Clinical and neuropsychological predictors of the diagnosis of dementia with Lewy bodies

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Abstract
Introduction: The pattern of clinical symptoms and cognitive impairment in dementia with Lewy bodies (DLB) is different from Alzheimer’s disease (AD). The aim of this study was to determine which clinical or neuropsychological features most accurately predicted the diagnosis of DLB or AD in the early stage of dementia.

Material and methods: Sixty-two subjects were included, 20 of those with clinically diagnosed DLB, 23 with AD and 19 cognitively intact controls. An elaborated battery of clinical and neuropsychological tools was applied.

Results: There were significant differences in clinical variables between the dementia groups despite similar duration of disease. In comparison to AD patients, the subjects with probable DLB achieved significantly worse scores in the NPI, HIS, UPDRS and ADL scales. The presence/recent history of apathy and visual hallucinations were significantly more frequent in DLB. The onset of neuropsychiatric symptoms was earlier in DLB and the symptoms were more severe in this group. The DLB cases had an increased prevalence of a positive history of REM sleep behaviour disorder and anosmia as well. The DLB group was more impaired in category fluency (animals), visuoperceptual, constructional, and attention tasks.

Conclusions: DLB patients have a different profile of clinical symptoms and neuropsychological deficits early in the course of dementia compared to the AD group. Neuropsychological evaluation in AD and DLB reveals multiple cognitive deficits even in early and moderate dementia.

Key words: dementia with Lewy bodies, Alzheimer’s disease, neuropsychology, differential diagnosis.

Introduction
Following Alzheimer’s disease (AD), dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia, accounting for approximately 20% of cases in autopsy series [1, 2], and about 10% in psychogeriatric outpatient unit cohorts [3]. Despite its high prevalence, DLB is seldomly diagnosed ante-mortem as no specific and sensitive biomarker has been identified to date. The third report of the DLB consortium concluded that there were no uniformly acceptable clinically applicable genetic or CSF markers to support the diagnosis of DLB [4]. However, according to that panel of renowned experts, neuroimaging (in particular, the preservation of hippocampal and medial temporal lobe volume on MRI, atrophy of the putamen, occipital hypoperfusion (SPECT) and hypometabolism (PET) without occipital atrophy on MRI) can be helpful in the differential diagnosis. Other features such as the degree of generalized atrophy, rate of progressive brain...
atrophy, and severity of white matter lesions do not aid in the discrimination of DLB from other dementia subtypes. Other imaging investigations [heart scintigraphy with [1-123] metaiodobenzyl guanidine (MIBG)] have been suggested to have high sensitivity and specificity in the differential diagnosis of DLB and AD [4]. The introduction of staining for ubiquitin and α-synuclein facilitated the detection of cortical Lewy bodies and improved the diagnostic accuracy at autopsy. Nonetheless, clinically there are constant problems with differentiating the presenting symptoms of DLB from those of both AD with Parkinsonism and Parkinson’s disease dementia (PDD). DLB and PDD share many clinical, genetic and neurobiological similarities, but there are differences as well. The diagnosis of DLB is based on clinical investigation, application of the Consensus Criteria and on an arbitrary distinction between the time of onset of motor and cognitive symptoms in DLB and PDD [4]. The consensus criteria for a clinical diagnosis of DLB state that DLB should be diagnosed when dementia occurs before or concurrently with Parkinsonism (the 1-year rule between the onset of dementia and Parkinsonism should be used for DLB). It has been criticized by those who regard the different clinical presentations as simply representing different points on a common spectrum of Lewy body disorders. The identification of differences during clinical and neuropsychological evaluations ought to be of value in the clinical separation of DLB and AD. Diagnostic accuracy is crucial in the context of specific and important treatment considerations for patients with DLB as compared to other dementias, particularly neuroleptic hypersensitivity reactions [5] and the symptoms of autonomic dysfunction [6] complicating DLB treatment interventions.

To determine the possible differences in clinical and cognitive features between DLB and AD we investigated patients with a clinical diagnosis of DLB or AD at the stage of early dementia.

Material and methods

The study group comprised 20 patients referred to a psychogeriatric outpatient unit who exhibited clinical features of DLB. All DLB subjects fulfilled the Consortium on DLB International Workshop Criteria for probable DLB [7]. In the present study, the diagnosis of DLB was established based on the previous version of the diagnostic criteria, since the current criteria [4] were published after we had finished the recruitment of study participants. Twenty-three patients with probable AD diagnosed with the NINCDS-ADRDA criteria [8] served as a comparison group. Nineteen cognitively intact control subjects also participated in the study, all of them without either subjective memory complaints or any neurological or unstable somatic disease. All demented subjects had an informant who provided an adequate clinical history.

All subjects underwent general medical, neurological, psychiatric and neuropsychological examinations.

Written informed consent for the study was obtained from all subjects before inclusion. The study was approved by the Ethics Committee of the Medical University of Lodz.

Clinical assessments

The clinical assessments included a structured interview (demographic data, age at onset, duration of illness, presence of REM sleep behaviour disorder, anosmia), vital signs, Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR), the Memory-Orientation-Concentration Test of Blessed (BIMC), the Clock Drawing Test (CDT), the Hachinski Ischaemic Scale (HIS), 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).

Neuropsychological assessments

The neuropsychological examination was designed to assess: working memory [forward and backward digit span – subscale from Wechsler Adult Intelligence Scale-Revised (WAIS-R)], serial subtraction – from MMSE, episodic memory (10-item word list x 5 trials with delayed recall), semantic memory [Boston Naming Test, category and letter fluency (FAS), Similarities subscale from WAIS-R], visuoconstructive skills (object assembly and block design subscales from WAIS-R, copy of the Interlocking pentagons from MMSE, copy and delayed recall of Rey complex figure, the Clock Drawing Test), abstraction reasoning (Similarities subscale from WAIS-R).

Procedure

At the time of the first visit all subjects underwent clinical assessment with the above described tools (RM). The neuropsychological examination was carried out independently of clinical history taking by an independent rater (IK). The evaluation of data and statistics was carried out by an independent rater (TS) not involved in any clinical contact with the patients.

Statistical analysis

Kruskal-Wallis H was used as a nonparametric alternative to one-way analysis of variance for testing the null hypothesis that the samples (continuous variables for groups of subjects diagnosed as AD or DLB or controls) did not differ in mean rank for the criterion variable. Data from all samples were ordered as in the Mann-Whitney U test used as a post-hoc procedure for direct between-the-groups comparisons with a finding of
significant difference understood that the two samples differed in the variable of interest.

Differences in frequency of clinical symptoms were measured with Fisher’s exact test.

**Results**

Sixty-two subjects matched for age, gender, years of formal education and dementia severity scores (MMSE & CDR) were examined. 20 of those were with clinically diagnosed DLB, 23 with AD and 19 were cognitively intact controls. The patients with AD were selected to be as closely matched to the DLB group as possible on a range of demographic and clinical variables (Table I). All three samples were enriched in women to the same extent (p=0.371). Controls were slightly younger than both AD and DLB subjects (AD vs. controls: Z=–2.4; p=0.014; DLB vs. controls: Z=–2.6, p=0.01). Similarly, controls had more years of education than both AD and DLB patients (χ²=6.150; df=2; p=0.046). Adjustments for age and education were applied to exclude the influence of these variables on final results.

**Clinical findings**

The global severity of dementia was comparable between the 2 dementia groups, as demonstrated by MMSE (DLB vs. AD: Z=–1.526; p=0.127); the CDR total score was, however, higher in the DLB group (1.2±0.5 vs. 1.6±0.7; p=0.017). The age of onset and the duration of dementia were similar in both dementia groups (DLB vs. AD; p=0.874 and p=0.540, respectively).

Significant differences in the clinical variables were revealed between the dementia groups despite similar duration of disease. The results of all clinical assessments in the groups with probable DLB and AD are presented in Table II.

The patients with probable DLB achieved significantly worse scores in the NPI, HIS, UPDRS and ADL scales than the subjects with probable AD. The NPI subscales scores analysis revealed that the presence/recent history of apathy (p<0.001) and visual hallucinations (p<0.001) were significantly more frequent in DLB compared to AD (Figure 1). The DLB group demonstrated a characteristic pattern of severity of neuropsychiatric symptoms. As shown in Figure 2, the onset of neuropsychiatric

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**Table I**. Demographic and clinical data of dementia with Lewy bodies (DLB), Alzheimer’s disease (AD) and control subjects*

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (y)</th>
<th>Gender (fraction of women)</th>
<th>Education (y)</th>
<th>Duration of dementia (mo)</th>
<th>Age at onset (y)</th>
<th>MMSE score</th>
<th>CDR score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (n=23)</td>
<td>76.0±5.4</td>
<td>0.6</td>
<td>9.7±3.9</td>
<td>41.5±14</td>
<td>73.1±6.2</td>
<td>21.2±4.1</td>
<td>1.2±0.5</td>
</tr>
<tr>
<td>DLB (n=20)</td>
<td>76.8±5.1</td>
<td>0.6</td>
<td>10.3±4.7</td>
<td>48.9±28</td>
<td>72.8±5.7</td>
<td>19.1±4.9</td>
<td>1.6±0.7</td>
</tr>
<tr>
<td>Controls</td>
<td>70.4±7.1</td>
<td>0.8</td>
<td>11.9±3.1</td>
<td>n/a</td>
<td>n/a</td>
<td>28.9±0.7</td>
<td>0±0</td>
</tr>
</tbody>
</table>

* Results are given as means ±SDs. MMSE – Mini Mental State Examination; CDR – Clinical Dementia Rating; y – years; mo – months; n/a – not applicable

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**Table II**. Differences in clinical test scores between probable DLB and probable AD (statistically significant differences in bold)*

<table>
<thead>
<tr>
<th>Test</th>
<th>AD</th>
<th>DLB</th>
<th>p#</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>21.2±4.1</td>
<td>19.1±4.9</td>
<td>0.1</td>
</tr>
<tr>
<td>CDR</td>
<td>1.2±0.6</td>
<td>1.6±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>BIMC</td>
<td>22.9±5.4</td>
<td>22.5±6.0</td>
<td>0.4</td>
</tr>
<tr>
<td>CDT</td>
<td>3.8±2.2</td>
<td>2.6±2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>HIS</td>
<td>1.7±0.8</td>
<td>3.1±1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GDS</td>
<td>8.6±5.6</td>
<td>11.6±5.2</td>
<td>0.06</td>
</tr>
<tr>
<td>NPI</td>
<td>8.9±9.4</td>
<td>20.3±14.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ADL</td>
<td>66.1±10.6</td>
<td>48.0±13.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UPDRS</td>
<td>3.2±3.3</td>
<td>19.2±12.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Results are given as means ±SDs. MMSE – Mini Mental State Examination; CDR – Clinical Dementia Rating; BIMC – the Memory-Orientation-Concentration Test of Blessed; CDT – the Clock Drawing Test; HIS – the Hachinski Ischaemic Scale; GDS – the Geriatric Depression Scale; NPI – the Neuropsychiatric Inventory; ADL – the Activities of Daily Living; UPDRS – the motor section of the Unified Parkinson’s Disease Rating Scale; y – years; mo – months; n/a – not applicable

# Mann-Whitney U test

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**Figure 1**. Mean composite scores (frequency x severity) for behavioural symptoms in patients with Alzheimer’s disease (AD), and dementia with Lewy bodies (DLB) measured by the Neuropsychiatric Inventory (NPI)*

* 1 – indicates Delusions; 2 – Hallucinations; 3 – Apathy or aggression; 4 – Depression or dysphoria; 5 – Anxiety; 6 – Elation or euphoria; 7 – Apathy or indifference; 8 – disinhibition; 9 – irritability or lability; 10 – Motor disturbance
Neuropsychological findings

The mean scores achieved by the DLB and AD groups on every neuropsychological test are presented in Table III.

Although the DLB and AD patients were matched for overall severity of dementia based on the MMSE result, their patterns of performance on neuropsychological tests differed.

As shown in Table III, the DLB and AD subjects performed comparably on tests assessing working memory (forward and backward digit span from WAIS-R), abstraction reasoning and problem solving (similarities subscale from WAIS-R), episodic memory (10-item word list x 5 trials with delayed recall), semantic memory (Boston Naming Test), letter fluency (FAS), and constructional functions (block design subscale from WAIS-R, delayed recall of the Rey

Figure 2. Relationship between Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI) scores: patients with Alzheimer’s disease (AD), (A); patients with dementia with Lewy bodies (DLB) (B)

Figure 3. Frequency of REM sleep behaviour disorder in patients with Alzheimer’s disease (AD), dementia with Lewy bodies (DLB), and the control group evaluated during a structured interview

Figure 4. Frequency of anosmia in patients with Alzheimer’s disease (AD), dementia with Lewy bodies (DLB), and the control group evaluated during a structured interview
The DLB group was more impaired in category fluency (animals), visuoconstructive and constructional (Object Assembly subscale from WAIS-R, copy of the interlocking pentagons from MMSE, copy of the Rey complex figure), and attention (serial subtraction from MMSE) tests.

Discussion

An early diagnosis of DLB is still a tall order in everyday clinical practice. According to the Consensus Criteria, the condition is characterized by a progressive decline in cognitive functions, sufficient to interfere with normal functioning (dementia). Symptoms of persistent or prominent memory impairment are not always present early in the course of the illness, although they are likely to develop in most patients with disease progression. Although neuropsychological assessment seems to be helpful in the differential diagnosis of dementing disorders, with the progression of dementia in DLB, the specific selective pattern of cognitive deficits may be lost, making differential diagnosis based on clinical examination difficult.

Our findings are consistent with the previous studies on DLB subjects. Evidence exists that the clinical course of DLB differs from that observed in AD, and early symptomatology could be a main clue in the DLB diagnostic process. In our group there were significant differences in the clinical variables between the dementia groups despite the similar age at onset and duration of disease. The NPI, HIS, UPDRS and ADL scores were significantly worse in the group with probable DLB compared to probable AD patients. The onset of neuropsychiatric symptoms was earlier and symptoms were more severe in the DLB group. These findings were similar to those reported by Del Ser et al., who found DLB subjects to have a higher frequency of acute-subacute onset of dementia, early parkinsonism, early and late hallucinations, fluctuating course, delusions, earlier urinary incontinence and shorter duration of dementia [9, 10]. However, Walker et al. concluded that the 3-year survival rate did not differ between patients with AD and DLB [11]. Delusions, depressed mood, sleep disturbance and auditory hallucinations are common neuropsychiatric features of DLB [12]. Similarly to previous papers [13-15], we confirmed a higher prevalence of the presence/recent history of apathy and visual hallucinations in DLB patients. It needs to be emphasized, however, that the difference in the frequency of hallucinations might, in part, stem from the clinical inclusion criteria and, as such, be spuriously accentuated (the so-called “circular argument” problem). On the other hand, the finding that apathy is overrepresented in the DLB group is new and might contribute to the future improvement of clinical diagnostic criteria.

Some authors have reported that DLB is typically accompanied by sleep disturbances [16, 17]. According to Turner [18], REM sleep behaviour disorder (RBD) is clinically associated with alpha-synucleinopathies: multiple system atrophy (MSA), Parkinson’s disease (PD) and DLB. Similarly, we demonstrated that RBD

<table>
<thead>
<tr>
<th>Test</th>
<th>Mann-Whitney U</th>
<th>Wilcoxon W</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R Forward and backward digit span</td>
<td>98.5</td>
<td>203.5</td>
<td>–0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>WAIS-R Similarities</td>
<td>97.5</td>
<td>202.5</td>
<td>–0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>WAIS-R Block design</td>
<td>38.5</td>
<td>83.5</td>
<td>–1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>WAIS-R Object Assembly</td>
<td>44.5</td>
<td>110.5</td>
<td>–2.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>10-item word list (5 trials with delayed recall)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total score</td>
<td>136.5</td>
<td>289.5</td>
<td>–0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>delayed recall</td>
<td>140.0</td>
<td>311.0</td>
<td>–0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>recognition</td>
<td>122.5</td>
<td>275.5</td>
<td>–1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>correct answers</td>
<td>115.5</td>
<td>251.5</td>
<td>–0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>incorrect answers</td>
<td>124.5</td>
<td>260.5</td>
<td>–0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Letter fluency (FAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>copy</td>
<td>93.5</td>
<td>246.5</td>
<td>–1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Category fluency (animals)</td>
<td>67.5</td>
<td>220.5</td>
<td>–2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>The Rey complex figure copy</td>
<td>68.0</td>
<td>204.0</td>
<td>–2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>delayed recall</td>
<td>33.5</td>
<td>61.5</td>
<td>–1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>MMSE copy of the interlocking pentagons</td>
<td>105.0</td>
<td>276.0</td>
<td>–2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>MMSE serial subtraction</td>
<td>71.0</td>
<td>242.0</td>
<td>–3.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Results are given as means ±SDs. MMSE – Mini Mental State Examination; CDR – Clinical Dementia Rating; y – years; mo – months; n/a – not applicable
is more common in DLB than both in AD and controls, although, again and similarly to hallucination frequency, the methodological problem of inclusion criteria might apply to that finding.

Finally, we should also stress that several other behavioural symptoms (particularly, delusions, depression or dysphoria and agitation or aggression) were numerically more frequent in DLB than in AD but, most probably due to insufficient sample size, the differences missed statistical significance.

McShane et al. having compared the olfactory function of patients with dementia (DLB and AD) and controls, suggested that DLB was associated with impaired odour detection and patients with Lewy bodies were more likely to be anosmic than those with AD or controls [19]. DLB subjects in our study (as well as their caregivers) similarly reported a greater prevalence of anosmia than in both AD subjects and cognitively intact healthy controls, supporting the above-mentioned clinical findings.

Patients with probable DB and those with probable AD were comparable in the global assessment of dementia severity as estimated by the MMSE score. Only two items from MMSE discriminated DLB from AD subjects. Firstly, the DLB group performed worse in copying the interlocking pentagons task from MMSE. Similarly, Ala et al. concluded that in patients with MMSE scores >13 the inability to accurately copy the pentagons was suggestive of DLB rather than AD [20]. Moreover, in a study by Cormack et al. patients with DLB were found to draw pentagons significantly worse than those with AD or PDD. Drawing scores were significantly correlated with MMSE scores for the AD and PDD groups but not for those with DB [21]. Secondly, DBL subjects turned out to perform worse on a serial subtraction item from MMSE as compared to AD. In a study by Robles [22] acalculia was seen in over half of the DLB patients. Furthermore, using items from assessment tools other than MMSE, the DLB group showed a greater level of impairment in comparison to AD on visuo-perceptual and constructional tests (Object Assembly subscale from WAIS-R, copy of the Rey complex figure). These results are concordant with other studies on visuospatial/constructional impairment in DLB [23, 24]. According to Noe et al., the profile of neuropsychological deficits in DBL (attentional, visuo-perceptive, and visuo-constructive) and PD (attentional) compared to AD (amnesic syndrome) can contribute to an accurate identification of these entities. Both attention deficits and fluctuation of attention are described in the consensus clinical criteria for DLB as characteristic features of the condition. Attention impairments, together with parkinsonism and visual hallucinations, are among the most typical symptoms of DLB. In our study, the assessment of fluctuations of attention was based on an interview with a caregiver; however, we did not examine attention deficits and fluctuation of attention separately. This type of impairment in DLB patients was only confirmed by the results of some subtests. Examination of that domain is still difficult in the absence of reliable tools. In some surveys a computerized test battery was used for this purpose [25, 26].

In the presented study, CDR was a more precise instrument in the evaluation of severity of dementia than MMSE. BIMC and CDT were proven to be ineffective in the differential diagnosis of AD and DBL. Similarly, Cahn-Weiner et al. noted that CDT provided only limited discrimination of DBL from AD and PD [27].

Several methodological issues limit the interpretation of the results of this study. Firstly, the diagnosis relied solely on the clinical picture, without pathologic confirmation. Secondly, the number of DBL patients included in this study was small and we decided to match a similar number of AD and control subjects. The small size of the DBL and AD groups resulted in modest statistical power. Thirdly, some of the demographic characteristics were significantly different among the three studied groups. For that purpose statistical adjustment needed to be performed.

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.

Conclusions

1. DLB patients have a different profile of clinical symptoms and neuropsychological deficits early in the course of dementia compared to the AD group. Clinically, DLB is a more malicious disorder than AD, with more pronounced behavioural and everyday-life (functional) problems despite a similar level of cognitive dysfunction.

2. Neuropsychological evaluation reveals multiple cognitive deficits in the AD and DBL groups, even in the early and moderate stages of dementia. Some neuropsychological features, including language and visuo-spatial perception (e.g. category fluency, copying interlocking pentagons, copying Rey complex figure), might be helpful in the differential diagnosis.

3. Compared to AD, DLB cases had an increased prevalence of a positive history of REM sleep behaviour disorder and anosmia.

4. Careful clinical evaluation with special reference to the typical features, enhanced with the use of behavioural and activities of daily living assessment tools and selected neuropsychological tests, might be helpful in the differential diagnosis.
of DLB versus the most commonly encountered dementia of AD type.

Acknowledgments

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References