Advances in Psychiatric Treatment (1998), vol. 4, pp. 360–363

Dementia with Lewy bodies

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Dementia with cortical Lewy bodies (LBD) was first described by Okazaki *et al* in 1961 and is now recognised as a relatively common cause of the dementia syndrome. The true prevalence of LBD is unknown. In post-mortem studies of patients diagnosed as having dementia in life, the mean frequency of Lewy body dementia is 12.5% (Byrne, 1997). Clinically diagnosed LBD (using operational clinical criteria) is found in 10–23% of patients presenting to, or in the care of, psychogeriatric services (Collerton *et al*, 1996). What is not yet certain is its nosological status; opinion is divided between regarding it as a variety of Alzheimer's disease (the Lewy body variant), a distinct disease (senile dementia of the Lewy body type) or a spectrum disorder related to both Parkinson's disease and to Alzheimer's disease (Byrne, 1992).

Much of this debate is due to the interpretation of the neuropathological findings. Lewy bodies are intracellular inclusions, composed of neurofilament proteins and various cell stress response proteins (e.g. ubiquitin and α–β crystalline), suggesting that they are the result of a cytoprotective process. In the cerebral cortex they have a predilection for the frontal, temporal, insula and anterior cingulate areas. In LBD the majority of cases have cortical and brainstem Lewy bodies in association with Alzheimer's type histological changes (senile plaques, neurofibrillary tangles) which in about half of these fulfil criteria for Alzheimer's disease.

However, a minority of cases (usually of a younger age of onset) have no Alzheimer's type histological changes and in rare cases cortical Lewy bodies are the only abnormal neuropathological finding.

Neurochemistry

There has been relatively little work in the area. Choline acetyltransferase (ChAT) levels are lower in LBD than in Alzheimer's disease (Dickson *et al*, 1996; Perry *et al*, 1990*a*). Perry *et al* (1990*a*) found that ChAT levels correlated with the antemortem degree of cognitive impairment. In addition, individuals experiencing hallucinations (with LBD) have significantly lower ChAT levels than those without hallucinations. Patients with Parkinson's disease who do not hallucinate, but have equally low ChAT levels as the LBD cases, have much lower dopamine levels (Perry *et al*, 1990*a*). Lipowski (1990), after reviewing the work on experimental delirium (induced by synthetic anticholinergic agents and reversed by dopamine blockade) concluded that: "an imbalance of central cholinergic and adrenergic neurotransmitters...represented a major pathogenic mechanism in delirium" – and possibly in LBD (Byrne, 1996; Perry & Perry, 1996).

Genetics of LBD

Several studies (see review by Saitoh & Katzman, 1996) have found a frequency of the apo E ε4 allele in LBD similar to that found in Alzheimer's disease. Saitoh *et al* (1995) found an increase in the CYP2D6B mutant allele of the gene that encodes debrisoquine 4-hydroxylase.

Some mutant CYP2D6 alleles correlate with reduced ability to metabolise debrisoquine and some drugs including neuroleptics. Further, the presence of the 'poor' metaboliser phenotype has been found to increase the risk of Parkinson's disease (Armstrong *et al*, 1992). LBD has been found in one large family cohort with familial Parkinson's disease (Denson *et al*, 1997).

The clinical syndrome

There is a surprising consistency in reports of the clinical features associated with LBD, in view of the heated nosological debate, and consensus clinical

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https://doi.org/10.1192/apt.4.6.360 Published online by Cambridge University Press

diagnostic criteria have been published, although they have not yet been validated (McKeith *et al*, 1996; see Box 1).

Cognitive decline is a feature of LBD. However, its type, severity and course are extremely variable, which may explain in part the contradictory reports in the literature. Some have suggested that the characteristic feature of cognitive change in LBD is fluctuation either from day to day or within episodes of 'delirium' (for which no apparent cause is ever identified). It is possible that some of this fluctuation in cognition is associated with a profound attentional disorder (Hansen *et al*, 1990).

When seen, the fluctuation can be dramatic. Patients suffering from LBD can go from a coherent involved conversation to incoherent mumbling in a matter of minutes (Byrne, 1997). Others describe a "transient period of reduced or entire loss of consciousness" (McKeith *et al*, 1992).

The fluctuations over time can be observed using visual analogue scales, the Mini Mental State Examination (MMSE; Cockrell & Folstein, 1988) and clock drawing tests. Of five cases only one had no variability in the MMSE, three varied by between three and five points and one by 17 points over a one-month assessment period (Williams *et al*, 1993).

Some authors report no such fluctuation in cognition in their cases (Förstl *et al*, 1993). In some case series the cognitive change is milder at onset than that seen in Alzheimer's disease (Crystal *et al*, 1990). Others have not found this to be the case (Förstl *et al*, 1993; Galasko *et al*, 1994).

Detailed neuropsychological studies in autopsy-proven cases of LBD and in clinically diagnosed cases of LBD show similarly conflicting results. Some found a quite distinct pattern of neuropsychological impairment when comparing LBD with Alzheimer's disease. In autopsy-diagnosed cases Salman & Galasko (1996) found that patients with LBD had significantly worse scores on the construction sub-tests of the Dementia Rating Scale (DRS; Mattis, 1976) than patients with Alzheimer's disease, whereas the patients with Alzheimer's disease were more impaired in the memory sub-test.

The individuals with LBD were also more impaired in terms of visuo-spatial and visuo-constructive tests. Other studies report similar findings (Hansen *et al*, 1990). However, no significant differences in cognitive function between LBD and Alzheimer's disease were found by Förstl *et al* (1993) or Gnanalingham *et al* (1997).

Electroencephalograms (EEGs) may be helpful in diagnosis. Several reports have found abnormalities (especially in the temporal area) very early in the course of the condition, whereas in the course of Alzheimer's disease the EEG is frequently normal.

Very little attention has yet focused on the carers of patients with LBD. It is well established that

Box 1. Consensus criteria for clinical diagnosis of probable and possible LBD (McKeith *et al*, 1996)

The central feature required for a diagnosis of LBD is 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 and of frontal–subcortical skills and visuo-spatial ability may be especially prominent.

Two of the following core features are essential for a diagnosis of probable LBD, and one is essential for possible LBD:

- fluctuating cognition with pronounced variations in attention and alertness
- recurrent visual hallucinations that are typically well formed and detailed
- spontaneous motor features of Parkinsonism

Features supportive of the diagnosis are:

- repeated falls
- syncope
- transient loss of consciousness
- neuroleptic sensitivity
- systematised delusions
- hallucinations in other modalities

A diagnosis of LBD is less likely in the presence of:

- stroke disease, evident as focal necrologic signs or on brain imaging
- evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

https://doi.org/10.1192/apt.4.6.360 Published online by Cambridge University Press

non-cognitive features in Alzheimer's disease sufferers relate to stress in their carers. Because of the prominence and severity of the non-cognitive features in LBD it is possible to hypothesise that their carers might be highly stressed.

Parkinsonism

About 20% of cases present with features of idiopathic Parkinson's disease (Lennox, 1992). In some case series the Parkinsonian features are described as mild or non-L-dopa responsive (Perry *et al*, 1990*b*; Hansen *et al*, 1990; Förstl *et al*, 1993). Others showed that the Parkinsonian features in LBD are more severe than Alzheimer's disease and closely resemble Parkinson's disease (Louis *et al*, 1995; Gnanalingham *et al*, 1997).

Other features, depression, delirium and hallucinations are not uncommon in dementia and are often seen in LBD. Visual hallucinations of dramatic complex form may be an early feature of LBD. One patient described the horses galloping through his living room as being 'like a videotape'. Another saw an African king and queen who arrived at his front door with their army. Complex hallucinatory experiences require a relatively intact level of higher cortical activity. Myoclonus, dysphagia, supranuclear palsy and disorders of sleep have also been described in a few cases.

Neuroleptic sensitivity

Neuroleptic sensitivity in LBD was first described by McKeith *et al* (1992). Fourteen of 21 people with LBD in the series received neuroleptics, of these 57% deteriorated rapidly either after the mutual prescription of neuroleptics or after an increase in the dosage.

The survival time in these people was significantly reduced (mean 7.4 months) compared with the people with LBD with no or only a mild reaction to neuroleptics (28.5 months) and the seven people with LBD who were not treated (mean 17.8 months). The syndrome of neuroleptic sensitivity is described by McKeith *et al* (1992) as initial sedation followed by severe rigidity and with postural instability and falls. This is followed by rapid deterioration in the overall clinical state with increased 'confusion' (not clearly defined) immobility and reduced fluid and food intake. The Newcastle group (Perry & Perry, 1996) suggest that the syndrome in LBD is based on nigrastriatal dopamine depletion associated with a failure of adaptive up-regulation of post-synaptic striatal D_2 receptors.

Treatment

Well-designed treatment trials are only just beginning. Most treatment has been empirical. Apart from the severity of the symptoms of LBD the other challenge posed is the variable baseline (cognitive deficit, psychotic symptoms and motor symptoms) from which outcome is to be measured. I have found it very helpful before commencing treatment to have a series of measures of the features of the illness.

Neurotransmitter strategies

The findings of very low levels of ChAT in people with LBD and the reports of some people who respond to tacrine being found to have cortical Lewy bodies suggests that anticholinesterase inhibitors may be helpful in the treatment of LBD. Controlled trials of such agents are now being undertaken.

Other strategies suggested on theoretical grounds that have not yet been evaluated have been 5-HT antagonists, nicotinic agonists and muscarinic agonists.

Treating the psychosis

Conventional neuroleptics are hazardous, and are probably best avoided. Some clinicians still use them in very small doses in treatment-resistant cases. Novel neuroleptics such as risperidone and clozapine have been used with benefit. However, risperidone can produce extrapyramidal symptoms.

Olanzapine has been reported to be less likely to induce extrapyramidal symptoms. Other empirical approaches have been used in patients with troublesome psychotic symptoms who are unable to tolerate novel neuroleptics.

Chlormethiazole can be very effective in some cases. It can be sedative in some patients and is unlikely to be tolerated in doses of higher than four capsules (192 mg each) per day.

Starting doses of all these agents (such as risperidone) should be low, 0.5 mg twice a day, for chlormethiazole 192 mg at night.

Patients with LBD may require antidepressant therapy. There is no indication yet that any particular group of antidepressants is superior in treating the symptoms of depression in these patients.

Agitation, which may be extreme, is sometimes improved by (short-term use of) benzodiazepines (preferably short-acting types such as lorazepam).

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Treating Parkinsonian symptoms

In patients with mild extrapyramidal symptoms it is probably best to withhold anti-Parkinsonian medication. In patients with moderate to severe symptoms treatment should be gradually introduced. As most patients with LBD are elderly, control of extrapyramidal symptoms may be obtained with relatively low doses of L-dopa preparations (Broe & Caird, 1973).

Starting doses should certainly be low, for example, L-dopa (100 mg) and carbidopa (10 mg), half a tablet, twice a day.

There is the risk of exacerbating psychotic symptoms by using L-dopa preparations, the treatment of extrapyramidal symptoms is a balance between improvement in mobility and independence and worsening of the psychosis. In patients with severe symptoms (both extrapyramidal symptoms and psychosis) it can be very difficult to achieve a balance and the temptation may be to proceed too quickly with dose increases. This should be resisted.

Treatment of sufferers of LBD also involves (as it does for sufferers of dementia of other aetiologies) supporting the carers both formally and informally. Information about LBD is in short supply, but it is always helpful to carers and often to sufferers. However, as in Alzheimer's disease, severe non-cognitive symptoms in LBD increase the chances of institutionalisation.

The treatment of LBD is in its very earliest stages and is empirical. The insights that can be gained from these attempts to help severely ill patients will hopefully generalise to more effective treatment for other dementia sufferers.

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