What best differentiates Lewy body from Alzheimer’s disease in early-stage dementia?

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To determine which clinical feature(s) [among visual hallucinations (VH), extrapyramidal signs (EPS) and visuospatial impairment] in the earliest stages of disease best predicted a diagnosis of dementia with Lewy bodies (DLB) at autopsy, first-visit data of 23 pathologically proven DLB and 94 Alzheimer’s disease cases were compared. There were no group differences with regard to age, gender, education or global severity of dementia at presentation (mean Mini-Mental State Examination: 24.0 versus 25.0, mean Dementia Rating Scale: 123.6 versus 125.7). DLB patients at initial presentation displayed an increased frequency of VH (P = 0.001), but not EPS (P = 0.3), compared to Alzheimer’s disease patients. However, only a minority of DLB cases had either VH (22%), EPS (26%) or both (13%). In contrast, although not a core feature, visuospatial/constructional impairment was observed in most of the DLB cases (74%). Among clinical variables, presence/recent history of VH was the most specific to DLB (99%), and visuospatial impairment was the most sensitive (74%). As a result, VH at presentation were the best positive predictor of DLB at autopsy (positive predictive value: 83% versus 32% or less for all other variables), while lack of visuospatial impairment was the best negative predictor (negative predictive value: 90%). We conclude that the best model for differentiating DLB from Alzheimer’s disease in the earliest stages of disease includes VH and visuospatial/constructional dysfunction, but not spontaneous EPS, as predictors. This suggests that clinical history plus a brief assessment of visuospatial function may be of the greatest value in correctly identifying DLB early during the course of disease.

Keywords: Alzheimer’s disease; dementia with Lewy bodies; core clinical features; diagnostic accuracy

Abbreviations: DLB = dementia with Lewy bodies; DRS = Dementia Rating Scale; DRS-C = DRS construction subscale; EPS = extrapyramidal signs; MMSE = Mini-Mental State Examination; NPV = negative predictive value; PPV = positive predictive value; VH = visual hallucinations


Introduction

Dementia with Lewy bodies (DLB) has been reported to be the second most common form of dementia, after Alzheimer’s disease. Much attention has focused on identifying reliable criteria that allow discrimination between DLB and Alzheimer’s disease during life (Hansen et al., 1990; McKeith et al., 1996). In addition to cognitive impairment, the core clinical features of DLB, according to the Consortium on DLB (McKeith et al., 1996), are visual hallucinations (VH), fluctuating attention and spontaneous extrapyramidal signs (EPS). Neuropsychologically, patients with DLB may display a different pattern of cognitive decline, with worse performances on attentional and executive tasks (Hansen et al., 1990, Walker et al., 2000a; Ballard et al., 2001; Doubleday et al., 2002) and, especially, on tests of visuospatial/constructional abilities (Salmon et al., 1996; Salmon and Galasko, 1996; Mori et al., 2000; Ala et al., 2001; Simard et al., 2003; Cormack et al., 2004). Furthermore, the progression of their deterioration on global measures of dementia (e.g. the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Mattis Dementia Rating Scale (DRS) (Mattis, 1976)) may be faster than that observed in patients with Alzheimer’s disease (Olichney et al., 1998).
Neuropathologically, Lewy bodies are requisite for a diagnosis of Alzheimer's disease, but most brains of patients with autopsy-proven DLB (i.e. cases with dementia during life and Alzheimer's disease at autopsy) also display concomitant Alzheimer's disease pathology in the form of diffuse plaques, neuritic plaques and neurofibrillary tangles [i.e. the Lewy body variant of Alzheimer's disease (Hansen et al., 1990)]. A few brains, however, have no more Alzheimer's disease pathological changes than age-matched controls (pure or diffuse Lewy body disease).

Differentiation between DLB and Alzheimer's disease during life is important because, compared to Alzheimer's disease, patients with DLB may show dissimilar response to acetylcholinesterase inhibitors (Levy et al., 1994) and abnormal sensitivity to neuroleptic drugs (Ballard et al., 1998). However, in studies using postmortem diagnosis as the gold standard, clinical diagnostic accuracy of DLB has been poor, ranging from 34 to 65% (Litvan et al., 1998; Lopez et al., 1999; Luis et al., 1999; Vergheese et al., 1999; Hohl et al., 2000). Only one prospective study to date has reported relatively higher values (83%) (McKeith et al., 2000). Pathological heterogeneity of patient populations may have influenced the clinician's ability to correctly identify DLB, since increased concomitant Alzheimer's disease changes have been associated with decreased frequency of core clinical features and lower diagnostic accuracy of DLB (Del Ser et al., 2001; Merdes et al., 2003).

Recognizing the current difficulty of correctly identifying DLB, and yet the importance of its differentiation from Alzheimer's disease as early as possible in the course of disease, we sought to determine which clinical feature(s) among VH, EPS and visuospatial impairment in the mildest stages of dementia most reliably predicted a diagnosis of DLB at autopsy. To explore this, we restricted our analyses to first-visit data of those patients with pathologically proven DLB or Alzheimer's disease whose DRS score at initial presentation to our centre was at least 115.

We should emphasize that, although other clinical features have been suggested as potentially useful markers of DLB, we focused on those most often highlighted by clinicians with regard to DLB as sufficiently characterized to be reliably identified (i.e. VH and EPS, but not fluctuations). Furthermore, although all cases included in this study had received a thorough neuropsychological examination, we limited our analyses to visuospatial function since, compared to Alzheimer's disease, DLB subjects have consistently been shown to perform more poorly in this area even on commonly used global measures of cognitive status (i.e. MMSE, DRS) (Salmon and Galasko, 1996; Ala et al., 2001; Cormack et al., 2004).

Our intent was to elucidate the best predictors for distinguishing DLB from Alzheimer's disease as early as possible in the course of dementia. Since VH, EPS and visuospatial deficits are not exclusive to DLB (occurring frequently in moderate to severe Alzheimer's disease), it is their appearance early in DLB that may be distinctive. Thus, the present study examined the frequency of these clinical features at first presentation rather than at later points during the course of these illnesses.

Methods

Subjects

The patients included in this study were followed clinically at the University of California San Diego Alzheimer's Disease Research Center. They represent approximately one-third of all patients who came for autopsy between 1985 and the present with a pathological diagnosis of DLB or Alzheimer's disease. To be included in our analyses, patients had to have no other confounding pathological diagnoses and their first clinical examination had to have occurred during the earliest stages of dementia (as defined by a DRS score of at least 115). Two DLB and 19 Alzheimer's disease subjects were excluded because of additional confounding pathological diagnoses to which clinical dementia could be attributed, including vascular disease (n = 17), hippocampal sclerosis (n = 2), Pick's disease (n = 1) or Huntington's disease (n = 1). There were 23 autopsy-proven DLB and 96 Alzheimer's disease patients who met all of the requirements for inclusion.

Subjects had been evaluated at the University of California San Diego Alzheimer's Disease Research Center with standardized medical, neurological, neuropsychological and laboratory examinations. All had fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria for a clinical diagnosis of dementia (American Psychiatric Association, 1987) at first visit, except for one subject in the DLB group and five subjects in the Alzheimer's disease group, who had been clinically diagnosed as 'at risk for dementia' at first presentation.

Procedures

Presence/absence of VH was assessed by the Diagnostic Interview Schedule (Robins et al., 1981), Neuropsychiatric Inventory (Cummings et al., 1994) or Behave-Alzheimer's disease (Reisberg et al., 1996). Spontaneous EPS were regarded as present when at least one among bradykinesia, masked facies, rigidity, action tremor, parkinsonian tremor and parkinsonian gait was rated in the motor examination subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) as ≥2, in the absence of neuroleptic or other dopamine blocker drugs. In the years before implementing the UPDRS at our centre, parkinsonian signs were rated as part of a structured neurological examination. Visuospatial/constructional function was rated on the basis of MMSE intersecting pentagons and/or DRS construction subscale (DRS-C). Following the original grading criteria, each patient's copy of the intersecting pentagons was regarded as acceptable when all ten angles were present and two intersected (Folstein et al., 1975). Ratings on the DRS-C, which is composed of six tasks including copy of two-dimensional figures, were also dichotomized, since each patient's performance was considered acceptable only when the maximal score was obtained. Testing procedures were modified in that all six subscale items were administered to all patients. As opposed to less restrictive original criteria (Mattis, 1976), the patient was given maximum credit when he/she accomplished all of the tasks, not the first one alone (reproduction of a diamond within a square).

Neuropathological examination

Pathological assessment was made by one observer (L.A.H.). Autopsy was performed within 12 h of death using a protocol described by...
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Terry et al. (1981). The left hemibrain was fixed by immersion in 10% formalin for 5–7 days. The paraffin-embedded blocks from mid-frontal, rostral superior temporal and inferior parietal areas of neocortex, anterior cingulate gyrus, posterior cingulate gyrus, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon and pons were cut at 7 μm thickness for haematoxylin and eosin (H–E) and thioflavin-S staining. Total plaque, neuritic plaque, neurofibrillary tangle and Lewy body counts were determined by the same examiner with the same criteria used consistently. Each brain was also staged for degree of neurofibrillary pathology according to a slight modification (Hansen and Samuel, 1997) of the scheme of Braak and Braak (1991).

All of the DLB cases included in this study met the Consortium on DLB criteria for a pathological diagnosis of DLB, based on the presence of brainstem and cortical Lewy bodies [identified by H–E and antiubiquitin immunostaining, as recommended by the Consortium on DLB (McKeith et al., 1996), and anti-alpha-synuclein immunostaining]. Nearly all would have been labelled, according to Lewy body distribution, as being “neocortical predominant” DLB.

Of the 23 patients with DLB included in the present analysis, two had no or negligible Alzheimer’s disease changes, while the remaining 21 also had enough senile plaques to meet the National Institute on Aging (NIA) criteria for Alzheimer’s disease (Khachaturian, 1985) or neuritic plaques to meet the criteria of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) for probable or definite Alzheimer’s disease (Mirra et al., 1991) (i.e. Lewy body variant of Alzheimer’s disease). However, approximately three quarters of the cases had no neocortical neurofibrillary tangle involvement (Braak stage IV or less), thereby meeting NIA-Reagan guidelines (1997) for only a low to intermediate likelihood that Alzheimer’s disease pathology contributed to their dementia.

The neuropathological diagnosis of Alzheimer’s disease was based on both NIA and CERAD criteria for Alzheimer’s disease, as well as on the exclusion of brainstem and cortical Lewy body. Almost all of the Alzheimer’s disease patients included in the present study displayed significant numbers of neurofibrillary tangles in each of the neocortical regions examined (Braak stages V or VI), thereby fulfilling NIA-Reagan guidelines for a high likelihood that their dementia was attributable to Alzheimer’s disease pathology. As mentioned above, DLB or Alzheimer’s disease cases with significant coexistent vascular (>10 ml of infarcted brain tissue, two or more cortical microinfarcts, two or more lacunes, or hippocampal sclerosis) or other pathology [that could by itself cause dementia] were excluded from analyses.

Statistical analysis

Mean values between groups were compared using unpaired t-test or Fisher exact test. For each clinical feature (VH, EPS and visuospatial impairment), sensitivity and specificity to DLB, as well as positive and negative predictive values were calculated using pathological diagnosis as the external validation. Sensitivity is the proportion of pathologically proved DLB patients with VH, EPS or visuospatial impairment. Specificity is the proportion of pathologically proved Alzheimer’s disease patients without VH, EPS or visuospatial impairment. Positive predictive value (PPV) is the proportion of patients with VH, EPS or visuospatial impairment who are correctly diagnosed as DLB; negative predictive value (NPV) is the proportion of patients without VH, EPS or visuospatial impairment who are correctly diagnosed as Alzheimer’s disease. The PPV and NPV were estimated assuming a DLB prevalence of 20%. An odds ratio with a 95% CI was also calculated for each clinical variable, using logistic regression.

Results

Because their EPS at first visit occurred in the presence of neuroleptic drugs, 2 patients from the Alzheimer’s disease group were excluded; thus, final analyses were based on 23 DLB and 94 Alzheimer’s disease patients.

There were no group differences with regard to age (at either onset, first visit or death), gender, education or global severity of dementia at presentation (Table 1). None of the DLB or Alzheimer’s disease patients was receiving dopaminergic therapy. Depression was judged to be severe enough to require specific treatment in two DLB and seven Alzheimer’s disease patients (P = 0.5). No significant visual deficits were reported in any of the subjects.

As shown in Table 2, compared to Alzheimer’s disease, DLB patients at initial presentation displayed an increased frequency of VH (P = 0.001) but not spontaneous EPS (P = 0.3). However, only a minority of DLB cases had either VH (22%), EPS (26%) or both (13%). In contrast, although not a core feature, visuospatial/constructional impairment was observed in most of the DLB cases. While differences in the frequency of flawed MMSE pentagon copying between...
DLB and Alzheimer’s disease patients only approached statistical significance (30% versus 16%, $P = 0.1$), an impaired performance on the DRS-C subscale was significantly more common in the DLB group (74% versus 45%, $P = 0.01$). Removal of cases who, at first visit, had been diagnosed as ‘at risk for dementia’ from each group did not result in any significant changes in these findings.

Sensitivity, specificity, PPV, NPV and odds ratios of each clinical feature for distinguishing DLB from Alzheimer’s disease cases are reported in Table 3. Presence/recent history of VH was the most specific (99%) to DLB. As a result, early VH emerged as the best positive predictor of DLB (PPV: 84% versus 32% or less for all other variables), while lack of visuospatial/constructional impairment on the DRS-C was the best negative predictor (NPV: 90%). In stepwise regression analyses, VH at presentation were confirmed to be by far the strongest predictor of DLB (PPV: 84% versus 16% for Alzheimer’s disease). The estimated PPV of VH for DLB was 0.83, implying that more than 8 out of 10 cases clinically diagnosed as DLB on the basis of early VH are likely to be correctly identified. However, due to extremely low sensitivity, the absence of VH in mild-stage dementia does not exclude a diagnosis of DLB. In fact, assuming a prevalence of ~20% for DLB in dementia populations, our estimated NPV of VH was 0.84. In other words, ~1 out of 6 cases clinically considered not to have DLB (on the basis of an absence of VH at presentation) will indeed have DLB at autopsy. On the other hand, as a result of their almost complete specificity (99%), the presence of early VH makes the diagnosis of DLB considerably more likely than that of Alzheimer’s disease (odds ratio = 25.8).

The presence of EPS, conversely, does not appear to significantly contribute to improved diagnostic accuracy of DLB in the earliest stages of dementia. In fact, in our analysis, EPS were not only poorly sensitive but also insufficiently specific to DLB, as indicated by the absence of significant differences in their prevalence between the DLB and Alzheimer’s disease groups. Consequently, the estimated PPV of EPS for DLB was only 0.26, implying that, in early-stage dementia, about three quarters of cases clinically labelled as DLB on the basis of this core feature alone are likely to be misdiagnosed. Had we used more stringent criteria for parkinsonism—such as the presence of at least two EPS—sensitivity to DLB would have declined from 26 to 13%, without any increase in specificity. Thus, parkinsonism in early-stage DLB is infrequent and, when present, relatively mild.

In support of these results is a recent study of mild DLB patients that described a frequency of spontaneous EPS as low as that observed in our DLB cohort (Weiner et al., 2003). Furthermore, at least four autopsy series of mild to moderately demented subjects have failed to observe any difference in the frequency of spontaneous EPS between DLB and Alzheimer’s disease (McKeith et al., 1992; Weiner et al., 1996; Stern et al., 2001; Weiner et al., 2003), despite greater frequencies for drug-induced parkinsonism in DLB (McKeith et al., 1992; Weiner et al., 2003). Nevertheless, this is the first study to highlight that spontaneous parkinsonism, even when apparent in the earliest stages of dementia, may not be a useful discriminator between the two entities.

The finding of only negligible differences in EPS frequency between DLB and Alzheimer’s disease, although somewhat unexpected, has several possible explanations. For example, Lewy bodies are not necessarily associated with clinical signs (Gibb and Lees 1988; Stern et al., 2001; Wakisaka et al., 2003; McKeith et al., 2003).

### Table 3

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual hallucinations</td>
<td>0.22</td>
<td>0.99</td>
<td>0.83</td>
<td>0.84</td>
<td>25.8 (2.8–234.6)</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>0.26</td>
<td>0.82</td>
<td>0.26</td>
<td>0.82</td>
<td>1.6 (0.5–4.7)</td>
</tr>
<tr>
<td>Visuospatial impairment on DRS-C</td>
<td>0.74</td>
<td>0.55</td>
<td>0.29</td>
<td>0.90</td>
<td>3.5 (1.3–9.7)</td>
</tr>
<tr>
<td>Wrong MMSE pentagon copy</td>
<td>0.30</td>
<td>0.84</td>
<td>0.32</td>
<td>0.83</td>
<td>2.3 (0.8–6.6)</td>
</tr>
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</table>

PPV = positive predictive value, NPV = negative predictive value. Other abbreviations are as in Table 1.

Discussion

The main finding of this study is that the best model for differentiating DLB from Alzheimer’s disease in the earliest stages of dementia includes VH and visuospatial/constructional dysfunction, but not spontaneous EPS, as predictors. Another important finding of this study is the extremely low frequency of Consortium core clinical features (McKeith et al., 1996) in mild-stage DLB, a factor that likely contributes considerably to its poor clinical diagnostic accuracy. In fact, only about a quarter of our patients with DLB exhibited VH or EPS at initial presentation. Although these frequencies increase to some degree if the entire course of disease is considered, as previously reported by ourselves and others (Litvan et al., 1998; Lopez et al., 1999; Luis et al., 1999; Verghese et al., 1999; Hohl et al., 2000; Lopez et al., 2000; McKeith et al., 2000; Merdes et al., 2003), up to 50% of DLB patients may never develop EPS or VH during life (Verghese et al., 1999; Merdes et al., 2003).

What definitely emerges from this study is that, among the features examined, early VH are by far the strongest positive predictor of DLB at autopsy. Our estimated PPV of VH for DLB was 0.83, implying that more than 8 out of 10 cases...
Parkkinen et al., 2005) and it may be that severity of cell loss in the substantia nigra, rather than the presence of Lewy bodies in surviving neurons, is a necessary concomitant of parkinsonism (Brown, 1999). DBL cases without EPS may be those in whom the threshold of cell loss for clinical symptomatology has not been exceeded, despite the presence of nigral Lewy body. In addition, it has been suggested that, in Alzheimer’s disease, several neuropathological substrates other than Lewy bodies may account for the presence of EPS (Scarmeas et al., 2004), including extranigral lesions involving mesocortical dopaminergic pathways (Morris et al., 1989), damage to striatal dopamine transporter sites (Murray et al., 1995), and decreased dopaminergic D2 receptors in the putamen (Cross et al., 1984). Alzheimer’s disease pathology itself, in the form of plaques or tangles, has been described in the putamen, caudate and substantia nigra of Alzheimer’s disease subjects and, in the absence of Lewy bodies, has been associated with EPS (Liu et al., 1997).

What also emerges from the present study is that emphasis on visuospatial impairment early in the course of dementia substantially improves the sensitivity of detecting DBL. Notably, most (74%) of our DBL patients, but only 45% of the Alzheimer’s disease subjects, showed some degree of visuospatial/constructional impairment on the DRS-C. An erroneous ‘vertical lines’ reproduction was by far the most frequent mistake in both groups. Fewer DBL subjects (30%) had difficulty with the MMSE pentagon copy, suggesting that the DRS-C may be more sensitive to visuospatial/constructional impairment early in the course of the disease.

Most investigators (Gnanalingham et al., 1996; Salmon and Galasko, 1996; Walker et al., 1997; Mori et al., 2000; Ala et al., 2001; Calderon et al., 2001; Lambon-Ralph et al., 2001; Collerton et al., 2003; Simard et al., 2003; Cormack et al., 2004; Mosimann et al., 2004; Noe et al., 2004), but not all (Cahn-Weiner et al., 2003), have previously reported greater visuospatial/constructional (and visual-perceptual) deficits for patients with DLB as compared to Alzheimer’s disease. In this study, visuospatial impairment on the DRS-C had the highest sensitivity (74%) and, consequently, the highest NPV (90%) for mild-stage DBL. These results imply that only 1 out of 10 subjects clinically considered not to have DBL (on the basis of intact visuospatial function at presentation) will have DBL at autopsy.

Although visuospatial deficits are mentioned in the Consortium on DLB criteria (McKeith et al., 1996), they have not been suggested as either a core or supportive feature. Our results strongly suggest that the addition of early visuospatial impairment to the traditional core clinical features of DBL can increase diagnostic accuracy for this entity. In fact, it appears that the best model for the early diagnosis of DBL includes the presence of VH as a positive predictor and the absence of visuospatial dysfunction as a negative predictor.

Some issues related to this study should be addressed. First, it is likely that greater frequencies of specific DBL core clinical features at initial presentation would have been observed had we been a psychiatric (VH) or movement disorder (EPS), rather than a memory, centre. These differences inevitably limit sample comparability since a clinical diagnosis of DBL applies equally well to cases with EPS preceding the onset of dementia. On the other hand, such an order of presentation of motor and cognitive disturbances poses considerably less challenge to the clinician’s diagnostic ability. In fact, discrimination of DBL from Alzheimer’s disease is only difficult when dementia occurs first in the clinical course of disease.

Secondly, we limited our evaluation of visuospatial impairment to the MMSE pentagon copy and the DRS-C subscale. Others from our institution (Salmon and Galasko, 1996; Salmon et al., 1996) have previously reported significantly more impaired visuospatial/constructional ability in DBL than Alzheimer’s disease utilizing tests such as the Wechsler Adult Intelligence Scale—Block Design and Clock Drawing or Copy-a-Cube. Since this study was intentionally weighted towards clinical rather than detailed neuropsychological examination, our analyses were restricted to the patient’s visuospatial performance on commonly used global measures of cognitive status.

A further limitation of this study stems from its retrospective analysis of prospectively collected data—in this case, sometimes many years before the core clinical features of DBL were even recognized. This is probably especially significant with regard to fluctuations; however, even today this symptom remains problematic to identify and difficult to define and reliably assess. In fact, while both VH and EPS have reached very high kappa scores in interrater reliability studies of DBL, fluctuations have not (Mega et al., 1996; Litvan et al., 1998; Luis et al., 1999; Verghese et al., 1999), reflecting the lack of well-defined operationalized criteria for their identification. In light of this, some investigators have attempted to better standardize the evaluation of fluctuating cognition (Walker et al., 2000a, b; Ferman et al., 2004). Although these authors have reported good discrimination between DBL and Alzheimer’s disease, confirmation of their findings through pathological verification of subjects’ clinical diagnoses is needed.

In summary, in the present study, we sought to determine which clinical feature(s) (among VH, EPS or visuospatial/constructional impairment) at initial presentation best predicted a diagnosis of DBL at autopsy. We conclude that the low frequency of current Consortium core clinical features (McKeith et al., 1996) in mild-stage DBL is a major obstacle to its identification. When present, though, early VH strongly predict DBL. While concomitant EPS at presentation do not appear to contribute significantly to improved clinical diagnostic accuracy, coexistent visuospatial dysfunction does. In particular, it appears that, in differentiating DBL from Alzheimer’s disease, the presence of intact visuospatial function at presentation makes the diagnosis of DBL less likely than does the absence of either VH or EPS. These results suggest that early visuospatial deficits should be considered as a core clinical feature of DBL and that clinical history plus a brief assessment of visuospatial function may be of
the greatest value in correctly identifying DLB early in the course of the disease.

Acknowledgements

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