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Frontotemporal Lobe Dementia

*By Dr. Louise Carrier
Medical Director
Geriatric Psychiatry Community Services of Ottawa*

Mr. B. is a 60 year old man, retired from politics, was previously sociable and described as congenial. He presents with a 4 year history of chronic depression difficult to treat not responding to several antidepressant medications. His family describes personality changes, apathy, antisocial behaviour, poor to almost non-existent speech, stereotypy in language and verbal perseveration. At times he presents with anxiety and agitation. His mood is labile. He shows lack of concern and poor judgment. He has no insight into his condition. He is neglected in his personal care. On cognitive testing, although he scores low on the MMSE 23/30, his memory recall is relatively preserved as well as praxis and spatial orientation.

This clinical presentation is typical of frontotemporal lobe dementia (FTLD). Other clinical presentations include primary progressive aphasia (PPA), corticobasal degeneration syndrome (CBD) and motor neuron disease. They represent up to 25% of cases of presenile dementia. Patients are often misdiagnosed due to pseudodepressive or pseudopsychotic presentations. It is an insidious disease with an age of onset in the 6th decade of life. Both familial and sporadic forms occur. The clinical history and examination remain the best diagnostic tools. Neuroimaging and neuropsychological testing are confirmatory.

Definitions

Frontotemporal lobe dementia

Syndrome characterized by an alteration of behaviour, personality and affect with relative sparing of the memory and spatial orientation.

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Frontotemporal Lobe Dementia

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Primary progressive aphasia

Progressive language deficit in the absence of other abnormalities of cognition for at least 2 years from onset, presentation may be non-fluent with word finding difficulties, anomia, paraphasia, and preserved comprehension. Semantic dementia is a fluent progressive aphasia presenting with a loss of meaning of words, face and object agnosia. Naming and comprehension are also impaired.

Corticobasal degeneration

This is an asymmetric, slowly progressive development of a limb apraxia, bradykinesia, rigidity, dystonia, tremors and myoclonus, alien limb phenomenon, dysesthesia and hemispatial neglect. Behaviour and cognitive changes are present in 30-50% of cases, with personality changes and speech problems.

Core diagnostic features

- **Onset**

Insidious with a slow progression; onset before 65; positive family history of similar disorder in first degree relatives

- **Behaviour disorder**

Early loss of personal and social awareness, disinhibition, mental rigidity and inflexibility, stereotyped and perseverative behaviour, distractibility, impulsivity, early loss of insight

- **Affective symptoms**

Depression, anxiety, fixed ideation, delusion, hypochondriasis, bizarre somatic preoccupation, emotional unconcern, inertia, asponaneity

- **Speech disorder**

Progressive reduction of speech, stereotypy, echolalia and perseveration, late mutism

- **Spatial orientation and praxis preserved**

- **Physical signs**

Early primitive reflexes, early incontinence, late akinesia, rigidity, tremor, low and labile blood pressure, bulbar palsy, muscular weakness and wasting, fasciculation (motor neuron disease)

- **Investigation**

Normal EEG, brain imaging predominant frontal or anterior temporal abnormality, asymmetrical, unilateral. Neuropsychology: profound failure on "frontal lobes" in absence of severe amnesia, aphasia or perceptual spatial disorder



Management

Frontotemporal lobe dementia is not associated with a deficit of the cholinergic neurons, therefore acetylcholinesterase inhibitors are not recommended. Actually, cholinergic boosting may exacerbate the psychiatric and behavioural symptoms of FTLT. Serotonin binding has been found to be decreased in the frontal cortex. The use of selective serotonin reuptake inhibitors (SSRI) may provide some symptom relief of the affective and behavioural manifestations. Caregiver education and support, including respite care, is most important in understanding and coping with this illness.

Reference

Neary, D et al. *Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria*. Neurology 1998; 51:1546-54.

The Lund and Manchester Groups. *Consensus Statement. Clinical and neuropathological criteria for frontotemporal dementia*. J Neurol Neurosurg Psychiatry 1994; 57:416-18

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Dementia with Lewy Bodies (DLB)

*By Tilak Mendis, MD FRCP FACP
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Neurodegenerative Disorders Clinic*

Dementia with Lewy bodies is a common cause of dementia, and has probably been under diagnosed in the past. Based on autopsy findings, McKeith et al suggest that 15-25% of elderly demented patients suffer from DLB. This condition is referred to by a variety of different names, including diffuse Lewy body disease, senile dementia of the Lewy body type, or Lewy body variant of Alzheimer disease.

One reason for the lack of consensus is that the condition falls between the areas of the movement disorder neurologist and that of the specialist in dementia. This has led to emphasis on either the cognitive deficits or parkinsonian motor features, at the expense of the other. A more recent trend has been to use the term DLB and to consider this a distinct entity with its own typical pathology. However, since DLB shares clinical and pathological features with Parkinson's disease and with Parkinson's dementia (PDD), it remains controversial as to whether it is indeed a distinct condition, or if the three conditions are simply variants of the same disorder. Furthermore DLB needs to be differentiated from the two common dementias, Alzheimer disease and vascular dementia. The diagnosis of DLB remains challenging.

Lewy bodies:

These are abnormal components of nerve cells, thought to be caused by the accumulation of neurofilament proteins. Lewy

bodies were thought to be a hallmark of Parkinson's disease. However, the presence of Lewy bodies in the cortex was linked to the presence of dementia, and this gave rise to the concept of DLB. It has subsequently been recognized that Lewy bodies are also seen in the brains of patients with other dementias, such as Alzheimer disease and vascular dementia.

Clinical:

Criteria for diagnosis: different criteria have been proposed, but the most widely accepted at the present time are consensus guidelines proposed by the consortium on DLB, published in 1996. These criteria include the following:

1. Cognitive impairment with attentional and visuospatial deficits.
2. Two of the following for probable DLB or one of the following for possible DLB:
 - fluctuating levels of cognition
 - visual hallucinations
 - parkinsonism

"Supportive" criteria for DLB include repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions and hallucinations other than visual.

Fluctuations result in changes in alertness and cognitive processes, and this may occur over a period of hours or days. In some cases, this picture needs to be differentiated from delirium, which also leads to changing levels of alertness. It is

important to differentiate these conditions, as delirium may be reversed by identifying and treating underlying medical conditions.

DLB shares with Parkinson's dementia the presence of parkinsonian motor symptoms, problems with attention, executive dysfunction, and visuospatial difficulties. In addition, common findings include visual hallucinations, delusions, mood changes and fluctuating levels of cognition. It may often be difficult to differentiate DLB from PDD. A rule of thumb is to require the diagnosis of parkinsonism to precede the cognitive changes in PDD, whereas in DLB, it is the dementing process that starts first.

Cholinergic hypothesis of DLB:

Although originally proposed as a theory to explain Alzheimer disease, it is now thought that many forms of dementia are associated with cholinergic deficits. Choline acetyltransferase (ChAT) levels are diminished in the cerebral cortex of DLB patients and the reductions tend to be more marked than those seen in Alzheimer patients. DLB patients with hallucinations have even greater reductions in ChAT levels than those without hallucinations. It has been suggested that an imbalance between cholinergic and monoaminergic neurotransmitters may be responsible for the visual hallucinations in DLB.

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Dementia with Lewy Bodies

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These findings provide theoretical basis for the use of cholinomimetic agents in DLB.

Management

The standard treatments used in Parkinson's disease are not helpful in treating the dementia associated with DLB. The possibility of managing the cognitive and behavioral symptoms of DLB with cholinesterase inhibitors, has therefore raised considerable interest.

There are several case series and individual case reports on the beneficial effects of cholinesterase inhibitors (CI) in the treatment of DLB symptoms. The only randomized clinical trial (RCT) has been with Rivastigmine. A 20-week prospective, randomized, double-blind, placebo controlled study was carried out in 120 patients, who were randomized to either rivastigmine 6-12 mg/day or placebo. The primary outcome measures were the Cognitive Drug Research computerized assessment system and the Neuropsychiatric Inventory. Significant benefits were seen in the rivastigmine treated group, on tests of attention, working memory and episodic secondary memory. These benefits were accompanied by improvements in

behavioral measures on the NPI. The behavioral benefits were seen in the following areas: apathy, indifference, anxiety, delusions, hallucinations and aberrant motor behavior. The benefits noted in DLB patients treated with rivastigmine, occurred without a deterioration in parkinsonian motor status. The cognitive improvements noted were in the areas of attention and short-term memory, considered "sub-cortical" functions.

Donepezil has also been reported to be of benefit in DLB. However, the evidence is based on case series and case reports. Furthermore, some of these case reports indicated an aggravation in extrapyramidal parkinsonian symptoms. Most suggested some clinical benefit in managing both psychotic and non-psychotic behavioral symptoms as well as improvement in MMSE scores. Delirium-like features in DLB have also been reported to respond to treatment with Donepezil. Galantamine has not been systematically studied in DLB at this time. Other cholinomimetic agents, currently not in common use in Canada, have shown benefits in the behavioral management of Alzheimer disease, but evidence for clinical efficacy in DLB is limited. These include Tacrine, physostigmine

and metrifonate.

There is a great amount of overlap between the different forms of dementia in which Lewy bodies are seen, and "pure" forms are less commonly seen than mixed forms of the dementias. Since most forms of dementia may be treated with cholinesterase inhibitors, one may ask if it is worthwhile differentiating one form of dementia from another. Management dictates that standard neuroleptic agents be avoided in DLB patients, as these patients are generally extremely sensitive to such drugs, and their mental as well as motor status may deteriorate. In this case, an accurate diagnosis is necessary in order to avoid aggravating symptoms.

In summary, DLB is a common cause of dementia in the elderly. The diagnosis cannot be made with certainty without autopsy confirmation. Consensus criteria in current use appear to correlate well with confirmation of "probable" DLB. Cholinesterase inhibitors are increasingly being used as first-line treatments in the management of DLB patients, and evidence for safety and efficacy has best been documented in the case of rivastigmine at the present time.

THANK YOU

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