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**Title: The incidence of recorded delirium episodes before and after dementia diagnosis:
Differences between dementia with Lewy bodies and Alzheimer's disease**

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The incidence of recorded delirium episodes before and after dementia diagnosis: Differences between dementia with Lewy bodies and Alzheimer's disease

Objectives: To describe the incidence of delirium recording before and after a diagnosis of dementia is established in patients with dementia with Lewy bodies (DLB) and compare findings to a matched cohort of patients with Alzheimer's disease (AD).

Design: Retrospective cohort study.

Setting and Participants: A cohort of patients with dementia from a large mental health and dementia care database in South London, linked to hospitalization and mortality data. We identified 194 patients with DLB and 1:4 matched these with 776 patients diagnosed with AD on age, gender, and cognitive status.

Measures: We identified delirium episodes recorded in mental health and hospital records from one year before to one year after dementia diagnosis. Using dementia diagnosis as an index date we followed patients until first episode of delirium, death or a censoring point.

Results: Patients with DLB had significantly more episodes of delirium recorded in the year before dementia diagnosis than patients with AD (incidence rate 17.6 vs 3.2; $p < 0.001$).

Whereas the incidence of recording of delirium episodes reduced substantially in patients with DLB after dementia diagnosis, it remained significantly higher than in patients with AD (incidence rate 6.2 vs. 2.3; $p = 0.032$). Cox regression models indicate that patients with DLB remain at a higher risk of delirium than patients with AD after a dementia diagnosis.

Conclusions/Relevance: Establishing a diagnosis of dementia reduces episodes classified as delirium in patients with DLB and might lead to fewer potentially harmful interventions as hospitalization or use of antipsychotic medication.

Introduction

Dementia and delirium are two of the most common neurocognitive disorders found in the older inpatient population¹. Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative dementia with a reported prevalence of 10-15% of all patients with dementia, whereby in clinical settings diagnostic rates are only at about 1/3rd of what is expected with substantial geographical variations^{2,3}. DLB is associated with a poor prognosis including increased long-term care requirements, hospitalization and an increased risk of mortality⁴⁻⁶. In the acute hospital setting, patients are often misdiagnosed and inappropriately treated with antipsychotics which result in detrimental clinical outcomes, as potentially fatal neuroleptic sensitivity⁷.

Delirium is an acute onset neuropsychiatric syndrome that occurs in the context of advanced age and critical illness⁸. Delirium is characterised by a heterogeneous phenomenology with core features such as inattention, arousal and cognitive fluctuations, and less frequently associated features such as delusions and hallucinations⁹. In the general hospital setting, it has a reported prevalence of 20% and which increases to over a 50% in the over 65 hospital inpatient population⁸. Delirium is associated with an increased risk of morbidity, mortality and the development of dementia^{10,11}. Despite these detrimental clinical outcomes, an estimated 2/3 of cases of delirium are missed and hence not treated¹².

Delirium also exists in the context of a mixed neuropsychiatric presentation, with delirium superimposed upon dementia (DSD) prevalence range reported at between 20-80%¹. DSD is associated with a significantly higher risk of mortality, institutionalisation, and cognitive and functional decline compared to delirium alone¹³. Once considered a transient disorder, it is now recognised that delirium is marked by incomplete recovery and approximately 20% of

patient have persistent delirium lasting months^{14,15}. DLB is cited as an example of the delirium-dementia continuum due to the presence of similar features such as disturbances in sleep-wake cycle, fluctuating neurocognitive impairment, and visual hallucinations¹. There is unfortunately a lack of consensus regarding the differentiation between delirium and dementia which impacts upon patient care and clinical outcomes¹⁶. It has been suggested that episodes diagnosed as delirium, may in fact be part of the prodromal presentation of DLB¹⁷. In a retrospective case note study of elderly patients undergoing review of dementia diagnosis at a tertiary referral unit, it was found that delirium was more closely associated with DLB than Alzheimer's disease (AD)¹⁸. However, it remains unclear whether the occurrence of delirium-like features typical for DLB leads to increased recording of delirium in dementia care and hospitalization records, and whether this practice changes once a diagnosis of dementia is established.

Using routinely collected data from a specialist mental health and dementia care provider linked to national hospitalization records, we aimed to investigate the incidence of delirium recording before and after a diagnosis of dementia is established, and whether this differed between DLB and AD.

Methods

Data source

Data for this study were extracted from the South London and Maudsley (SLaM) NHS Foundation Trust Clinical Record Interactive Search (CRIS) system. SLaM is one of the largest mental health and dementia care providers in Europe covering a catchment area in South East London with over 1.36 million residents, providing largely community, but also psychiatric inpatient care. The CRIS system has received ethical approval as an anonymised data resource (Oxford Research Ethics Committee C, reference 08/H0606/71+5) and provides research access to anonymized copies of SLaM's electronic health records within a robust governance framework^{19,20}. Data is extracted from structured fields in the source record and from free text fields through natural language processing algorithms using General Architecture for Text Engineering (GATE) software (<https://gate.ac.uk>)²⁰. Further, linkages have been established to national data on hospitalisation, the so-called Hospital Episode Statistics (HES) database²¹. HES records all admissions to all National Health Service (NHS) hospitals in England, including diagnoses and procedures.

Study Cohort

Using CRIS we identified a sample of patients 65 years or older receiving a first dementia diagnosis within SLaM services between 1st January 2006 and 31st March 2013. Cases of Alzheimer's disease were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) codes²². As no ICD-10 code for DLB exists, we identified cases of DLB using text strings associated with a diagnostic statement of dementia with Lewy bodies using GATE natural language processing software²⁰. DLB and randomly selected AD

cases were matched on a 1:4 ratio according to gender, age bands (5-year bands from 55-59 to 95+ years) and Mini Mental State Examination (MMSE)²³ score categories (0-9, 10-14, 15-19, 20-24, and 25-30 score points) at dementia diagnosis. The performance of the diagnosis identification software and the matching procedures in this cohort have been described in a previous study⁶.

Covariates

We extracted demographic factors including age, gender, marital status, a neighbourhood-level index of socio-economic deprivation²⁴ as well as data from the Health of the Nation Outcome Scales (HoNOS65+) instrument. The HoNOS65+ is a validated routinely administered measure of patient mental and physical wellbeing as well as functioning used in UK mental health services^{25,26}. Subscales are each rated zero (no problem) to four (severe or very severe problem). To facilitate interpretation, these subscale scores were dichotomised to 'minor or no problem' (0-1) and 'mild to severe problems' (2-4).

Outcomes

We identified episodes of delirium coded as F05 according to ICD-10²⁰ both in mental health (CRIS) and hospitalization records (HES), between one year before the first dementia diagnosis until date of death or a censoring point on 31st March 2013 (after which no hospitalisation data was available). For the purpose of this analysis we counted all delirium episodes and defined the subgroup of hospitalized delirium episodes. A delirium episode recorded in CRIS, that did not occur within two weeks of a discharge or admission date of a hospitalized (HES) episode, was considered as non-hospitalized.

At least two weeks needed to elapse between two delirium episodes in order for them to be considered distinct episodes. We further defined a delirium episode as occurring before the patient's first dementia diagnosis when the date of delirium diagnosis recorded on CRIS or the discharge date recorded in HES lay before or on the date of first dementia diagnosis recording. All other episodes of delirium were considered to occur after the first dementia diagnosis date.

Statistical Analysis

The STATA 13 software (Stata Corp LP, 2014) was used. The date of first dementia diagnosis served as index date. We assessed baseline differences between the DLB and AD cohort using t-tests and the Wilcoxon rank sum tests for continuous data and chi-squared tests for categorical variables. We further compared the number of all and hospitalized delirium episodes in the year before and after dementia diagnosis. Not restricting the follow-up time to one year, we applied stratified Cox regression models to determine risk of and time to first delirium episode in the follow-up period after dementia diagnosis until censoring date or death.

Results

We identified 10,159 patients diagnosed with dementia in the observation period. Of these 6,300 had a diagnosis of AD and 200 a diagnosis of DLB. Six DLB cases were excluded as no MMSE score was recorded at the time of dementia diagnosis and the remaining 194 DLB cases were matched to 776 with patients diagnosed with AD according to gender, age and cognitive score categories.

Participant characteristics

No significant differences between patients with DLB and AD were detected in sociodemographic variables (see Table 1). According to HoNOS65+ scores patients with DLB were more likely to present with aggressive behaviour, non-accidental self-injury, hallucinations or delusions and depressed mood at the time of dementia diagnosis. Further, a higher proportion of patients with DLB had a functional or physical health problem.

Incidence rate of delirium episodes in the year before and after dementia diagnosis

The 194 patients with DLB contributed 187.1 person-years before and 162.5 person-years after dementia diagnosis. The AD cohort, consisting of 776 patients, contributed 718.6 person-years before and 733.1 person-years after dementia diagnosis.

Both in the year before and after dementia diagnosis patients with DLB had a significantly higher incidence rate of delirium recording than patients with AD (see Table 2). The most striking difference was noted in the year before dementia diagnosis, whereby the incidence rate of delirium recording was almost six times higher in the DLB group. While the incidence

rate of delirium recording after dementia diagnosis largely remained unchanged in patients with AD ($p=0.393$), it dropped significantly to about one third in patients with DLB ($p=0.003$).

Only before dementia diagnosis there were significant differences between incidence rates of recording of hospitalised delirium episodes, and no significant reductions in neither the DLB ($p=0.332$) nor the AD ($p=0.965$) group occurred after dementia diagnosis (see Table 3).

Stratified Cox regression models assessing risk of and time to first delirium episode after dementia diagnosis

When we did not restrict the follow-up time after dementia diagnosis to one year, mean time to the first recorded delirium episode or censoring was 3.24 (SD 2.03) years. In 36 (18.6%) patients with DLB and 88 (11.3%) patients with AD at least one recorded episode of delirium occurred in the follow-up period. Over a mean follow-up time of 3.35 (SD 2.02) years, 19 (9.8%) patients with DLB had at least one recorded hospitalised delirium episode and 53 (6.8%) in patients with AD. Cox regression models assessing risk of first recorded delirium episode and first recorded hospitalised delirium episode in relation to dementia subtype diagnosis are presented in Table 4. Taking time to first delirium episode into consideration, patients with DLB had a substantially increased hazard to develop a recorded delirium earlier than patients with AD, also after a wide range of potential confounders had been taken into consideration (see Table 4).

Discussion

Patients with dementia have a higher frequency of hospital admissions compared to the general population and hence understanding the relationship between delirium and dementia is warranted. In a naturalistic sample of patients diagnosed with DLB, we showed that episodes of delirium are more frequently recorded in patients with DLB than in patients with AD. This association is more pronounced before the diagnosis of dementia is established, whereby the incidence rate of recorded delirium episodes was close to six times higher in patients with DLB than in patients with AD. While the incidence rate of recorded delirium in patients with AD did not change significantly after dementia diagnosis, it reduced to approximately one third in patients with DLB. Cox regression models demonstrated that patients with DLB remain at an increased risk of delirium after dementia diagnosis, suggesting that these occur earlier in the follow-up time than in AD.

Previous studies exploring the relationship between DLB and delirium are scarce. In a retrospective study conducted by Vardy et al.,¹⁸ it was found that the proportion of inpatient episodes of delirium was higher for DLB (62%) when compared to AD (43%). In a study of early symptom presentation of DLB conducted by Rongve et al.²⁷ showed that prior to DLB diagnosis, 43% of patients had delirium.

There are several possible reasons for this close relationship between DLB and delirium. Firstly, episodes diagnosed as delirium may in fact be prodromal DLB given the nonspecific features of delirium and the lack of any pathognomonic feature. According to McKeith et al.,²⁸ there may be three subtypes of DLB with one of these being a *delirium onset DLB subtype*, whereby delirium is the presenting feature prior to formal DLB diagnosis. Other authors have also found a high frequency of delirium prior to DLB diagnosis which suggests

that delirium may be part of the DLB prodrome^{29,30}. Moreover, patients with DLB may have increased risk of delirium due to the underlying pathophysiological impact of Lewy body proteins upon neuronal functioning in cortical and subcortical regions³¹. This is supported by evidence reporting that dementia and cognitive impairment are highly potent risk factors for the development of delirium due to the diminished neurocognitive reserve in an older patient's brain¹.

Most importantly, the decrease in delirium recording after dementia diagnosis might reflect a change in clinician behavior. Features common to both delirium and DLB as fluctuating cognition, visual hallucinations or sleep-wake cycle disturbances¹, are less likely to be misattributed to a delirium and more appropriately recognized as features of DLB⁷. Subsequently, establishing a diagnosis of dementia in patients with DLB might reduce potentially harmful treatment with antipsychotic medication and prolonged hospitalizations, and further allow appropriate treatment with a cholinesterase inhibitor³². It is, however, of equal importance not to automatically attribute the above-mentioned features to the DLB state and risk overlooking a delirium due an acute medical condition. Vigilance is necessary in order to timely instigate investigations and treatments for potentially life-threatening conditions and common causes of delirium in the elderly ^{7,18,32}.

Limitations of the study

There are several limitations of this study that need to be considered and these include the use of routine electronic records for data pertaining to reason for admission, delirium and DLB diagnosis. With regards to the reason for admission, hospitalization data as recorded by HES is based upon ICD-10 codes applied at the point of patient discharge and may not

accurately explain the reason for admission in the context of dementia e.g., behavioural and/or functional decline or DSD²². More complicated still, the neurodegenerative process underlying dementia often exists many years before formal diagnosis and may impact upon the demographic presenting to hospital. In other words, given that this is a survivor cohort, patients need to survive until a formal dementia diagnosis is established. Another shortcoming relates to the rate of clinical diagnosis of DLB and delirium which is often cited as being under reported in the hospital setting^{3,33,34}. Further, some patients might have protracted episodes of delirium¹⁵, lasting longer than the two weeks used in this analysis to distinguish separate episodes in this analysis. However, those patients tend to be followed-up by the same SLAM service without repeated recording of the ICD-10 code unless the patient is discharged. These limitations could be overcome with stringent diagnostic criteria for delirium and recruitment into a prospective study. 'Further, a history of episodes of delirium itself might lead to clinicians falsely establishing a diagnosis of DLB. However, in our sample the performance of the case identification was assessed in a subset of one third of the DLB cases by clinicians and senior experts. This process is described elsewhere (Mueller et al., 2018) and only 4.3% of case records identified as DLB contained false positives not suffering from any Lewy body dementia. The low prevalence of DLB in our sample compared to the literature (Kane et al., 2018; Vann Jones and O'Brien, 2014) suggests that clinicians were more likely to recognise patients with typical DLB rather than those with mixed AD and DLB pathologies, which might be more common given the mean age of our sample (McKeith et al., 2016).'

Although this study is representative of the target population in South East London and results are applicable to patients in long-term care, the generalisability of these findings outside the UK may be limited due to differences in the delivery of dementia care. Multi-centred studies using standardised criteria and study design may further elucidate the interface between DLB and delirium. Previous studies exploring delirium phenomenology in particular have demonstrated that multi-centred studies have been instrumental in understanding the complex heterogeneous phenomenology of delirium in the context of dementia in hospital inpatients^{35,36}.

Future studies and recommendations

Future studies may explore the interface between DLB and delirium in depth using a prospective longitudinal design to investigate the relationship between prevalent and incident delirium in patients with and without DLB. Understanding the differences in clinical profiles for example, reason for referral or hospital admission and functional ability, between these patients may further help researchers stratify this vulnerable subgroup. Moreover, further study should investigate the phenomenology of delirium and DLB, both at point of admission into hospital or referral to community care providers, and the trajectory of these features over the course of their treatment. Particular areas that may be explored would be the circadian domain which is composed of motor behaviour and sleep-wake cycle disturbances, both of which are core features of delirium and DLB¹⁷. Use of bioelectronics measures such as actigraphy and psychometric measures have shown to have utility in exploring delirium circadian phenomenology and progress our understanding of the interface between delirium and dementia^{37,38}. This would enable researchers to identify specific areas

to implement routine delirium screening to aid frontline staff in parsing out suspected delirium from DLB and hence initiate appropriate management for each patient.

Conclusions/Relevance:

Key findings from this study include the significantly higher occurrence of delirium recording prior to dementia diagnosis in patients with DLB compared to patients with AD. Following dementia diagnosis, the high rate of delirium recording abruptly declines by approximately two-thirds in patients with DLB and establishing a diagnosis of dementia might reduce episodes misclassified as delirium in patients with DLB, but not AD. Given that patients with DLB are at a higher risk of severe sensitivity reactions to antipsychotics, which are commonly prescribed for delirium, a proactive diagnosis of dementia in this group might mitigate those risks. Further research is required in factors which might allow a clearer distinction of DLB and delirium. Closer and systematic follow-up of patients who presented with delirium might also allow earlier diagnosis of dementia.

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The relationship between Delirium and dementia with Lewy bodies: A retrospective cohort analysis

Table 1: Sample characteristics (see also Mueller et al., 2018)

Risk factors	DLB cohort (n=194)	AD cohort (n=776)	P*
<i>Socio-demographic status and cognitive function[§]</i>			
Mean age at dementia diagnosis (95% CI) [†]	79.9 (78.8-81.0)	80.3 (79.7-80.8)	0.560
Female gender (%) [†]	50.0%	50.0%	1.000
Non-White ethnicity (%)	22.2%	20.9%	0.694
Married or cohabiting status (%)	43.1%	41.4%	0.648
Mean index of deprivation (95% CI)	26.6 (25.0-28.1)	26.2 (25.4-27.0)	0.618
Mean MMSE score at diagnosis (95% CI) [†]	19.2 (18.3-20.1)	18.7 (18.2-19.1)	0.307
<i>HoNOS65+ symptoms/disorders (%)[±]</i>			
Overactive, aggressive behaviour	38.0%	17.7%	<0.001
Non-accidental self-injury	3.1%	0.7%	0.005
Problem-drinking or drug taking	2.1%	4.2%	0.167
Hallucinations or delusions	59.2%	10.0%	<0.001
Depressed mood	22.9%	11.4%	<0.001
<i>HoNOS65+ functional problems (%)[±]</i>			
Activities of daily living	63.4%	52.3%	0.001
Living conditions	10.9%	10.9%	0.973
Occupational and recreational activities	37.0%	28.2%	0.019
Social relationships	25.0%	15.1%	<0.001
<i>HoNOS65+ Physical illness or disability (%)[±]</i>	64.1%	38.1%	<0.001

* t-test (age), Wilcoxon rank sum (MMSE, index of deprivation) or chi² test (categorical variables)

[§] at the time of index dementia diagnosis

[†] cohorts matched on categories of these variables

[±] whether problem present at dementia diagnosis

Table 2: Incidence rates of delirium episodes per person 100 person-years in the year before or after dementia diagnosis (95% CIs; n=total number of delirium episodes)

	DLB	AD	P*
Before Dementia Diagnosis	17.64 (12.14-24.77; n=33)	3.20 (2.03-4.80; n=23)	<0.001
After dementia diagnosis	6.15 (2.95-11.32; n=10)	2.32 (1.35-3.71; n=17)	0.032

*P calculated using Fisher's exact test

Table 3: Incidence rates of hospitalized delirium episodes per person 100 person-years in the year before or after dementia diagnosis (95% CIs; n=total number of hospitalized delirium episodes)

	DLB	AD	P*
Before Dementia Diagnosis	5.88 (2.93-10.52; n=11)	1.39 (0.66-2.56; n=10)	0.003
After dementia diagnosis	3.08 (0.99-7.18; n=5)	1.23 (0.56-2.33; n=9)	0.187

*P calculated using Fisher's exact test

Table 4: Cox regression models assessing risk of first delirium / hospitalised delirium in DLB compared to AD

Having a diagnosis of DLB	Any delirium episode - Hazard ratio (95% CI)	Hospitalised delirium episode – Hazard ratio (95% CI)
Crude	3.47 (2.15-5.62)	3.18 (1.65-6.17)
Adjusted for ethnicity, marital status and deprivation score	4.72 (2.71-8.21)	3.53 (1.70-7.33)
Adjusted for demographics and HoNOS65+ mental health symptom scores	5.21 (2.57-10.53)	3.84 (1.61-9.14)
Adjusted for demographics and HoNOS65+ functional problem scores	4.84 (2.69-8.72)	3.82 (1.73-8.49)
Adjusted for demographics and previous delirium HoNOS65+ physical health symptom scores	4.36 (2.48-7.69)	3.46 (1.64-7.26)
Fully adjusted	5.49 (2.55-11.85)	3.34 (1.29-8.64)

bold: $p < 0.05$