Parkinson-Plus Syndromes

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Cameron Miller-Patterson, Kathryn E. Krobot, Edward A. Burton, and Libby J. Smith

A summary comparison of typical clinical features of Parkinson disease (PD), progressive supranuclear palsy (PSP), and multiple system atrophy is shown in Table 13.1. These differences are elaborated in depth within this chapter.

Progressive Supranuclear Palsy

Clinical Features

PSP is characterized clinically by progressive parkinsonism, supranuclear ocular gaze palsy, bulbar symptoms, axial rigidity, early postural instability with frequent falls, and frontotemporal dementia [1]. Supranuclear gaze palsy refers to a condition in which voluntary ocular movements are impaired, but reflex movements are preserved. The typical ocular motor disorder of PSP includes prominent impairment of voluntary vertical saccadic and pursuit movements, particularly for downgaze, with preservation of oculocephalic reflexes (movements of the eyes when the patient fixes gaze on a distant object while the examiner rotates the patient's head up and down in a nodding motion). Axial rigidity occurs in association with hyperextension of the neck. Gait is stiff, hypokinetic, and disorganized, with significant lateral deviation, instability, and often prominent gait freezing. Loss of postural reflexes leads to frequent falls, often backward, which typically occurs early during the clinical course and may be the first symptom. Dementia often develops within the first few years of disease onset and is characterized by frontotemporal deficits such as apathy, poor planning, difficulty multitasking, and decreased verbal fluency. Other features include facial bradykinesia and dystonia, which produces a characteristic "startled" expression, eyelid opening apraxia, small rapid handwriting, and pseudobulbar affect (mood-incongruent crying or laughing) [2]. Prominent speech and swallowing deficits are a significant cause of morbidity and mortality in PSP and are described below.

Corticobasal degeneration (CBD) shares some clinical and pathologic overlap with PSP but is much less common. In addition to progressive asymmetric parkinsonism and early falls, CBD most frequently presents with dystonia, myoclonus, alien limb phenomena, and dementia. Cortical sensory deficits are frequently found, including inability to identify objects placed in

C. Miller-Patterson · E. A. Burton
Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

K. E. Krobot · L. J. Smith (✉)
Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: smithlj2@upmc.edu

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Table 13.1 A comparison of the typical clinical features of Parkinson disease, progressive supranuclear palsy, and multiple system atrophy. The three diseases show extensive clinical overlap, especially early in disease course, and the clinical presentation of an individual disease can vary significantly between patients. Consequently, definite diagnosis depends on neuropathological evaluation at autopsy

	Parkinson's disease	Progressive supranuclear palsy	Multiple system atrophy
Shared motor features	Bradykinesia, akinesia, rigidity		
Distinguishing motor features	Unilateral onset; pill-rolling rest tremor	Symmetric onset; axial > appendicular rigidity; early backward falls	Symmetric onset; cerebellar ataxia; pyramidal signs or irregular postural kinetic tremor
L-DOPA response	Excellent, sustained	Usually poor or absent	Some patients respond but may require high doses
Autonomic	Early constipation; urinary/erectile dysfunction and orthostatic hypotension tend to occur late	Urinary incontinence common late in disease	Constipation, urinary/erectile dysfunction, and orthostatic hypotension may be severe and occur early
Cognitive/behavioral	Anxiety/depression frequently precede motor symptoms; dementia common in advanced disease and associated with visual hallucinations	Frontotemporal dementia nearly always present; may be presenting symptom and severe	Frontal dysexecutive syndrome may be present; severe dementia uncommon
Other typical features	REM sleep behavior disorder, anosmia	Supranuclear downgaze palsy	REM sleep behavior disorder, central sleep apnea (may be life-threatening)
Voice/swallow/airway	Hypophonia and hypokinetic dysarthria; severe swallowing difficulties uncommon	Mixed spastic/hypokinetic dysarthria; pseudobulbar palsy and progressive dysphagia	Spastic/hypokinetic or ataxic dysarthria; progressive dysphagia; dysphonia, nocturnal stridor, obstructive sleep apnea; bilateral vocal fold paralysis

REM Rapid eye movement

the hand (astereognosis) or figures drawn on the palm (agraphesthesia) with eyes closed, despite having apparently normal somatic sensation [2].

Epidemiology

PSP is the most common neurodegenerative cause of parkinsonism after Parkinson disease, comprising around 5% of all parkinsonian patients seen in a movement disorders clinic. The reported prevalence is 1.39–14.3/100,000 and incidence is 0.3–1.1/100,000/year [3]. Median onset is 63 and median survival from symptom onset is 6.9 years [4]. The sex ratio is unclear, with different studies reporting varying data [3].

Pathophysiology

The pathology of PSP is characterized by neuronal loss in the basal ganglia, midbrain, pons, dentate nucleus, and inferior olive, causing the characteristic movement, gait, and oculomotor abnormalities. Frontal cortical and adjacent subcortical white matter involvement occurs and is typically associated with prominent cognitive and behavioral changes [4]. Pseudobulbar palsy is caused by degeneration of corticobulbar fibers innervating relevant cranial nerve nuclei in the brainstem [5]. Inclusion body pathology in PSP includes neurofibrillary tangles and neuropil threads [6], tufted astrocytes, and coiled bodies within oligodendrocytes [7]. These pathological inclusions contain insoluble, hyperphosphorylated aggregates of the microtubule-associated protein tau, leading to PSP being classified as a tauopathy. CBD is also a tauopathy, although there is more prominent pathology in motor cortical areas and the putamen, and ballooned neurons in the cortex, and the inclusion body pathology differs, including corticobasal bodies in the brainstem and accumulations of tau in distal astrocytic processes called astrocytic

plaques [7]. The origin and role of the extensive tau pathology seen in PSP and CBD are currently unclear.

Genetics

Tau is encoded by the *MAPT* gene located on chromosome 17. Mutations in this gene have been associated with an autosomal dominant tauopathy that can overlap clinically and pathologically with PSP [8, 9]. However, most PSP cases have no family history and no *MAPT* gene mutation. Inversion of the genomic locus containing *MAPT* is present in 20% human chromosomes and appears protective against PSP. Genome-wide association studies have identified genetic variants that confer an increased risk of PSP, including non-coding variants adjacent to the *MAPT* gene and several other genes [10].

Voice-, Airway-, and Swallow-Specific Symptoms: Findings or Sequela

Voice Dysarthria is present universally early in the disease, although of variable severity. Speech is characterized by mixed spastic and extrapyramidal hypophonia and dysarthria, resulting in quiet, slow, strained, and sometimes nasal speech [11]. Spastic dysarthria and hypokinetic features usually predominate over ataxic features [12, 13].

Airway Airway obstruction is not an expected feature of PSP.

Dysphagia Dysphagia in PSP involves the oral phase of swallowing more than the pharyngeal phase, contrary to patients with PD [14]. The onset of dysphagia in PSP occurs with a mean latency after initial presentation of 42 months [15]. Only 18% of patients complained of dysphagia 2 years after symptom onset, but nearly 50% had dysphagia at 5 years [16]. Given the relatively rapid progression of PSP, it is imperative to begin dysphagia education, evaluation, and treatment prior to onset of symptomatic problems.

Oral Phase Oral phase complaints are common in PSP. Abnormalities include excessive pooling of saliva in the oral cavity, sialorrhea, difficulty with mastication and bolus formation, unintentional bolus loss, and residue throughout the oral cavity after swallow. Excessive saliva has been reported in 63% of PSP patients [17], while only 20% of patients were found to have pharyngeal pooling of secretions [18] on FEES exam, illustrating the importance of oral dysphagia in PSP. Interestingly, dysarthria severity did not correlate with dysphagia severity on endoscopic evaluation (FEES) [17]. Oral phase dysphagia in PSP is characterized by incomplete mastication, forceful lingual pressing of food against the hard palate, lingual pumping, uncoordinated lingual movements, reduced lingual strength, extra movements of the velum, non-cohesive bolus transfer, delayed or uncoordinated bolus transfer, piecemeal deglutition, and passive bolus transfer prior to swallow (which is worsened by retrocollis) [17, 19, 20]. On clinical swallowing evaluation, mastication is prolonged in the early stages of dysphagia; however, once the disease has progressed, oral preparation and mastication are essentially absent. Lingual movement also appears to diminish over time.

Pharyngeal Phase Common pharyngeal findings in patients with PSP include delayed swallow initiation and vallecular residue. Aspiration due to pharyngeal deficits is less common. Pharyngeal contraction, base of tongue retraction, and hyolaryngeal elevation and excursion are relatively preserved, especially in the early stages of the disease. FEES examination showed that laryngeal penetration/aspiration events occurred frequently prior to swallow initiation in patients in the early stages of PSP; this suggests that passive bolus transfer due to poor bolus formation, reduced posterior oral control, discoordination, and oral residue (oral dysphagia) contributes to laryngeal penetration/aspiration [18]. The link between poor bolus control and aspiration was

confirmed in another study [17]. Importantly, half of the episodes of penetration/aspiration were silent, greatly elevating the risk of aspiration pneumonia, which is a major cause of morbidity and mortality in PSP.

Pharmacology/Medical Management

Treatment of PSP is symptomatic and includes fall prevention, management of complications such as eyelid opening apraxia and sialorrhea with botulinum toxin injections, and management of pseudobulbar affect with dextromethorphan/quinidine. The movement disorder of PSP rarely responds to L-DOPA or amantadine.

Voice-, Airway-, and Swallow-Specific Procedures: Treatment Outcomes

Voice Early in the course of PSP, enhancing vocal intensity by increasing subglottic air pressure during phonation may help ameliorate hypokinetic dysarthric features, though to a lesser degree than with PD [21]. Long-term efficacy has yet to be proven. As dysarthria progresses and speech becomes unintelligible, computer-assisted technologies may be useful to maintain communication.

Dysphagia Progressive dysphagia may lead to poor oral intake, dehydration, and malnutrition. There is no research showing improvement or slower swallowing decline with swallowing therapy. Despite this, periodic swallowing evaluation via videofluoroscopy or endoscopic evaluation (FEES) may assist with developing a plan to reduce or prevent aspiration. Compensatory strategies including chin tuck, cough–swallow, breath hold, or head turn can be tried. The nature of the deficits should determine compensatory strategies. For example, cough–swallow is unlikely to be effective in a patient with severe hypophonia, and chin tuck is challenging in the presence of retrocollis. Simpler swallowing strategies may be needed as cognitive deficits worsen. Overall, a softer diet is often used as the disease progresses. High-risk foods for aspiration include nuts, dry meats, rice, and bread. "Mixed" consistencies (such as cereal with mild, chunky soups) can be challenging. If thin liquids become an issue due to poor posterior oral control or discoordination, nectar liquids can be used. However, nectar liquids increase the risk of dehydration due to poor fluid intake. In the presence of downgaze palsy, raising the level of a meal tray may improve the ability to self-feed, which in turn lowers aspiration risk [22, 23]. As the disease advances, enteral nutrition usually via percutaneous endoscopic gastrostomy (PEG) is frequently required, not only to ensure proper daily caloric intake but also for safety (aspiration, asphyxiation from food bolus). Patients and families, however, must be cautioned that PEG placement does not eliminate the risk of developing aspiration pneumonia, since the risks of aspirating secretions or tube feeds via gastroesophageal reflux remain.

Dysphagia complications may be mitigated by patient and family education regarding signs of dysphagia, aspiration, or pneumonia and the importance of oral care. Through dietary modification, use of compensatory swallowing strategies, and patient education guided by a speech–language pathologist, a plan can be developed to maximize swallowing safety, improve quality of life, and prevent aspiration pneumonia for as long as possible.

Management options for sialorrhoea can include off-label use of antimuscarinic medications such as 1% atropine ophthalmic solution applied sublingually and oral glycopyrrolate, although the use of these agents is derived from evidence for PD and they are often poorly tolerated [24]. Botulinum toxin injected into the parotid glands can be effective in treating sialorrhoea in parkinsonian disorders including PSP [25].

Frontiers

One major goal of recent research has been to identify disease-modifying therapies for PSP through development of agents that target tau pathology. Two recent double-blind placebo-controlled clinical trials of putative disease-modifying treatments did not show efficacy [26, 27]. However, these

studies demonstrated that large, multicenter, randomized trials are possible in PSP, despite it being a comparatively rare disease, and validated the PSP rating scale [28] as a replicable way to monitor clinical progression. Several other clinical trials are underway, or in planning stages, involving agents that may inhibit tau aggregation, stabilize neuronal microtubules, or prevent cell-to-cell transmission of aggregated tau [29]. Other approaches such as accelerating degradation of pathological forms of tau are also under preclinical development. This is a very active area of research that is likely to evolve rapidly in the next few years.

Multiple System Atrophy

Clinical Features

MSA is a neurodegenerative disorder characterized clinically by various combinations of parkinsonism, autonomic failure, and cerebellar ataxia, all caused by a common underlying pathology. Depending on the predominant movement disorder, MSA is categorized clinically as MSA-parkinsonism (MSA-P) or MSA-cerebellar (MSA-C) types. MSA-P is characterized by rapidly progressive parkinsonism with early postural instability and poor response to L-DOPA. MSA-C is characterized by progressive ataxia, including cerebellar oculomotor signs and gait ataxia [30]. Dysautonomia occurs in both types of MSA and can appear early during the course of the disease, causing urinary incontinence, male erectile dysfunction, orthostatic hypotension, and syncope. In addition, central sleep apnea, orofacial dystonia (especially following exposure to L-DOPA), axial dystonia, and hyperreflexia with extensor plantar responses are typical. Dementia may occur uncommonly, but is not usually a prominent feature [2]. Prominent deficits in speech and swallowing are typical in MSA and are discussed below.

Epidemiology

The reported prevalence of MSA is 3.4–4.9/100,000 and incidence is 0.1–2.4/100,000/year. Peak age of onset is in the early 50s, and the median survival from symptom onset is 6–10 years. MSA affects males and females equally. MSP-P is more common than MSA-C in most countries, although the converse is true in Japan [31].

Pathophysiology

Neuronal loss, astrogliosis, and microglial infiltration in MSA occurs in different topological patterns reflecting the clinical phenotype. In MSA-P, prominent neuronal loss is seen in the putamen and substantia nigra (striatonigral degeneration; SND). In MSA-C, neuronal degeneration is more obvious in the pons, inferior olives, and cerebellum (olivopontocerebellar atrophy; OPCA) [32]. Neuronal loss is usually also present in the autonomic nuclei of the hypothalamus and brainstem and in the intermediolateral columns and Onuf's nucleus of the spinal cord, resulting in autonomic symptoms [32]. Central sleep apnea is likely due to degeneration of respiratory centers in the brainstem [33]. Prominent inclusion body pathology in MSA occurs in CNS oligodendrocytes as perinuclear crescent-shaped structures called glial cytoplasmic inclusions (CGIs, also known as Papp–Lantos bodies) [34]. GCIs occur in CNS regions undergoing neurodegeneration in MSA and are found in both MSA-P and MSA-C. Interestingly, GCIs are composed of aggregates of the protein α-synuclein [35], which is also a major component of Lewy bodies, the neuronal cytoplasmic inclusion body of PD. The origin and consequences of oligodendroglial α-synuclein accumulation in MSA are controversial.

Genetics

MSA is a sporadic disease, and pathologically proven cases with clear monogenic Mendelian inheritance have not been described. A recent large unbiased GWAS study in samples from sporadic MSA cases of European ancestry found no significant associations after stringent correction for multiple comparisons [36].

Voice-, Airway-, and Swallow-Specific Symptoms: Findings or Sequela

Voice Ataxic and spastic vocal features predominate over hypokinetic features [13]. Ataxic dysarthria is characterized by fluctuations in pitch and intensity. With prolonged exposure, listeners are often able to understand ataxic speech better than hypokinetic speech, which may explain the perception of dysarthria in MSA being rated as less severe than in PSP, even though many markers of dysarthria are greater in MSA [37].

Airway Sleep-disordered breathing is common in MSA. Over half of patients have obstructive sleep apnea (OSA) or central sleep apnea (CSA), with OSA being more common. Of those with OSA, approximately 10% eventually develop CSA [38]. Most patients have REM sleep behavior disorder [31]. About one-third of patients have nocturnal stridor, which is a frequent cause of death in MSA if left untreated.

Dysphagia Dysphagia has been identified as an early symptom of MSA, which implies that it is either more common than in other neurological disorders or that awareness is greater than in other parkinsonian disorders [39]. Dysphagia symptoms begin around 3 years after onset of MSA symptoms, with no difference in latency between patients with MSA-C and MSA-P [38]. About 75% of patients eventually have dysphagia complaints [15]. The characteristics of swallowing deficits in patients with MSA may differ between clinical subtype.

Oral Phase Oral phase dysphagia is prominent in MSA. Prolonged oral preparation, incomplete mastication, oral holding, and lingual residue are typical findings on instrumental swallowing examinations. Delayed bolus transit is common 1–3 years following onset of MSA symptoms but becomes nearly universal by 7 years. Tongue pressures in both MSA-P and MSA-C cases are lower than normal controls. Patients with MSA-P demonstrated longer oropharyngeal transit times and more difficulty propelling the bolus posteriorly in the oral cavity than patients with MSA-C, correlating with more severe oral phase complaints, such as increased meal time, drooling, sensory changes in the oral cavity, and difficulty with mastication [38]. MSA-C patients demonstrated discoordinated oropharyngeal bolus transit but not obviously prolonged AP transfer within the oral cavity.

Pharyngeal Phase Two-thirds of patients have either laryngeal penetration or aspiration on videofluoroscopic study, with no difference noted between MSA subtypes [38]. Vallecular residue was the most common finding on videofluoroscopic study (90%). Vallecular residue is more severe in patients with MSA-P, likely due to reduced base of tongue retraction and poor ability to form and transfer a cohesive bolus. Upward movement of the laryngeal complex during swallow is also slowed, although hyolaryngeal elevation was not found to be reduced in either the superior or anterior planes. Patients with MSA-C had more frequent aspiration symptoms, such as coughing, throat clearing, etc., than patients with MSA-P, suggesting these instances of laryngeal penetration and aspiration were likely more related to oropharyngeal transit, discoordination, and delayed laryngeal elevation and closure.

Esophageal Phase Upper esophageal sphincter opening seems to remain stable throughout the course of MSA [40] and thus is not a factor in dysphagia.

Pharmacology/Medical Management

Management of MSA is symptomatic and includes fall prevention, treatment of complications such as sialorrhea, and cervical dystonia with botulinum toxin injections. Bradykinesia and rigidity in approximately 30% MSA-P patients show a significant response to L-DOPA, although high doses may be necessary, and this commonly precipitates unusual craniofacial dyskinesias. Orthostatic hypotension is managed by compression stockings, increased salt intake,

pyridostigmine, fludrocortisone, or midodrine. Urinary incontinence can be managed by antimuscarinic medications or catheterization depending the underlying mechanism.

Voice-, Airway-, and Swallow-Specific Procedures: Treatment Outcomes

Voice Vocal fold motion impairment is common with the progression of MSA [41]. The etiology is unclear, but a laryngeal examination is recommended for all patients with MSA. Decreased or absent bilateral vocal fold motion is likely a contributing factor to hypophonia, nocturnal stridor, and OSA. The presence of decreased or absent vocal fold motion is a relative contraindication for vocal fold augmentation (injection, laryngoplasty) due to the risk of further airway compromise.

Airway Previously, tracheotomy was the recommended treatment for nocturnal stridor. However, more recently, continuous positive airway pressure (CPAP) has been found useful in the nonsurgical management of stridor [42, 43]. Different variations of CPAP can help to address stridor, OSA, and to a less extent CSA [44], but CPAP is ineffective for central hypoventilation. A formal sleep evaluation and appropriate treatment is recommended in the care of MSA patients.

Dysphagia Dysphagia in MSA can cause significant difficulties with nutrition, hydration, and airway protection. There is no evidence showing swallowing therapy to be beneficial. Periodic swallowing evaluations (videofluoroscopy or FEES) are recommended to guide appropriate compensatory strategies, which often change as the disease progresses. Transition to a softer diet is often necessary as mastication and oral transfer deteriorate. Thickened liquids are recommended as posterior oral control and incoordination become challenging. Enteral nutrition is often needed as swallowing function deteriorates. Attention to oral hygiene is recommended. Coordinated care with a speech language pathologist can help the patient and their caregivers to understand the signs of aspiration. Compensatory swallowing strategies and diet modifications can maximize swallowing safety, thus reducing the risk of aspiration pneumonia.

Frontiers

A variety of therapeutic interventions directed at different aspects of MSA pathogenesis, and supported by preclinical studies, showed no evidence of efficacy. Evaluation of active immunization against α-synuclein is currently in progress after promising results in preclinical studies [45]. A recent phase 3 randomized clinical trial found that droxidopa, a norepinephrine precursor, significantly reduced orthostatic symptoms compared to placebo [46]. This drug is now FDA approved for treating neurogenic orthostatic hypotension in adult patients.

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