BERLIN—Aggregates of superoxide dismutase 1 (SOD1) were found in postmortem tissue from people with Parkinson’s disease (PD) for the first time, researchers from the University of Sydney in Australia reported here June 21 at the International Congress of Parkinson’s Disease and Movement Disorders. 

The scientists believe that aggregates of the mutant SOD1, which is also implicated in amyotrophic lateral sclerosis (ALS), might also play a role in brain cell death in PD.

Protein aggregates found immunopositive for SOD1 were significantly more abundant in degenerating regions of the PD brain, with a greater than five-fold increase in the substantia nigra and a greater than 2.5-fold increase in the locus coeruleus, compared with non-degenerating PD brain regions or in control brains.

Kay Double, PhD, associate professor at the University of Sydney and lead researcher on this work, told Neurology Today Conference Reporter that this discovery began when she was studying dopamine-producing cells of the substantia nigra. "They contain a melanin pigment and melanin binds metals," she explained. "There was an increase in iron and a decrease in copper levels specifically within the degenerating brain regions in PD, and this change in copper led us to consider that SOD1 might be involved."

SOD1 is a key antioxidant in the brain, and low levels of copper can alter the functioning of SOD1, she explained.

Working with colleagues at the Florey Institute of Neuroscience and Mental Health in Melbourne and at the University of Bordeaux in France, the scientists conducted studies to characterize the aggregates and to count their distribution throughout the PD brains and those of normal controls.

Using immunohistochemistry, they identified Lewy body pathology and SOD1-immunopositive protein aggregates in regions of significant neuronal loss in the PD brain, Dr. Double said.

The aggregates contained significant amounts of SOD1, copper chaperone for SOD1, and ubiquitin, but not alpha-synuclein. A positive isoelectric point shift in SOD1 was also observed in the PD brains, compared with control brains, she said.

Dr. Double said she suspects that the SOD1 pathology could play a role in the vulnerability of the substantia nigra in PD. "We found a 60 percent loss of copper in neurons in the substantia nigra in PD, so it makes sense that part of the problem with SOD1 in PD is that it is not binding adequate amounts of copper to enable the enzyme to function normally."

She noted that an intermediate number of SOD1 aggregates were found in two brains from people with PD (with intermediate scores on the Hoehn and Yahr scale) who had no evidence of clinical disease. This suggests that the formation of the aggregates occurs very early in the disease process, she said.

If the pathology is similar to what is seen in ALS, Dr. Double said, it is possible that the two diseases could respond to the same treatment.

Commenting on the study, ALS researcher Jeffrey Rothstein, MD, professor of neurology and neuroscience and director of the Brain Science Institute at Johns Hopkins University, said that when aggregates form, they can trap other cytosolic protein in them. Since SOD1 is a highly abundant cytosolic protein — 1 percent of all body protein is SOD1 — it's not surprising that it could "decorate these inclusions."

Dr. Rothstein said the finding of the aggregates calls for "additional experiments aimed at reducing SOD1 aggregation: A pathological link between Parkinson's disease and amyotrophic lateral sclerosis."

Robert H. Brown, Jr., MD, PhD, chair of the department of neurology at the University of Massachusetts Medical School, agreed. "This study would appear to show that misfolding of SOD1 is not specific. If it is not specific to ALS, one might envision two very different interpretations (and there are probably many others). Perhaps misfolding of SOD1 is neurotoxic and drives pathogenesis in many neurodegenerative diseases, linking ALS, PD, and other disorders as a common, disease-triggering, miscreant protein. At the other end of the spectrum, the study may suggest that misfolding of SOD1 is simply a byproduct pathology in a dying neuron, which is completely unrelated to causing disease."

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