**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 adults over age 85 (up to 1 million Americans).5,6 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.7,8

Cause and Pathology

The cause of LBD is unknown. Brain pathological changes in LBD involve selective damage and loss of nerve cells in certain regions of the brain (example: substantia nigra in the brainstem). Affected, but less damaged cells contain Lewy bodies, which are a microscopic aggregation of a specific protein (α-synuclein). The Lewy body is the pathological signature of LBD that overwhelms the cell’s normal biological functions and causes it to die.9 There are many possible causes of LBD but researchers are just beginning to understand the reasons why some people are more susceptible to developing LBD. One important reason that has recently come to light is the discovery of an increasing number of genetic variants that increase the likelihood that a person will develop LBD. DLB and PDD are clinically similar, except for the timing of onset of cognitive impairment, 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. The clinical overlap between AD and DLB in the absence of a specific diagnostic test leads to misdiagnosis in a significant minority of patients. Currently, the only way to definitively diagnose LBD is with an 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.10 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.11 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. Parkinson’s disease is a risk factor for developing dementia, since the majority of those with PD will eventually suffer from cognitive impairment

Genetics

Mutations in over a dozen genes have been shown to “cause” PD.12,13 Individuals with such rare genetic variants have a very high risk of developing PD during their lifetime, and many of them will later develop dementia. Mutations in one of these genes (SNCA) can occasionally result in a clinical picture that resembles DLB.14 However, no more than 2% of patients with PD, and likely

even fewer with DLB, carry a disease-causing mutation in a known gene. In most instances PD and DLB are thought to arise through a complex interaction between common genetic and environmental factors, each one with a small-to-modest effect. Two important common genetic risk factors that have recently come to light are variants in the APOE and GBA genes. The APOE ε4 allele has long been known to increase the risk of developing AD, but there is now strong evidence that it does the same for DLB.15,16 Furthermore, patients with PD who carry APOE ε4 have (on average) more severe cognitive problems.17 A number of variants in the GBA gene have been shown to increase risk for both PD and DLB.18–20 In addition, patients with PD who have one of these GBA variants have a more rapid cognitive decline and are more likely to develop dementia.21,22 Since mutations that cause LBD are rare, and no treatments have been discovered to reverse the effects of known genetic risk factors, genetic testing is not currently recommended for routine screening. However, if a family has multiple individuals with PD (with or without dementia) and/or DLB, it is reasonable to consider genetic testing for some or all of the known 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 healthcare provider. It is prudent to undergo pre- and post-testing counseling so that the individual fully understands the risks and benefits of learning about their genetic status. In addition, certain research centers at academic institutions and the National Institutes of Health are investigating genetic risk and are actively seeking people who would like to volunteer as research subjects.