses more rapidly than AD and to compare the differences in mortality between dementia groups as related to diabetes and other vascular risk factors.

Using well-characterized, and demographically well-matched groups of AD and DLB subjects, we demonstrated that individuals with DLB have shorter time to death, either as overall mortality or from disease onset, compared with AD. The same findings were reported by Williams *et al.* [11], based on examination of a neuropathologically defined sample of subjects with AD and DLB.

We also examined the effect of a number of covariates on survival. The presence of diabetes had a significant survival time modifying effect in AD cases, which is difficult to explain. There is a well-known association between vascular risk factors, clinically overt cognitive decline and vascular dementia but also AD [17]. The risk of AD is increased in cases with diabetes mellitus, hypertension, atherosclerotic disease and AF [18]. Lu *et al.* have published a meta-analysis of data on the association between diabetes and the risk of various geriatric conditions [19]. They found that diabetes was associated with a 47% increased risk for all dementia, 39% for Alzheimer dementia, and more than two-fold higher risk for vascular dementia among community-dwelling older adults. The association between diabetes and dementia was independent of cardiovascular comorbidities. AD and diabetes share several molecular pathways. Disturbances in insulin signalling, insulin growth factor (IGF) and transforming growth factor (TGF) dysfunctions, misfolding of proteins and deposition of fibrillar protein aggregates, and specific cell degeneration and death appear to be essential for both conditions [20,21]. Evidence on the association between diabetes and cognitive decline in DLB has not been published yet.

Similarly to diabetes, the presence of hypertension had a modifying effect on survival time in AD cases. Other analysed vascular risk factors did not differentiate between the examined groups.

Our study also demonstrates a significant gender effect on outcomes. Survival time was longer for women when compared to men in the DLB group; surprisingly, the opposite was observed in the AD group, with longer survival time for men. The between-dementia difference in survival time (DLB vs. AD) was more pronounced in males than in females. Opposite results were published by Williams *et al.* [11]. They found that the overall mortality was higher in men with DLB, whereas time after diagnosis and survival time were shorter for nursing home female patients with DLB. In each case, the longest surviving group was women with AD.

Several methodological issues limit the interpretation of the results of this study. Firstly, only a retrospective analysis was performed. Secondly, the diagnosis relied solely on the clinical picture, without pathologi-

cal confirmation. The consensus clinical criteria for the diagnosis of DLB [12] suffer from poor sensitivity, particularly for individuals with concurrent AD pathology [22-24]. The majority of patients with DLB have mixed AD and Lewy body pathologies while only a small subset of DLB patients demonstrate pure Lewy body pathology at autopsy [23]. As patients with mixed pathology are often difficult to distinguish clinically from those with AD, some researchers decide to examine outcomes only in neuropathologically, rather than clinically defined groups [11].

Thirdly, the number of DLB patients included in this study was small when compared to the AD group, and for that reason they were matched to a larger number of AD subjects.

Finally, the majority of participants underwent elaborate neuropsychological examination and examination with a clinical test battery at diagnosis and follow-up but only MMSE could be traced for all subjects included in the study. For this reason, the projected disease progression was expressed as MMSE decline/year.

Despite these limitations, we are confident about the reliability of our findings, with diagnosis being carefully established with widely accepted clinical criteria and magnetic resonance imaging (data not presented in this paper), and a comprehensive set of tools for clinical and neuropsychological evaluation being used.

The strengths of this study include the large number of individuals well matched clinically and demographically and the long period of follow-up (median follow-up time was 8 years, range 4-13 years). Other studies followed up the patients only for one or three years [9,16].

The presence of psychotic symptoms, parkinsonism, depression and antipsychotic treatment can influence survival time and mortality rate in demented patients. A systematic analysis of the presence and severity of parkinsonism, psychotic symptoms and depression was performed for the representative and well matched subgroups of AD and DLB subjects (AD, $n = 23$; DLB, $n = 20$). These data were published in a separate paper [25]. A motor subscale of UPDRS was used for the assessment of neurological symptoms. More expressed symptoms in all domains except postural instability were found in the DLB group when compared to AD patients. The severity of neurological symptoms did not correlate with dementia severity (rated with the MMSE and CDR scales). The severity of psychotic symptoms was assessed with the NPI scale. Psychotic symptoms were more expressed in the DLB patients when compared to AD. Antipsychotic treatment was used for these features in some cases before admission to our outpatient clinic. Small doses of phenothiazines, sulpiride or haloperidol were usually used. At the time of admission to our outpatient clinic antipsychotic treatment was withdrawn and not continued during the study.

Cholinesterase inhibitors are the drugs of choice for AD and DLB patients. The tolerability of pro-cognitive treatment in the group presented in this paper was analysed as well. In a retrospective chart analysis of a relatively large population of patients no meaningful differences in tolerability were detected between donepezil and rivastigmine treatments in DLB and AD [26]. The intolerability of any prescribed dose and discontinuation rates as well as the side effect profile were similar. Neither serious adverse reactions nor the exacerbation of extrapyramidal symptoms were observed in the DLB group. Adverse reactions were rare and mild, resulting in drug discontinuation only in a few cases. In our opinion cholinesterase inhibitors, considered a gold standard in the treatment of AD, might constitute a therapeutic option in DLB as well.

Our paper is the first to focus on the influence of diabetes on survival in AD and DLB patients. The mortality rate was altered in AD but not DLB subjects. This may suggest distinct biology of the two dementias. We hope it will provide inspiration for further research and possibly a meta-analysis.

Conclusions

1. DLB seems to be a more aggressive disease when survival is taken into account. Mean estimated survival time is about 2 years shorter for DLB as compared to AD subjects, with comparable baseline demographic characteristics.
2. The difference in survival is substantially larger in men, who are at a greater risk of premature death due to DLB.
3. AD patients with diabetes are at a greater risk of premature death compared to AD patients without diabetes.
4. Higher calculated pre-treatment rate of disease progression might be helpful in the identification of subjects with a higher risk of premature death.

Acknowledgments

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Disclosure

Authors report no conflict of interest.

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