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Gene therapy reverses symptoms of Parkinson's disease

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A gene therapy called NLX-P101 dramatically reduces movement impairment in Parkinson's patients, according to results of a Phase 2 study published today in the journal *Lancet Neurology*. The approach introduces a gene into the brain to normalize chemical signaling.

The study is the first successful randomized, double-blind clinical trial of a gene therapy for Parkinson's or any neurologic disorder, and it represents the culmination of 20 years of research by study co-authors Dr. Michael Kaplitt, vice chairman for research in the Department of Neurological Surgery at Weill Cornell Medical College and a neurosurgeon at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and Dr. Matthew During, originally at Yale University and now professor of molecular virology, immunology and medical genetics, neuroscience and neurological surgery at the Ohio State University.

"Patients who received NLX-P101 showed a significant reduction in the motor symptoms of Parkinson's, including tremor, rigidity and difficulty initiating movement," says Dr. Kaplitt, who pioneered the approach and helped design the clinical trial. "This not only confirms the results of our Phase 1 trial performed at NewYork-Presbyterian/Weill Cornell but also represents a major milestone in the development of gene therapy for a wide range of neurological diseases."

"This is great news for the 1.5 million Americans living with Parkinson's disease," adds Dr. During, who is the co-inventor, with Dr. Kaplitt, of the gene therapy procedure. "Since this is also the first gene therapy

study for a neurological disease to achieve success in a rigorous randomized, double-blind design compared with a sham group, this is also a crucial step forward toward finally bringing gene therapy into clinical practice for patients with debilitating brain disorders."

Although medical therapy is usually effective for most symptoms of Parkinson's early in the disease, over time many patients become resistant to treatment or develop disabling side effects. An alternative treatment is electrical deep brain stimulation, which requires the implantation of permanent medical devices in the brain.

In the current study, 45 patients with moderate to advanced Parkinson's disease who were not adequately controlled with current therapies were enrolled in the double-blind trial, with half randomized to receive the gene therapy and the other half to a "sham surgery" -- a mock procedure designed to make patients think they could have received the experimental approach.

The results were significant. Half of patients receiving gene therapy achieved dramatic symptom improvements, compared with just 14 percent in the control group. Overall, patients receiving gene therapy had a 23.1 percent improvement in motor score, compared to a 12.7 percent improvement in the control group. This greater improvement in the gene therapy patients compared with the sham patients was statistically significant over the entire six-month blinded study period. (Dr. Kaplitt explains that the improvements in the control group were likely a chimera, the result of placebo effect or a similar phenomenon called regression to the mean.)

"Improved motor control was seen at one month and continued virtually unchanged throughout the six-month study period," says Dr. Kaplitt, who also serves as associate professor of neurological surgery and director of the Laboratory of Molecular Neurosurgery at Weill Cornell Medical

College. "Patients also reported better control of their medication and no worsening of non-motor symptoms."

How NLX-P101 Gene Therapy Works

Gene therapy is the use of a gene to change the function of cells or organs to improve or prevent disease. To transfer genes into cells, an inert virus is used to deliver the gene into a target cell. In this case, the glutamic acid decarboxylase (GAD) gene was used because GAD makes a chemical called GABA, a major inhibitory neurotransmitter in the brain that helps "quiet" excessive neuronal firing related to Parkinson's disease.

"In Parkinson's disease, not only do patients lose many dopamine-producing brain cells, but they also develop substantial reductions in the activity and amount of GABA in their brains. This causes a dysfunction in brain circuitry responsible for coordinating movement," explains Dr. During.

In the Phase 2 study, each patient in the experimental group received an infusion of the genetic material directly into their subthalamic nucleus, a key brain region involved in motor function. The GAD gene instructed cells in that area to begin making GABA neurotransmitters in order to re-establish the normal chemical balance which becomes dysfunctional within circuits that control movement.

While patients in the Phase 1 study only received the therapy on one side of their brain, patients in the Phase 2 were infused on both sides. And while the infusion happened entirely in the operating room in the previous phase, the current study made use of a novel delivery system conceived by Drs. Kaplitt and During that allowed for the infusion to take place outside of the OR -- at the hospital bedside -- something Dr. Kaplitt says makes for a more comfortable patient experience.

Drs. Kaplitt and During also designed the sham surgery, one of the most complex of its kind. The challenge was especially great because patients were required to remain awake to enable surgeons to locate the targeted brain area. In the sham procedure, a small indentation was drilled partway into their skull. Pre-recorded audio of a subthalamic nucleus mapping procedure was played while patients were asked to move various body parts, leading them to believe that an actual brain procedure was being performed. Lastly patients were attached to an infusion system that appeared identical to the system used in the gene therapy group but were subcutaneously injected with saline solution instead of the gene therapy.

The NLX-P101 gene therapy was pioneered by Neurologix Inc. scientific founders Drs. Kaplitt and During. The two researchers have been at the forefront of gene therapy research since 1989. They were the first to demonstrate that the viral vector AAV could be an effective gene therapy agent in the brain, which they reported in a landmark Nature Genetics paper in 1994. Drs. During, Kaplitt and colleagues subsequently published additional research demonstrating the beneficial effects of AAV-GAD gene therapy for Parkinson's in the journal Science in 2002. The Phase 1 clinical trial, performed at NewYork-Presbyterian/Weill Cornell, was the first ever clinical gene therapy trial for Parkinson's or any other adult neurological disorder. Results of that study appeared in 2007 as a cover article in The Lancet and in a second article in the Proceedings of the National Academy of Sciences.

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