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Case Series

Parkinson's disease with dementia: A biochemical and pathophysiological treatment approach

John D Young, M.D.[1,*]

[1]Young Foundational Health Center, USA

*Author for correspondence:
Email: maria@dryoungfhc.com

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Abstract

About three years ago, Memorial Sloan Kettering Cancer Center (MSK) developed a stem cell-based therapy that may help advance the treatment of Parkinson's disease. Researchers took embryonic stem cells and manipulated them to produce neurons that could be implanted into the brains of patients with mild Parkinson's disease. These cells were designed to produce dopamine, a neurotransmitter that Parkinson's patients have in very low amounts. A major component of the procedure was an MRI-guided surgical technique that allowed surgeons to remove a small portion of the skull and use a specialized needle to inject neural stem cells into the putamen, a region of the brain involved in dopamine production and motor control. The primary objective of the trial was to demonstrate the safety and tolerability of the implanted cells without significant adverse effects. After eighteen months, fluorodopa positron emission tomography (PET) scans showed that the grafts had survived. Patients also demonstrated stability or improvement on the Movement Disorder Society Unified Parkinson's Disease Rating Scale, particularly those receiving the higher dose of cells. A secondary objective was to evaluate motor function. Participants reported feeling well, experiencing minimal signs of disease progression, and spending less time in the "off" period when their medications wore off and more times in the "on period" or feeling better. The estimated cost of the treatment and surgical procedure is approximately fifty thousand dollars. Our approach uses umbilical cord-derived stem cells. Research has shown that umbilical cord stem cells can develop into multiple tissue types, including muscle, bone, and nerve tissue, and they are also capable of producing Brain-Derived Neurotrophic Factor (BDNF). Which is thought responsible for neuron proliferation and differentiation and neuron survival especially with dopamine. Rather than focusing on mild Parkinson's disease, we treated patients with moderate to severe Parkinson's disease, including those with Parkinson's disease dementia. Patients received stem cells along with either exosomes, which are naturally produced by stem cells, or Enbrel to help reduce brain inflammation. These therapies were delivered through the vertebral venous system. Because this venous system contains no valves, the infused products can reach the brain in less than a minute. This allows stem cells, exosomes, or Enbrel to be delivered rapidly to the central nervous system, where they may exert their therapeutic effects by reducing inflammation. This allows the stem cells to be delivered to the brain where they can make BDNF. In the 6th study, five of the six patients showed reversal of the Parkinsons Disease and Dementia. They were able to live independently, drive and truly socialize without difficulty. All the patients had one treatment and one of the six had the treatment done twice. Over the three-year study, only one patient showed no improvement. The cost associated with this treatment was $7,500.

Introduction

Parkinson's disease affects approximately 1.1 million individuals in the United States and occurs more frequently in males than females. Approximately 90,000 new cases are diagnosed annually [1]. It is the second most common neurodegenerative disorder after Alzheimer's disease [1]. Patients living with Parkinson's disease for more than ten years have an estimated 50–80% probability of developing dementia [2]. Parkinson's disease dementia may manifest with depression, anxiety, apathy, hallucinations, and delusional thinking [5].

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It is believed that Parkinson's disease dementia is associated with the accumulation of alpha-synuclein protein, which damages neurons within the basal ganglia—an area of the brain responsible for movement control. This pathological process may subsequently spread to brain regions responsible for cognitive function [3]. At present, there is no established cure.

Many within the scientific community have concluded that Parkinson's disease and Parkinson's disease with dementia are progressive disorders without curative treatment. The hypothesis presented here challenges that conclusion. Rather than focusing exclusively on pharmaceutical symptom management, we examined this condition from a biochemical and pathophysiological perspective. Neuropathologically, Parkinson's disease is characterized by degeneration of neurons in the midbrain substantia nigra pars compacta and the presence of eosinophilic, alpha-synuclein–positive inclusion bodies known as Lewy pathology. Mitochondria within neuronal cells perform several essential functions. One of their primary roles is the generation of adenosine triphosphate (ATP), which provides the energy required for basic cellular processes. ATP production supports the electrical signaling necessary for neuronal function [6].

In Parkinson's disease, neurons of the substantia nigra—responsible for dopamine production—require large amounts of mitochondrial ATP to maintain normal neuronal activity. Potassium ATP (K/ATP) channels have been identified as important regulators of depolarization within dopaminergic neurons. These channels may influence neuronal depolarization and therefore affect neuronal electrical output or energy production [4]. If neuronal electrical energy production decreases, dopaminergic neurons may become vulnerable to damage [5].

Alpha-synuclein has been widely implicated as a key protein involved in neuronal degeneration within the substantia nigra, where dopamine is produced [6]. Natural Killer Cells (NKCs) have been shown to remove alpha-synuclein aggregates [7]. Umbilical cord stem cells have the capacity to generate Natural Killer Cells [8]. Dementia is a broad clinical term describing impairments in memory, language, problem-solving ability, and other cognitive functions [9]. Multiple underlying etiologies may contribute, including vascular disease [10]. Lewy bodies and synucleinopathies [11] also play a significant role in Parkinson's disease dementia [10]. In evaluating dementia broadly, we sought to identify common pathological mechanisms that might be addressed therapeutically. If such mechanisms could be corrected, it is possible that disease progression might be slowed or potentially reversed. In this small study of Parkinson's disease with dementia, we hypothesized that multiple pathological mechanisms contribute to disease progression and that correcting several of these mechanisms simultaneously may arrest or potentially reverse aspects of the disease process.

Proposed Mechanistic Targets

Potassium channel function

Potassium channels are transmembrane ion channels that regulate the movement of potassium ions across cell membranes. When these channels open, hyperpolarization of the cell membrane occurs. Potassium channels play a major role in regulating cellular electrical activity and contribute significantly to the generation of action potentials. In disease states, the ability of neurons to generate electrical activity may be compromised. Blocking potassium channels can transiently prolong the action potential by less than a second, thereby increasing electrical activity within neurons. This mechanism is conceptually similar to how calcium channel blockers influence vascular function in blood pressure regulation. 4-Aminopyridine can be used to facilitate neuronal depolarization and enhance electrical signaling within brain cells. Potassium channel dysfunction has been observed in Parkinson's disease [12].

Brain-Derived neurotrophic factor (BDNF)

BDNF plays a central role in the development and maintenance of the central nervous system and is essential for neuronal repair and regeneration. BDNF is also a critical mediator of neuroplasticity [13]. Neuroplasticity refers to the capacity of the nervous system to modify its structure and function in response to internal and external stimuli, experiential learning, or injury. It plays a significant role in neuronal growth, survival, neurotransmission, and synaptic plasticity [14]. High concentrations of BDNF are found in the cerebellum and hippocampus [15]. Animal studies suggest that BDNF is essential for learning and memory due to its influence on hippocampal function [16]. Reduced levels of BDNF have been associated with several neurological disorders, including Huntington's disease, Alzheimer's disease, and major depressive disorder [17].

Alpha-synuclein pathology

Alpha-synuclein is widely distributed throughout the body but is most abundant within the brain. It is located primarily at neuronal synapses, where it helps regulate neurotransmitter release. It also participates in mitochondrial function and gene expression within neurons, influencing DNA repair processes. However, alpha-synuclein can misfold, resulting in the formation of toxic oligomers. These aggregates disrupt mitochondrial function and impair normal cellular activity. Misfolded proteins may accumulate into larger inclusions known as Lewy bodies. Lewy bodies are characteristic pathological features of several neurodegenerative conditions, including Parkinson's disease with dementia, dementia with Lewy bodies, multiple system atrophy, and Alzheimer's disease. In Parkinson's disease, overexpression of alpha-synuclein may contribute to DNA damage and cellular senescence. This DNA damage within the substantia nigra ultimately leads to degeneration of dopaminergic neurons and the development of motor deficits. Examination of Lewy bodies in brain tissue from Parkinson's patients demonstrates evidence of DNA degradation [18].

Neuroinflammation

Patients with Parkinson's disease frequently demonstrate inflammatory markers in both brain tissue and peripheral blood [19]. Inflammation is believed to contribute to the pathogenesis of Parkinson's disease [20]. Etanercept (Enbrel) inhibits the binding of tumor necrosis factor (TNF) to cell-surface TNF receptors, rendering TNF biologically inactive [21]. To reduce inflammatory activity within the brain, Enbrel was administered via the vertebral vascular system. Exosomes derived from umbilical cord stem cells [22] have also demonstrated anti-inflammatory effects [23]. In our treatment protocol, either Enbrel or exosomes were utilized because both specifically target inflammatory components of the disease process.

Safety of umbilical cord stem cells and their derivatives

Following research conducted at Sloan Kettering investigating Parkinson's disease, a larger study was proposed to evaluate the long-

term safety of BDNF-related therapies. Umbilical cord–derived cellular therapies have been utilized clinically for more than a decade and have received regulatory authorization from the U.S. Food and Drug Administration for specific transplant applications. Umbilical cord stem cells naturally produce BDNF, and their clinical safety has been extensively studied.

- 1990 – The first unrelated donor cord blood transplant in the United States was performed on a young boy with leukemia at Duke University [24].
- 1992 – The first umbilical cord blood bank was established by the New York Blood Center, allowing donated cord blood to be distributed to transplant centers [25].
- 1992 – The *New England Journal of Medicine* reported the first 25 cord blood transplants performed at Duke University [24].
- 1993 – More than 400 unrelated donor transplants had been supported, demonstrating event-free survival across multiple diagnoses and age groups [26].
- 2009 – The FDA designated cord blood as an approved biologic for unrelated recipients [27].
- 2011 – The FDA licensed the clinical use of cord blood for unrelated recipients [25].

The Study

Patient A

A 79-year-old white male presented with his wife with a diagnosis of Parkinson's disease with dementia. His Parkinsonian symptoms were being managed with escalating doses of Sinemet in an effort to control tremors and rigidity. Cognitive decline had become a major concern. His treating neurologist indicated that continued deterioration was expected. According to his wife, the patient's behavior had become increasingly childlike. Physical examination revealed a slow shuffling gait, bilateral tremors, speech difficulty, marked confusion, and inability to follow commands. The patient slept for approximately half of the consultation. Examination demonstrated a positive glabellar tap, bilateral cogwheel rigidity in the upper extremities, and significant somnolence.

Baseline laboratory evaluation included vitamin D, total iron and percent saturation, and screening for metabolic causes of fatigue including CBC, CMP, lithium level, TSH, Free T3, Total T4, testosterone, DHEA-S, and fasting insulin. Medication review confirmed that the patient was not taking statin therapy due to reported associations between statins and cognitive decline [28]. Treatment consisted of 30 million umbilical cord stem cells obtained from unrelated donor cord blood, administered along with 25 mg of Enbrel through the vertebral vascular system. At 6-week follow-up, no significant clinical changes were observed. Treatment was then augmented with 4-aminopyridine, a potassium channel blocker intended to enhance neuronal electrical signaling by increasing cellular depolarization.

At 16 weeks post-treatment, the patient returned to the clinic walking independently without a walker and without a shuffling gait. He appeared alert, energetic, socially interactive, and cognitively appropriate. No cognitive deficits or motor impairments were noted during the examination. His wife reported, "My husband is back."

Patient B

A 77-year-old female with Parkinson's disease presented with worsening functional decline despite treatment with Sinemet. According to her husband, she had developed severe confusion and could not be left unattended, prompting consideration of 24-hour nursing care.

Her tremors were severe, significantly impairing her ability to feed herself or drink from a cup. Examination revealed cervical rigidity with severely restricted head rotation, slow speech, dependence on a walker, and extreme fatigue. Treatment consisted of 30 million umbilical cord stem cells combined with 250 billion exosomes administered through the vertebral vascular system. One week later, treatment with 4-aminopyridine was initiated and titrated to 10 mg twice daily.

At 6-week follow-up, physical examination demonstrated decreased tremor activity, reduced cogwheel rigidity, improved energy levels, and improved cervical mobility. Both the patient and her husband reported normalization of cognitive function. Due to occasional anxiety, the 4-aminopyridine dose was reduced to 10 mg once daily. At 6 months post-treatment, tremors were minimal. The patient was able to feed herself and drink normally from a cup. She reported good energy levels and no functional restrictions in daily activities. She resumed independent living and was able to return to her regular social activities, including participation in her Bridge club.

Patient C

A 64-year-old Caucasian male with a diagnosis of Parkinson's disease and Lewy body dementia presented with significant cognitive impairment, including poor memory, visual hallucinations, and decreased energy levels. The patient underwent treatment with stem cells and exosomes in November 2025, with noted clinical improvement. On February 9, 2026, 4-aminopyridine therapy was initiated. Following initiation, the patient demonstrated improved balance and increased energy.

Patient D

A 76-year-old Caucasian female diagnosed with Parkinson's disease presented with severe tremors, significantly impairing her ability to perform activities of daily living, including drinking from a cup. On June 10, 2024, she received treatment with stem cells and exosomes. One week later, 4-aminopyridine therapy was initiated. By September 18, 2024, the patient exhibited improved gait, increased facial expressivity, reduced tremors, and regained the ability to drink without spillage. A second treatment with stem cells and exosomes was administered on December 18, 2024, after which tremors were reported to be essentially resolved.

Patient E

A 75-year-old Caucasian male with Parkinson's disease and associated dementia was initiated on 4-aminopyridine therapy on October 9, 2025. Initial response included increased alertness and improvement in right-hand tremor. The patient continued therapy, and by February 11, 2026, demonstrated slight improvement in short-term memory, maintained functional status, and modest improvement in motor function. Consideration is being given to future treatment with stem cells.

Conclusion

A total of five patients were treated using this protocol. All patients demonstrated some degree of clinical improvement, with no evidence of deterioration during the observation period. Parkinsonian symptoms appeared to stabilize across all cases and showed improvement.

Among patients with Parkinson's disease with dementia, hallucinations were either eliminated or significantly reduced. Overall, dementia-related symptoms were resolved in 4 of 5 cases. Four of the five patients received combination therapy consisting of stem cells, exosomes, and 4-aminopyridine, while one patient was treated with 4-aminopyridine alone. Although the patient receiving only 4-aminopyradine exhibited slight improvement, the degree of clinical response was less pronounced compared to those who underwent the full combination protocol. These findings suggest a potential additive or synergistic effect of combination therapy; however, further study with larger patient populations and controlled conditions is warranted. No serious adverse effects were observed. In one patient, the dosage of 4-aminopyridine was reduced from 20 mg/day to 10 mg/day due to mild anxiety. The cost per patient ranged between $7,000 and $8,000. This non-surgical approach represents a potentially more accessible and less costly alternative to procedures currently being investigated at major academic medical centers. Research conducted at Sloan Kettering has suggested that Parkinson's disease may be reversible under certain conditions, we would agree. Their findings challenge the longstanding assumption that Parkinson's disease is inevitably progressive and irreversible. Continued investigation into these mechanisms may provide further insight into other potential therapeutic strategies.

Conflict of Interest & Disclosure Statement

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Artificial intelligence (AI) tools were used solely to assist with language editing, grammar, spelling, and improving readability. AI was not used to generate the scientific content, analyze data, interpret results, draw conclusions, or write the manuscript. The authors take full responsibility for the accuracy, originality, and integrity of the work.

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