

ABOUT LEWY BODY DEMENTIA

The LBD spectrum

Lewy body dementia (LBD) is a disease of the brain characterized by a spectrum of symptoms involving disturbances of movement, cognition, behavior, sleep and autonomic function. Two related clinical disorders make up the LBD spectrum: dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

Parkinsonism and cognitive impairment (CI) are present in both DLB and PDD, but the two clinical entities have been separated arbitrarily by a consensus of experts based on the time when CI starts in relation to parkinsonism. If dementia precedes or is concurrent with parkinsonism, then DLB is diagnosed, whereas if motor symptoms precede dementia by more than 12 months, PDD is diagnosed.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is second to Alzheimer's disease in prevalence of degenerative dementias in the elderly. Biologically related to Parkinson's disease (PD), the most common features are progressive cognitive impairment leading eventually to full blown dementia, parkinsonian motor symptoms (tremor, slowed mobility, stiffness of muscles, stooped posture, shuffling gait), visual hallucinations and fluctuations in levels of alertness and cognitive acuity. REM sleep behavior disorder, disturbances of autonomic function (low blood pressure, constipation and urinary frequency) and severe sensitivity or over-reaction to antipsychotic drugs (aka neuroleptics) are also common.

DLB is often misdiagnosed as Alzheimer's disease, especially in those individuals who have little or no sign of parkinsonism. Diagnosis is challenging because the order of symptom appearance, severity and combination varies among individuals.

Parkinson's Disease Dementia

PD is a common movement disorder that affects 1 in 100 individuals over the age of 60 and 4-5% of older adults over age 85 (approximately 1 million Americans).

Original descriptions of PD in the medical literature did not recognize cognitive problems as an important clinical feature. More recently, clinicians have come to realize that PDD occurs often and is among the most debilitating symptoms associated with disease progression.

Each year an estimated 14% of PD patients over age 65 will develop at least mild dementia. In one study, almost 80% of PD patients developed dementia over an 8 year period. ⁴

Cause and Pathology

The cause of Lewy body dementia (LBD) is unknown. When the brain of an individual with LBD is examined by a pathologist, it shows damage to most nerve cells in certain regions of the brain (example: substantia nigra in the brainstem), and some of the remaining, less damaged cells contain Lewy bodies, which are easily recognized by a pathologist with a special microscope. The Lewy body is the pathological signature of LBD. It contains an abnormal and lethal buildup of a naturally occurring protein (alphasynuclein) that overwhelms the cell's normal biological functions and causes it to die. There are many possible reasons why LBD occurs, but no one has yet been able to explain why some people are

more susceptible to developing LBD. One important reason that has most recently come to light is the discovery of an increasing number of genetic mutations in people with PD, especially those that have other family members affected by the disease. However, genetic PD is still uncommon, accounting for < 10% of all cases.

DLB and PDD are clinically similar, except for the timing of onset of cognitive impairment, as described above, but the pathology of the two is almost identical. This is both a surprise and a mystery, since there is no good explanation for the variability of the motor-cognitive interval among people with LBD. In other words, why do some people develop serious cognitive impairment at the earliest stage of a Lewy body disorder, whereas others remain cognitively normal for many years before impairment develops or never develop dementia?

Another puzzling fact is the frequent coexistence of the pathology of AD (amyloid plaques and neurofibrillary tangles) in DLB compared with PDD. AD differs from LBD clinically because of its distinctive cognitive profile (mostly a disorder of memory without the other features typical of LBD) and its lack of parkinsonian features except in late stages, but clinical LBD does not seem to be influenced by this co-existence. In the final analysis, clinical overlap is a real confounder, leading to misdiagnosis in a significant minority of patients, only to be definitively corrected by the diagnostic “gold standard” of autopsy. . These facts underscore the current concept of a neurodegenerative continuum with boundaries that are frequently blurred. . It is only through research that these and other fundamental questions will be answered.

Risk factors

Older age is the greatest risk factor for LBD, with most diagnoses being made in individuals over the age of 50. There is some evidence that the age of onset of the symptoms of DLB is younger than in PDD and the rate of progression/duration of disease is slightly faster in DLB.

Parkinson’s disease is a risk factor for PDD, since the majority of those with PD will eventually develop cognitive impairment.

Rapid eye movement (REM) sleep behavior disorder (RBD), a condition characterized by dream enactment, is a common risk factor for DLB, PD and other synucleinopathies, often occurring many years before the onset of parkinsonism or cognitive impairment. Pre-Parkinson’s RBD is thought to increase the risk of cognitive impairment when the motor phase of PD evolves, compared with PD that has no RBD prodrome.

Genetics

Researchers have identified rare genes that cause Parkinson’s disease (PD) and Alzheimer’s disease (AD), but no causative genes have been identified, except indirectly (i.e. genetic mutations can cause PD in a small minority of people; PD is a risk factor for PDD). Two examples of genetic markers that may increase risk of LBD are the Alzheimer-associated apolipoprotein E4 genotype and a particular mutation of the glucocerebrosidase gene, which in full strength causes Gaucher’s disease.

Given that there are no known causative genes definitely associated with LBD and that no treatments have been discovered to reverse the effects of known LBD risk factors, genetic testing is not currently recommended for routine screening.

However, if a family has multiple individuals across several generations with PD, AD, or LBD, it might be reasonable to consider genetic testing for one of the known rare genes. The rationale for considering

such testing would be to (1) confirm a diagnosis and (2) provide genetic counseling for family members, if the results are positive. These decisions need to be made carefully with family members and the individual's health care provider. It is prudent to undergo pre- and post-testing counseling so that the individual fully understands the risks and benefits. In addition, certain research centers at universities and the National Institutes of Health are investigating genetic risk and are accessible to people who would like to volunteer as research subjects.

Research

In 2013 the National Institutes of Health developed a research strategy for LBD. Research priorities for LBD include:

- Developing new drugs for clinical trials.
- Establishing longitudinal studies culminating in autopsy studies to improve diagnosis of DLB
- Determining which individuals with PD have a high risk of progressing to dementia.
- Developing a better understanding of the disease mechanisms through brain mapping and genetics
- Identifying validated biological and imaging biomarkers to detect disease presence, measure progression and advance the development of safe and effective symptomatic and disease modifying therapies.

Acknowledgment

LBDA would like to acknowledge the contribution of Dr. Howard Hurtig in the preparation of this handout.