Long-term cognitive outcome of Alzheimer’s disease and dementia with Lewy bodies: dual disease is worse

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Abstract

Background: Longitudinal studies of dementia with Lewy bodies (DLB) are rare. Clinically, DLB is usually considered to worsen into Alzheimer’s disease (AD). The aim of our study was to compare the rate of the cognitive decline in DLB, AD, and the association of the two diseases (AD + DLB).

Methods: Using the Regional Network for Diagnostic Aid and Management of Patients with Cognitive Impairment database, which includes all the patients seen at all memory clinics (medical consultation and day hospitals) in four French regions, and beta regression, we compared the longitudinal the Mini-Mental State Examination scores of 1159 patients with AD (n = 1000), DLB (n = 131) and AD + DLB (association of the two) (n = 28) during follow-up of at least 4 years.

Results: The mean follow-up of the patients was 5.88 years. Using beta regression without propensity scores, the comparison of the decline of patients with AD and patients with DLB did not show a significant difference, but the decline of patients with AD + DLB was worse than that of either patients with DLB (P = 0.006) or patients with AD (P < 0.001). Using beta regression weighted by a propensity score, comparison of patients with AD and patients with DLB showed a faster decline for patients with DLB (P < 0.001). The comparison of the decline of patients with AD + DLB with that of patients with DLB (P < 0.001) and patients with AD (P < 0.001) showed that the decline was clearly worse in the patients with dual disease.

Conclusions: Whatever the analysis, the rate of decline is faster in patients with AD + DLB dual disease. The identification of such patients is important to enable clinicians to optimise treatment and care and to better inform and help patients and caregivers.

Keywords: Dementia with Lewy bodies, Alzheimer’s disease, Alzheimer’s dementia, Lewy body disease, MMSE, Outcome

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Background

Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB) are the two main neurodegenerative diseases responsible for dementia and account, respectively, for 70–80% and 15–20% of neuropathologically defined cases [1]. Diagnostic classification of DLB is based on revised consensus criteria, with the core features being: (1) recurrent visual hallucinations, (2) cognitive fluctuations and (3) spontaneous motor features of parkinsonism [1]. The presence of two or three of these core signs is sufficient for a diagnosis of probable DLB [1] at the stage of dementia. The outcome of patients with DLB is known to impact survival more than AD [2], particularly when patients have autonomic dysfunction [3].

The cognitive outcome of AD and DLB has previously been measured in longitudinal studies with fewer than 200 patients, with contradictory results. Some demonstrated a faster rate of decline for DLB than for AD [4, 5]. One study demonstrated a faster rate of decline solely for patients with dual disease (AD + DLB) compared with patients with either AD or DLB [6, 7]. However, most studies showed a similar rate of decline in patients with AD and patients with DLB. Thus, a recent meta-analysis of six studies in which researchers used the Mini Mental State Examination (MMSE), the rate of decline showed no significant difference between patients with AD and patients with DLB (annual declines of 3.4 and 3.3 MMSE points, respectively) [8]. The biggest study, with 315 patients (AD, n = 252; DLB, n = 63), likewise showed no difference in terms of cognitive outcome between AD and DLB [9].

To the best of our knowledge, no study has previously been done using data of a naturalistic longitudinal cohort. The primary aim of this study was thus to compare patients with AD, patients with DLB, and patients with AD + DLB in terms of cognitive rate of decline using the MMSE score as the outcome measure in a naturalistic cohort from a group of regions in north-eastern France.

Methods

Study design

Patients were consecutively recruited via the database of the Regional Network for Diagnostic Aid and Management of Patients with Cognitive Impairment (RAPID-Fr network), where all memory clinics in the French regions of Alsace, Champagne-Ardenne, Lorraine (starting from 2016, these three regions are known as “Région Grand Est”) and Franche-Comté register all patients who consult for cognitive complaints [10]. According to the French National Institute for Statistics and Economic Studies, at 1 January 2012, these four regions had a population of 8,307,000, corresponding to 12.6% of the population of France. Between 2003 and 2016, 222,202 consultations (by geriatricians, neurologists and psychiatrists) or geriatrics day hospital visits were recorded in the RAPID-Fr database for 100,698 patients. All memory clinics (including neurologists in liberal, memory centres and tertiary memory centres named memory resource and research centres [CM2R]) in the four French regions participate in the RAPID-Fr database, and all have been validated by the French Ministry of Health. We extracted from the database data recorded between 1 January 2003 and 1 July 2016 for patients with follow-up of at least 4 years and a declared diagnosis of AD alone, DLB alone or AD and DLB together (AD + DLB).

Patients, assessments and diagnosis

Among 4422 patients followed for at least 4 years for cognitive complaints (see Fig. 1), we found 1159 patients

![Flowchart of the present study on cognitive outcome in dementia with Lewy, Alzheimer's disease and double disease. AD Alzheimer's disease, DLB Dementia with Lewy bodies, AD + DLB Dual disease, RAPID Regional Network for Diagnostic Aid and Management of Patients with Cognitive Impairment.](image-url)
with AD (n = 1000 among 16,389 patients with AD seen at least once), DLB (n = 131 among 1692 patients with DLB seen at least once) and AD + DLB (dual disease) (n = 28 among 301 patients with AD + DLB seen at least once).

An aetiopathological diagnosis of the neurocognitive disorder for each patient was made using McKhann’s criteria for AD [11], McKeith’s criteria for DLB [12] and both sets of criteria for AD + DLB. The diagnosis was made by a multidisciplinary team at each memory centre, including geriatricians, neurologists, psychiatrists and neuropsychologists.

The MMSE version used was the French consensus version of the French Working Group on Cognitive Evaluation (GRECO) [13]. Among the sociodemographic data, we considered age in years, sex, and education level with five levels (no schooling, primary school level [equivalent to 1–5 years of education], collège [equivalent to secondary school level with 6–9 years of education], lycée [equivalent to secondary school level with 10–12 years of education] or university level [over 12 years of education]).

**Statistical analysis**

Differences in demographic and clinical data at baseline were assessed for continuous variables using parametric analysis of variance. In post hoc analyses between diseases, we employed the Holm adjustment on analysis of variance. In post hoc analyses between diseases, but, when relevant, we back-transformed means, SEMs and 5% CIs of parameters.

To deal with potential differences between subjects in each group at their time of inclusion in the study, we carried out two different analyses: (1) a “ground reality” beta regression as described above and (2) the same beta regression but using propensity scores based on demographic and clinical variables as weights (age, sex, education level). Calculation of this score was done using boosted logistic regression [15]. All statistical analyses were performed using the R version 3.2.3 statistical software package [16] with ad hoc packages (betareg, multcomp and twang). Results are shown to four significant digits.

**Results**

**Subject characteristics and propensity scores**

The demographic data for patients are summarised in Table 1. Subject groups differed among the three disease groups with regard to age, sex and education level.

|                          | AD        | AD + DLB  | p value   |
|--------------------------|-----------|-----------|-----------|
| Age, years               | 74.4 ± 8.4| 77.3 ± 8.1| <0.001    |
| Sex, male                | 52.2      | 34.9      | <0.001    |
| Education levela         | 3.1 ± 1.1 | 2.8 ± 1.1 | <0.001    |

Continuous variables are shown as mean (SD) and categorical variables as percent

*AD Alzheimer’s disease, DLB Dementia with Lewy bodies

<sup>a</sup> Considered as a discrete variable

|                          | AD        | AD + DLB  | p value   |
|--------------------------|-----------|-----------|-----------|
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| Education level          | 3.1 ± 1.1 | 2.8 ± 1.1 | <0.001    |

<sup>a</sup> Considered as a discrete variable

<sup>p</sup> 0.05 was regarded as significant. Descriptive results are shown as mean ± SD for continuous variables and as number and percent for categorical variables.

Because MMSE has discrete values bounded by 0 and 30, we relied on beta regression for modelling a transformation of the score on (0, 1). MMSE was divided by 30 and, to exclude 0 and 1 values, transformed using the Smithson and Verkuilen method [14]. The transformed scores were assumed to be beta-distributed. The precision of these distributions was not modelled, but in the logit of its mean, we added several terms: a specific intercept for each disease (DLB, AD, and AD + DLB) and a specific temporal linear (on the logit scale) trend for each disease. All post hoc comparisons between intercepts and slopes were simultaneously inferred using contrasts and accurate corrections for type I error. On a logit scale, the values of the parameters are meaningless. When necessary, the back-transformation on the natural scale was achieved using the “expit” function (inverse function of logit) for the mean estimates and the delta method for the variance. We retrieved only the P value of different statistical comparisons (intercepts and trends between diseases), but, when relevant, we back-transformed means, SEMs and 5% CIs of parameters.

**MMSE outcome**

Showing data retrieved from the beta regression weighted by propensity score (though results with unweighted regression were very similar), Table 2 summarises estimates for intercept of each disease on the natural scale (the value of MMSE at inclusion in the study). The intercept AD + DLB was intermediate (mean 20.81) between AD (19.34) and DLB (21.85). The intercept for AD was significantly lower than the intercept for AD + DLB (P < 0.001), which was significantly lower than that for DLB (P < 0.001).

On the logit scale, all the three temporal trends (hence taking into account baseline differences in MMSE) were significantly decreasing (P < 0.001). When using beta regression without propensity score, we found that the results were as follows: −0.013 for AD, −0.017 for DLB and −0.030 for AD + DLB. These trends were not different between AD and DLB (P = 0.086), but the trend for

Table 1. Baseline characteristics of patients in the three disease groups: dementia with Lewy bodies, Alzheimer’s disease and dual pathology

|                          | DLB       | AD        | AD + DLB  | p value   |
|--------------------------|-----------|-----------|-----------|-----------|
| Age, years               | 74.4 ± 8.4| 77.3 ± 8.1| 79.1 ± 7.46| <0.001    |
| Sex, male                | 52.2      | 34.9      | 43.6      | <0.001    |
| Education level          | 3.1 ± 1.1 | 2.8 ± 1.1 | 2.9 ± 1.1 | <0.001    |

Continuous variables are shown as mean (SD) and categorical variables as percent

<sup>a</sup> Considered as a discrete variable

**Results**

Subject characteristics and propensity scores

The demographic data for patients are summarised in Table 1. Subject groups differed among the three disease groups with regard to age, sex and education level.

Whereas ages were different between each of the three disease groups, sex and education level were different only between the AD and DLB groups. The propensity score was built on these three variables. It ranged between 1 and 55.26, with a median at 1.136, the 75th percentile at 1.286 and the 90th percentile at 4.894.
AD + DLB was significantly lower with respect to the trend for AD \((P < 0.001)\) and DLB \((P = 0.006)\). When using beta regression with propensity score, we found that the results were as follows: \(-0.012\) for AD, \(-0.019\) for DLB and \(-0.025\) for AD + DLB. All these trends were significantly different from each other \((P < 0.001)\).

Figure 2a (without propensity score) and Fig. 2b (with propensity score) show the three trends on a natural scale. Values of MMSE were difficult to compare on this scale. If we assumed that the MMSE values were 20 at inclusion using the beta regression without propensity score, for a subject with AD, the values were 18.94, 16.70, 14.39 and 8.94 at 1, 3, 5 and 10 years, respectively. For a subject with DLB with the same initial value and at the same times, the corresponding values were 18.59, 15.57, 12.51 and 6.11, and for a subject with AD + DLB, the corresponding values were 17.49, 12.17, 7.50 and 1.58. If we assumed that the MMSE values were 20 at inclusion using the beta regression with propensity score, for a subject with AD, the values were 18.99, 16.85, 14.63 and 9.36 at 1, 3, 5 and 10 years, respectively. For a subject with DLB with the same initial value and at the same times, the corresponding values were 18.43, 15.07, 11.70 and 5.09, and for a subject with AD + DLB, the corresponding values were 17.93, 13.50, 9.32 and 2.76 (see Fig. 3).

When we considered a linear decrease of MMSE (which did not appear to be the case) and considered the rate of cognitive decline, we found that (1) in beta regression without propensity score, the

| Disease | Mean | SEM  | 95% CI   |
|---------|------|------|----------|
| AD      | 19.44| 0.1522| 19.15 19.79 |
| DLB     | 21.67| 0.1526| 21.87 23.38 |
| AD + DLB| 20.41| 0.1963| 19.32 22.68 |

*AD* Alzheimer’s disease, *DLB* Dementia with Lewy bodies

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**Fig. 2** Estimated MMSE temporal evolution with beta regression without propensity score (a) and with propensity score (b) of patients with AD, patients with DLB and patients with AD + DLB. *AD* Alzheimer’s disease, *DLB* Dementia with Lewy bodies, *MMSE* Mini Mental State Examination.
MMSE decreased by 65.56% in 12 years (or 1.06 points per year) for AD, by 72.58% (or 1.37 points per year) for DLB and by 95.57% (or 1.68 points per year) for AD + DLB; and (2) in beta regression with propensity score, the MMSE decreased by 63.47% in 12 years (or 1.02 points per year) for AD, by 80.04% (or 1.45 points per year) for DLB and by 91.74% (1.56 per year) for AD + DLB. At the end of follow-up (a mean of 59.06 months for AD, 55.53 months for DLB and 50.69 months for AD + DLB), the mean MMSE values were 18.23 for DLB, 14.53 for AD and 14.04 for AD + DLB.

Differences between centres for the rate of diagnosis
CM2Rs diagnosed proportionally more patients with DLB than memory centres or neurologists in liberal than patients with AD (Table 3). For the AD + DLB diagnosis, there was no statistically significant difference between the different types of centres when compared with AD diagnosis or DLB diagnosis. For details on AD + DLB diagnosis, see Table 4, which shows the clinical and paraclinical characteristics of the 19 patients diagnosed in the CM2R of Strasbourg.

Discussion
We report a clearly more significant cognitive decline in dual-disease patients, associating AD and DLB, than observed in patients with either pure AD or pure DLB. These results confirm the logical notion that the outcome is worse for patients with two neurodegenerative diseases than for patients with one neurodegenerative disease. There was no statistical difference between the decline in patients with DLB and the decline in patients with AD when the beta regression was without propensity score; however, when the beta regression was with a
propensity score that took into account sex, education level and age, the decline was more marked in patients with DLB than in patients with AD.

Assuming a linear temporal evolution in MMSE score, the rate of cognitive decline was 1.02–1.06 points per year for AD, 1.37–1.45 points for DLB and 1.56–1.68 points for AD + DLB. However, because patients with DLB had a better MMSE score at the beginning of the study, the final MMSE score of patients with DLB was better than AD and also AD + DLB patients at the end of follow-up: 18.23 for DLB, 14.53 for AD and 14.04 for AD + DLB after a mean 56, 59 and 51 months of follow-up, respectively.

Nelson et al. previously demonstrated that patients with AD + DLB have a worse cognitive decline than patients with either pure AD or pure DLB [6, 7]. Their study was autopsy-proven, which explains why only 9 patients were included in the pure DLB group compared with 107 in the AD group and 27 in the AD + DLB group.

In our study, the three groups were different in terms of age, sex and education level. However, these differences are consistent with previous publications on AD and DLB [8]. Thus, in our cohort, there were more women in the AD group than in the DLB group. The sex ratio in AD cohorts usually shows a predominance of women [17]. In contrast, there is either a predominance of men or a balanced sex ratio in DBL cohorts [18, 19]. In our cohort, the AD + DLB group was the oldest. There is an increase in the reported prevalence of clinical AD as well as in DLB with age [20]. In our cohort, patients with DLB had a higher education level. However, the relationship between education level and dementia is unclear [21]. Most studies report a positive effect of education on cognitive performance but a lack of association with the rate of cognitive decline [22].

Thus, it would be quite artificial to consider only the beta regression with propensity score in our study and to conclude that the rate of cognitive decline in DLB is greater than the rate of decline in AD. As described above, the characteristics of patients with DLB differed from those of patients with AD, with, for instance, more women in the AD group than in the DBL group; these intrinsic characteristics must be preserved. This explains why the beta regression without propensity score is most likely a better reflection of the ground reality, showing that AD and DBL had roughly the same rate of decline. Moreover, in this respect, our study is consistent with previous studies, in particular with a meta-analysis of six studies [8], as well as with the previous biggest study [9], showing no difference in terms of cognitive decline between DBL and AD.

The diagnosis of AD + DBL is not crisply defined. That is the reason why most of the patients diagnosed as AD + DBL came from CM2R (tertiary memory clinic; 86%), and particularly from Strasbourg (68%) (see Table 4), which specialises in patients with DBL. Interestingly, the diagnosis of one of the diseases was done before the other one; thus, AD was usually first diagnosed (79%), and then DBL was diagnosed in addition to AD. Therefore, to diagnose patients with AD + DBL, the clinician had to be demanding of himself: Systematic interrogation of fluctuations, visual hallucinations and RBD, as well as a search for parkinsonism, was done even if the patient was previously diagnosed with AD. In the same way, if the first diagnosis was DBL (21%), the search for AD had to be done, particularly if on neuropsychological tests a memory storage deficit was found. In this situation, hippocampal atrophy raised interest in arguing for an AD diagnosis, but cerebrospinal fluid (CSF) analysis was clearly of importance [23].

Our study has two advantages: It is the first study with more than 350 patients (n = 1159), and it is the first naturalistic study including patients of all the memory clinics within a coherent geographical area (four large regions in north-eastern France). Our study has some limitations. Firstly, we do not have any autopsy verification of the patients. Thus, we cannot exclude the

| Centre responsible for diagnosis of each of the diseases | Alzheimer's disease | Dementia with Lewy bodies | Alzheimer's disease and dementia with Lewy bodies |
|--------------------------------------------------------|---------------------|---------------------------|-----------------------------------------------|
| Neurologist in liberal                                  | n=30 | 3 | n=3 | 2 | n=0 | 0 |
| Memory centre                                           | n=300 | 30 | n=26 | 20 | n=4 | 14 |
| Memory Resource and Research Centre                    | n=670 | 67 | n=102 | 78 | n=24 | 86 |
| Total                                                   | n=1000 | 100 | n=131 | 100 | n=28 | 100 |

Fisher’s exact test

*a* Means statistically significant difference in terms of centre responsible for the diagnosis of AD versus DLB

*b* The difference between Alzheimer’s disease and dementia with Lewy bodies

*c* (NS), it is the difference between Alzheimer’s disease and (AD and DLB)

*d* (NS), it is the difference between Dementia with Lewy bodies and (AD and DLB)
Table 4: Characteristics of the patients with dual disease (Alzheimer's disease and dementia with Lewy bodies) from the Memory Resource and Research Centre of Strasbourg

| Patients Initial MMSE score | Memory storage deficit | Language deficit | Executive deficit | Visual hallucinations | Fluctuations | Parkinsonism | RBD | Hypocampal atrophy on brain MRI | CSF | FDG-PET or perfusion SPECT | AD or DLB diagnosed first | Years between diagnoses | DAT, flutemetamol, EEG |
|-----------------------------|------------------------|------------------|-------------------|----------------------|--------------|--------------|-----|-------------------------------|-----|-----------------------------|-------------------------|------------------------|--------------------------|
| 1 18                        | Yes                    | Yes              | Yes               | Yes                   | Yes          | No           | Yes (left) | 3 Hypometabolism frontal, parietal, insular | AD  | 4                           |                         |                        |                          |
| 2 22                        | Yes                    | Yes              | Yes               | Yes                   | Yes          | No           | Yes   | Hypometabolism temporal, occipital | AD  | 3                           |                         |                        |                          |
| 3 24                        | No                     | No               | Yes               | Yes                   | Yes          | No           | Yes   | Hypometabolism frontal, temporal, parietal | DLB | 1 Slow wave EEG             |                         |                        |                          |
| 4 26                        | Yes                    | No               | Yes               | No                    | No           | No           | Yes   | 1 (P-Tau) hypometabolism frontal, parietal, occipital | AD  | 6                           |                         |                        |                          |
| 5 25                        | Yes                    | Yes              | Yes               | ND                   | Yes          | No           | Yes   | 1 (Aβ) hypometabolism frontal, parietal, occipital | AD  | 5                           |                         |                        |                          |
| 6 24                        | Yes                    | No               | Yes               | Yes                   | Yes          | No           | Yes (left) | 2 (tau, p-tau) hypometabolism temporal, parietal, occipital | AD  | 5                           |                         |                        |                          |
| 7 16                        | Yes                    | Yes              | Yes               | Yes                   | Yes          | No           | Yes (right) 3 Hypometabolism temporal, parietal | AD  | 2                           |                         |                        |                          |
| 8 24                        | Yes                    | No               | Yes               | No                    | Yes          | No           | No     | 2 (tau, p-tau) Hypoperfusion frontal, temporal, occipital | AD  | 4                           |                         |                        | Pathological DAT slow wave EEG |
| 9 21                        | Yes                    | Yes              | Yes               | Yes                   | Yes          | Yes          | Yes   | 2 (p-tau, Aβ) Hypoperfusion frontal, temporal, occipital | DLB | 3 Pathological DAT slow wave EEG |                         |                        |                          |
| 10 25                       | Yes                    | Yes              | Yes               | Yes                   | Yes          | No           | No     | ND                            | AD  | 1 Pathological DAT slow wave EEG |                         |                        |                          |
| 11 25                       | No                     | No               | Yes               | No                    | Yes          | No           | No     | ND                            | AD  | 6 Pathological PET with flutemetamol |                         |                        |                          |
| 12 26                       | Yes                    | Yes              | Yes               | Yes                   | Yes          | No           | No     | 3 Hypometabolism temporal, occipital | AD  | 4 Pathological PET with flutemetamol |                         |                        |                          |
| 13 28                       | No                     | Yes              | Yes               | Yes                   | Yes          | No           | Yes   | ND                            | AD  | 3 Pathological DAT scan |                         |                        |                          |
| 14 24                       | No                     | No               | Yes               | Yes                   | Yes          | No           | No     | 3 Hypometabolism temporal, occipital | AD  | 5                           |                         |                        |                          |
| 15 20                       | Yes                    | No               | Yes               | Yes                   | Yes          | Yes          | No     | 3 Hypometabolism temporal, parietal, insular | AD  | 2 Pathological DAT scan |                         |                        |                          |
| 16 22                       | Yes                    | No               | No                | No                    | Yes          | No           | No     | 3 Hypometabolism temporal | AD  | 7                           |                         |                        |                          |
| 17 26                       | Yes                    | No               | Yes               | No                    | Yes          | No           | No     | ND                            | AD  | 1 Pathological PET with flutemetamol |                         |                        |                          |
| 18 24                       | No                     | No               | Yes               | No                    | Yes          | Yes (right) 0 | No     | ND                            | AD  | 3                           |                         |                        |                          |
| 19 24                       | No                     | No               | Yes               | No                    | Yes          | No           | 0     | Hypoperfusion temporal, parietal, insular | DLB | 4 Pathological PET with flutemetamol |                         |                        |                          |

Abbreviations: Aβ Amyloid-β, AD Alzheimer’s disease, CSF Cerebrospinal fluid, DAT Dopamine transporter scan, DLB Dementia with Lewy bodies, EEG Electroencephalogram, FDG-PET Fluorodeoxyglucose positron emission tomography, MMSE Mini Mental State Examination, MRI Magnetic resonance imaging, ND Not done, p-tau Phosphorylated tau, RBD Rapid eye movement sleep behaviour disorder SPECT Single-photon emission computed tomography

* Symptoms arising during follow-up and not at the beginning.
Conclusions
Our data suggest that patients with dual disease (AD + DLB) have a higher rate of cognitive decline and are consistent with previous studies showing that AD and DLB have a similar rate of decline. The identification of dual-disease patients is of importance to enable clinicians to optimise treatment and care and to better inform and help patients and caregivers. The next steps would be, firstly, to better understand the role of symptomatic treatment such as cholinesterase inhibitors or memantine in the two diseases, secondly to explore the functional outcome of these patients, and thirdly to explore the cognitive outcome of patients at the prodromal stage of AD, DLB and AD + DLB.

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Availability of data and materials
Data used in the article are available from the corresponding author upon request.

Authors’ contributions
FB conceived of the study; participated in its design and coordination; diagnosed patients with DLB, AD, and AD with DLB; analysed patients’ records; and drafted the manuscript. EAS performed the statistical analysis and drafted the manuscript. RM, TJ, XG, GC, BC, CD, CMH, NP, FS, JMM, PV, EM, JLN, GK, and AB diagnosed patients with DLB, AD, and AD with DLB; analysed patients’ records; and revised the manuscript. GT and MS helped to organise the study and revised the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This research was approved by the French committee Centre National informatique et Liberté (CNIL), and all the patients gave their consent to participate.

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