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COMMENTARY

Challenges and Opportunities in Atypical Parkinsonian Syndromes: Call to Action

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Abstract: Neurodegenerative diseases are a leading cause of disability and death in the United States, and the burden of rare neurodegenerative conditions such as atypical Parkinsonian syndromes is expected to grow in the coming years as the size of the older population increases at an unprecedented rate. Atypical Parkinsonian syndromes encompass a collective of rare neurodegenerative diseases that are often misdiagnosed as Parkinson's disease due to similar signs and symptoms. These syndromes include progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD), and are characterized by rapid disease progression and decreased life expectancy. In this paper, we describe the substantial burden atypical Parkinsonian syndromes pose to the healthcare system and patients attributable to challenges in diagnosis, ineffective treatment options, and rapid functional decline. Despite increased understanding and recognition of these disorders, there remains significant unmet need for patients with atypical Parkinsonian syndromes. We provide recommendations to policymakers to support access to effective disease management of atypical Parkinsonian syndromes through legislative efforts that i) prioritize development of disease-modifying treatments, ii) focus on objectively assessing disease progression in addition to symptom management, and iii) bring forth economic frameworks that capture the full value of treatments.

Keywords: atypical Parkinsonian syndromes, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, disease-modifying treatments

Introduction

Neurodegenerative diseases inflict a substantial burden on patients, caregivers, and the healthcare system as a whole. Already a leading cause of disability and death in the United States, the impact of these diseases is only expected to grow as baby boomers age and life expectancy increases.[1,2] Considerable research has been conducted to better understand and manage more common neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (PD). However, rare neurodegenerative diseases, such as atypical Parkinsonian syndromes, can be particularly debilitating and are not yet well understood. Atypical Parkinsonian syndromes encompass a collective of rare neurodegenerative diseases that are often misdiagnosed as PD due to similar signs and symptoms including resting tremors, muscle stiffness, and slowed or difficult movements such as walking.[3,4] These syndromes include progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD), along with other rarer diseases such as dementia with Lewy bodies (DLB). Despite some overlapping features, atypical Parkinsonian syndromes are distinct disorders, which, while less common than PD,

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often have more rapid disease progressions, greater functional decline, an absence of effective therapies, and poorer life expectancy.

Atypical Parkinsonian syndromes pose substantial burden on the healthcare system and to patients, attributable to challenges in diagnosis, ineffective treatment options, and rapid functional decline. Despite increased understanding and recognition of these disorders, both individually and collectively, there remains significant unmet need for patients with atypical Parkinsonian syndromes. In this paper, we aim to describe the patient journey and challenges accompanying PSP, MSA, and CBD, and present actionable opportunities to support the development of disease-modifying treatments.

Understanding and Managing Atypical Parkinsonian Syndromes

Atypical Parkinsonian syndromes fall into two broad categories – tauopathies (PSP and CBD) and synucleinopathies (MSA) – which indicate a build-up in the brain of the tau and alpha-synuclein proteins, respectively. Among atypical Parkinsonian syndromes, diagnostic accuracy is lowest for CBD (approximately 50%), due to substantial overlap in clinical presentation with Alzheimer's disease.[3] To further complicate the diagnostic process, PD is a synucleinopathy, thus presenting similar signs associated with alpha-synuclein protein accumulation as MSA.

Currently, there are no effective Food and Drug Administration (FDA) approved symptomatic or disease-modifying treatments for atypical Parkinsonian syndromes.[5] Physicians often prescribe treatment regimens indicated for Parkinson's disease (e.g., levodopa), but these treatments are not as effective for atypical Parkinsonian syndromes.[3] In a recent study, less than 25% of PSP and MSA patients reported that levodopa improved their symptoms.[6] Recent clinical trials for new therapies failed to demonstrate efficacy on clinical outcome measures.[6–9]

Developing an effective treatment requires an understanding of the causal mechanism and progression of disease. However, like Alzheimer's and Parkinson's disease, the etiology of atypical Parkinsonian syndromes is unknown. Causal mechanisms of tau and alpha-synuclein protein accumulations are not understood, nor are the processes in which the protein accumulation serves as a catalyst for select neurodegenerative diseases.[10,11] Researchers believe that multiple factors may contribute to the development of atypical Parkinsonian syndromes, including genetic factors and occupational and environmental exposures.[10,12,13] Atypical Parkinsonian syndromes are generally considered to be sporadic while further research aims to find conclusive evidence of risk factors. As such, therapeutic choices for atypical Parkinsonian syndromes remain limited due to the lack of understanding of disease etiology and the absence of appropriate disease progression models.

Exploring the Patient Journey

Delays in Diagnosis and Misdiagnosis

Although pathologically distinct, clinical features of atypical Parkinsonian syndromes often overlap with PD. This can lead to delays in diagnosis and misdiagnosis.[11] On average, it takes 3.6–4.9 years from the onset of clinical symptoms to an accurate diagnosis of PSP.[10] More than 90% of PSP patients are seen by three or more physicians before a diagnosis of PSP is made.[10] Among MSA patients, 44% reported that it took greater than two years to receive a diagnosis of MSA, and more than half of MSA patients required consultation with three or more neurologists to receive the diagnosis.[14]

Additionally, diagnostic tools have not found a simple way to differentiate between atypical Parkinsonian syndromes and PD or other neurodegenerative diseases. Diagnostic imaging scans and tests can measure neuron loss, brain stem shrinkage, and brain glucose metabolism, which may be indicative of atypical Parkinsonian syndromes.[3,11] However, there is no single diagnostic biomarker for each of the distinct atypical Parkinsonian syndromes.[11] Identification of specific biomarkers would be a significant step toward earlier diagnosis, tracking of disease progression, and measuring the treatment response in patients with atypical Parkinsonian syndromes.

Diagnosis is further complicated by heterogeneous presentations of these disorders. For example, PSP presents in at least seven clinically distinct phenotypes, with varying regional pathologies and clinical features.[11] CBD and MSA have at least four and three different phenotype categories, respectively.[7,8] Given the overlapping but distinct clinical features of atypical Parkinsonian syndromes, it is critical to understand the heterogeneity and varied phenotypes in order to improve the diagnostic odyssey these patients face.

Timely and accurate diagnosis is critical for starting treatment. The typical delay in making an accurate diagnosis of PSP and MSA may mean that patients do not receive treatment until it is too late to prevent or delay disease progression. While effective treatments do not currently exist, identifying the specific atypical Parkinsonian syndrome is necessary to understand disease

progression and could be important in selecting the appropriate treatment in the future.

High Burden of Symptoms and Comorbidities

In the absence of effective treatment, health care providers currently rely on medications to alleviate some of the symptoms and attempt to prevent complications related to atypical Parkinsonian syndromes. However, patients with atypical Parkinsonian syndromes have a high frequency of symptoms and comorbidities, making even basic symptom reduction difficult.[15] For example, sleep apnea and nocturnal stridor, urinary incontinence, erectile dysfunction, and orthostatic hypotension (i.e. a severe drop in blood pressure upon standing) are common symptoms of MSA.[3,4] Additionally, many patients with PSP, CBD, and MSA frequently have sleep behavior disorders.[16] In one study, the majority of patients with either PSP or MSA reported spasms, fatigue, pain, difficulty swallowing, difficulty communicating, and constipation.[17]

Mental illnesses are common among people with atypical Parkinsonian syndromes. Depression is present in approximately 58%, 62%, and 73% of patients with PSP, MSA, and CBD, respectively.[18–20] Anxiety is estimated to be present in 72% of MSA patients.[19] A recent study found that approximately half of patients with PSP experience some form of sleep disorder, and one-third experience eating disorders.[18]

Due to the extensive symptoms, comorbidities, and complications associated with atypical Parkinsonian syndromes, management of a patient with an atypical Parkinsonian syndrome often incorporates a broad multidisciplinary team. Atypical Parkinsonian syndrome patients may require coordinated care from a combination of psychiatrists, physical therapists, speech pathologists, cardiologists, urologists, sleep specialists, as well as their neurologist and primary care physician. Thus, the complexity of treating patients with atypical Parkinsonian syndromes imposes substantial burden on formal and informal caregivers, the healthcare system, and payers.

Rapid Disease Progression and Functional Decline

Disease progression and functional decline occur more rapidly in atypical Parkinsonian syndromes than in PD.[11,21] Atypical Parkinsonian syndromes are characterized by motor and non-motor functional decline, resulting in approximately 50% of MSA patients requiring a walking aid within three years of symptom onset.[16] Most MSA patients are bedridden within 6 to 8 years of symptom onset.[16] A recent study found that among PSP and MSA patients who had not yet retired, all were unable to work due to their illness.[17]

Informal caregivers are relied upon to provide daily care to people with atypical Parkinsonian syndromes. Among PSP and MSA patients, 93% relied upon informal caregivers.[17] High rates of depression, apathy, and other psychiatric comorbidities among patients with atypical Parkinsonian syndromes, together with the substantial reliance on caregivers in this population, suggest a great risk of caregiver strain.[15]

Caregivers of patients with PSP report high psychological burden and depressive symptoms themselves.[22] Caregiver burden is associated with caregiver stress, depression, and healthcare utilization, and has a psychological and performance impact on their own daily activities at work and at home.[23]

Modifying the Disease Course

While the average age of onset varies from 55 (MSA) to 60s (PSP and CBD) for atypical Parkinsonian syndromes, Medicare will likely see a growing financial burden as the number of people with atypical Parkinsonian syndromes grows.[3,4,8] The rapid functional decline of patients with atypical Parkinsonian syndromes will also place an economic strain on the Medicaid system, a primary payer for long-term care. Delaying utilization of a skilled nursing facility by one year can save Medicaid approximately $76,000 per patient.[24] Thus, treatments that delay or mitigate disease progression could reduce or defer the need for both formal and informal care, thereby reducing healthcare utilization and caregiver burden.

Early, accurate diagnosis and effective disease management will become critical as treatments are developed. For patients with atypical Parkinsonian syndromes, it often takes several years to achieve a proper diagnosis, during which time their disease continues to progress.[10] Thus, early and ongoing treatment with disease-modifying therapies is crucial to modifying the disease course and preventing progression of disability.

Prioritizing Development of Disease-Modifying Treatments

Currently the FDA's Office of Orphan Products Development provides funding for clinical research for treatments of rare diseases through the Orphan Products

Grants Program.[25] However, of the $1.61 billion allocated for the FDA's Human Drugs Program in fiscal year 2018, just $29.1 million is appropriated for the Office of Orphan Products Development, a number that has not changed since 2016.[26]

The National Institute of Neurological Disorders and Stroke (NINDS), National Center for Advancing Translational Sciences (NCATS), and the National Institute on Aging (NIA), all subsets of the National Institutes of Health (NIH), provide additional funding for atypical Parkinsonian syndromes. The NIH should encourage interdepartmental collaboration by allocating funding for disease-modifying treatments through existing NIH programs such as the Rare Diseases Clinical Research Network or the Trans-NIH RNAi Facility, which develops genomic screenings to advance disease knowledge and drug development.

Developing effective treatments is not a challenge unique to atypical Parkinsonian syndromes. Similarly, Alzheimer's and Parkinson's diseases also lack effective symptomatic and disease-modifying treatments. Atypical Parkinsonian syndromes, however, are distinctively positioned for research due to the more rapid progression of the disease, which allows clinical trials to detect meaningful differences over a shorter time period, thus reducing cost and resource burden. Advancements in treatments for CBD, MSA, or PSP could have implications for neurodegenerative conditions beyond atypical Parkinsonian syndromes.

Assessing Disease Progression and Symptom Reduction in Patient Outcomes

While symptom management is important for patient quality of life, ultimately, disease progression must be slowed or delayed, positively affecting the bleak disability and mortality outcomes that accompany atypical Parkinsonian syndromes. Currently, the US healthcare system emphasizes symptom management. However, it is imperative that the narrative broadens to incorporate delaying the progression of disease in addition to suppressing symptoms with a focus on disease modifying interventions.

Several scales have been developed to assess disease severity and disease progression, including the Parkinson's Plus Scale, the Unified MSA Rating Scale, and the PSP Rating Scale.[27–30] Each of these scales assesses physical and mental functionality as surrogate measures for disease progression. However, due to lack of clinical biomarkers, objective measures of disease progression have not been established.

Additionally, while these scales were developed to be used in both interventional trials and clinical practice, data are lacking on the rate of their use. Consistent use of objective measures of disease severity and progression would inform clinical decision-making and quantify the extent to which a treatment is producing the intended response.

Developing an Economic Framework to Capture Value

Due to the lack of current treatments for atypical Parkinsonian syndromes, models to establish and quantify the value of disease-modifying treatments are lacking. New treatments are scrutinized via cost-effectiveness analyses, which are often limited in their measurement of patient, caregiver, or payer value.

An economic framework that captures novel elements of value – such as indirect costs involved with lost work years, informal caregiver burden, and formal skilled nursing – is needed to fully understand the potential impact of disease-modifying treatments. The unique burden imposed on formal and informal caregiving is a key component of both healthcare utilization and societal costs that needs to be accounted for when quantifying the value of treatments.

Given the high lifetime burden of illness and diminished length and quality of life involved with each of these diseases, a robust economic framework is critical to characterizing the value of disease-modifying treatments. In addition, such an economic framework can be used to inform reimbursement decisions once treatments are developed.

Conclusion

Our collective understanding of atypical Parkinsonian syndromes has grown substantially in recent years with developments of more advanced research and diagnostic tools. However, much remains unknown about these disorders. The burden of rare neurodegenerative conditions such as atypical Parkinsonian syndromes is expected to grow in the coming years as the size of the older population grows. Efforts to develop new disease-modifying treatments for atypical Parkinsonian syndromes are crucial to meeting current and future demand.

Heterogeneity within these disorders, along with numerous comorbidities and rapid disease progression, complicate management of atypical Parkinsonian syndromes. As such, stakeholders must align regarding the importance of supporting innovation to understand, diagnose, and treat atypical Parkinsonian syndromes.

Policymakers have the unique opportunity to support each of the above recommendations through legislative efforts that prioritize atypical Parkinsonian syndromes as well as other rare diseases. Policies that prioritize development of disease-modifying treatments, focus on objectively assessing disease progression in addition to symptom management, and bring forth economic frameworks that capture the full value of treatments can promote access to effective disease management.

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