REVIEW OPEN ACCESS

A General Neurologist's Practical Diagnostic Algorithm for Atypical Parkinsonian Disorders

A Consensus Statement

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Abstract

Purpose of Review

The most common four neurodegenerative atypical parkinsonian disorders (APDs) are progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal syndrome (CBS), and dementia with Lewy bodies (DLB). Their formal diagnostic criteria often require subspecialty experience to implement as designed and all require excluding competing diagnoses without clearly specifying how to do that. Validated diagnostic criteria are not available at all for many of the other common APDs, including normal pressure hydrocephalus (NPH), vascular parkinsonism (VP), or drug-induced parkinsonism (DIP). APDs also include conditions of structural, genetic, vascular, toxic/metabolic, infectious, and autoimmune origin. Their differential diagnosis can be challenging early in the course, if the presentation is atypical, or if a rare or non-neurodegenerative condition is present. This review equips community general neurologists to make an early provisional diagnosis before, or in place of, referral to a tertiary center. Early diagnosis would allay diagnostic uncertainty, allow prompt symptomatic management, provide disease-specific information and support resources, avoid further pointless testing and treatments, and create the possibility of trial referral.

Recent Findings

We address 64 APDs using one over-arching flow diagram and a series of detailed tables. Most instances of APDs can be diagnosed with a careful history and neurological exam, along with a non-contrast brain MRI. Additional diagnostic tests are rarely needed but are delineated where applicable. Our diagnostic algorithm encourages referral to a tertiary center whenever the general neurologist feels it would be in the patient's best interest. Our algorithm emphasizes that the diagnosis of APDs is an iterative process, refined with the appearance of new diagnostic features, availability of new technology, and advances in scientific understanding of the disorders. Clinicians' proposals for all diagnostic tests for the APDs, including repeat visits, should be discussed with patients and their families to ensure that the potential information to be gained aligns with their larger clinical goals.

Summary

We designed this differential diagnostic algorithm for the APDs to enhance general neurologists' diagnostic skills and confidence and to help them address the less common or more ambiguous cases.

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Introduction

In 2017, CurePSP established its Centers of Care (CoCs) network with a mission to improve the quality and availability of care and support for progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and multiple system atrophy (MSA). The CoCs pursue this mission by providing state-of-the-art clinical care, collaborating to discover ways to enhance care and research, and educating other professionals both locally and globally. In 2021, the CoCs published a "best practices" consensus statement for clinical management of PSP and CBS,[1] but that document did not address diagnosis, a complex and rapidly changing area.

CurePSP's recent anonymous, online, community survey of 234 patients and care partners with Atypical Parkinsonian Disorders (APDs) revealed that the most important perceived barrier to care was lack of familiarity with APDs on the part of medical professionals, followed by the lengthy process to diagnosis.[2] Latencies from symptom onset to even a recorded suspicion of PSP, for example, can average 3–4 years,[3] about half of the average survival duration postonset.[4] Wait times for subspecialists can be especially long, and access is even more difficult for rural, socioeconomically disadvantaged, and underinsured populations. Furthermore, until we have better diagnostic markers, diagnosis of the APDs will remain largely an iterative process requiring multiple visits that may be inconvenient or impossible if they must occur at a distant academic center.

This project attempts to equip community general neurologists or subspecialists outside of movement disorders or behavioral neurology to provide at least a provisional diagnosis to allay uncertainty, allow prompt symptomatic management, provide disease-specific information and support resources, avoid further pointless testing and treatments, and create the possibility of trial referral.[5-7] The last can be implemented using contact information in clinicaltrials.gov, curepsp.org, michaeljfox.org/trial-finder, or other sources.

APDs include not only neurodegenerative diseases but also conditions of structural, genetic, vascular, toxic/metabolic, infectious, and autoimmune origin. Their differential diagnosis is challenging, especially early in the course.[7-9] Among the neurodegenerative conditions, PSP, MSA, CBS, and dementia with Lewy bodies (DLB) are the most commonly recognized. Their formal, published diagnostic criteria often require subspecialty experience to implement, and all require excluding competing diagnoses without clearly specifying how to do that.[10-12] For these reasons, the formal criteria have largely been relegated to research use. Validated diagnostic criteria are not available for many of the other common APDs, including normal pressure hydrocephalus (NPH), vascular Parkinsonism (VP), or drug-induced Parkinsonism (DIP).

To replicate real-world diagnostic dilemmas, we include conditions of all pathogenetic classes.[13-15] We do not discuss each disorder or diagnostic test in detail. Rather, our algorithm is oriented around the many clinical features that might prompt a suspicion of an APD. We then provide guidance on the predictive value of each feature in ruling each candidate diagnosis in or out and suggest any ancillary tests. The Figure and Tables can be used as a convenient reference, while the text provides additional instructions and serves as a more in-depth review.

Methods

General Comments

The authors form the Diagnosis and Treatment Working Group of the CurePSP CoCs. Most are academic subspecialists in movement disorders or cognitive/behavioral neurology. We searched the PubMed, Cochrane, Medline, and Google Scholar databases for articles published in English since 2013 on the differential diagnosis of the Parkinsonian disorders, using keywords "diagnosis" and "atypical parkinsonism" OR "Parkinson-plus" OR "PSP" OR "CBS/CBD" OR "MSA" OR "DLB" and expanded the references in online meetings. Next, a writing committee comprising authors MB and LG drafted the Figures and Tables and submitted them to 3 rounds of comments from the coauthors. The writing committee then drafted the text to conform to the algorithm and submitted it for edits by the coauthors. Finally, we asked 3 academic general neurologists for comments and implemented most of their suggestions.

We included disorders presenting in adulthood in which motor parkinsonism develops in most cases at some point. We included very rare disorders only where some action by the physician could help the patient or family.

As shown in the Figure, we advise clinicians to consider subspecialty referral at any point in the diagnostic process. If the undiagnosed patient's progress is unusually rapid, we advise to visit every 1 or 2 months or an inpatient work-up.

Overall Strategy of the Algorithm

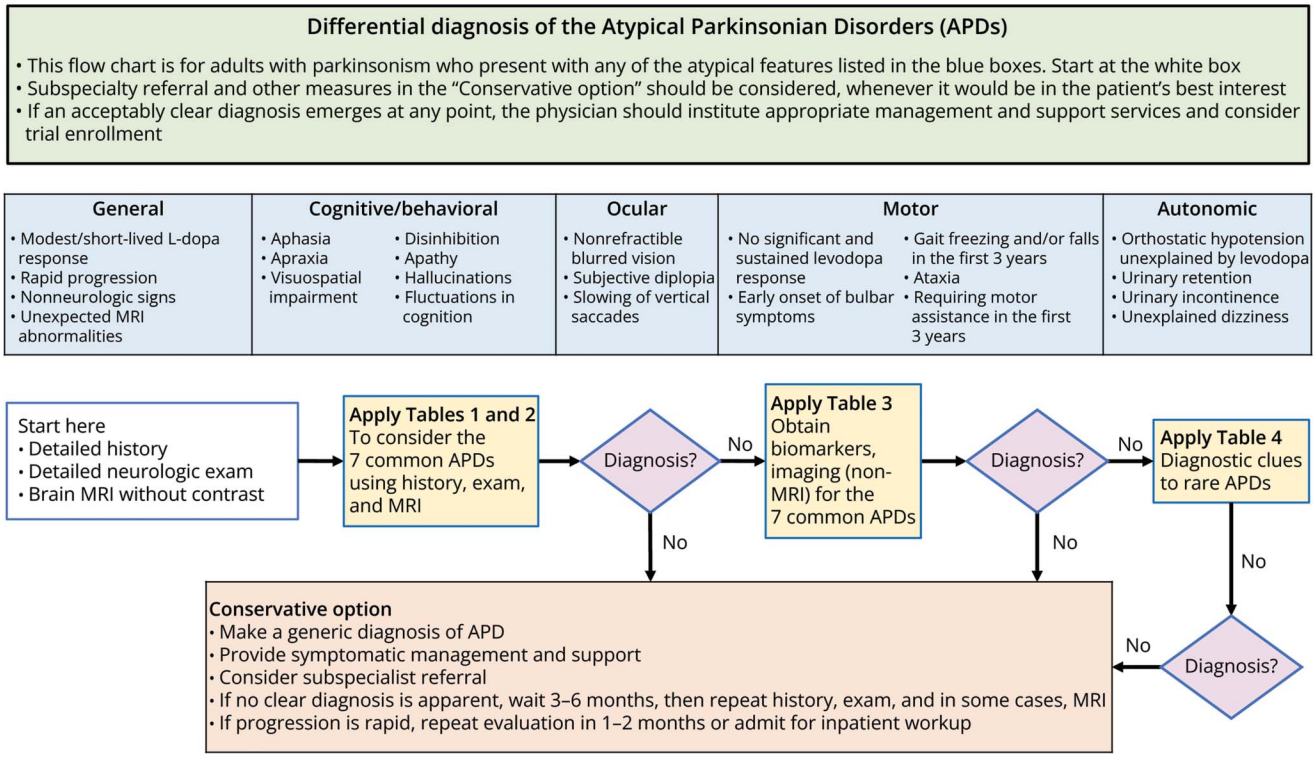
The Figures and Tables are designed to be self-explanatory. However, the following section presents the pathophysiologic, clinical, and epidemiologic justifications for our recommendations, with emphasis on the 7 APDs most relevant to the general neurologist.

The Figure's green box lists general strategy. The blue box lists features atypical for PD that should prompt use of the algorithm. They are divided into 5 categories:

General Features

The most common reason to suspect an APD in a patient with an existing diagnosis of PD is a modest or short-lived response to levodopa. Published MDS-PD,[16] MDS-PSP,[9] and MDS-MSA[10] criteria differ slightly on the definition of levodopa responsiveness, but a typical definition is failure of

Figure Differential Diagnosis of the Atypical Parkinsonian Disorders (APDs)



the UPDRS III motor score to improve at least 25% after 1–2 months of levodopa ≥1,000 mg per day.[17]

We list certain "nonneurological features" as predictors of an APD. They are rare in the overall APD population but may have high positive predictive values. Similarly, we mention "unexpected MRI abnormalities" as suggesting an APD rather than PD. Some of these can precede clinical signs and symptoms suggesting an APD. Perhaps the most salient example is normal pressure hydrocephalus (NPH). This is further detailed in Table 2.

Cognitive/Behavioral Features

These are common early in PSP and CBS as well as in DLB. Predominant impairment of episodic memory is more suggestive of AD, and predominant visual hallucinations or fluctuations in alertness suggest DLB.[12] PSP's cognitive presentation is characterized as frontal or behavioral dysfunction and includes apathy, bradyphrenia, executive dysfunction, impulsivity, disinhibition, perseveration, socially inappropriate behaviors, motor recklessness, palilalia, and echolalia. The applause sign,[9] an inability to limit the number of claps to the 3 demonstrated by the examiner, occurs in many disorders with frontotemporal dysfunction,[18] as does pathologic laughter and crying.

CBS may present with focal, usually highly asymmetric cortical dysfunction, including visuospatial impairment, frontal syndrome, aphasia (primary progressive aphasia), apraxia (ideomotor, limb, speech, and gait), cortical sensory loss, and alien limb syndrome. Neurocognitive testing may be helpful in differentiating the cognitive pattern of APDs. Patients with NPH and VP may present with varying degrees and types of cognitive dysfunction.

Ocular Features

Problems in fixation, ocular motility, or eyelid control can produce blurred vision, double vision, nonspecific reading difficulty, ptosis, photophobia, dry eye sensation, and apraxia of eyelid opening. Square wave jerks and decreased saccadic speed and amplitude, worse vertically than horizontally and worse downward than upward, are common in early PSP and occasionally in CBS even before limitation of voluntary gaze. In "round the houses" sign, the eyes are unable to make pure vertical saccades, taking a curved path instead.[19] Difficulties with downward saccades can also be elicited on optokinetic nystagmus testing. MSA may produce cerebellar ocular motor abnormalities such as sustained gaze-evoked nystagmus, macrosquare wave jerks, and hypermetric saccades. Both PSP and MSA can display "eyelid opening apraxia," an inability to voluntarily initiate eyelid opening after a period of lid closure, possibly a form of dystonia called pretarsal blepharospasm.

Motor Features

PSP, especially the Richardson syndrome phenotype (PSP-RS), often presents with falls unexplainable by the patient's

neurologic findings. Patients with MSA-cerebellar type (MSA-C) can also experience falls early in the course, but in the setting of ataxia or orthostatic hypotension. Typical pill-rolling tremor is uncommon in APDs. Tremor in MSA-parkinsonism (MSA-P) is often of higher frequency and lower amplitude, often with a jerky, stimulus-sensitive, myoclonic quality. In general, a decrement in amplitude over a few seconds of finger-tap or handwriting is characteristic of PD, while the initial loss of amplitude does not worsen during the task in the degenerative APDs. Parkinsonism tends to be more symmetric in PSP and MSA and progresses faster compared with PD, although PSP-parkinsonism and MSA-P can be clinically indistinguishable from PD,[13] especially early in the course. CBS strongly tends to have a very asymmetrical presentation with limb dystonia and myoclonus.

Rigidity and bradykinesia of APDs are less responsive to levodopa than in PD, although patients with DLB, PSP-P, MSA-P, postencephalitic parkinsonism, and anatomical lesions of the substantia nigra can respond. Levodopa-induced dyskinesia is far less common than in PD, but MSA-P can produce levodopa-induced orofacial dystonia without limb dyskinesia.[11] Cerebellar limb ataxia and hypermetria are common in MSA-C and may also occur in MSA-P.

Gait ataxia, primary freezing of gait, apraxic gait, and severely impaired balance early in the disease all suggest an APD. The gait in PSP is irregular and stiff, with a broad base, extended knees, and abducted arms, with a major impulsive component. In MSA-C, ataxic gait occurs early on. Those with NPH can present with gait apraxia in many forms, especially the "magnetic gait," where the feet slide along the floor.[20] The gait of VP is also pleiomorphic, with freezing or apraxia.[21] In MSA, axial dystonia in the form of Pisa syndrome, with lateral bending, or camptocormia, with forward flexion at the neck or trunk, is very common.[11]

Early bulbar dysfunction in the form of dysphonia, dysarthria, or dysphagia can occur early in the APDs. Hypokinetic and spastic dysarthria, slow or strained speech, low or high volume, and harsh dysphonia may occur in PSP,[22] as can stuttering, echolalia, and involuntary vocalizations. Speech in MSA-P is characterized by a mixed spastic, hypokinetic dysarthria, or dysphonia. MSA-C patients in early stages can have staccato speech or cerebellar "scanning" speech.

APDs may display prominent facial dystonia, contrasting with the slack facies of PD, as well as cervical dystonia, although facial contortions may occur in advanced PD as a form of motor complications of levodopa therapy. In PSP and CBS, common features are very low blink rates and evidence of facial hyperinnervation such as raised eyebrows and vertical wrinkles at the glabellar region.[23] Nuchal dystonia with disproportionate retrocollis or anterocollis is commonly seen in PSP and MSA, respectively.

Autonomic Features

PD may include early dysautonomia but more severe dysautonomia should raise suspicion for MSA. This includes neurogenic orthostatic hypotension (nOH) early on, severe urinary retention, incomplete bladder emptying, urinary incontinence, and erectile dysfunction.[10] Bedside orthostatic blood pressure (BP) measurement should be routine in suspected APD. nOH is defined as a drop in systolic (≥20 mm Hg) and/or diastolic (≥10 mm Hg) BP within 3 min of active standing from the supine position, with failure to increase the heart rate by at least 1 beat per minute for every 2 mm Hg drop in SBP.[24]

MSA often includes a cold sensation and cyanosis in acral areas such as finger, toes, and nose, with blanching on pressure and poor circulatory return. Patients with MSA may develop respiratory or laryngeal stridor. In NPH, urinary incontinence is a cardinal feature.[20]

History, Neurologic Examination, and Brain MRI

Once an APD is suspected, a detailed history, neurologic examination, and noncontrast brain MRI usually are adequate. The neurologic examination should include, in addition to the elements of the "standard" examination, evaluation of orthostatic blood pressure and pulse; frontal cognitive function; eye movements to a command rather than a following task; inspection for square wave jerks; nystagmus; and Kayser-Fleischer rings; testing for rigidity of all 4 limbs and neck; balance evaluation using the pull test with proper precautions; evaluation of cerebellar control in lowers and uppers; and observation of the gait with pivots.

Table 1 lists clinical features along with an indication of their predictive diagnostic importance for the 7 APDs most commonly encountered in clinical practice.

PSP: PSP-RS accounts for over half of all PSP and is the form originally described.[25] Other subtypes include PSP-parkinsonism, PSP with progressive gait freezing, PSP-frontal, PSP-ocular motor, PSP-speech/language, PSP-CBS, PSP-cerebellar (PSP-C), and PSP-primary lateral sclerosis (PSP-PLS). Formal criteria providing high levels of clinical certainty have not been published for some of the phenotypes, and a patient may satisfy descriptions of multiple phenotypes.[26] In their final stages, the phenotypes all converge over time to a PSP-RS picture.[25] We conclude that the application of the formal MDS-PSP criteria in everyday clinical practice poses challenges and recommend only that clinicians be aware of the diverse array of PSP phenotypes and their clinical evolution over time.

MSA: Cardiovascular autonomic findings in MSA and PD with OH overlap, but autonomic failure is often more severe and generalized in MSA.[24] Cardiac [^{123}I]metaiodobenzylguanidine (123I-MIBG) scintigraphy reflects postganglionic cardiac sympathetic innervation[27] but is unavailable in many centers. It shows a reduced myocardial signal in PD with autonomic

Table 1 Diagnostic Clues to the 7 Major APDs

	Features atypical for PD	PSP	CBS	MSA	DLB	NPH	VP	DIP
History								
Disease course	Major vascular risk factors or stroke history						++	
	Modest to moderate, or short-lived, levodopa benefit	+		+	++			
	Recent or current neuroleptic or other dopamine-blocking drug							++
Cognitive/behavioral	Speech and language impairment	+	++		++			
	Dream enactment without recall (RBD)			++	++			
	Visual hallucinations not otherwise explained				++			
Visual	Nonrefractible blurring or diplopia	++		+				
Motor	Unexplained falls within 3 y of onset	++		+				
	Asymmetric loss of "coordination" or alien limb		++					
	Dysphagia within 3 y of motor onset	++		+				
	Ataxia otherwise unexplained			++				
Autonomic	Orthostatic lightheadedness or syncope			++	+			
	Unexplained issues besides nOH, such as urinary changes, constipation, ED, temperature intolerance			++	+	+		
	Stridor			++				
Examination								
Cognitive/behavioral	Aphasia or other cognitive speech deficit		++				+	
	Impulsivity, manipulating objects	++		+				
	Palilalia	++						
Ocular motor	Vertical > horizontal gaze palsy, reduced speed/size of downward saccades, or curved downward saccades	++	+					
	Equally reduced upward and downward gaze, or upward worse		+	+	++	+	+	
	Apraxia of up or down saccades (difficulty initiating movement)	+	++				+	
	Square-wave jerks large and/or frequent	++		+				
	Blepharospasm, excessive blinking or photophobia	++		+				
Limb motor or sensory	Antecollis disproportionate to parkinsonism			++	+			
	Balance loss disproportionate to parkinsonism	++		++	+	+	++	
	Gait apraxia/frontal gait syndrome	+	+			++	++	
	Wide-based or ataxic gait without other obvious explanation	+		++				
	Asymmetric pyramidal signs		++				+	
	Asymmetric dystonia	+	++	+				
	Myoclonus		++	+	+			
	Asymmetric astereognosis		++		+			
	Asymmetric limb apraxia	+	++				+	

Continued

Table 1 Diagnostic Clues to the 7 Major APDs *(continued)*

	Features atypical for PD	PSP	CBS	MSA	DLB	NPH	VP	DIP
Autonomic	nOH, especially without compensatory tachycardia			++	++			

Abbreviations: CBS = corticobasal syndrome; DIP = drug-induced parkinsonism; DLB = dementia with Lewy bodies; ED = erectile disturbance; LOC = loss of consciousness; MSA = multiple system atrophy; nOH = neurogenic orthostatic hypotension; NPH = normal pressure hydrocephalus; PSP = progressive supranuclear palsy; RBD = rapid eye movement behavioral disorder; VP = vascular parkinsonism.
Predictive value of atypical features in a patient with a tentative diagnosis of Parkinson disease: +: modest; ++: moderate.

failure but not in MSA, where the defect is central. Lower urinary tract symptoms can be the initial manifestation of MSA. Elevated postvoid residual is the most specific sign of bladder dysfunction in MSA vs PD (but not PSP).[28]

CBS: The clinical entity called CBS can be caused not only by the pathologic entity called corticobasal degeneration (CBD, in 32%) but also by other pathologic entities, including PSP (31%), Alzheimer disease (AD) (20%), and low frequencies of others, including DLB, Creutzfeldt-Jakob disease (CJD), and cerebrovascular disease. Conversely, CBD may present not only with CBS (37%) but also with PSP-RS (23%), frontotemporal dementia (14%) AD-like dementia (8%), aphasia (4%), and other or mixed pathologies.[29] In the differential diagnosis of the APDs, CBS with underlying AD neuropathology can be detected by CSF assays for elevated total tau/phospho-tau protein, reduced aβ 42/40 ratio, and elevated a T-tau:aβ(1–42) ratio.[30] The positron emission scan for beta-amyloid is in routine research use and may enter clinical use soon. The current gradual emergence of monoclonal anti–beta-amyloid antibody treatment for AD will increase the need for patients with CBS to be evaluated for underlying AD pathology.

DLB: As part of the α-synuclein-associated disease spectrum, this entity closely overlaps both clinically and pathologically with PD dementia (PDD). DLB was initially distinguished from PDD by a history of cognitive/behavioral symptoms starting no later than 1 year after, and often even before, motor parkinsonism. Diagnostic criteria have been since refined[12] to include executive or visuospatial dysfunction, cognitive fluctuations, visual hallucinations, and REM sleep behavior disorder (RBD) as central features. RBD may present years before any other feature. Supportive clinical features include severe sensitivity to antipsychotic agents, postural instability, repeated falls, severe autonomic dysfunction, hypersomnia, hyposmia, nonvisual hallucinations, delusions, apathy, anxiety, depression, syncope, or other transient episodes of unresponsiveness.

Normal pressure hydrocephalus (NPH): This presents with a canonical clinical triad of magnetic gait, urinary incontinence, and dementia. Recent opinion has proposed that the triad be expanded to include parkinsonism. We included NPH, along with VP and DIP, among the leading APDs because of their prevalence in neurologic practice. All 3 have been nosologically controversial,[31,32] but all are relatively common and amenable to treatment or to secondary prevention in the case of VP.

NPH-like presentations are common in other APDs such as PSP, DLB, and VP. DaT scans have been reported to be abnormal in some patients with a clinical diagnosis of NPH, suggesting striatal-nigral degeneration, although normalization of DaT imaging after VP shunting has also been reported.[33] AD pathology and other neurodegenerative dementias are overrepresented in NPH, raising the possibility that NPH can somehow be a result of underlying neurodegenerative disease.[34]

VP: This diagnosis is frequently applied to patients with progressive ambulatory impairment (typically described as "lower-body parkinsonism") with poor levodopa response and abnormal white matter signal.[21] No widely accepted diagnostic criteria exist, however, and clinicopathologic studies show only modest correlation between MRI hyperintensities and microangiopathic brain disease.[32] Microvascular changes in the basal ganglia are frequent in the general population,[35] and the published prevalence of VP ranges from 2% to 29% of all parkinsonism, depending on population and criteria. A clear history of ischemic or hemorrhagic stroke in the substantia nigra or nigrostriatal pathway with unilateral parkinsonism, presynaptic nigral-striatal pathway damage, and abnormal DaT scan can be considered "pure" or "definite" VP.[36] However, the majority of patients carrying this diagnosis have bilateral deep cerebral white matter or basal ganglia lesions on MRI, with a normal DaT scan.[37] The motor parkinsonism is attributed to frontal lobe higher-level gait dysfunction or basal ganglia postsynaptic abnormalities. We recommend that any diagnosis of VP remains informal and that such patients receive constant vigilance for other APDs.

DIP: Parkinsonism may occur shortly after starting dopamine-blocking or dopamine-depleting medications, especially antipsychotics. It is readily reversible after the offending drug is reduced or converted to quetiapine or clozapine, antipsychotics with much less DIP risk. Patients are at increased risk of developing degenerative parkinsonism probably because a presymptomatic stage of the latter predisposes to the DIP.[38] DIP is usually but not always symmetric. Gait slowing is common but gait

Table 2 Brain MRI Findings in More (Bold) and Less Common Atypical Parkinsonian Disorders (APDs) With Diagnostic Candidates They Suggest

Finding	Diagnostic candidate
Structural lesions	
Midbrain or basal ganglia mass	Tumor
Lateral/3rd ventriculomegaly	Pineal region mass
Enlarged lateral and 3rd ventricles with normal sulci, widened Sylvian fissures and sulcal crowding at vertex	**NPH**
Thalamic T2 lesions	Mitochondrial disorders
Severe, multiple basal ganglia lesions	Wilson disease
Enhancing lesions in hypothalamus	Whipple disease
Stroke/vascular changes	
Marked vascular changes in basal ganglia or brainstem	**VP**
Multifocal vascular lesions, especially anterior temporal	CADASIL
Strokes in nonvascular distributions	Mitochondrial disorders
Other parenchymal signal changes	
Abnormal DWI signal in basal ganglia	CJD
Basal ganglia calcifications	Hypoparathyroidism
Inflammation of striatum	SLE/APLS/Sjögren
Limbic/extralimbic inflammation	Autoimmune encephalitis
Iron in dentate, basal ganglia, thalamus	Aceruloplasminemia, NBIA
Diffuse or multifocal white matter loss	B12 deficiency
Atrophy	
Asymmetric cortical atrophy	**CBS**
Medial temporal preceding frontal atrophy	FTD-ALS
Caudate and cortical atrophy	Juvenile HD, HD-like 2, lubag
Diffuse atrophy worst in basal ganglia	HIV
Cerebellar and/or pontine atrophy, putaminal iron deposition	**MSA**
Posterior fossa atrophy	SCAs, DRPLA
Posterior fossa atrophy with demyelination in middle cerebellar peduncle	FXTAS
Cerebellar atrophy or inflammation	Paraneoplastic cerebellar degeneration

Abbreviations: APLS = antiphospholipid antibody syndrome; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBS = corticobasal syndrome; CJD = Creutzfeldt-Jacob disease; DRPLA = dentato-rubro-pallido-Luysian atrophy; DWI = diffusion-weighted imaging; FTD-ALS = frontotemporal dementia-amyotrophic lateral sclerosis; FXTAS = fragile X-associated tremor/ataxia syndrome; HD = Huntington disease; MSA = multiple system atrophy; NBIA = neurodegeneration with brain iron accumulation; NPH = normal pressure hydrocephalus; PSP = progressive supranuclear palsy; SCA = spinocerebellar atrophy; SLE = systemic lupus encephalitis; VP = vascular parkinsonism.

freezing is rare.[39] DIP is not disproportionately associated with anosmia, orthostasis, or RBD. Clues to DIP may be sedation and tardive dyskinesia from the offending medication.

Table 2 lists the MRI abnormalities to be considered in both the common and rare APDs. In clinical practice, it is not uncommon to reach a specific diagnosis from an MRI, once APD is suspected.

In PSP, relatively sensitive and specific signs are striking midbrain atrophy in the form of the "hummingbird" sign (atrophy of dorsal midbrain in the midsagittal plane resembling a slim hummingbird's head and bill), "Mickey Mouse" sign (rounded rather than rectangular midbrain peduncles in the axial plane), and "morning glory" sign (concavity of the lateral margin of the midbrain tegmentum in the axial plane).[40] Certain quantitative measures improve the accuracy of the MRI here. The midbrain-pons ratio uses

Table 3 Biomarkers and Non-MRI Imaging for the 7 Major Atypical Parkinsonian Disorders

	PSP	CBS	MSA	DLB	NPH	VP	DIP
Widely available							
Dopamine transporter (DaT) SPECT	Usually positive	Sometimes positive	Usually positive	Usually positive	Usually negative	Usually negative	Usually negative
CSF amyloid/tau/p-tau for Alzheimer pathology	Unhelpful	Positive if AD pathology underlies the CBS	No clear value	Positive or negative	Unhelpful	Negative	Negative
Trial of large-volume LP or continuous drainage (see text)	Negative	Negative	Negative	Negative	Usually positive	Negative	Negative
Less available							
Autonomic testing (see text)	Usually negative	Negative	Positive	Positive	Negative	Negative	Negative
FDG PET or HMPAO SPECT	Bilateral frontal, insula, caudate and brainstem loss	Asymmetric frontoparietal, striatum, thalamus loss	Bifrontal putamen, pons, cerebellar loss	Bioccipital loss, cingulate island sign	Usually negative	Usually negative	Usually negative
Amyloid PET	Unhelpful	Positive if AD pathology underlies the CBS	Unhelpful	Positive if AD copathology present	Unhelpful	Unhelpful	Unhelpful
αS assays in CSF or skin	Usually negative	Usually negative	Usually positive	Usually positive	Insufficient data	Insufficient data	Negative

Abbreviations: FDG PET = fluorodeoxyglucose positron emission tomography; LP = lumbar puncture; PD = Parkinson disease; p-tau = phosphorylated tau; SAA = seed amplification assay; SPECT = single-photon emission-computed tomography; VDRL = venereal disease research laboratory test; αS = alpha-synuclein. Advised only if prompted by specific findings on history, examination, or MRI.

the anteroposterior width of those structures in the midsagittal plane to differentiate PSP-RS from MSA-P, given that MSA-P is associated with atrophy of the pons and sparing of the midbrain, a ratio opposite that of PSP-RS. In PSP, superior cerebellar peduncles (SCP) are atrophic in contrast to relative sparing of the middle cerebellar peduncles (MCP). The magnetic resonance parkinsonism index (MRPI) combines both ratios and can differentiate PSP-RS from MSA-P, PD, and VP, even very early in the course, before a diagnosis is possible using standard criteria.[40] However, the MRPI is limited by the difficulty in performing the measurements in the prescribed imaging planes and by a relative paucity of data on both the early-phase non-Richardson PSP and the differentiation of PSP from NPH.

In MSA, radiologic hallmarks are atrophy of the putamen (with signal changes indicating increased iron content), pons, MCP, and cerebellum, along with the "hot-cross bun" sign (a cruciform hyperintensity in the pons on T2 images) and increased diffusivity in the putamen and MCP.[10]

In CBS, neuroimaging typically shows asymmetric cortical and subcortical abnormalities, most commonly gray matter atrophy of peri-Rolandic and parietal regions encompassing premotor, motor, and sensory association cortex, and typically develops contralateral to the more affected side of the body.[41]

MRI imaging features of NPH include evidence of hydrocephalus, defined by an Evans index greater than 0.3.[31] Additional specific neuroimaging findings include disproportionate enlargement of the subarachnoid space (DESH) and tightening of the sulci over the midline convexity. CSF removal by large volume tap or lumbar drainage to test clinical response is essential for the diagnosis and the decision to pursue VP shunt surgery. However, there is no consensus on the optimal diagnostic procedure or on its criteria for positivity.

Table 3: Biomarkers and imaging.

For the APDs, diagnostic testing beyond the brain MRI should be undertaken only by clinicians familiar with the implications of the results in the APDs and their limitations. The laboratory pathologist or radiologist should not be relied on to provide the findings' implications for specific patients.

Serum: As a practical matter, by far the most commonly indicated fluid biomarkers in the differential diagnosis of the APDs are serum ceruloplasmin and copper and 24-hour urine

copper level to rule out Wilson disease in patients presenting before age 50 with any movement disorder. Other tests to be considered for younger patients with parkinsonism in appropriate settings (especially with dystonia) include serum thyroid and parathyroid hormone levels, blood smear for neuroacanthocytosis,[42] immunodeficiency virus (HIV) titer, and serum RPR. Reversible causes of parkinsonism with cerebellar ataxia can be revealed by tests of vitamin E, HIV, antinuclear antibodies (ANA), anti-gliadin antibodies, thyroid hormones, antiphospholipid antibodies, liver function, and autoimmune encephalitis antibodies (Table 4).

CSF: When autoimmune cerebellar ataxia with or without parkinsonism is suspected, CSF is routinely screened for cells, total protein, oligoclonal bands, IgG index, the Venereal Disease Research Laboratory test (VDRL), and PCR for Epstein-Barr virus (EBV) and *Varicella zoster* virus (VZV). For prion diseases such as CJD, CSF real-time quaking-induced conversion (RT-QulC) can be diagnostic and CSF 14-3-3 protein, neuron-specific enolase and tau are less specific. Many textbooks recommend ruling out Whipple disease in patients with suspected PSP because there can be a superficial clinical resemblance,[43] CSF *T. whipplei* DNA PCR can be diagnostic and antibiotics curative. However, few experienced movement disorders specialists with busy PSP referral practices have ever diagnosed such a case, and we do not recommend LP purely for this purpose in a patient with apparent PSP.

Emerging diagnostic methods such as CSF tau, total tau (t-tau), and phosphorylated tau (p-tau) have been validated as markers for AD but are not reliably altered in PSP. CSF/serum neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) are perhaps the leading biomarkers under study for differentiating the APDs from PD and from one another.[44,45]

DaT scan: This measure of nigral axonal integrity in the caudate and putamen can be investigated using different radiotracers. DaT density is reduced in PD, PSP, MSA, and DLB. The test may help distinguish DLB from AD.[46] PD and DLB show asymmetric loss, worse in the posterior putamen, while in PSP, DaT loss is more nearly symmetric, with a higher putamen-to-caudate ratio than in PD. In CBS, DaT can be normal or mildly affected.[44] The DaT scan can also help distinguish DIP and other nonneurodegenerative APDs from neurodegenerative and nigral structural causes.[38]

18F-fluorodeoxyglucose (FDG) PET and technetium 99m hexamethylpropyleneamine oxime (HMPAO) SPECT: FDG PET measures glucose metabolism and may be able to differentiate PD from APDs and to differentiate among APDs.[8,47] FDG PET is not available everywhere, and third-party payors vary in their coverage for this indication. A good substitute albeit with lower resolution is measurement of variations of cerebral blood flow and metabolism with SPECT imaging using 99mTc-HMPAO.[48]

Amyloid PET: This modality can identify Alzheimer pathology in CBS, although healthy elderly and patients with DLB, NPH, and VP can also give positive scans.[49] Its role in routine work-ups for APDs remains unclear, and we list it only to help neurologists remain alert to future developments.

Tau-PET is likely to become a clinically useful marker for PSP and CBD. Currently, the only FDA-approved tau tracer is 18F-flortaucipir, but it is approved only for the differential diagnosis of AD, is not widely available for clinical use, and is not sufficiently accurate in the diagnosis of non-AD tauopathy.[50] The next-generation tau tracers ^{18}F-THK5351, ^{18}F-PI-2620, and ^{18}F-APN-1607 have performed well in early-phase clinical trials for PSP and CBS and will soon enter pivotal, late-phase trials.[51] Seed amplification assays (SAAs) for tau are in an earlier stage of development.[52]

Skin biopsies: The immunohistochemical detection of phospho-α-synuclein in skin biopsies is direct evidence of synucleinopathy, and its topographic distribution may differentiate MSA from PD.[53] It is generally available in routine practice and requires only a bit of training.

Future tests for alpha-synucleinopathy: SAAs, including real-time quaking-induced conversion (RTqIC), are promising biomarkers for alpha-synuclein (α-syn) deposits in skin biopsies.[54] SAAs have also been successfully applied to detect misfolded α-syn in CSF, olfactory mucosa, submandibular gland biopsies, skin, saliva, and most recently, serum.[55] SAAs differentiate PD, DLB, and MSA from nonsynucleinopathic parkinsonism, although the diagnostic specificity depends on the kinetic features of amplification process of different α-syn fibril strains. The sensitivity and specificity of SAAs to detect MSA is slightly lower than for PD and DLB. Detection and differentiation of the synucleinopathies using CSF SAA represents a major advance and is becoming more widely adopted. PET tracers to detect brain alpha-synuclein are also in development.[56]

Table 4 is an overview of clinical characteristics of the less common APDs. Some are quite rare or limited to certain geographical regions or populations. However, this resource addresses the desire of neurologists to be thorough and to minimize unnecessary referrals.

Within each pathophysiologic entity, the diseases appear in descending order of estimated frequency as a cause of APDs, and we also list diagnostic tests to be considered. Some of the diseases have actionable implications, defined either as having specific available treatment directed at the pathogenesis or requiring specific management such as genetic counseling for monogenic disease[57] or prion transmission precautions. Early diagnosis of immune-mediated neurologic syndromes[58] is imperative because these are potentially treatable and may signal early-stage neoplasia. The movement disorders in these syndromes are typically accompanied or overshadowed by other signs such as encephalopathy, seizures, and neuropathy. The

Table 4 Rare Atypical Parkinsonian Disorders: Clinical Features Suggesting Various Pathogenetic Categories, With Differential Diagnosis and Diagnostic Tests to Consider

	Features atypical for the 7 major Atypical Parkinsonian Disorders								
Pathogenesis	Family history	Rapidly progressive	Multisystem	Neuropsychiatric	Ataxia prominent	Neuromuscular	Specific population	Diagnoses to consider (in approximate descending order of frequency)	Tests to consider
Autoimmune	x	x	x	x	x			Systemic lupus, Sjögren antiphospholipid syndrome, anti-NMDA, anti-IgLON5, anti-Hu (ANNA1), anti-Ri (ANNA2), anti-Caspr2, anti-CRMP5, anti-DPPX, anti-LGI1, anti-Ma, anti-GAD65, gluten ataxia	Serum: ANA, Sjögren anti-phospholipid, anti-gliadin antibodies encephalitis panel CSF: oligoclonal bands, IgG index autoimmune encephalitis antibodies
Degenerative				x			x	FTD/ALS spectrum, familial basal ganglia calcification, motor neuron disease with congophilic angiopathy, glial globular tauopathy, Guadeloupean tauopathy (Caribbean), lytico-bodig (Chamorro Guamanian)	EMG/NCS (for ALS/PLS)
Genetic	x		x	x	x	x	x	FTD with parkinsonism, Huntington disease, fragile-X ataxia syndrome, spinocerebellar ataxias 2, 3, 17, CADASIL dopa-responsive dystonia, choreoacathocytosis, DRPLA (Japanese), Haw River syndrome (US North Carolina African American), Lubag (Filipinos) mitochondrial disease, Niemann-Pick type C-3, Perry syndrome, Wilson disease aceruloplasminemia, genetic CJD, Huntington disease-like 2	Genetic testing Screen for Wilson with serum ceruloplasmin, 24-h urine copper Screen for NPC with serum cholestane triol or other oxysterol Blood smear for neuroacanthocytosis
Infectious		x	x	x		x		Creutzfeldt-Jakob disease, HIV, neurosyphilis, Whipple disease postencephalitic parkinsonism	Serum: RPR and HIV CSF: cell count/protein/glucose Viral tests *T. whipplei* PCR and RT-QuIC for prion disease
Metabolic		x	x			x		Hypothyroidism, vitamin B 12/folate deficiency, liver/renal disease, vitamin E deficiency, hypoparathyroidism, extrapontine myelinolysis	Serum: TSH vitamin B12, folate, chemistry/calcium vitamin E, parathyroid hormone
Toxic						x	x	Manganese, carbon disulfide, carbon monoxide, cyanide, methanol, organic solvents, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	

diagnosis relies on assays of antibodies against antigens in serum and CSF. Most commercial laboratories offer paraneoplastic and autoimmune panels. Those without specific treatment may benefit from prognostic counseling and potential referral to research opportunities. Patients with many of these conditions may benefit from referral to a specialist outside of movement disorders or even outside of neurology.

Not included in Table 4 is functional parkinsonism. Although functional movement disorders are not very rare, they rarely include parkinsonism. Their most important features are entrainable tremor, dystonia, non-Parkinsonian gait change, myoclonus, tics, pain, variability, distractibility, and sudden onset, especially after minor peripheral trauma.[59]

eTables 1–3 present the content on the rare APDs differently and in more detail. Although Tables 1-4 mimic the diagnostic process by starting from clinical findings, the 3 eTables start with the specific diagnoses, showing for each (rather than as groups) the leading diagnostic clinical features, the relative prevalence in a general neurology practice, and diagnostic tests beyond brain MRI. This level of detail is not necessary for the general neurologist; we present it only as an optional reference tool.

The "Conservative Option"

Our algorithm (Figure) offers the option of discontinuing the process and referring to a subspecialist at any point where it would be in the patient's best interest. This may occur, for example, at the point where the clinician's training and experience are insufficient to continue, or after the treatable APDs have been ruled out. An alternative is not to refer to a subspecialist but simply to offer a diagnosis of "atypical Parkinsonian disorder" along with the option to re-evaluate in 3–6 months or sooner if new features emerge or if progression in rapid. This may occur when the patient and family prefer to focus on symptomatic management and comfort, with no wish or ability to travel to a possibly distant subspecialist.[6,60] Patients suffering from dementia, far-advanced motor disability, or severe concomitant illnesses may prefer this option. For such patients, the neurologist must remain available and should encourage telephone reporting of any new clinical features as they emerge.

Conclusion

We emphasize that the diagnosis of APDs is an iterative process, refined with the appearance of new diagnostic features, availability of new technology, and advances in scientific understanding of the disorders. We cannot state strongly enough that for the APDs, a good history and neurologic examination, along with tincture of time, are the best diagnostic tests. It is also important to realize that "atypical atypicals" are not rare and that some patients' clinical features fall outside the canonical descriptions or published diagnostic criteria. Perhaps most important, we strongly advise that proposals for all diagnostic tests for the APDs, including repeat visits, be discussed with patients and their families to ensure that the potential information to be gained aligns with their larger clinical goals. These important points are just as easily applied by the general neurologist in the community as by the distant academic subspecialist.

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