EXPERT OPINON

Parkinson's Plus Syndrome Treatment: Are We There Yet?

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In contrast to conventional idiopathic Parkinson's disease, the neurodegenerative disorders comprising Parkinsonism Plus Syndrome (i.e., atypical parkinsonism-AP) share several characteristics in common, including a clustering of symptoms, a lack of response to levodopa, distinctive pathological abnormalities, rapid disease progression, and a dismal prognosis. Clinical features include asymmetrical onset; infrequent or unusual tremor; prominent rigidity in the axial muscles; bradykinesia; early postural instability; supranuclear gaze palsy; early autonomic failure; pyramidal affection; cerebellar involvement; alien limb phenomenon; apraxia; and in some cases, significant early cognitive dysfunction. Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and Dementia with Lewy Bodies (DLB) are the most common forms of AP. Less frequent forms include cortico-basal ganglionic degeneration (CBGD), frontotemporal dementia with chromosome 17 (FTDP-17), pick's disease, Guam Parkinson's-dementia complex, pallidonigral degeneration, Wilson's disease, and a severe variant of Huntington's disease. In the past three decades, researchers have made significant discoveries in the tau disorders, including PSP, CBGD, and FTDP-17. Idiopathic Parkinson's disease, multiple system atrophy, and dementia with lewy bodies are all examples of alpha-synucleinopathies.

According to recent research, using stringent diagnostic criteria enhances the ability to diagnose these Parkinsonism plus disorders. Unusual appearances, however, can make diagnosis difficult. The limitations of the existing investigations highlight the need for more investigation to find biologic indicators that can enable early identification and comprehend the causes of alpha-synuclein or tau aggregation.[1] It has been emphasized to identify treatment approaches that could stop the aggregation of these proteins and save defective cells. The clinical, neuroimaging, pathologic, genetic, and treatment aspects of these illnesses are still challenging to clinicians. Although the exact origin of these cluster-forming tauopathies is unknown, many believe it is related to post-infectious events that resemble post-encephalitic parkinsonism or to cumulative neurotoxins that may be present in the diet. Alkaloids' pharmacology and neurotoxicity need to be better understood, as well as their function in PSP and other associated tauopathies.[2]

Most drug therapies for AP are ineffectual. The effects of dopaminergic replacement therapy are often brief and minimal. Levodopa, dopamine agonists, amantadine, tricyclic antidepressants, anticholinergic drugs, and selective serotonin-reuptake inhibitors were shown to be ineffective and to have adverse effects in a study of 12 PSP patients.[3] Also, there is no improvement to motor function by pramipexole.[4] According to research using donepezil there was a little improvement in cognitive tests but a decline in motor performance.[5] However, no improvement on cognitive performance was shown in a different investigation.[6] A zolpidem study[7] found that both saccadic eye movements and motor skills had improved. Interestingly, people with PSP have been proven to benefit with tandospirone citrate (5-HT1A agonist) reported to exist.[8] Myoclonus in CBGD has been reported to be helped by clonazepam, and both CBGD and PSP patients may benefit from botulinum toxin injections to treat their blepharospasm and painful limb dystonia. Positive findings in PD research, like those attained with direct brain infusion of glial cell derived neurotrophic factor (GDNF)[9], are expected to spur treatment trials with similarly promising medicines in other neurodegenerative diseases, such the tauopathies.

Since our understanding of PD is still far from complete, new promising therapeutics must be explored to better improve patients' quality of life and maybe slow down the neurodegenerative process. Animal models of PD are required to address all these issues in this context. "Classic" models are based on neurotoxins that selectively target catecholaminergic neurons (6-hydroxydopamine, 1-methyl-1,2,3,6-tetrahydropiridine, agricultural pesticides, etc.), while "modern" models use genetic manipulations to

introduce mutations like those found in familial cases of PD (a-synuclein, DJ-1, PINK1, Parkin, etc.) or to disrupt nigrostriatal neurons (MitoPark, Pitx3, Nurr1, etc.). While some of these models are more adapted to studying the pathophysiology of Parkinson's disease, others are better suited for evaluating therapeutic approaches because to their unique advantages and disadvantages.

Despite their limitations, animal models of Parkinson's disease (PD) have been useful for exploring the mechanisms of "traditional" treatments like L-dopa, testing the efficacy of experimental antiparkinsonian medications, and clarifying certain pathophysiological concepts. The most important message to take away from this article is that different PD animal models may be better suited to investigating different aspects of the disease, such as its pathogenesis (genetic models), neuroprotection (genetic and other models), and symptomatic therapy (toxin models). It's feasible that in the future, a hybrid of many of these models may emerge. This could allow for the development of innovative models that are more suited to the complexity of the etiology, pathophysiology, and symptoms of PD, by, for example, simulating the impact of genetic and environmental variables.

Conclusively, as biomarkers become increasingly used to assist clinical diagnosis, new opportunities for early detection of Parkinson's disease will arise, and diagnostic accuracy at the initial neurological consultation will be significantly improved over the current state of the art. One day soon, maybe, neurologists will be able to correctly identify the many Parkinson's disease subtypes, each of which has a varied prognosis and reacts differently to treatment. However, there will be more complications, the most significant of which will occur when a diagnosis may be made in asymptomatic people, but no preventative treatment is available. There has never been a greater variety of potential drugs for disease modification under clinical development.

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