Be Proactive in Treating Parkinson's Dementia

BY DAMIAN McNAMARA

MIAMI BEACH — Early and aggressive treatment of dementia in people with Parkinson's disease could optimize outcomes and quality of life for patients and their caregivers, growing evidence suggests.

About one-third of people with Parkinson's disease experience dementia. "We know there is such high risk for dementia in this population. We need to be proactive," Dr. David J. Burn said at the World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders.

Hallucinations are a major concern. These can arise when mild cognitive impairment, common in people with Parkinson's disease, progresses to dementia.

How you deliver a dementia diagnosis to the patient and family members is important, said Dr. Burn, professor of movement disorder neurology at Newcastle University, Newcastle-Upon-Tyne, England. "There is some reluctance to give the diagnosis. You have to be sure [that] the dementia exists. But giving this in a reasonable way might reassure people with hallucinations they are not going mad."

In addition, a definitive diagnosis can provide a sense of relief to caregivers.

Current patient age is the dominant risk factor for dementia in Parkinson's disease. Cognitive impairments (attention, executive functioning, visuospatial perception, and memory) and behavioral effects (apathy, mood) are clinical features often associated with this classic "dysexecutive visuoperceptual" dementia.

"There is a high psychiatric burden in that dementia, which is important in the management of the disease," said Dr. Burn.

General and specific diagnostic instruments such as the Mini-Mental State Examination or the Mini-Mental Parkinson test can be helpful in this population. Dr. Burn recommended also using the Neuropsychiatric Inventory–4. "It is fairly quick to administer to the caregiver [together] with the Caregiver Distress Scale. It is a neat, compact way of assessing a lot quite quickly."

Despite the usefulness of such scales, Dr. Burn advised that clinicians should not feel comfortable even if the resulting score is robust. "Always follow-up with an interview with the patient and the informant—that is essential."

Fluctuation in symptoms presents one of the diagnostic challenges, Dr. Burn said. "These patients can have good hours or days versus bad hours or days, which can [yield] widely different values on neurologic testing. These fluctuations may be the biggest determinant of [the impact on] activities of daily living in the setting of Parkinson's disease dementia."

Giving a diagnosis of dementia to patients with hallucinations might reassure them 'they are not going mad.'

DR. BURN

Other confounding factors that can complicate diagnosis include an insidious onset, slow progression, motor effects of Parkinson's disease, and whether the impairment is the result of cognitive dysfunction, Dr. Burn said.

Multiple medications have been studied for efficacy in this comorbid population. These include clozapine (Clozaril); quetiapine (Seroquel); memantine (Namenda); rivastigmine (Exelon); and donepezil (Aricept). Dr. Burn disclosed that he was recently a member of the advisory board for Eisai Inc., the manufacturer of Aricept.

However, the level of evidence to support a particular agent varies in the literature, and many drugs have side effects that need to be considered.

Cholinesterase inhibitors can have effects on the heart, including reports of hospital visits for syncope and bradycardia, for example.

"Most of us, when we diagnose Parkinson's disease dementia, would reach for a cholinesterase inhibitor if patients are symptomatic," Dr. Burn said. "You need to push the dose to the maximum."

Keep in mind that patients do not always respond to the first agent, so a switch to a different agent in this class or to a different type of medication may be warranted for some patients, he added.

Evidence-based guidelines in the United Kingdom support the use of clozapine, but sedation and falls are possible, Dr. Burn said.

The choice of agent is unclear in part because randomized, controlled trials of antipsychotics in Parkinson's disease frequently exclude demented cases, he said.

In addition, there is a lack of randomized, controlled trials to support use of quetiapine.

"The jury is out on memantine, but for the moment … studies are favoring [its] use," Dr. Burn said.

He added that he and his colleagues are planning a study in which they will randomize 500 patients with Parkinson's disease and dementia to either donepezil or placebo. Secondary measures will include caregiver distress, strain, and health economics. ■

Protein Aggregation May Drive PD Development, Progression

BY DAMIAN McNAMARA

MIAMI BEACH — Aggregation of proteins within dopaminergic and other neuronal cells may play an important role in the development and progression of Parkinson's disease.

Although the etiology of Parkinson's disease is likely multifactorial, these findings point researchers toward one important group of candidate targets for future therapies, Dr. C. Warren Olanow said at the World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders.

"Although we have not yet found a neuroprotective drug for Parkinson's disease, the future is looking brighter," he said. "Gene studies are directing us to look at mitochondria and proteins that lead to misfolding and prion-like activity. This may lead to very promising therapies."

Dr. Olanow is chairman emeritus of the department of neurology at Mount Sinai School of Medicine, New York. He disclosed that he is a consultant for Boehringer Ingelheim GmbH, Ceregene Inc., Merck Serono S.A., Novartis Pharmaceuticals Corp., and Teva Neuroscience Inc., all of which manufacture or are developing medications for Parkinson's disease.

Normally, there is a balance between the number of proteins being formed and the ability to clear them, said Dr. Olanow. "Protein aggregation is much more than what we appreciated. Of the systems for clearing accumulated protein, the ubiquitin-proteasome system is the most important. This is a series of enzymes that signal for protein to be transported to a proteasome, where it is broken down."

Healthy embryonic cells transferred to the substantia nigra of a person with Parkinson's disease have shown characteristic features of the disease (Nat. Med. 2008;14:504-6). In that study, the transplants showed hallmark signs of Parkinson's disease, including Lewy body pathology; increased levels of the protein alpha-synuclein, a protein of unknown function found abundantly in Lewy bodies; and reduced amounts of dopamine transporter in a post mortem examination 14 years later. The grafted cells had adopted the features of the host dopaminergic neurons, suggesting that ongoing changes occur with Parkinson's disease.

Gene study data suggest looking at 'mitochondria and proteins that lead to misfolding and prion-like activity.'

DR. OLANOW

Aggregation and misfolding may occur when excess protein overwhelms the clearance system and/or a neuron with normal levels has an impaired clearance system. Lysosomal or proteasomal degradation of alpha-synuclein is likely the clearance mechanism in healthy individuals. "Overproduction of alpha-synuclein alone is shown to be enough to start the cell death process in Parkinson's disease," Dr. Olanow noted.

Although alpha-synuclein is a major focus of research, other proteins are likely involved in Parkinson's disease as well, Dr. Olanow said. "With respect to the lysosome system, as you increase protein accumulation, it begins to block the LAMP [lysosome-associated membrane protein] receptors and other proteins can start to accumulate as well."

Neuron-to-neuron transmission of alpha-synuclein has been demonstrated (Proc. Natl. Acad. Sci. USA 2009;106:13010-15). In that study, a substantial number of transplanted healthy embryonic cells overexpressed alpha-synuclein from host cells in a relatively short time, Dr. Olanow said. "This showed that alpha-synuclein can travel across a neuron and be taken up by a healthy neuron, leading to protein uptake, aggregation, and cell death." This endocytosis of alpha-synuclein from one neuron to another might play a role in the progressive spread of Lewy pathology in the nervous systems of people with Parkinson's disease.

"With that in mind, we can perhaps revise the hypothesized model [to say] that alpha-synuclein itself can act as a prion to promote protein accumulation," said Dr. Olanow (Proc. Natl. Acad. Sci. USA 2009;106:12571-2).

"This could perhaps explain the fascinating observations suggested by Braak and his colleagues [Neurobiol. Aging. 2003;24:197-211] where [effects of the disease are] first seen in the olfactory bulb and the brain stem, then spread to other brain regions," he said. "Could it be a prion-like effect?"

An attendee asked why some brain regions are not included in Braak's hypothesis about connections between different anatomic areas playing a role in progression of Parkinson's disease. "I don't know the answer," Dr. Olanow said. "[This] is pure speculation, but one type of cell might have a better ability to clear proteins than another."

The sobering news is that much about the pathogenesis of Parkinson's disease remains unknown. "We are not sure which factor, if any, is the primary driver of cell death. And the primary factor may be different in different individuals," Dr. Olanow said. In addition, there may be a network of different, interactive pathogenic factors that initiate the disease process, "so blocking any one of them might not halt the process."

Even so, these recent findings could lead to neuroprotective therapies directed at proteins and/or agents that prevent protein misfolding, promote refolding, and/or facilitate clearance of aggregated proteins, he said. ■