

Dementia with Lewy Bodies

Victor W. Henderson, MD, MS

Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences
Stanford University

Director, Stanford Alzheimer's Disease Research Center

A Lewy body is an abnormal, round structure found inside nerve cells and composed largely of a protein called alpha-synuclein (Figure). Lewy bodies are associated with two important brain disorders, Parkinson's disease and dementia with Lewy bodies (DLB). DLB is classified as a neurodegenerative disease, because it involves the progressive impairment and loss of nerve cells.

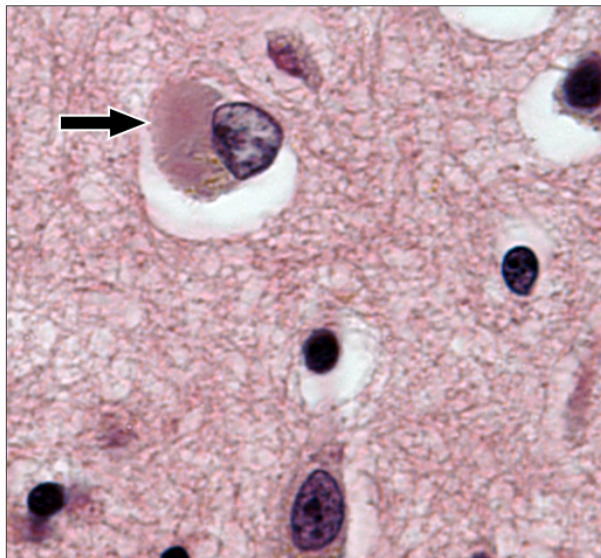


Figure. Cortical Lewy body. A single Lewy body (arrow) is shown within a pyramidal nerve cell in the cerebral cortex. H&E stain. Image courtesy of Dr. Edward D. Plowey, Stanford University.

Dementia and mild cognitive impairment

DLB is one of several causes of dementia. The most common cause is Alzheimer's disease, which is an entirely separate neurodegenerative disease. Vascular dementia is the second most common cause of

dementia, and here the pathological changes are due to stroke and to related changes that impair blood circulation in the brain. DLB is the third most common cause. Changes of all three disorders can occur in the same brain.

Dementia can be defined as cognitive (mental) decline that has an adverse impact on daily function or independence. The term mild cognitive impairment is used to describe lesser cognitive decline that is not explained by age alone, but the decline does not impair daily function or affects function only minimally. Although DLB is a type of dementia, Lewy bodies can cause milder symptoms that might be better characterized as mild cognitive impairment.

Clinical criteria for dementia with Lewy bodies

The dementia of DLB differs from that of Alzheimer's disease. In Alzheimer's disease, trouble remembering recent events is often an early, prominent symptom. In DLB, memory is often good early in the course of the illness. Instead, there can be confusion, mental slowness, visual problems, trouble with spatial relations, and difficulty with problem solving.

The Dementia with Lewy Bodies Consortium has recommended criteria for the diagnosis of probable DLB (Table 1). The consortium used the word "probable" to indicate that a definite diagnosis of DLB usually requires documentation of Lewy bodies during a brain

autopsy. There are four "core features" of DLB, and the diagnosis of DLB requires at least two of these features, plus dementia.

One core feature is "fluctuating cognition." This term refers to periods of confusion or lack of alertness that come and go. A person with DLB may be drowsy off and on during the daytime, stare off into space (zone out), or speak in a disorganized manner.

The second core feature is visual hallucinations. These also come and go. Often, the hallucinations are of people or animals. Even though these can be realistic, the patient sometimes knows quite well that these cannot be real.

Although not a core feature, some people with DLB have other mental problems. These include delusions (fixed, false beliefs like paranoia), illusions (misperceptions), or a false sense of presence or passage. (Presence refers to the experience that someone is nearby when no one is actually there. Passage refers to a fleeting, vague image of someone or something moving off to the side.)

The third core feature is called REM sleep behavior disorder. REM stands for rapid eye movements, the stage of sleep during which dreams occur. During REM sleep, only the eyes move; the arms and legs are still. In REM sleep behavior disorder, dreaming and staying still are disconnected. A person with this disorder will act out dreams and thrash about, and may even strike a bed partner. It is not uncommon for a spouse to move to a separate bed to keep from being kicked or punched. Interestingly, REM sleep behavior disorder sometimes appears years before other problems of DLB. REM sleep behavior disorder is often associated with DLB or Parkinson's disease, but it can occur on its

own and is occasionally seen with other brain disorders.

DLB and Parkinson's disease overlap in several ways, and the final core clinical feature of DLB is abnormal movement. In Parkinson's disease, there are three cardinal types of abnormal movements, and any one of these qualifies as a core feature of DLB. These three are bradykinesia (slowness), tremor (shaking), and rigidity (stiffness).

Bradykinesia refers to slowness in facial expression, moving the arms and legs, or walking. It also refers to small movements, such as separating the hands less than usual when clapping. Another key feature is tremor, especially when resting quietly and not otherwise moving. The final key feature of Parkinson's disease is stiffness, which is not painful and contributes to slowness. To test for rigidity, the doctor might first ask the person to relax. The doctor should be able to move a relaxed arm or leg freely, with very little resistance. When there is rigidity, the movement will feel stiff and have a ratchet quality.

Specialized laboratory tests can also be used to help meet consortium criteria for probable DLB.

Table. Clinical criteria for probable dementia with Lewy bodies

- A. Dementia, established by clinical examination
- B. Two or more of the following core features:
 - Fluctuating cognition
 - Visual hallucinations
 - REM sleep behavior disorder
 - One or more cardinal feature of Parkinson's disease: bradykinesia (slowness of movement), tremor at rest, or rigidity (stiffness)

(after McKeith et al., 2017)

Relation between DLB, Parkinson's disease, and Parkinson's disease dementia

DLB, Parkinson's disease, and Parkinson's disease dementia are closely related. In each, the main problem is with alpha-synuclein. This is a protein is found inside nerve cells at sites where one nerve cell communicates with the next. In each disorder, alpha-synuclein clumps to form abnormal fibers and larger, round Lewy bodies. It is not known why clumping takes place. These clumps affect nerve cells in the brainstem (in an area called the substantia nigra), the cerebral cortex, and certain other regions of the nervous system.

Nerve cells in the substantia nigra use dopamine as a chemical transmitter, and damage and death of the dopamine nerve cells cause movement symptoms of Parkinson's disease. The main symptoms of Parkinson's disease are bradykinesia, tremor, and rigidity. Nerve cells in the cerebral cortex use different chemical transmitters, and damage and death of these nerve cells contribute to the mental symptoms of DLB. Nerve cells in the substantia nigra and cerebral cortex can be affected more or less separately, or they can be affected at the same time.

Lewy body dementia

Lewy body dementia (LBD) is an umbrella term for both DLB and Parkinson's disease dementia. This term — LBD — is confusingly similar to DLB. When dementia occurs in someone who already has Parkinson's disease, physicians speak of Parkinson's disease dementia. DLB is diagnosed when dementia occurs before movement symptoms of Parkinson's disease, or at the same time. Some people with DLB

will have mild movement symptoms, or none at all.

Evaluation and diagnosis

In most instances, a diagnosis of DLB is made or confirmed by a neurologist, geriatrician, or geriatric psychiatrist. A neurologist is best qualified to recognize and diagnose other neurological conditions causing dementia or affecting movement and mimicking DLB.

The physician's evaluation is directed towards documentation of dementia, looking for changes in movement, and determining the underlying cause. The assessment includes a careful medical, neurological, and psychiatric history; a family history to see whether close family members have a similar or related disorder; a general physical examination; and a neurological examination. The physician reviews the use of prescription and over-the-counter medications. Many older adults take multiple drugs, some of which can cause confusion, impair mental function, and affect movement.

The neurological examination includes assessment of bradykinesia, tremor, rigidity, ataxia (poor coordination), and walking balance.

The evaluation also includes a mental status examination of memory and other cognitive abilities, sometimes supplemented by more detailed testing by a neuropsychologist. The physician should consider the possibility of depression and look for evidence of anxiety.

Laboratory tests depend on the individual circumstances but usually include a screening blood test for kidney, liver, and related metabolic functions; a blood test for thyroid function; a blood test to determine the level of

vitamin B12; and brain imaging. Brain imaging with a CT (computed tomography) scan or MRI (magnetic resonance imaging) scan is used to evaluate brain structures and to help exclude stroke, tumor, and other less common causes of dementia and abnormal movement. None of these tests can prove the presence or absence of DLB.

Specialized laboratory tests

Specialized tests can help firm up a diagnosis of DLB when the extra information is needed for research. The Dementia with Lewy Bodies Consortium mentions tests that can be used to indicate a diagnosis of DLB (McKeith et al., 2017). These are a dopamine transporter brain scan, a type of heart scan, and a sleep study. Physicians typically do not rely on these tests to diagnose DLB.

Dopamine transporter scan

PET (positron emission tomography) scans provide images of the brain based on specific molecules with radioactive labels. The dopamine transporter (DAT) is a protein molecule that helps move dopamine back into the nerve cell after this chemical messenger is released. Nerve cells that use dopamine are lost in Parkinson's disease and DLB. In these disorders, DAT-PET usually shows low dopamine transporter labeling in the putamen, a brain area deep in the cerebral hemispheres. This finding is not fully specific and can be abnormal in other diseases that affect brain dopamine. Some patients with DLB will have a normal scan.

DAT-SPECT (single photon emission computed tomography) provides similar information, but brain details are clearer with PET than SPECT.

Cardiac scintigraphy

Parkinson's disease and DLB affect nerve cells outside the brain. ¹²³Iodine-metaiodobenzylguanidine (MIBG) is a radioactively-labeled chemical. After it is injected into the blood, MIBG is stored in nerve cells that release norepinephrine. Norepinephrine, like dopamine, is a chemical messenger that travels a very short distance to activate a second nerve cell. In Parkinson's disease and DLB, the number of these second nerve cells is often reduced in the heart. A scan (MIBG cardiac scintigraphy) showing low levels of MIBG in the heart indicates a loss of nerve cells that receive norepinephrine. No laboratory test is perfect, and MIBG cardiac scintigraphy can be abnormal in certain other diseases and it is sometimes normal in DLB.

Sleep study

A sleep study test, also called polysomnography, is done at a specialized sleep center or in a hospital. Various recordings are done while falling asleep and throughout the night. The measurements include brain waves (electroencephalogram), oxygen level in the blood, heart rate, breathing, and eye and leg movements. A sleep study that shows body movements during REM sleep will confirm a diagnosis of REM sleep behavior disorder. REM sleep behavior disorder is one of the core features of DLB (Table).

Treatment and management

There is not yet a cure for DLB. People with DLB can be helped by changes in their environment, by lifestyle changes, and by prescription drugs.

Environmental adjustments and lifestyle changes

Environmental adjustments help compensate for declining mental abilities. A bulletin board or white board, or a written or electronic calendar can help some patients keep track of appointments and upcoming events.

Compartmentalized pill boxes can be used to organize medications. A person with dementia almost always requires help with more complex tasks like managing bills and finances, or simply maintaining a household. People with more severe dementia often need help with bathing, dressing, toileting, and eating.

Driving skills can deteriorate, and people with even mild dementia have a higher risk of accidents. In DLB, poor spatial skills and fluctuating attention can affect driving safety. In California, physicians are required by law to report a dementia diagnosis. The loss of a driver's license is not automatic, however, and some people with mild dementia can retain their licenses.

Reassurance, distraction, and redirection sometimes help agitation or hallucinations or delusions. Changing the environment to a more familiar, quieter, or less distracting setting can help. People with dementia often benefit from a simpler, more peaceful, more structured daily routine.

Although the evidence for benefit is circumstantial, most physicians recommend regular physical exercise, mental stimulation, social engagement, and good nutrition. Brisk walking and other forms of aerobic exercise are usually recommended when there are no health problems standing in the way. One target goal is to walk about 150 minutes each week, divided into 30 minute intervals, five

days each week. Exercise also helps depressive symptoms.

Mental activity is potentially important. People obtain mental stimulation through social interactions, hobbies, card games and board games, and reading. There is no evidence that one form of mental stimulation — such as a set of computerized tasks — is better than another.

Drug treatment

The Food and Drug Administration has not approved any drugs for the treatment of DLB.

One drug is approved for mild to moderate dementia associated with Parkinson's disease. This is rivastigmine, a cholinesterase inhibitor, which it is also approved for dementia due to Alzheimer's disease. This drug acts to increase brain levels of acetylcholine (another chemical messenger between nerve cells). It does not reverse or halt disease progression in Parkinson's disease dementia or DLB, but it can improve some of the symptoms.

Two other cholinesterase inhibitors are approved for use in Alzheimer's disease (donepezil and galantamine) but not specifically for Parkinson's disease dementia or DLB. There is no evidence that one cholinesterase inhibitor is more effective than another. These drugs are usually well tolerated, but some people have loss of appetite, nausea, or diarrhea.

The Food and Drug Administration has approved pimavanserin for the treatment of hallucinations and delusions in the setting of psychosis in people with Parkinson's disease. This approval does not extend to DLB. The Food and Drug Administration refers to pimavanserin as an atypical antipsychotic. All atypical antipsychotic drugs carry a warning

of increased mortality (death) in people with psychosis and dementia. This risk is rare.

Quetiapine, another atypical antipsychotic drug, is often tried for mental symptoms in DLB that cannot be managed by environmental adjustments. It is not approved by the Food and Drug Administration for this purpose either.

People with DLB are very sensitive to antipsychotic drugs like haloperidol, risperidone or olanzapine, which may increase confusion and increase motor symptoms of Parkinson's disease, even at low doses. These drugs should be avoided.

Other drugs can be used if there are problems with mood or disruptive behaviors. An antidepressant may help depression, even though it may have little or no effect on cognitive impairment in DLB.

A few people with dementia become agitated or aggressive. These symptoms are sometimes triggered by a medical illness like a bladder infection, by a medication side-effect, or by a change in daily routine. It is important to search carefully for these underlying conditions. When no specific cause can be found and when agitation or aggression poses a safety risk or is distressful to the patient, the physician may try other prescription medications for these symptoms. The concern, of course, is that other medications have potential side effects, as well. Some drugs used for agitation can increase confusion and risk of falling.

Patients and their families are sometimes tempted to try dietary supplements and herbal remedies. These alternative therapies have not undergone rigorous testing in humans, and there is no evidence that they are effective. Alternative therapies can be expensive. Like

prescription drugs, they can cause side effects, and they can be dangerous when taken with other medicines. Most physicians advise against these products.

Reference

McKeith IG, Boeve BF, Dickson DW, et al. (2017) Diagnosis and management of dementia with Lewy bodies. *Neurology*, 89, 88-100.

Resources

Alzheimer's Association
www.alz.org

Lewy Body Dementia Association
www.lbda.org/contact

National Institute on Aging, Alzheimer's Disease Centers
www.nia.nih.gov/research/dn/alzheimers-disease-centers

National Institute on Aging, Lewy body dementia
www.nia.nih.gov/health/topics/lewy-body-dementia

Stanford Alzheimer's Disease Research Center
adrc.stanford.edu

Stanford Center for Memory Disorders
stanfordhealthcare.org/medical-clinics/memory-disorders-center.html

Stanford Health Care Aging Adult Services
stanfordhealthcare.org/medical-clinics/aging-adult-services.html

Stanford Movement Disorders Center
stanfordhealthcare.org/medical-clinics/movement-disorders-center.html

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