

Dementia with Lewy bodies and Parkinson's disease dementia - two synucleinopathies

Background

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are two common syndromes with overlapping clinical symptoms suggesting that they represent different points on a spectrum of Lewy body (LB) disease and that they share similar, underlying neuropathological processes. Parkinson's disease (PD) is associated with a six fold higher risk of developing dementia when compared to healthy elderly controls and longitudinal studies suggest that up to 78% of Parkinson's disease (PD) patients will develop dementia after an average of a decade of motor symptoms^{1,2}. Potential predictors for the development of dementia in PD include older age at the onset of motor symptoms, bradykinetic, not tremor dominant parkinsonism, bilateral onset of parkinsonism and declining response to levodopa. Depression, visual hallucinations, executive and visuospatial impairments early in the course of PD are putative risk factors for subsequent cognitive decline³⁻⁶. Operationalised criteria to define the clinical boundaries between PD and PDD are lacking, although this distinction may have profound clinical implications for prognosis and treatment strategies⁷.

Clinical diagnosis

Consensus guidelines for DLB^{8,9} suggest that PD patients who develop dementia more than 12 months after the initial motor symptoms should be diagnosed as PDD rather than DLB. The central feature required for a diagnosis of DLB is progressive cognitive decline, severe enough to cause social and occupational functional impairment. Core features are fluctuating cognition, recurrent and persistent visual hallucinations and extrapyramidal motor symptoms (EPS). Guidelines recommend that two of the core clinical features have to be present for a diagnosis of probable and one for a diagnosis of possible DLB⁸ (Table 1). Supportive features may increase diagnostic sensitivity. They are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematised delusions and hallucinations in other modalities. Depression and REM sleep behaviour disorder have also been suggested as additions to this list⁹. A history of stroke, focal neurological signs, and the presence of significant comorbid physical illness and brain disorder reduce the certainty with which a diagnosis of DLB can be made.

Studies comparing clinical symptoms of DLB and PDD reveal significant overlap between the two disorders. Fluctuating cognition measured using computerised tests of attentional speed show no differences between DLB and PDD patients¹⁰. All PDD patients have parkinsonian features and this proportion is less (80-100%) in DLB, but when present, EPS seem to be equally severe. PDD patients develop dementia about 10 years after initial motor features¹¹ and the arbitrary distinction suggested by the Consensus guidelines possibly reflects diagnostic convenience rather than any significant biological or clinical differences.

Neuropathology

Brainstem and cortical Lewy bodies (LB) are the only features considered essential for a pathologic diagnosis of DLB, although Lewy neurites (LN), concomitant cortical senile plaques, sparse tau-pathology and spongiform changes may also be seen^{12,13}. Coincident AD or vascular pathology fulfilling neuropathological diagnosis of AD or vascular dementia also occurs in DLB and PDD and may

modify the clinical presentation. Lewy bodies and LN contain alpha-synuclein (Figure 1) and suggest neurobiological links with other synucleinopathies such as multiple system atrophy. In DLB cortical LB density has been associated with cognitive impairment and visual hallucinations¹⁴, but better correlates of symptom formation are with LN, neurone loss, dopaminergic and cholinergic deficits. Alpha-synuclein positive, neuritic degeneration of the striatum has recently been described in DLB and PDD and may explain reduced levodopa responsiveness and neuroleptic sensitivity, in the two syndromes.

Neuropsychology

Prominent executive, attentional and visuospatial dysfunctions, with relatively preserved memory functions are characteristic neuropsychological findings in DLB and PDD. Fluctuation of cognition and attention interfere with cognitive assessments and lead to high variability of cognitive performance¹⁵. As most PD patients have some executive and visual impairment it is also difficult to set a threshold between PD and PDD.

Neuroimaging

Structural neuroimaging studies find relative preservation of the medial temporal lobes and the hippocampus in DLB compared to AD¹⁶ and functional neuroimaging studies reveal occipital¹⁷ and pronounced nigro-striatal dopaminergic dysfunction in caudate nucleus and putamen^{18,19}. In DLB as well as PDD bilateral temporal and parietal perfusion deficits have been reported.

Genetics

Most cases occur sporadically and there are only a few reports of autosomal dominant LB disease families. The Apo-ε4 allele is over-represented in DLB as in AD but not in PD without dementia²⁰. Most studies find no associations between polymorphism in genes involved in familial AD (e.g. presenilin 1 or 2) or genes involved in familial PD (parkin and alpha-synuclein mutations) and DLB or PDD.



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Table 1

Consensus guidelines for the clinical diagnosis of probable and possible DLB^{8,9}

1. Central feature

Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function

2. Core features (two core features essential for a diagnosis of probable, one for possible DLB)

Fluctuation of cognition

Recurrent visual hallucinations

Spontaneous features of parkinsonism

3. Supportive features

Repeated falls

Syncope

Transient loss of consciousness

Neuroleptic sensitivity

Systematised delusions

Hallucinations of other modalities

REM sleep behaviour disorder

Depression

4. Features less likely to be present

History of stroke

Any other physical illness or brain disorder sufficient enough to interfere with cognitive performance

Differential diagnosis

Major syndromes to be considered for differential diagnosis are other degenerative brain disorders with EPS, neuropsychiatric syndromes with visual hallucinations, and syndromes with profound fluctuation in cognition. A list of possible differential diagnoses is summarised in Table 2.

Table 2

Differential diagnosis of DLB

1. Other neuropsychiatric syndromes with extrapyramidal motor symptoms

Parkinson's disease with / without dementia
Fronto-temporal dementia with Parkinsonism
Multi system atrophy
Progressive supranuclear palsy
Corticobasal ganglionic degeneration
Creutzfeldt-Jacob Disease

2. Other neuropsychiatric syndromes with visual hallucination

Delirium tremens of different aetiologies
Parkinson's disease with / without dementia
Psychotic depression
Charles-Bonnet-Syndrome
Creutzfeldt-Jacob Disease

3. Other neuropsychiatric syndromes with profound fluctuation

Vascular dementia
Delirium tremens

Table 3

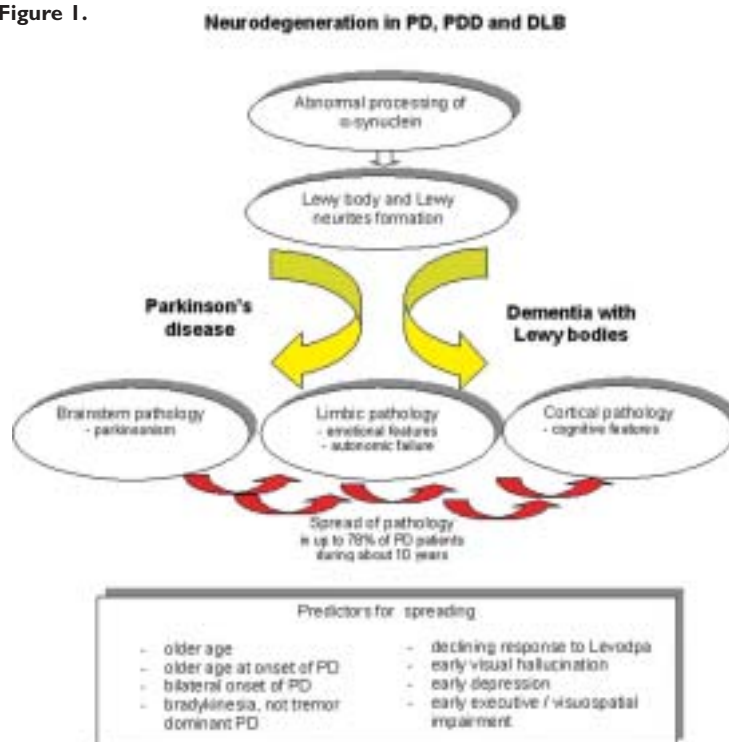
Five recommendations for pharmacological treatment of DLB and PDD

1. Identify the key symptom to be treated
2. Avoid drugs with anticholinergic side effects such as: tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, antispasmodics for bladder or gastrointestinal tract
3. Use neuroleptics with caution
4. Prefer L-Dopa monotherapy whenever possible
5. Consider cholinesterase inhibitors for neuropsychiatric and cognitive symptoms

Clinical management

It is the combination of EPS and neuropsychiatric features, which makes pharmacological treatment of DLB and PDD patients very difficult, and often leads to a situation where the improvement of one symptom may only be achieved at the expense of another. The neurochemical dysfunction in DLB and PDD suggest combined cholinergic and dopaminergic deficits implying a need to avoid medications with anticholinergic actions or side effects or dopaminergic antagonism. Tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, antispasmodics for bladder or gastrointestinal tract symptoms should therefore be avoided as they have the potential to impair cognition, exacerbate psychotic symptoms and may be associated with orthostatic hypotension. About 50% of treated patients develop severe side effects when treated with typical or atypical neuroleptics and it is not possible to predict these

Figure 1.



neuroleptic sensitivity reactions in an individual patient before treatment starts. Reported side effects of increased rigidity, immobility, confusion, sedation and postural falls are associated with a 2-3 fold increased mortality risk²¹. Effects and side effects of neuroleptics are poorly investigated in PDD, but caution in their use is urged until more is known. There is converging and consistent evidence that cholinesterase inhibitors (ChE-I) are effective and relatively safe for the treatment of neuropsychiatric and cognitive symptoms in DLB and PDD²² with major side effects similar to those reported in AD; mainly gastrointestinal symptoms, with nausea, vomiting and diarrhoea. Progression of EPS is uncommon, but hypersalivation, somnolence, orthostatic hypotension and syncope may be more frequent in this population. Whether ChE-I should be the first choice of treatment and which patients are likely to respond remain as open questions.

Conclusion

DLB and PDD share similar clinical and neuropathological features. The aetiology of both disorders and mechanisms triggering the spread of subcortical pathology in PD are unknown. Ongoing and future research has to clarify whether PDD and DLB are different representations of the same neurobiological process, with different initial manifestations or whether they are more independent diseases ending in a similar common pathway. Accumulating evidence favours the former option. Current clinical Consensus guidelines recommend an arbitrary distinction between the two disorders based on the duration of EPS (B1 year) before the manifestation of dementia and even if this does not reflect biological differences it may remain useful in clinical diagnostic practice.

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For a case study on dementia with lewy bodies, see our website
www.acnr.co.uk/case%20report.htm

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New Neurosciences forum

The Royal College of Nursing has over 355,000 members and seeks to support member's professional development through education and training programmes at all stages of their careers. In pursuit of this goal over 70 forums exist to bring together a nation-wide network of members with shared interests. A newly formed forum will concentrate on Neurosciences and even before it went live earlier this year it had around 1,400 members.

Specifically the Neuroscience Forum aims to

- Develop a base of expertise responding to current topical debates within neurosciences
- Promote the art and science of nursing in neurosciences and promote the development of specialist and consultant nurses
- Establish good liaisons with other organisations
- Promote awareness of the specific legal framework of care
- Share good practice in the spirit of mutual support

Background

There has been significant work undertaken by the RCN with the Department of Health on the risk sharing programme for disease modifying therapies for multiple sclerosis. At the forefront of this scheme are MS nurse specialists one of whom is on the new forum executive. The RCN is a registered stakeholder for the NICE guideline development on MS. NICE are also developing guidelines for the administration of the newer epilepsy therapies and the RCN, jointly with the Epilepsy Specialist Nurse Association, was offered two stakeholder places for development of the guidelines.

Other special interest groups including Parkinson's Disease Nurse specialists, Dystonia Nurse specialists, Motor Neurone Disease Nurses and advisers and those with an interest in disability issues have been working closely with the RCN.

Specialist Nurses

Within nursing using the title 'specialist' is contestable, however England's Chief Nursing Officer Sarah Mullally said "They are providing high quality care and information, and patients appreciate that" (Parish 2003). While specialist nurses are playing an increasing role in prescribing and medication management, many patients have limited access to specialist services and are sometimes misunderstood and poorly managed.

People with neurological impairments may well experience stigma and be judged wrongly, even by health professionals. Yet people living with chronic neurological conditions are often very knowledgeable about themselves and as such are beginning to be acknowledged as 'expert'. It is important that we form alliances both across health care disciplines, between generic and specialist services and, of increasing importance, with patients and their representative groups (Scullion 2002).

In 2001 Alan Milburn, the then Health Secretary, announced that there would be a National Service Framework for people with long term neurological conditions. The RCN neurosciences forum has a keen interest in this and plans to hold a national event in 2004 to examine its implications. This NSF was welcomed by the Neurological Alliance who called for improved access to services for patients and more neurologists and other specialists including nurses.

With around 350,000 people requiring help with most of their daily activities and over one million people disabled by their neurological condition (Neurological Alliance 2003), the Neurosciences forum looks set to have a busy first term.

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