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Diagnosis and Management of NEURODEGENERATIVE ATYPICAL PARKINSONISM

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"Parkinsonism" and "parkinsonian" are terms broadly used to describe the motor features (i.e., bradykinesia, rigidity, resting tremor) typically associated with idiopathic Parkinson's disease (PD). While there are other causes of parkinsonism (e.g., drugs that block dopamine receptors, cerebrovascular disease), the neurodegenerative diseases that can cause parkinsonism are deserving of deeper consideration.* These conditions, frequently referred to as the atypical parkinsonian—or Parkinson's plus—syndromes (APS), include dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Early in the course, APS can be easily misdiagnosed as idiopathic PD because of the symptom overlap, lack of objective diagnostic biomarkers and, for some patients, a symptomatic improvement with levodopa. Waning medication benefit, development of additional characteristic signs and symptoms, and more rapid progression of disease may eventually differentiate these conditions from PD, although this can take years. Diagnosis is based solely on history and physical examination but ancillary testing—specifically neuroimaging—may support clinical impression and/or exclude conditions that may require (or respond better) to other treatments. Structural imaging (CT or MRI), for example, may reveal vascular disease or normal pressure hydrocephalus (both of which may present with clinical features similar to those seen in neurodegenerative parkinsonism). MRI may be normal or show mild diffuse atrophy in PD or DLB but demonstrate distinct patterns of atrophy in the other APS, particularly with advancing disease (e.g., midbrain atrophy in PSP). DaTscans, which approximate the presynaptic binding activity of dopamine transporters, may be helpful to distinguish neurodegenerative (PD or APS) from drug-induced or vascular forms of parkinsonism or essential tremor, but cannot differentiate among APS, or between them and PD.

Definitive diagnosis of APS can be made only through neuropathological confirmation, the hallmark of which is intracellular protein deposition. Abnormal accumulation of alpha-synuclein is characteristic of PD, DLB, and MSA (the synucleinopathies); tau protein aggregates in PSP and CBD (the tauopathies).[1] The clinical relevance of differentiating synucleinopathies from tauopathies requires further study, but certain generalizations (e.g., the correlation of synucleopathies with premotor symptoms and autonomic dysfunction) may help clinicians focus on potentially relevant aspects of the history and physical examination and thereby narrow the differential diagnosis.

Regardless of diagnosis, however, no disease-modifying therapy has been demonstrated effective for any of the APS, so management is symptomatic and supportive. A variety of drugs are utilized to target individual symptoms—levodopa being the first-line for parkinsonism—and physical, occupational and speech therapy are often beneficial adjunctive treatments for motor and bulbar symptoms. These conditions represent a diagnostic and therapeutic challenge that demands a careful and comprehensive approach.

Synucleinopathies (DLB and MSA)

Multiple System Atrophy

Clinical Features. MSA often presents in the sixth decade with parkinsonism (MSA-P) but may, less commonly, occur in an alternate form characterized by cerebellar dysfunction (MSA-C).[1] Both subtypes are associated with autonomic dysfunction.[1,2] Parkinsonism, which tends to be—but is by no means exclusively—symmetric, manifests as bradykinesia with rigidity, gait and postural instability, and/or tremor. Tremor, if present, is more apt to be irregular and may be greater with posture and action rather than rest.[3,4] Autonomic symptoms, which often precede motor symptoms, include orthostatic hypotension (OH) and urinary and/or erectile dysfunction (ED). Although PD patients can experience dysautonomia, that associated with MSA usually (but not always) presents earlier in the disease course and is more severe. OH due to autonomic impairment is demonstrated by a blood pressure drop upon arising (SBP > 20 mmHg and DBP > 10 mmHg) without the compensatory heart rate increase seen in patients who are simply volume depleted or treated with alpha-adrenergic blockers. It may be exacerbated by dopaminergic medications (i.e., levodopa or dopamine agonists). Genitourinary problems increase with aging, making ED and urinary disturbances nonspecific, but normal function of either would make MSA less likely.[4] Symptoms are more severe in MSA (versus PD) and the type of urinary dysfunction is different—in PD it is most often frequency and urgency, whereas in MSA it is retention.[4,5,6]

Additional supportive features include characteristic postural abnormalities (e.g., lateral spinal flexion and/or disproportionate anterocollis), early bulbar dysfunction (e.g., dysphonia, dysarthria, dysphagia), and nighttime laryngeal stridor. Mild cognitive impairment involving memory and executive function may also be seen but dementia appears to be less common than in PD and is certainly not a fundamental feature as it is at some stage in most of the other APS.[7]

MSA progresses over an average of six to 10 years and death typically results from aspiration pneumonia or nocturnal cardiorespiratory arrest.[1,2]

Diagnosis. Diagnostic criteria for MSA, revised in 2008, provide guidelines for making a diagnosis on three levels of certainty—possible, probable or definite. At the core, MSA is an adult-onset (age greater than 30 years), sporadic, and progressive condition. Depending on whether it is possible or probable MSA, symptoms of autonomic failure, poorly levodopa-responsive parkinsonism or a cerebellar syndrome, and/or a characteristic clinical or neuroimaging abnormality are required.[4] Definite MSA can be diagnosed only by neuropathological examination, which demonstrates degeneration of striatonigral and olivopontocerebellar structures along with profuse alpha-synuclein-positive glial cytoplasmic inclusions.[4]

Based on whether MSA is of the parkinsonian or cerebellar subtype, the brain MRI may show focal atrophy of the putamen, middle cerebellar peduncles, lower portion of the basis pontis, medulla and cerebellar hemispheres. T2 hyperintensity can also be seen in the basis pontis—the "hot cross bun sign"—and in the posterolateral putamen.[8,9] Structural changes may, unfortunately, be most evident when disease is well-established and diagnosis is no longer in doubt.[4] Therefore, neuroimaging can typically support clinical suspicion, but not render an actual diagnosis. Autonomic function testing may be similarly helpful to aid with diagnosis and could also potentially serve as a prognostic marker.[10]

Tauopathies (PSP and CBD)

Progressive Supranuclear Palsy

Clinical Features. The classical symptoms of PSP are postural and gait instability with falls, symmetric akinetic-rigid parkinsonism of the axial musculature, and vertical gaze paresis.[1,11] Imbalance, gait difficulties and a tendency to fall backwards are the first and the most frequent symptoms of the disease, with a mean age of onset in the early to mid-60s.[1,7] Gait is typically stiff and broad-based with truncal extension.[7] Limitation of voluntary vertical eye movements leads to falls when descending stairs (due to downgaze palsy coupled with neck extension) and difficulty reading (secondary to problems scanning text). Visual disturbances (e.g., diplopia, blurred vision, photophobia) are typical complaints at disease onset or within the first year.[3] Cognitive and/or behavioral changes—impaired executive function, loss of insight and apathy—usually begin within the first year as well.[11] Other common features include bulbar symptoms (e.g., dysarthria, dysphagia, pseudobulbar affect) and blepharospasm.[7]

Less frequently, PSP patients may exhibit an asymmetric, limb-predominant, levodopa-responsive parkinsonism (initially indistinguishable from idiopathic PD), pure akinesia with gait freezing (i.e., lack of rigidity or tremor), behavioral variant of frontotemporal dementia, progressive non-fluent aphasia or corticobasal syndrome (CBS). When (and if) vertical gaze palsy and postural instability and falls arise, these syndromes might be recognized as PSP. One exception is CBS, in which symptoms may remain clinically identical regardless of whether the underlying pathology is that of PSP or corticobasal degeneration.[1,11] (See below.)

Length of survival with PSP is an average of five to eight years; death is most often a consequence of aspiration pneumonia.[1,7,11]

Diagnosis. Consensus guidelines, created in 1996, denote that PSP is a gradually progressive disorder with onset at age 40 or later. Diagnoses of probable or possible PSP are based on the presence of oculomotor dysfunction (vertical supranuclear gaze palsy and slowing of vertical saccades) and prominent postural instability with a tendency to fall within the first year of disease onset.[11] Definite PSP is diagnosed histopathologically, when tau-positive neurofibrillary tangles in neurons and neuropil threads in neuronal processes, as well as accumulations of phosphorylated tau in astrocytes and oligodendrocytes, are found in a characteristic distribution throughout the brainstem and basal ganglia.[1,11]

Examination of eye movements typically reveals slowed vertical saccades, an intact vestibulo-ocular reflex and/or limited vertical gaze. A constricted downgaze is more specific for PSP (some limitation in upgaze occurs with aging and may be present in other neurodegenerative disorders).[11] Other supportive physical examination findings include a positive pull test (and often also a spontaneous tendency to fall), upper motor neuron signs, decreased verbal fluency, perseveration and frontalis dystonia.[1]

Brain MRI may show midbrain atrophy, third ventricular dilatation and an intact pons, giving rise to the classic "hummingbird" or "penguin" sign. Superior cerebellar peduncle atrophy and/or increased FLAIR signal are sometimes also visualized.[8,9]

Corticobasal Degeneration

Clinical Features. CBD is a neuropathological disorder that expresses at least four different clinical phenotypes. The most common is corticobasal syndrome (CBS) and the others are frontal behavioral spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA) and progressive supranuclear palsy syndrome (PSPS).[12,13] Symptoms usually arise in the sixth or seventh decade and progress over an average of six to eight years.[1,12] Death typically results from aspiration due to dysphagia.[1]

CBS is marked by motor symptoms—parkinsonism, dystonia and myoclonus—and lateralized cortical features.[12,13] The parkinsonism is a strikingly asymmetric levodopa-resistant rigidity and bradykinesia, predominantly involving one upper extremity. Dystonia usually produces a fixed posture in which the arm is adducted at the shoulder, and the elbow, forearm and hand are flexed. It often results in pain, secondary contractures, palm lesions and/or functional limitations.[13] Myoclonus may be focal, action or stimulus-sensitive; it can also be superimposed on tremor which, if present, is poorly characterized and usually unlike the classic resting tremor of PD.[1,12] Gait abnormalities, postural instability and falls also occur in CBS, but not typically in the early stages of disease.[12]

Cortical symptoms of CBS may include one or more of the following:[1,3,12]

- Apraxia, or impaired performance of learned, skilled motor acts despite intact sensory, motor and language function. Ideomotor apraxia, specifically impacting the limbs, is the most frequent form in CBS. Orofacial muscles can also be involved, though, especially later in the course.[14,15] Apraxia can be demonstrated by having patients perform a gesture (e.g., wave goodbye, use a hammer or blow out a match) although limb dystonia and parkinsonism can make accurate assessment challenging.[12]
- Alien limb phenomenon—involuntary motor activity of a limb combined with a feeling of estrangement from that limb.[15] Movements are typically complex, unintentional and interfere with normal tasks. The limb may be described as foreign or as having a will of its own.[12] If they occur, alien limb symptoms typically present an average of [12] months into the disease course.[12]

- Cortical sensory loss, or inability to correctly interpret sensation despite intact primary sensory modalities. This can manifest as impairment of two-point discrimination, astereognosis, agraphesthesia and/or extinction to double simultaneous stimulation.[1,16]
- Language impairments, such as aphasia or speech apraxia.
- Cognitive disturbances, predominantly in executive function, which range from mild cognitive impairment at disease onset to frank dementia in later stages, with preservation of semantic memory.[7] Behavioral changes and mood alterations may be associated.[12]

Diagnosis. CBD is a pathological diagnosis, characterized by widespread deposition of hyperphosphorylated tau in neurons, astrocytes and oligodendrocytes throughout the neocortex and basal ganglia.[1,12] Criteria for the diagnosis of CBD were updated in 2013 to characterize the multiple clinical phenotypes of CBD (listed above) and potentially enable pre-mortem recognition of the disease. (This is in contrast to diagnosing CBS—a clinical syndrome with multiple underlying pathologies, including CBD, PSP and others.) The CBD guidelines specify an insidious onset of disease and minimum duration of one year along with gradual symptom progression. Age, family history of neurodegenerative disease, presence of tau genetic mutations, and specific symptoms characteristic of the individual CBD phenotypes are considered to make diagnoses of probable or possible CBD.[3.12]

Supplementary testing cannot diagnose CBD syndromes or CBS but could provide supportive evidence. In CBS, brain MRI may demonstrate asymmetric atrophy of the posterior frontal and parietal lobes, even in early stages of disease, and the lack of midbrain atrophy and basal ganglia changes may serve to differentiate it from PSP and other APS, respectively.[8,9] Neuropsychological testing might also be beneficial to delineate cognitive deficits.

Symptomatic Management of Atypical Parkinsonism

Parkinsonism. Despite the fact that benefit is transient and is usually modest at best, levodopa is the first-line therapy for parkinsonism in the APS. To adequately assess responsiveness, a trial of at least 1g/day levodopa (in combination with carbidopa) for a period of two to three months is recommended.[3,11] High doses may not be tolerated, however, and in MSA, levodopa is likely to exacerbate orthostatic hypotension and induce early orofacial dyskinesia or dystonia.[2,3] Dopamine agonists, amantadine and MAO-B inhibitors may be alternatives to levodopa, but these have variable, and oftentimes limited, efficacy and are frequently poorly tolerated.[1,2,3,13] Physical and occupational therapy (PT and OT) are important complementary components in the management of parkinsonism.

Dystonia. Botulinum toxin injections are a good option for focal dystonia—blepharospasm in PSP, upper extremity dystonia in CBD, and select cases of anterocollis and laryngeal stridor in MSA.[7] Systemic side effects are usually minimal and treatment response is high.[1] Oral agents (e.g., benzodiazepines, anticholinergics, muscle relaxants, baclofen) are rarely effective for dystonia in APS.[1,13] PT and OT can be helpful adjuncts to pharmacologic therapy.

Myoclonus. Myoclonus—most commonly encountered in CBD—can often be alleviated with benzodiazepines (especially clonazepam) but levetiracetam, gabapentin and valproic acid may be alternative options.[1,13]

Gait and Balance Impairment. Even before gait disturbances and postural instability are present or prominent, physical and occupational therapy may be beneficial. Early in the course of APS, therapists can teach patients exercises to help maintain strength, flexibility and mobility, as well as enhance the performance of activities of daily living. They can also instruct patients in fall prevention and assess the need for an ambulation aid (i.e., cane or walker, sometimes weighted for PSP patients). In later phases of disease, therapists can perform home safety evaluations (and propose modifications and/or adaptive equipment to make daily routines safer and easier), train caregivers in range of motion exercises and direct proper wheelchair selection, if required.[13]

Speech and Swallowing Disturbances. Speech therapists can treat language dysfunction with speech exercises and suggest devices to facilitate communication. Dysphagia is addressed with recommendations for appropriate dietary consistency, behavioral adjustments at mealtimes, and/or

techniques to promote adequate nutrition and reduce the risk of aspiration. Percutaneous endoscopic gastrostomy (PEG) tubes are not always necessary, but it is generally worthwhile to consider them proactively rather than after choking or overt aspiration has occurred, as these can result in potentially fatal pneumonia. Raising the possibility of a PEG tube early allows the patient and caregiver ample time to make an unpressured and informed decision regarding the therapy.

Dysautonomia. The autonomic symptoms of MSA are individually targeted in efforts to improve quality of life and maximize overall care (i.e., untreated orthostatic hypotension would undoubtedly worsen gait disturbances and postural instability).

Erectile Dysfunction. Medications (such as sildenafil) may be prescribed but those with symptomatic OH must be instructed to remain supine during intercourse and for the subsequent four hours. Intracavernosal injections of papaverine or prostaglandin E1 are alternative options.[2]

Urinary Dysfunction. Urinary urgency, frequency and/or incontinence with postvoid residual less than 100 mL (i.e., detrusor hyperactivity) are often treated with anticholinergics but the side effect profile of these agents may limit use, especially in the elderly.[2] Other considerations may include mirabegron (Myrbetriq)—a beta-3 adrenergic receptor agonist, detrusor muscle botulinum toxin injections or electrical stimulation (i.e., TENS units or implanted neurostimulators). Nasal desmopressin is occasionally utilized off-label to limit nocturia and increase morning blood pressure; hyponatremia and water intoxication are potential adverse effects.[2]

Urinary retention (i.e., postvoid residual greater than 100 mL) may necessitate intermittent self-catheterization to prevent urinary tract infection. Alpha-adrenergic antagonists are rarely used because of their potential to exacerbate OH.

Orthostatic Hypotension. The initial treatment of OH is non-pharmacologic:[5,6]

- discontinuation of blood-pressure lowering drugs (e.g., antihypertensive agents, diuretics, alpha-adrenergic blockers for prostatic hyperplasia)
- avoidance of precipitating factors (e.g., sudden position changes, large meals, alcohol and heat)
- dietary modifications, including the addition of salt to meals (10-20 g/day) and increased water and fluid intake (eight or more 8-ounce glasses per day)
- physical activity (i.e., regular exercise—without excessive perspiration—to prevent deconditioning and performance of countermaneuvers, such as 30 seconds of thigh muscle contraction, when symptomatic or with prolonged standing)
- daily application of abdominal binders and/or thigh or waist-high compression stockings

If the above are inadequate, pharmacological therapy is added. The most commonly prescribed medications are fludrocortisone (synthetic mineralocorticoid and plasma volume expander), midodrine ([1]-adrenoreceptor agonist), droxidopa (norepinephrine precursor) or pyridostigmine (cholinesterase inhibitor).[2,5,6] Supine and nighttime hypertension (a potential risk primarily with the first two drugs) can be avoided by administering the last medication dose more than four hours prior to bedtime and holding if supine or sitting blood pressure is greater than 180/100 mmHg.[2,5] It can also be managed with a short-acting nighttime anti-hypertensive. Electrolytes should be monitored while on fludrocortisone.

Pseudobulbar Affect. The pseudobulbar affect (inappropriate laughing and crying) of PSP may respond to combination drug therapy with dextromethorphan/quinidine.

Visual Disturbances. Oculomotor deficits are especially challenging to treat. Zolpidem was found to improve voluntary saccadic eye movements in a small group of patients[7] and amitriptyline reportedly affords a mild to moderate symptomatic improvement in about one-third of patients.[1]

Cognitive Impairment. For prominent cognitive dysfunction and dementia, cholinesterase inhibitors and memantine are sometimes tried based on experience with these drugs in related diseases, but their role in APS is still unclear.

Mood and Behavioral Symptoms. Mood disturbances could include depression and/or anxiety; these may respond to one or more of the following: cognitive behavioral therapy, selective serotonin reuptake inhibitors (SSRIs) or mood-stabilizing agents. Symptoms such as apathy are often more

difficult to treat and may require lifestyle adjustments (e.g., maintaining sleep and daytime schedules, exercising regularly) rather than medication management. Psychosis (mainly visual hallucinations and/or paranoid delusions) may incite personality changes or aggressive behavior, particularly in DLB. Symptoms of psychosis are particularly challenging to treat. As dopaminergic medications can contribute, these are first adjusted if possible. Oftentimes atypical antipsychotics are then prescribed, although these drugs can exacerbate parkinsonism.[13] Clozapine and low-dose quetiapine are least likely to worsen motor symptoms, but as clozapine can cause agranulocytosis (and therefore requires regular blood monitoring), most opt for quetiapine (despite the lack of convincing support for efficacy from randomized controlled trials).[17] At the time of this writing, pimavanserin—a 5-HT2A receptor inverse agonist—is under review by the FDA for approval to treat PD psychosis. A final decision is expected no later than May 1, 2016.

Conclusion

Neurodegenerative atypical parkinsonisms can pose a diagnostic dilemma for clinicians and a management challenge for clinicians, patients and families. Treatment of progressive neurodegenerative disease requires a holistic approach that encompasses the patient, caregiver and entire family unit. The type and level of care will, of course, change as ongoing symptoms advance and new symptoms develop.

Patients should be actively engaged in their care (e.g., shared decision-making regarding management, participation in exercise and social programs) as much as possible. If interested, they should also be offered the opportunity to contribute to research, which gives them an even more direct role in their disease and within the larger community of patients and researchers. (Available APS trials can be found on clinicaltrials.gov and soon also foxtrialfinder.org.) Caregivers play a crucial part in the management of patients with APS, and clinicians must routinely assess their levels of stress and ask about symptoms of caregiver burnout.

The care team must include allied healthcare professionals and palliative care specialists as soon as deemed necessary. Physical, occupational, and speech therapists can assist at nearly every stage of the disease and social workers can supply additional resources and support, particularly with regard to in-home care services, alternative living arrangements and long-term care. Palliative care specialists can help optimize symptom management, lend emotional and spiritual support, and coordinate communication among patients, families and providers in order to align the goals and directions of current and future care.

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**For a review of DLB, see the article entitled "Dementia with Lewy Bodies: In the News and In the Clinic" in the January/February 2015 issue of* Practical Neurology®, *available at practicalneurology.com.*