Changes in Brain May Herald Dementia in PD

A decrease in the volume of the hippocampus could predict which patients will progress to dementia.

BY DAMIAN McNAMARA

MIAMI BEACH — Changes in brain volume and networks could someday predict which patients with Parkinson's disease are at highest risk to develop dementia, according to recent studies.

It has been known for some time that hippocampal atrophy, for example, is a common feature of Parkinson's disease with dementia. However, a recent study is the first to show that the decrease in hippocampal volume could predict which patients are at a higher risk for development of dementia, Irena Rektorová, Ph.D., said at the World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders.

"What is important from a practical point of view is that atrophy of hippocampus probably predicts a switch to dementia," said Dr. Rektorová, who is on the neurology faculty at Masaryk University in Brno, Czech Republic.

A Swiss research team calculated that the risk for dementia increases almost 25% with every 0.1 mL decrease in hippocampal volume, based on a study of 70 patients who had subthalamic deep brain stimulation (Parkinsonism Relat. Disord. 2009;15:521-4). The 14 patients in this cohort who later developed dementia had significantly smaller preoperative hippocampal volumes than did those who did not develop dementia.

Dr. Rektorová provided some additional perspective on the extent of volume changes. "Hippocampal atrophy is definitely present in those with Parkinson's disease, and especially those with Parkinson's disease dementia, but it is lower than atrophy with Alzheimer's disease."

Using voxel-based morphometry, other researchers have reported gray matter loss in the frontal areas of the brain in patients with Parkinson's disease that extends to the temporal, occipital, and subcortical areas with comorbid dementia (Brain 2004;127:791-800). Occipital atrophy, in particular, may be an important distinction between Parkinson's patients with and without dementia.

Mild cognitive impairment (MCI) is common among people affected by Parkinson's disease. A goal for researchers is to identify "the malignant form" of MCI that will progress to dementia, said Dr. Rektorová, who had no relevant disclosures.

"Would brain imaging of mild cognitive impairment or dementia in Parkinson's disease be of any help?" Dr. Rektorová asked. It is possible, she said, based on the promising results of multiple studies using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography or functional MRI.

"These studies show posterior rather than anterior cortical involvement in Parkinson's disease dementia versus Parkinson's disease alone," Dr. Rektorová said.

A study using ^{18}F-FDG PET, for example, revealed metabolic network changes consistent with a Parkinson's disease-related cognitive pattern (NeuroImage 2007;34:714-23). These researchers found hyperactivation in the cerebellar vermis and dentate nuclei and reduced activation in the medial frontal and parietal regions. This cognitive pattern was not altered by routine Parkinson's disease treatment (for example, levodopa).

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In a study currently in preparation, Dr. Rektorová and her colleagues found decreased activity in certain brain areas of patients with Parkinson's disease, compared with controls, while performing the Stroop test. During this measure of executive function, decreases were seen in the cuneus, middle temporal gyrus, inferior parietal lobule, insula, and medial dorsal nucleus of thalamus.

"It is worth mentioning that these Parkinson's disease patients were medicated and they had no cognitive impairment in this task," Dr. Rektorová said. "They actually performed as well as healthy controls."

It also could be that what is not turned off during executive functioning in Parkinson's disease plays a role in cognitive impairment, Dr. Rektorová said. During executive task performance in healthy volunteers, fMRI shows deactivation of the medial prefrontal cortex, posterior cingulate cortex, precuneus, and medial temporal cortices.

However, this imaging also shows that people with Parkinson's disease may fail to shut off this resting brain activity, called the "default mode network." Dr. Rektorová said the full function of the default mode network is not yet known.

For the first time, other researchers have used fMRI to assess the potential contribution of the default mode network in patients with Parkinson's disease (Arch. Neurol. 2009;66:877-83). They demonstrated a decrease in ventral medial prefrontal cortex activity similar to controls during executive functioning. But participants with Parkinson's disease featured increased precuneus and posterior cingulate cortex activity, whereas controls showed deactivation in these regions. ■

Major Genetic Risk Factor Is Discovered for Parkinson's

BY JEFF EVANS

Mutations in the gene encoding the lysosomal enzyme glucocerebrosidase confer the single strongest risk for developing Parkinson's disease of any gene that has been discovered, according to a multicenter analysis of patients from around the world.

A single mutant copy of the gene, GBA, was found in 15% of Ashkenazi Jewish patients with Parkinson's disease and in 3% of Parkinson's patients of other ethnicities, compared with 3% of control patients with Ashkenazi ethnicity and less than 1% with non-Ashkenazi background.

This is the first time it has been conclusively shown that even a single mutant copy of the GBA gene can contribute to the disease in ethnically diverse, heterogenous cohorts of patients.

"The high frequency of mutations among ethnically diverse, heterogeneous cohorts of patients with Parkinson's disease makes the mutations in this gene the most common genetic risk factor for Parkinson's disease that has been identified to date," Dr. Ellen Sidransky of the National Human Genome Research Institute and her associates wrote in the the New England Journal of Medicine.

Although previous smaller studies have indicated a potential association between heterozygous carriers of a single defective copy of GBA and the risk of Parkinson's disease, this is the first time that it has been conclusively shown that even a single copy of the mutated gene can contribute to disease.

Holders of two defective GBA alleles develop Gaucher's disease, which is characterized by an accumulation of glucocerebroside, an essential component of cell membranes. This can lead to a broad spectrum of disease manifestations, including hepatosplenomegaly, anemia, thrombocytopenia, bone disease, and neurologic impairment.

Dr. Mark Hallett, chief of the medical neurology branch of the National Institute of Neurological Disorders and Stroke, said in an interview that the discovery of the contribution of GBA mutations to Parkinson's disease risk is "far from the whole answer, but it's a piece of the puzzle that I think is becoming clearer now. It seems very clear that there's going to be a number of risk genes that all add up together that will lead to Parkinson's disease."

Dr. Hallett, who was not involved in the study, likened the GBA finding to the discovery of the apolipoprotein E gene's contribution to the increased risk for developing Alzheimer's disease, in combination with other susceptibility alleles and various environmental factors.

In the study, Dr. Sidransky and her colleagues pooled data from 16 centers that had genotyped 5,691 patients with Parkinson's disease and 4,898 control patients for mutations in GBA. The centers were located in North America (4), South America (1), Asia (3), Israel (2), and Europe (6).The analysis included 980 Ashkenazi Jewish patients with Parkinson's disease and 387 Ashkenazi Jewish control patients (N. Engl. J. Med. 2009;361:1651-61).

At least 6 out of 100 people of Ashkenazi descent carry a defective GBA allele, compared with fewer than 1 out of 100 people in the general population.

Among all patients, carriers of any GBA mutation had more than five times greater odds of developing Parkinson's disease than did noncarriers. Two mutations in particular—N370S and L444P—accounted for most of the GBA mutations and were most prevalent in Ashkenazi patients.

Individuals with the N370S or L444P mutation were nearly four times or nearly seven times more likely, respectively, to develop Parkinson's disease than were noncarriers.

The investigators found that incomplete sequencing of GBA, such as only screening for the N370S or L444P mutations, could miss many mutant alleles in non-Ashkenazi ethnic groups. For example, complete sequencing of GBA in non-Ashkenazi Jewish patients indicated that up to 45% of mutant alleles could be missed if only N370S and L444P were targeted.

Patients with GBA mutations developed Parkinson's disease at a significantly earlier mean age than did noncarriers (54.9 years vs. 58.8 years). A significantly higher proportion of patients with a GBA mutation also reported having a first- or second-degree relative with Parkinson's disease, compared with noncarriers (24% vs. 18%).

Some disease features showed up significantly more often among those with GBA mutations than in those without mutations, such as asymmetric onset, bradykinesia, resting tremor, rigidity, and cognitive changes.

The study was funded impart by large number of international grants. Dr. Sidransky had no disclosures to report, but many other investigators reported potential conflicts of interest. ■