Gruppo di ricerca geriatrica

Seminari del Venerdì
31 Agosto 2007

Demenza a corpi di Lewy
Inquadramento clinico

Renato Turco

Definition

DLB (dementia with Lewy bodies) is a *syndrome associated with underlying LBD (Lewy body disease), with manifestations in the cognitive, neuropsychiatric, motor, sleep and autonomic domains*.

Bradley F. Boeve. *Clinical Science* 2005

Cellular and molecular pathology

- **Cortical Lewy bodies and Lewy neurites** are often widespread in PDD and DLB and correlate with the severity of the dementia.

- **α-Synuclein** aggregates into fibrils in Lewy bodies and Lewy neurites in *PDD, DLB, and PD*. The structure of the Lewy body is indistinguishable in all three conditions, with α-synuclein as its principal pathologic protein. Solubility and epitope studies show similar features in α-synuclein between diseases.

- The *mechanism* by which α-synuclein leads to neuronal death is the subject of intense investigation. α-synuclein is abundant in the normal brain at the synaptic terminal. It may regulate dopamine release or work with other molecules to protect presynaptic nerve terminals from injury. Because Lewy body pathology is composed of fibrillar α–synuclein and several autosomal dominant mutations in α-synuclein lead to enhanced rates of protein fibrillization, this conformational change in the structure of α-synuclein may render it neurotoxic.

C. F. Lippa et al. Neurology 2007

Epidemiologia

Incidenza e prevalenza

- The only estimate for DLB ***incidence*** is 0.1% a year for the general population and 3.2% a year for all new dementia cases

  J. Zaccai. *Age and Ageing* 2005

- ***Prevalence*** estimates, depending on case criteria, range from 0 to 5% with regard to the general population, and from 0 to 30.5% of all dementia cases

  J. Zaccai. *Age and Ageing* 2005

- Community study of people aged ***over 85 years*** found that 5.0% met consensus criteria for DLB (3.3% probable, 1.7% possible) representing 22% of a demented cases

  I. McKeith et al. The Lancet Neurology 2004

- Estimates from ***autopsy*** series have ranged between 15 and 25% of degenerative dementia in older people

  J. Zaccai. *Age and Ageing* 2005

Nursing home placement and survival

- Median time to *nursing home placement* of 6.1 years (95% CI: 4.4 to 7.8) after diagnosis

- *Median survival in a nursing home* of 28.93 months (95% CI: 14.4 to 43.6)
  - *women* with DLB surviving for a shorter period of time (median survival *12.17 months*; 95% CI: 9.5 to 14.8)

Monique M. Williams et al. *Neurology* 2006

DLB: survival and mortality

- DLB group had a median age at death of 78.0 years (95% CI:76.3 to 79.8) mortality
- *Men* with DLB had the shortest median survival time (76.8 years; 95% CI: 73.6 to 80.2); *women* with DLB (81.4 years; 95% CI: 77.8 to 84.9)
- The median survival following diagnosis of dementia for DLB was 7.28 years (95% CI: 5.7 to 8.8)
  - DLB *men* (8.12 years; 95% CI: 5.7 to 10.7)
  - DLB *women* (6.61 years; 95% CI: 5.3 to 7.9)

Monique M. Williams et al. *Neurology* 2006

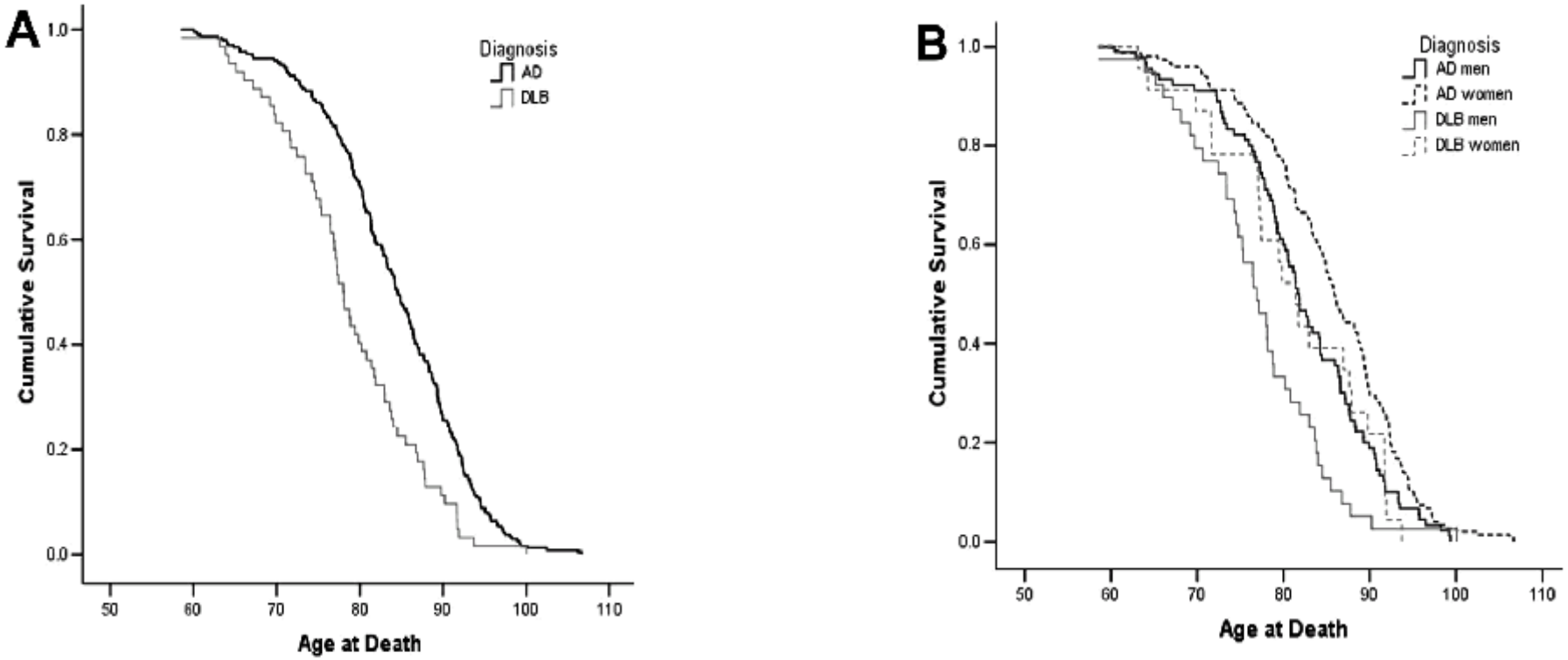

Figure 1. Kaplan–Meier survival curves comparing the **mortality rates for diagnosis** (A) and for **diagnosis–gender interactions** (B). The dementia with Lewy bodies (DLB) group had earlier ages at death than the Alzheimer dis-ease (AD) group (A) with a median age at death of 78.0 vs 84.6 years (χ^2 19.9, p 0.001 by log-rank test). There was a significant interaction effect of group and gender on mortality (B). DLB men had the shortest times to death (76.8 years; 95% CI: 73.6 to 83.7), whereas AD women (85.9 years; 95% CI: 84.3 to 87.5) had the longest survival times (χ^2 33.5, p 0.001 by log-rank test). AD groups are represented by black lines and DLB groups are represented by gray lines. Men are depicted as solid lines and women as dashed lines.

Monique M. Williams et al. *Neurology* 2006

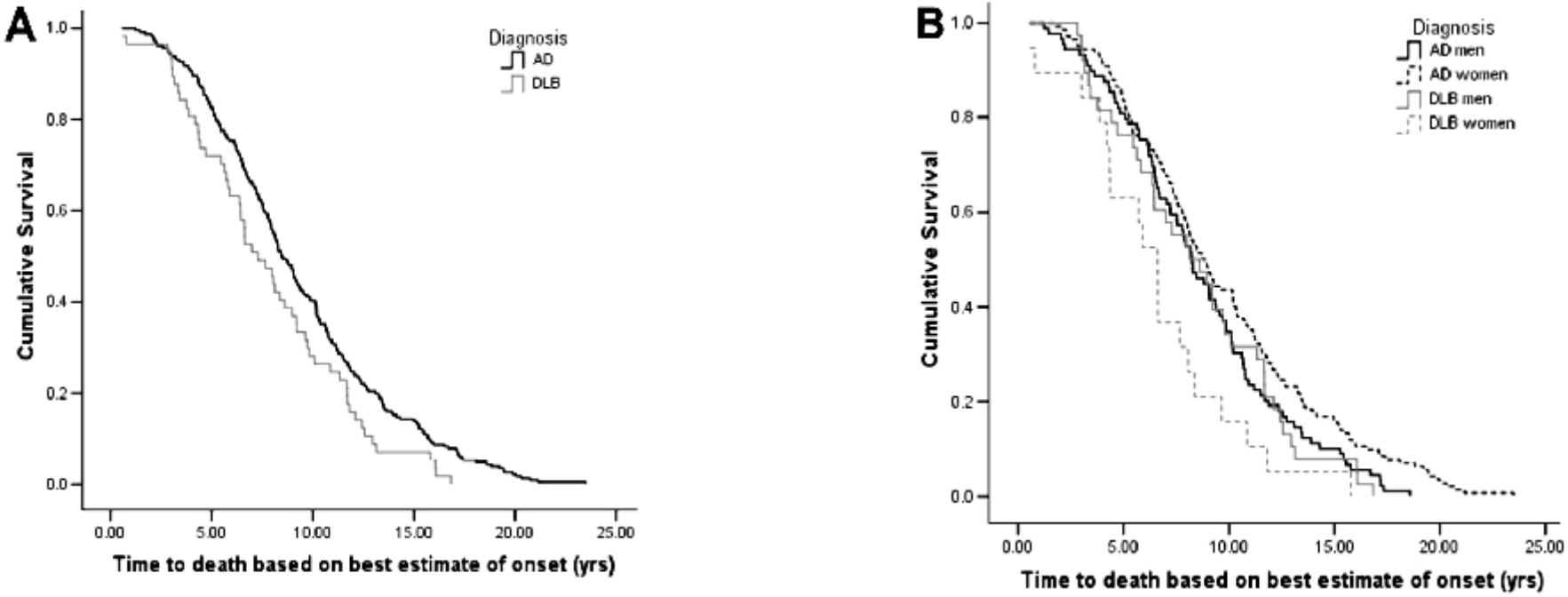

Figure 2. Kaplan–Meier survival curves comparing the survival after dementia onset for diagnosis (A) and for di-agnosis– gender interactions (B). The dementia with Lewy bodies (DLB) group had shorter survival times than the Alzheimer disease (AD) group (A) with a median survival of death after onset of 7.28 vs 8.47 years (χ^2 5.42, p 0.02 by log-rank test). There was a significant interaction effect of group and gender on mortality (B). DLB women had the shortest times to death following onset (6.61 years; 95% CI: 5.3 to 7.9). AD groups are represented by black lines and DLB groups are represented by gray lines. Men are depicted as solid lines and women as dashed lines.

Monique M. Williams et al. *Neurology* 2006

Sintomatologia clinica

Clinical Features

- Clinical symptomatology is wide, with most features falling into one of five categories:
  - *cognitive impairment,*
  - *neuropsychiatric features,*
  - *motor dysfunction,*
  - *sleep disorders,*
  - *autonomic dysfunction*

Bradley F. Boeve. *Clinical Science* 2005

Cognitive disfunction (I)

- Cognitive impairment is the presenting feature of DLB in **most, but not all, cases**

- Composite global cognitive assessment tools such as the Mini Mental State Examination (MMSE) cannot be relied upon to distinguish DLB from other common dementia syndromes and some patients who meet criteria for DLB will score in the normal range

- In contrast with Alzheimer's disease, in which anterograde memory dysfunction and then language dysfunction typically evolves, the domains of **attention/concentration**, **executive functioning** and **visuospatial functioning** are the most consistent domains impaired in DLB

McKeith et al. The Lancet Neurology 2004
Bradley F. Boeve. *Clinical Science* 2005
I. McKeith et al. *Neurology* 2005

Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease

J Calderon, R J Perry, S W Erzinclioglu, G E Berrios, T R Dening, J R Hodges

Abstract

Objective—To test the hypotheses that visuoperceptual and attentional ability are disproportionately impaired in patients having dementia with Lewy Bodies (DLB) compared with Alzheimer's disease (AD). ***Methods***—A comprehensive battery of neuropsychological tasks designed to assess working, episodic, and semantic memory, and visuoperceptual and attentional functions was given to groups of patients with DLB (n=10) and AD (n=9), matched for age, education, and mini mental state examination (MMSE), and to normal controls (n=17). ***Results***—Both patient groups performed equally poorly on tests of episodic and semantic memory with the exception of immediate and delayed story recall, which was worse in the AD group. Digit span was by contrast spared in AD. The most striking differences were on tests of visuoperceptual/spatial ability and attention. Whereas patients with AD performed normally on several subtests of the visual object and space perception battery, the DLB group showed substantial impairments. In keeping with previous studies, the AD group showed deficits in selective attention and set shifting, but patients with DLB were more impaired on virtually every test of attention with deficits in sustained, selective, and divided attention. ***Conclusions***—Patients with DLB have substantially greater impairment of attention, working memory, and visuoperceptual ability than patients with AD matched for overall dementia severity. Semantic memory seems to be equally affected in DLB and AD, unlike episodic memory, which is worse in AD. These findings may have relevance for our understanding of the genesis of visual hallucinations, and the differential diagnosis of AD and DLB.

J Neurol Neurosurg Psychiatry 2001

Cognitive disfunction (II)

- Problems with performing **sequential tasks**, for example, ordering from a menu, using remote controls, navigating in familiar surroundings and lying in the correct orientation in a bed, are typical symptoms.

- On examination in the office setting, patients tend to do **poorly on attention** (performing simple calculations, serial subtraction and digit span), **learning** (requiring several trials to learn short word lists) and **constructional praxis** (drawing the intersecting pentagons, clocks or cubes)

McKeith et al. The Lancet Neurology 2004
Bradley F. Boeve. *Clinical Science* 2005
I. McKeith et al. *Neurology* 2005

Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease

T A Ala, L F Hughes, G A Kyrouac, M W Ghobrial, R J Elble

Abstract

Objectives—In many cases the clinical differentiation of patients with dementia with Lewy bodies (DLB) from those with Alzheimer's disease (AD) has been diffi-cult. Because many neuropsychological studies have reported greater visuospatial/constructional impairment in DLB than in AD, it was determined whether accuracy in copying the interlocking pentagons item on the mini mental state examination (MMSE) may be helpful in distinguishing patients with DLB from those with AD relatively early in the course of the dementia. *Methods*—All cases of neuropathologically proved DLB and AD in the Center for Alzheimer Disease and Related Disorders brain bank were retrospectively re-viewed, and the first available MMSE for each was retrieved. Only patients with *MMSE scores>13* were included, indicating mild to moderate dementia. The patients' copies of the interlocking penta-gons were analyzed and graded as acceptable orunacceptable according to the original instructions for grading the MMSE. *Results*—Seventeen patients with DLB and 27 patients with AD were identified for whom MMSE with copies of the interlocking pentagons were available. Two patients with DLB (MMSEs 22 and 27) drew the pentagons acceptably, by contrast with 16 of the patients with AD (MMSEs 13–28). **An unacceptable copy was associated with DLB with a sensitivity of 88% and a specificity of 59% (p=0.002)**. *Conclusions*—**For patients with MMSE scores>13, an inability to accurately copy the pentagons suggests that the diagnosis is more likely DLB than AD**. The results confirm the work of others on visuospatial/constructional impairment in DLB and indicate that this feature may be helpful in its diagnosis.

J Neurol Neurosurg Psychiatry, 2001

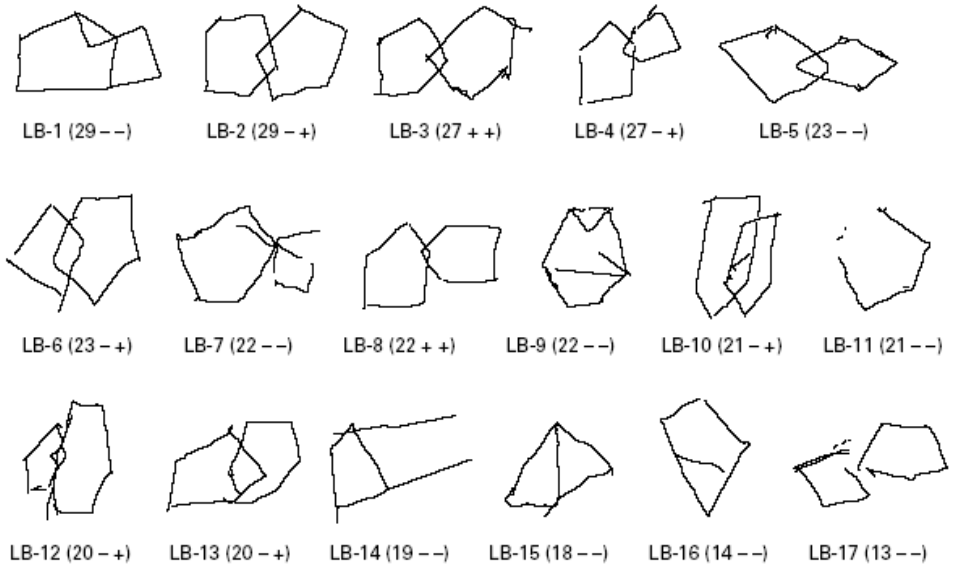

*Figure 1 Copies of the interlocking pentagons performed by the patients in the **DLB group**. The code beneath each copy indicates the patient identifier, the patient's overall score on the mini mental state examination (MMSE)18, and how the copy was graded according to the original grading criteria (first grade) and the relaxed grading criteria (second grade). For example, "LB-2 (29- +)" indicates that the copy was done by patient 2 in the LBD group, that the patient's overall MMSE score was 29, and that the copy was considered unacceptable (-) by the original criteria and acceptable (+) by the relaxed criteria. See table 1 for details of the two grading criteria. The models shown to the patients for them to copy are not included. The original copies have been reduced in size for this figure.*

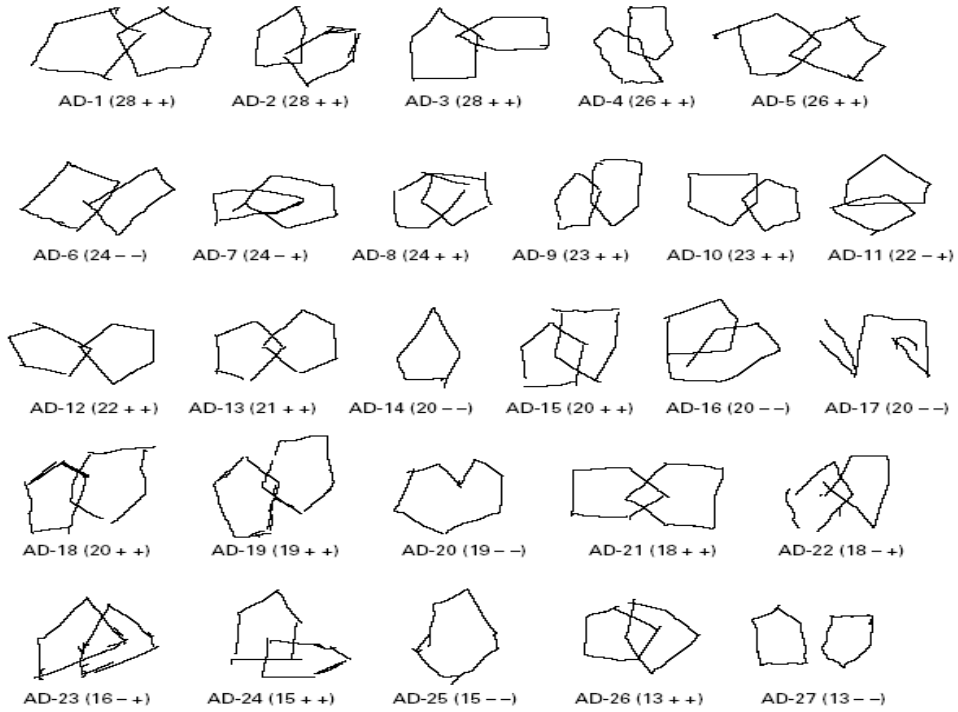

*Figure 2 Copies of the interlocking pentagons performed by the patients in the **AD group**. See the legend for fig 1 for an explanation of the code beneath each copy. The models shown to the patients for them to copy are not included. The original copies have been reduced in size for this figure.*

T A Ala et al. *J Neurol Neurosurg Psychiatry* 2001

Cognitive disfunction (III)

- Many also complain of losing one's train of thought or having *difficulty verbalizing simple words or phrases*, which some have termed **'verbal blocking'**, and this is often readily apparent during interviews in the office. This may be misinterpreted as aphasia or dysarthria, but this is more likely to be due to frontosub-cortical dysfunction

- A phenomenon known as **misidentification** can occur in which spouses or children are not recognized as such

- **Reflections in mirrors** can be particularly **distressing** in which patients attempt to communicate with their own reflection

- **Fluctuations** are considered a core feature of DLB. May vary over *minutes, hours, or days*. Fluctuations refer to periods of time when cognition and arousal are clearly abnormal contrasting with other periods with normal or near-normal functioning.

McKeith et al. The Lancet Neurology 2004
Bradley F. Boeve. *Clinical Science* 2005
I. McKeith et al. *Neurology* 2005

PAPER

Fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease is qualitatively distinct

J Bradshaw, M Saling, M Hopwood, V Anderson, A Brodtmann

J Neurol Neurosurg Psychiatry 2004;**75**:382–387. doi: 10.1136/jnnp.2002.002576

Objectives: To document and illustrate qualitative features of fluctuating cognition as described by care givers of patients with probable dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). To determine whether the quality of the fluctuations differs between DLB and AD. To examine the clinical utility of two recently developed rating scales. **Methods**: Care givers of 13 patients with early probable DLB and 12 patients with early probable AD were interviewed using the Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale, both developed recently. Descriptions of fluctuating cognition were recorded verbatim, analysed, and rated. **Results**: Descriptions of fluctuating cognition in DLB had a spontaneous, periodic, transient quality, which appeared to reflect an interruption in the ongoing flow of awareness or attention that impacted on functional abilities. Descriptions of fluctuations in AD frequently highlighted episodes of memory failure, or a more enduring state shift in the form of ''good'' and ''bad'' days, typically occurring in response to the cognitive demands of the immediate environment. These qualitative differences could be detected reliably by independent raters, but were not always captured in standard severity scores. **Conclusion**: Fluctuations occuring in DLB have particular characteristics that are distinguishable from fluctuations occurring in AD. Interpretation and application of the fluctuation criterion continues to limit the diagnostic sensitivity of the consensus criteria for DLB. Findings suggest that explicit documentation and a wider appreciation of these distinctions could improve the reliability with which less experienced clinicians identify this core diagnostic feature in the clinical setting.

Table 4 Care giver descriptions of FC in response to question two of the One Day Fluctuation Assessment Scale (''Has the patient had a period (or periods) today when he or she seemed to be confused and muddled and then a period (or periods) when he or she seemed to be improved and functioning better? Give examples of the worst and best period of function.'')

Probable DLB	Probable AD
Worst: He was hallucinating, his character changed and he got loud, almost aggressive. Best: He was only slightly muddled.	Worst: She repeated the same question over and over 5–8 times in an hour. Best: She didn't repeat herself so much.
Worst: She required full direction with ADLs, was lethargic, dribbling and confused to time, place and routine. Best: She was alert, aware of her routine and familiar with the other residents.	Worst: He forgot the time and date and asked me 10 times in an hour. Best: He remembered the day.
Worst: He couldn't work our how to charge his electric razor or plug it in. Best: He attended to clerical work and paid the bills.	Worst: She repeated the same question numerous times over a few hours. Best: She recognised people by name.
Worst: She was nonsensical, confused, and mumbled incoherently. Best: She was almost as she was.	Worst: She was unsure of where she was going and why. Best: She was fleetingly objective and less repetitive.
Worst: She got up at 2:30 am and got dressed for an appointment. Best: Periods where she seems to think quite clearly, made sense and remembered things.	Worst: When he had to sort things out himself and remember what to do. Best: When there was someone to guide and remind him.
Worst: He woke in the morning and thought there was a drama somewhere and he had to be there, I couldn't convince him otherwise. Best: He woke up calm, and was more easily convinced not to worry.	Worst: He got snappy, agitated and couldn't think of what he wanted to say. Best: He was talkative and productive, making his own bread.
Worst: He kept looking for ''the exit'', couldn't find the bedroom or the bathroom and had trouble recognising me (wife) Best: He was alert, opened the door, and greeted me after work. He knew me and seemed pleased to see me.	Worst: After an argument she got agitated and couldn't think Best: Normal conversation and presented well to others who don't live with her.
Worst: She was seeing people, preparing extra meals, and asking how many people to cook for. Best: Normal conversation, made sense, nothing unusual.	Worst: After a small amount of alcohol she became confused and unsteady Best: When she relaxed and things were highly organised or centred around her.
Worst: Illogical discussion, all jumbled, and didn't make sense. Best: Made himself clearly understood.	

J. Bradshaw et al. *JNNP*, 2004

DLB fluctuations

Specific features that reliably differentiate DLB from AD and normal aging

T.J. Ferman, PhD; G.E. Smith, PhD; B.F. Boeve, MD; R.J. Ivnik, PhD; R.C. Petersen, MD, PhD; D. Knopman, MD; N. Graff-Radford, MBBCh, MRCP; J. Parisi, MD; and D.W. Dickson, MD

Abstract—*Objective*: To determine whether certain aspects of fluctuations reliably distinguish dementia with Lewy bodies (DLB) from Alzheimer's disease (AD) and normal aging. *Methods*: Participants included 200 community-dwelling cognitively normal elderly persons, 70 DLB patients, and 70 AD patients with collateral informants. A 19-item questionnaire was administered to the informants that queried about symptoms of fluctuations and delirium. *Results*: Fluctuations occur infrequently in nondemented elderly persons aged 58 to 98 years. In contrast, four characteristics of fluctuations were found to significantly differentiate AD from DLB. These composite features include ***daytime drowsiness and lethargy***, ***daytime sleep of 2 or more hours***, ***staring into space for long periods***, and ***episodes of disorganized speech***. The presence of three or four features of this composite occurred in 63% of DLB patients compared with 12% of AD patients and 0.5% of normal elderly persons. Informant endorsement of **three or four** of these items yielded a positive predictive value of 83% for the clinical diagnosis of DLB against an alternate diagnosis of AD. Endorsement of **fewer than three** items had a negative predictive value of 70% for the absence of a clinical diagnosis of DLB in favor of AD. The authors present evidence of test- etest reliability, convergent validity, and empirical verification with a separate cross-validation sample. Fluctuations were not associated with any particular combination of hallucinations, parkinsonism, or REM sleep behavior disorder. *Conclusions*: Based on informant report, disturbed arousal and disorganized speech are specific aspects of fluctuations in dementia with Lewy bodies that reliably distinguish dementia with Lewy bodies from Alzheimer's disease and normal aging.

Neurology, 2004

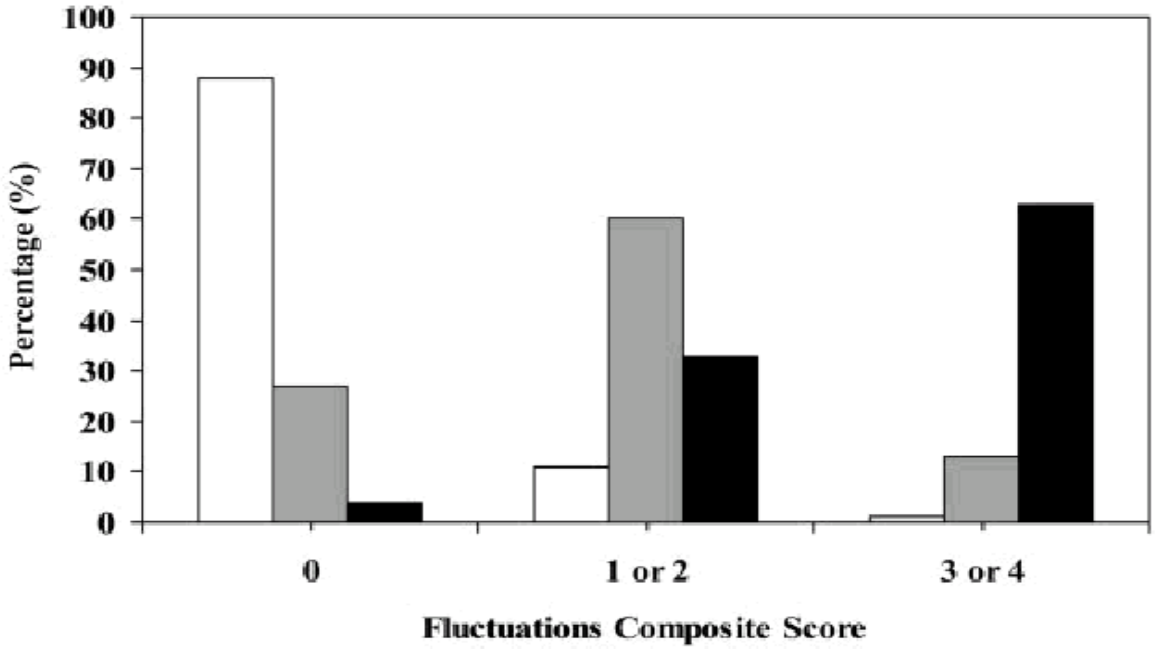

Figure 2. Percentage of normal elderly control subjects, dementia with Lewy bodies (DLB) patients, and Alzheimer's disease (AD) patients with Fluctuations Composite Score. White columns = normal elderly; gray columns = AD; black columns = DLB.

FCS=3 or 4: positive predictive value of 83% for identifying those with clinically diagnosed DLB from those with AD.
FCS<3: negative predictive value of 70% for identifying patients not considered to have a clinical diagnosis of DLB from those with AD.

Ferman et al. *Neurology*, 2004

Neuropsychiatric features

- Visual hallucinations
- Illusions
- Delusions
- Capgras' syndrome
- Depression
- Anxiety
- Auditory, tactile or olfactory hallucinations
- Agitation or aggressive behaviour

Bradley F. Boeve. *Clinical Science* 2005

- **Visual hallucinations**
  - 62% of DLB
  - They are generally present early in the course of illness.
  - They are similar to those reported in PDD in that they are vivid, colourful, three-dimensional, and generally mute images of animate objects.
  - Since these images are so vivid, patients often cannot be convinced that the images are truly not present.
  - In most patients, hallucinations begin during nocturnal hours in dimmed lighting, which is typically the bedroom. Over time, hallucinations tend to occur during the day and night independently of the surroundings and intensity of ambient light.
  - Barnes and colleagues suggested that the hallucinations arise from a combination of faulty perceptual processing of environmental stimuli and less detailed recollection of experience, combined with intact image generation.
  - Visual hallucinations are associated with greater deficits in cortical acetylcholine and predict better response to cholinesterase inhibitors.

McKeith et al. The Lancet Neurology 2004
Bradley F. Boeve. *Clinical Science* 2005
I. McKeith et al. *Neurology* 2005
Ferman et al. *Neurology*, 2004

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

Pietro Tiraboschi, David P. Salmon, Lawrence A. Hansen, Richard C. Hofstetter, Leon J. Thal and Jody Corey-Bloom

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 VHand 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.

Brain 2006

Table 3 Sensitivity, specificity, predictive values, and odds ratios of clinical variables for distinguishing DLB from Alzheimer's disease

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

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

Pietro Tirboschi et al. Braian 2006

- **Visual illusions**
  - Are also common in which patients perceive objects differently from the their true identity (e.g. a chair appearing to be a dog). Infact visual illusions and hallucinations often coincide, suggesting a common or overlapping neural basis.

- **Paranoid delusions**
  - Occur with some frequency as well.

- **Capgras' syndrome**
  - An uncommon but striking phenomenon that can also occur in which the patient believes that a relative or friend (usually spouse) has been replaced by an identical-appearing imposter.

- **Depression**
  - Is also common in DLB and may appear years before the onset of dementia.

- Other features include:
  - **anxiety**,
  - **hallucinations in other sensory modalities**,
  - **agitation/aggressive behaviour**,
  - **hypo-mania**.

Bradley F. Boeve. *Clinical Science* 2005

Motor disfunction

- Tremor (often postural and symmetric)
- Bradykinesia
- Rigidity
- Shuffling gait
- Stooped posture
- Difficulty with fine motor skills
- Masked facies.

Bradley F. Boeve. *Clinical Science* 2005

Motor disfunction

- There is an axial tendency with greater postural instability, gait difficulty, and facial immobility than in non-demented patients with PD

- Rest tremor is less common

- Levodopa responsiveness in DLB is almost certainly less than in uncomplicated PD, possibly because of intrinsic striatal degeneration and the fact that a significant proportion of the parkinsonian symptoms may be non-dopaminergic in origin

I. McKeith et al. *Neurology* 2005

Motor disfunction

- Extrapyramidal signs are reported in 25–50% of patients with DLB at diagnosis, and most develop some such signs during the natural course.

- In up to 25% of autopsy-confirmed cases, however, there may be no record of extrapyramidal signs, which shows that parkinsonism is not necessary for clinical diagnosis of DLB.

McKeith et al. The Lancet Neurology 2004

Sleep disorders

- RBD (REM sleep behaviour disorder)
- Excessive daytime somnolence
- Insomnia
- OSA (obstructive sleep apnoea)
- Central sleep apnoea
- Restless legs syndrome
- Periodic limb movement in sleep

Bradley F. Boeve. *Clinical Science* 2005

Sleep disorders

- In one polysomnographic series of DLB patients, at least one sleep disorder was present in almost every case.
- Excessive daytime somnolence is also common
- Excessive daytime drowsiness may also contribute to the fluctuating pattern

Bradley F. Boeve. *Clinical Science* 2005
I. McKeith et al. *Neurology* 2005

RBD (REM sleep behaviour disorder)

- RBD is a parasomnia manifested by dream-enactment behaviour in which patients will scream, swear, flail their limbs, punch, kick and lunge out of bed. The dreams tend to have a nightmarish quality, with a remarkable tendency for the dreams to have a chasing or attacking theme. The patient is very rarely the perpetrator; he/she is usually protecting himself/herself against aggressors.

- RBD often begins years or even decades before any cognitive or motor symptoms develop and, therefore, RBD may be the first sign of an evolving neurodegenerative disorder in many individuals.

- Since RBD is frequent in DLB and almost non-existent in Alzheimer's disease and frontotemporal dementia, some have argued that RBD co-existing with dementia is diagnostic of DLB, even in the absence of parkinsonism and visual hallucination, and RBD should be considered a core feature of DLB.

Bradley F. Boeve. *Clinical Science* 2005

Autonomic dysfunction

- OH (Orthostatic hypotension)
- Impotence
- Urinary incontinence
- Constipation

Bradley F. Boeve. *Clinical Science* 2005

Autonomic dysfunction (I)

- Severe autonomic dysfunction ***may occur early*** in disease, producing orthostatic hypotension, neuro-cardiovascular instability, urinary incontinence, constipation, and impotence, as well as eating and swallowing difficulties

I. McKeith et al. *Neurology* 2005

Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies

Horacio Kaufmann, MD; Kirsty Nahm, MD; Dushyant Purohit, MD; and David Wolfe, MD

NEUROLOGY 63 **September (2 of 2) 2004**

Autonomic dysfunction (II)

- Autonomic dysfunction may also contribute to repeated falls and syncope and the transient losses of consciousness that are seen in some patients with DLB

I. McKeith et al. *Neurology* 2005

The prevalence of autonomic symptoms in dementia and their association with physical activity, activities of daily living and quality of life

BACKGROUND/AIMS: There is little published data regarding autonomic symptoms in dementia. This study aimed to examine the prevalence and severity of autonomic symptoms in patients with different subtypes of dementia in comparison with healthy controls, and their association with levels of physical activity, depression, quality of life and ability to carry out activities of daily living. **METHODS**: Prevalence and severity of autonomic symptoms in Parkinson's disease dementia (PDD, n = 46), dementia with Lewy bodies (DLB, n = 32), vascular dementia (VAD, n = 38), Alzheimer's disease (AD, n = 40) and healthy controls (n = 42) were assessed using a structured symptom scale. The associations between autonomic symptoms and physical activity, Bristol Activities of Daily Living Score, Geriatric and Cornell Depression Scores and quality of life (Medical Outcomes Study 36-Item Short Form Health Survey, SF-36) were examined by multiple linear regressions. **RESULTS**: Total autonomic symptom scores, urinary symptoms, constipation and postural dizziness were significantly higher in PDD, DLB and VAD patients than either controls or AD patients (all $p < 0.05$). Higher autonomic symptom scores were associated with poorer outcomes in all measures of physical activity, activities of daily living, depression and quality of life. **CONCLUSION**: The burden of autonomic symptoms is high in non-Alzheimer's dementias. The identification of such symptoms is of importance because of the detrimental effect of these symptoms upon physical activity, depression, activities of daily living and quality of life.

Allan L. et al. *Dement Geriatr Cogn Disord*, 2006

Severe neuroleptic sensitivity

Deliberate pharmacologic challenge with D2 receptor blocking agents should not be used as a diagnostic strategy for DLB because of the high morbidity and mortality associated with neuroleptic sensitivity reactions, which are characterized by the acute onset or exacerbation of parkinsonism and impaired consciousness. Approximately 50% of patients with DLB receiving typical or atypical antipsychotic agents do not react so adversely and a history of neuroleptic tolerance does not therefore exclude a diagnosis of DLB. A positive history of severe neuroleptic sensitivity is, by contrast, strongly suggestive of DLB.

I. McKeith et al. *Neurology* 2005

Anosmia in dementia is associated with Lewy bodies rather than Alzheimer's pathology

R H McShane, Z Nagy, M M Esiri, E King, C Joachim, N Sullivan, A D Smith

J Neurol Neurosurg Psychiatry 2001;70:739–743 739

Abstract

Objectives—To assess olfactory function of patients with dementia. Odour detection ability is impaired in clinical Parkinson's disease. Evidence of impaired detection in patients with clinically diagnosed Alzheimer's disease is inconsistent. No studies of olfaction have been neuropathologically validated. ***Methods***—The olfactory function of 92 patients with dementia and 94 controls was assessed using a simple bedside test as part of the Oxford Project To Investigate Memory and Ageing (OPTIMA). Neuropathological assessment was made of cortical Lewy bodies and substantia nigra (SN) cell counts and of Alzheimer's disease in all 92 patients, 22 of whom had SN Lewy bodies and 43 of whom had only Alzheimer's disease. ***Results***—**Patients with Lewy bodies were more likely to be anosmic than those with Alzheimer's disease or controls**. Patients with Alzheimer's disease were not more likely to be anosmic than controls. Nor was anosmia associated with degree of neurofibrillary tangles, as assessed by Braak stage. Among subjects with Lewy bodies, overall cortical Lewy body scores and Lewy body density in the cingulate were higher in those who were anosmic. Consensus clinical criteria for dementia with Lewy bodies had a sensitivity of 64% and specificity of 89%. In the absence of definite Alzheimer's disease, the criteria had sensitivity of 100%. In patients with definite Alzheimer's disease, anosmia was slightly more sensitive (55%) than the consensus criteria (33%). However, the addition of anosmia to the consensus criteria did not improve their overall performance. ***Conclusion***—**Dementia with Lewy bodies is associated with impaired odour detection**. Misdiagnosis may have accounted for some previous reports of impaired odour detection in Alzheimer's disease. Simple but more sensitive tests of anosmia are required if they are to be clinically useful in identifying patients with dementia with Lewy bodies.

Diagnosi di DLB

Tim Stevens et al.
British Journal of Psychiatry, 2002.

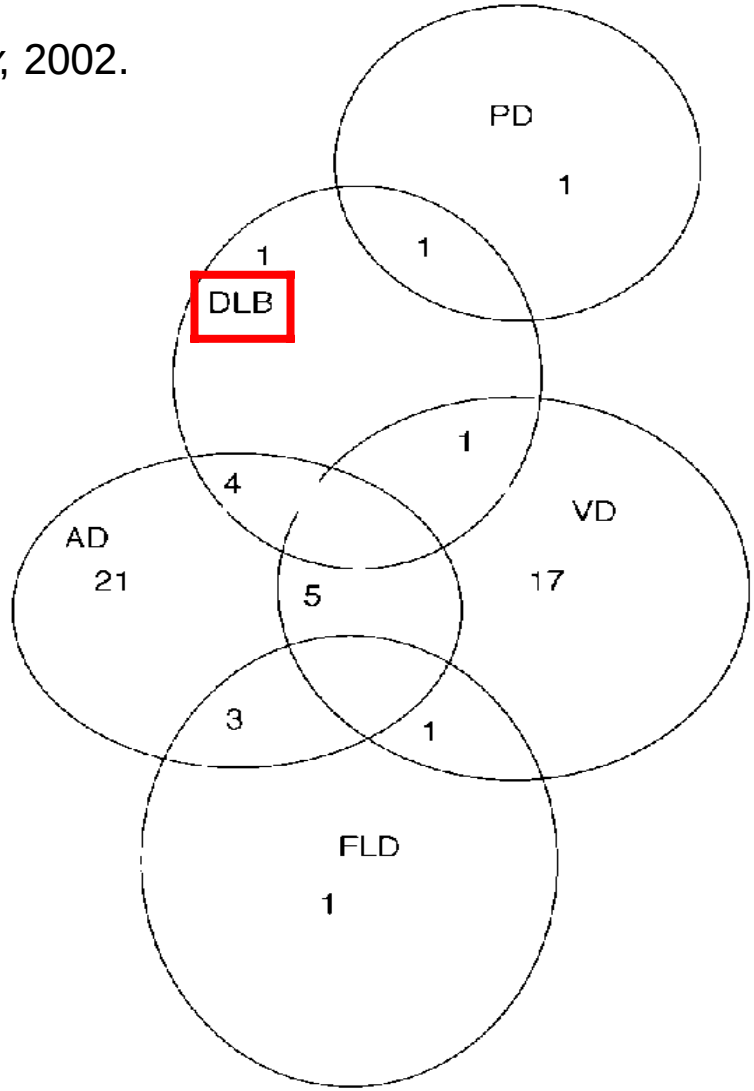

Fig. 1 Overlap of diagnoses: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FLD, frontal lobe dementia; PD, dementia in Parkinson's disease; VD, vascular dementia.

DLB vs PDD

There is no clinical symptom that absolutely distinguishes DLB and PDD as both may have psychiatric symptomatology, autonomic symptoms, REM-sleep behavior disorder, cognitive fluctuations, and neuroleptic sensitivity reactions. **The neuropsychological profiles in PDD and DLB share basic similarities including prominent abnormalities in attention, executive function, visuospatial function, language function, memory retrieval, and behavior**. However, differences in clinical features have been described in studies of DLB and PDD patients characterized by consensus criteria. Subtle cognitive differences have been found between PDD and DLB, with *DLB subjects making more conceptual and attentional errors than PDD subjects*, even after controlling for dementia severity. Psychiatric symptoms that differ quantitatively more than qualitatively occur in DLB and PDD, with *DLB patients having more hallucinations and psychoses* than those with PDD. *Adverse reactions to antipsychotic agents may also be more frequent in DLB*, whereas patients with PDD are more likely to be taking a wider variety of potentially psychotogenic doses of antiparkinson drugs. Saccadic eye movements are similar in DLB and PDD. *PDD subjects have more asymmetry in motor features, at least initially*, and *DLB subjects tend to have fewer signs of parkinsonism*, although the majority of DLB patients eventually develop parkinsonism characterized by generalized slowing and postural and gait disturbances, without prominent tremor. The clinical diagnostic criteria set forth in the third DLB consensus conference 7 can be applied to PDD, although there are no published validation studies.

C. F. Lippa et al. Neurology 2007

Probable Lewy Body Dementia Presenting as “Delirium”

Symptoms of prominent or persistent memory impairment are not always present early in the course of DLB. Rather, early cognitive impairment is often marked by prominent attentional deficits and visuospatial dysfunction. Fluctuation in cognitive function is common in DLB. This includes varia-tions in attention and alertness, excessive daytime drowsiness, and transient confusional states. The fluctuations may be observed within a day or from day to day. Additional features for consideration include rapid eye move-ment sleep behavior disorder and depressive symptoms. These clinical features of DLB look similar to the clinical presentation of delirium, which is defined as a disturbance in consciousness, with reduced ability to focus, sustain, or shift attention; and a change in cognition, or the development of a perceptual disturance.

Michael J. Robinson. *Psychosomatics*, 2002

Special investigations

- There are as yet no clinically applicable **genotypic or CSF markers** to support a diagnosis of DLB.

- Other imaging investigations can also be helpful, including preservation of hippocampal and medial temporal lobe volume on **MRI** atrophy of the putamen, and occipital hypoperfusion (**SPECT**) and hypometabolism (**PET**) without occipital atrophy on MRI.

- Other features such as the degree of generalized atrophy, rate of progressive brain atrophy, and severity of white matter lesions do not aid in differential diagnosis from other dementia subtypes.

- The **standard EEG** may show early slowing, epoch by epoch fluctuation, and transient temporal slow wave activity.

- Scintigraphy with metaiodobenzyl guanidine (**MIBG**), which enables the quantification of post-ganglionic sympathetic cardiac innervation, is reduced in DLB and has been suggested to have high sensitivity and specificity in the differential diagnosis from AD. Confirmatory studies with larger patient numbers are required.

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Laboratory and neuroimaging investigations

- Dopamine transporter loss in the caudate and putamen, a marker of nigrostriatal degeneration, can be detected by **dopaminergic SPECT** and can prove helpful in clinical differential diagnosis. A sensitivity of 83% and specificity of 100% has been reported for the association of an abnormal scan with an autopsy diagnosis of DLB.

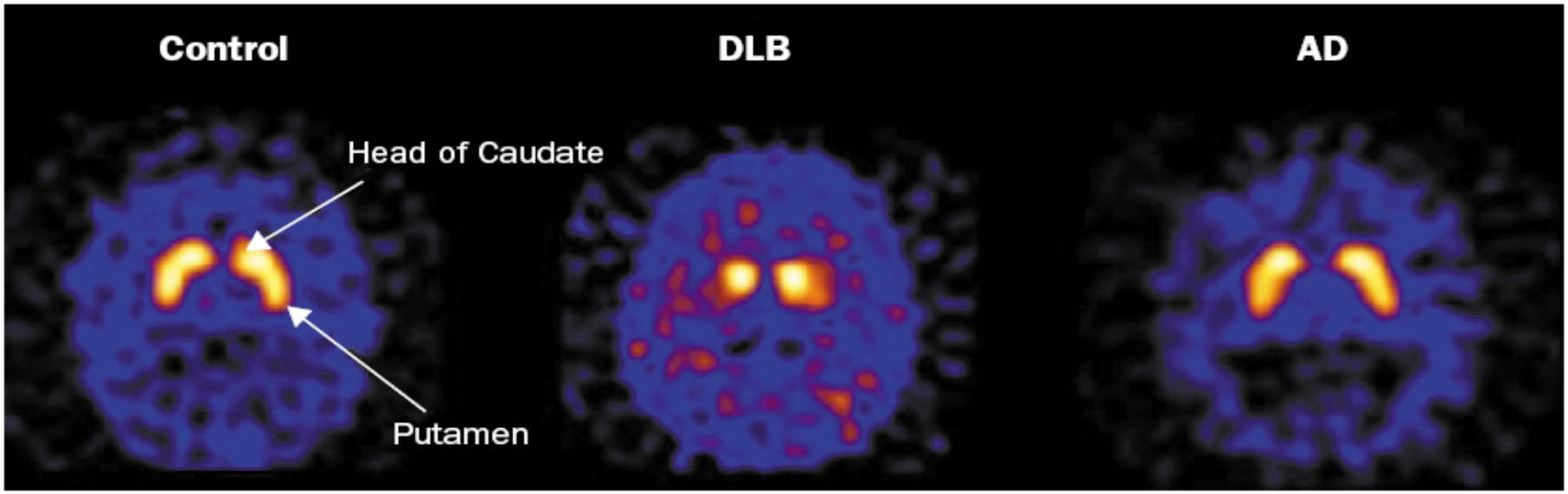

Figure 2. SPECT images of the dopamine transporter at the level of the striatum by use of fluoropropyl-CIT show striking reduction of activity in DLB compared with normal activity in Alzheimer's disease and normal ageing. Images courtesy of Prof J T O'Brien.

McKeith et al. The Lancet Neurology 2004

Clinical assessment

- Detailed history (from the patient and an informant)
- Full mental-state examinations
- Full cognitive examinations
- Full physical (including neurological) examinations

McKeith et al. The Lancet Neurology 2004

Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

I. McKeith et al. *Neurology* 2005

Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

1. ***Central feature*** (essential for a diagnosis of possible or probable DLB)
   - Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
   - Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
   - Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

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2. ***Core* features** (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)
   - Fluctuating cognition with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous features of parkinsonism

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3. ***Suggestive features*** (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)
   - REM sleep behavior disorder
   - Severe neuroleptic sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

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Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

4. ***Supportive features*** (commonly present but not proven to have diagnostic specificity)
   - Repeated falls and syncope
   - Transient, unexplained loss of consciousness
   - Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence
   - Hallucinations in other modalities
   - Systematized delusions
   - Depression
   - Relative preservation of medial temporal lobe structures on CT/MRI scan
   - Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
   - Abnormal (low uptake) MIBG myocardial scintigraphy
   - Prominent slow wave activity on EEG with temporal lobe transient sharp waves

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5. A diagnosis of DLB is ***less likely***
   - In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
   - In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
   - If parkinsonism only appears for the first time at a stage of severe dementia

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Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

6. ***Temporal sequence* of symptoms**

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term **Parkinson disease dementia (PDD)** should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

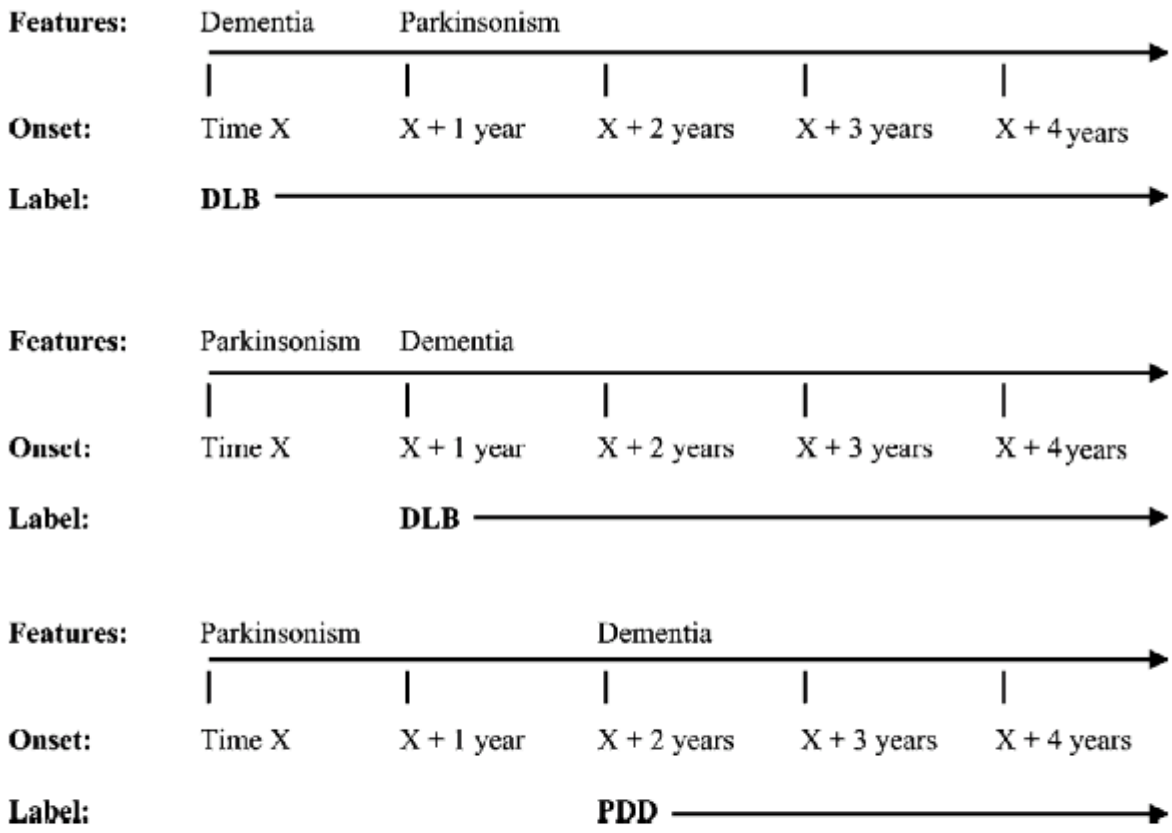

Figure 1 Schematic diagram of the '1 year rule'

Diagnosis of DLB applies to those who meet criteria for DLB [6] and develop parkinsonism at any time after the onset of dementia (upper panel) or develop dementia no more than 1 year after the onset of parkinsonism (middle panel). The term PDD refers to those patients who develop dementia more than 1 year after the onset of parkinsonism (lower panel).

Bradley F. Boeve. *Clinical Science* 2005

Management della DLB

Management clinico della DLB

- Trattamento non farmacologico
- Trattamento farmacologico

Nonpharmacologic interventions

Nonpharmacologic interventions have the potential to ameliorate many of the symptoms and functional impairments associated with DLB, but none has yet been systematically evaluated. Cognitive dysfunction and associated symptoms such as VH can for example be exacerbated by low levels of arousal and attention and strategies to increase these by **social interaction** and **environmental** novelty may reduce their presence and impact.

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Pharmacologic interventions

- Cognitive symptoms
- Neuropsychiatric symptoms
- Sleep disorders
- Motor parkinsonism
- Autonomic disfunction

Cognitive symptoms

Symptomatic treatment with cholinesterase inhibitors is currently the only treatment strategy for the cognitive symptoms of DLB with demonstration of *modest efficacy* in several randomized, placebo-controlled, double-blind studies. The largest randomized studies have used **rivastigmine (up to 12 mg/day)** in subjects with mild to moderate disease.

Neuropsychiatric symptoms

- When pharmacologic intervention is required the options include **cholinesterase inhibitors** (CHEIs) or atypical antipsychotic medications. Open label studies have demonstrated the effectiveness of all three generally available CHEIs in DLB but placebo controlled trial data are only available to date for rivastigmine. The reported reduction in symptom frequency and intensity of VH appears to be mediated at least in part by improved attentional function and the presence of VH is associated with greater cognitive improvement. *Side effects* of hypersalivation, lacrimation, and urinary frequency may occur, in addition to the usual gastrointestinal symptoms, and a dose dependent exacerbation of extrapyramidal motor features may occur in a minority.

- If CHEIs are ineffective or if more acute symptom control of behavior is required, it may be difficult to avoid a cautious trial of an **atypical antipsychotic**. The clinician should warn both the carer and patient of the possibility of a severe sensitivity reaction.

- **Typical antipsychotics** *should be avoided*. Novel atypicals with potentially more favorable pharmacologic properties, such as quetiapine, clozapine, and aripiprazole, may have theoretical advantages over traditional agents in LB disease but controlled clinical trial data are needed.

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Neuropsychiatric symptoms

- Depression: there have been no systematic studies of its management. At the present time **SSRI** and **SNRIs** are probably preferred pharmacologic treatment. Tricyclic antidepressants and those with anticholinergic prop-erties should generally be avoided.

- Apathy: may improve with **CHEIs**.

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Sleep disorders

- Some patients with moderate-to-severe OSA can exhibit dream enactment behaviour identical with those with RBD. **Clonazepam**, *the most effective agent for RBD*, can worsen OSA, so most patients should undergo polysomnography with or without nasal CPAP (continuous positive airway pressure) trial if there is a history suggesting RBD and/or OSA. Since the dreams associated with RBD are usually unpleasant, one goal of therapy is to reduce or eliminate nightmares. Serious injuries can occur to patients and bed partners, thus the more prominent goal of therapy for RBD are to minimize the abnormal behaviour. Moving lamps and furniture away from the bed and placing cushions on the floor beside the bed are simple ways to minimize injury. When drug therapy is appropriate, clonazepam (usually effective at 0.25–1.0 mg/night), **melatonin** (usually effective at 3–12 mg/night either as monotherapy or in conjunction with clonazepam [96]) or **quetiapine** (usually effective at 25–100 mg/night) are warranted.

- When attempting to manage insomnia, one first must sort out if this is due to one or more primary sleep disorders (e.g. restless legs syndrome, periodic limb movement in sleep, OSA or central sleep apnoea syndrome), by depression, by a circadian dysrhythmia or by medication. If no clear cause can be identified, polysomnography may be appropriate. If the findings are most consistent with idiopathic or psychophysiological insomnia, agents to consider include **trazodone**, **chloral hydrate**, **zolpidem**, **zaleplon** and the **atypical neuroleptics** (e.g. quetiapine, olanzapine, clozapine or risperidone). **Melatonin** may be effective in some patients.

Bradley F. Boeve. *Clinical Science* 2005

Motor parkinsonism

- Clinicians must decide what degree of parkinsonism is acceptable compared with what should be treated, as *dopaminergic agents can worsen psychotic symptoms, hypersomnolence and orthostatism*.
- **Dopamine agonists** are *generally poorly tolerated* in DLB patients.
- **L-dopa** was recently shown to be *well-tolerated in most, but only a third experienced significant improvement in parkinsonism*.
- There is genera agreement that if antiparkinsonian drugs are prescribed, the clinician should aim for ***the lowest acceptable dose of levodopa monotherapy***.

Bradley F. Boeve. *Clinical Science* 2005
McKeith et al. The Lancet Neurology 2004

Autonomic disfunction

- **Liberalizing fluid in-take** as well as salt in the diet, salt tablets, thigh-high compression stockings, fludrocortisone and midodrine are all potential treatments for OH.

- The **cholinesterase inhibitors** may improve OH, although this has not been rigorously studied in DLB subjects.

- Strategies for managing constipation include **increased water intake**, **increased fibre**, a variety of **laxative** formulations and **mosapride**.

Bradley F. Boeve. *Clinical Science* 2005

Conclusioni

- La DLB è una sindrome con una ampia sintomatologia clinica
- La diagnosi di DLB è sottostimata (i dati autoptici lo confermano)
- Importanza dell'assessment clinico (anamnesi, test cognitivi, esame obiettivo), tenendo conto, ai fini di una maggior affidabilità diagnostica, di valutare in modo dettagliato la qualità, la frequenza e la severità dei vari criteri diagnostici, in particolar modo di quelli core e di supporto