DIAGNOSIS AND MANAGEMENT OF ATYPICAL PARKINSONIAN SYNDROMES

David J Brooks

Parkinsonian syndromes are characterised by slowness of initiation (akinesia), movement (bradykinesia), and thought (bradyphrenia), tremor at rest (3–5 Hz) and on posture (4–8 Hz), and extrapyramidal rigidity. It is now recognised that a number of diverse pathologies can manifest with these signs making clinical diagnosis complex, especially in early disease (table 1). By searching for certain clinical characteristics, however, and with the aid of physiological and radiological examinations, these syndromes can now be separated with a reasonable degree of specificity. To diagnose atypical parkinsonism, it is first necessary to be familiar with the spectrum of typical Parkinson's disease.

IDIOPATHIC PARKINSON'S DISEASE

Typical late onset idiopathic Parkinson's disease (IPD) is characterised by insidious onset, generally in one limb, spreading over 2–5 years to become bilateral. Clinical asymmetry is retained as the disease progresses over 10 or more years. Initially postural reflexes are spared but later balance difficulties emerge.

Tremor

Forty per cent of patients will complain of tremor at presentation and 80% will have an asymmetrical rest tremor evident on examination. This is best brought out by asking the patient to relax, close their eyes, and count down from 100 or by asking them to walk with their arms hanging freely. A 4–8 Hz postural tremor is as frequent as the characteristic 3–5 Hz rest tremor and generally more disabling, though often less embarrassing for the patient. Occasionally IPD presents as an isolated postural tremor, and clues that it may represent early parkinsonism rather than essential tremor are that the tremor tends to be late onset, start in one limb, and there is generally a latency of a few seconds when the arm is extended before the oscillation appears. A common cause of diagnostic confusion is the breakthrough "rest" component of severe essential tremor. This can be discriminated from the rest tremor of IPD as the amplitude of the breakthrough rest tremor associated with essential tremor is always reduced compared to that of the postural component, and the frequency is similar. In IPD the rest tremor has a higher amplitude and lower frequency than the postural component and suppresses on limb movement.

The tremor of IPD can affect the eyelids (blepharoclonus), jaw, chin, and legs, while essential tremor targets the head, voice, and upper limbs. Parkinsonian tremor is not associated with incoordination, is increased by anxiety, and abolished by sleep. Limb activity attenuates rest but increases postural tremor. Around 50% of rest tremors respond well to dopaminergic and anticholinergic agents, though rarely completely, and a minority are refractory. Postural tremors of IPD, like essential tremor, may respond to both β blockers and ethanol.

Rigidity

The rigidity of IPD is "lead pipe" in character—that is, constant throughout a full range of passive movement. If a postural tremor is superimposed it takes on a ratchet characteristic described as "cogwheel" rigidity. The presence of rigidity can result in complaints of muscular aching and stiffness of limbs and back and, in the absence of tremor, some cases may initially be referred to a rheumatologist in error. The majority of patients have rigidity on examination, especially if synkinesis of the opposite limb is performed; the increased tone is often unilateral at presentation spreading to become bilateral over 3–5 years, but maintaining an asymmetrical emphasis.

The rigidity initially targets limbs but later spreads axially. A predominant involvement of limb and trunk flexors leads to characteristic "dystonic" posturing with trunk, neck, and arm flexion, and foot inversion. The rigidity is abolished by sleep and in 80% of cases responds well to dopaminergic agents.

Slowness

Fifty per cent of IPD patients complain of slowing up at presentation. Writing becomes smaller (micrographia). Later on they develop difficulty washing, feeding, dressing, and turning in bed, but

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Table 1 Classification of Parkinsonism

Idiopathic Parkinson's disease	(Lewy body disease)
Genetic Parkinson's disease	α Synuclein mutations AD Parkin mutations AR UCHL1 mutations AD
Subcortical degenerations	Striatonigral degeneration Multiple system atrophy Progressive supranuclear palsy Corticobasal degeneration Guamanian dementia Huntington's disease Hallervorden-Spatz disease Pallidal atrophy
Cortical degenerations:	Alzheimer's disease Creuzfeldt-Jakob disease Hydrocephalus Hemiparkinsonism—hemiatrophy
Metabolic disorders:	Dopa responsive dystonia Wilson's disease Chronic liver failure Hypoparathyroidism
Basal ganglia lesions	Multi-infarct disease Tumours, Fahr's syndrome
Encephalitis	Encephalitis lethargica, Other viral infections
Toxins	MPTP, CO, hypoxia, Mn^{II}, CS_2, solvents, pesticides
Drugs	Dopamine receptor blockers (neuroleptics and vestibular sedatives), L dopamine depleting agents

MPTP, 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine; CO; carbon monoxide, Mn^{II}, manganese; CS_2, carbon disulfide.

these functions are rarely problematic at presentation. Loss of facial expression occurs early, causing social embarrassment, while decreased eye blinking, hypophonia, and impaired swallowing leading to sialorrhoea are later features. The slowness of IPD involves both initiation and execution of movements, particularly sequential and volitional actions. Characteristically the patient will perform finger–thumb opposition movements well a few times and then the amplitude will diminish and motor arrest may occur. A common clinical mistake is to allow the patient insufficient time to overcome their bradykinesia when testing power and so eliciting artefactual weakness. Limb bradykinesia generally responds well to dopaminergic agents.

Gait and postural reflexes
While gait is frequently slowed at presentation, this first manifests as a non-specific feeling of taking longer to get around or of one leg occasionally dragging or catching. Reduced arm swing on the affected side is usually evident. Later a tendency to shuffle develops, followed by gait initiation difficulties, freezing, and festination—involuntary acceleration while walking. At the same time, postural instability and retropulsion lead to difficulties turning and rising from a chair. While early slowing of gait responds to dopaminergic agents the later complications do not, though they may be helped by the presence of external cues—such as walking across lines or listening to a metronome ticking or marching music on a walkman tape.

Ocular movements
Pursuit eye movements are preserved though later may become hypometric with saccadic intrusion. Reflexive saccades to targets remain intact but formal testing of remembered saccades to an occluded target or anti-saccades

reveals slowing. A frank supranuclear gaze problem is rarely seen but has occasionally been described in association with diffuse Lewy body disease. Restricted voluntary upgaze and convergence can, however, be seen and, indeed, is present in a minority of elderly normal subjects.

Voice
This initially becomes quiet and speech loses its natural cadence and prosody. Later lingual and labial bradykinesia leads to problems with articulation and speech becomes indistinct. Pallilalia is a feature of end stage disease.

Dystonia
Younger onset IPD cases (including genetic Parkinson's disease associated with *parkin* mutations) are particularly prone to exhibit limb dystonia. This can be early morning or wearing off dystonia with a predilection for painful foot inversion, but can also manifest as a variety of segmental syndromes. Levodopa and dopamine agonists may worsen rather than improve dystonia in some of these young onset IPD cases, and anticholinergic treatment or amantadine can be helpful.

Dysautonomia
Impairment of cardiovascular reflexes leading to symptomatic orthostatic hypotension is rare initially, but patients frequently admit to impotence and have slowed bowel motility with associated constipation and abdominal pain. Impotence may respond well to sildenafil (Viagra). As the disease progresses and dopaminergic treatment is instituted, symptomatic orthostatic hypotension may develop but is rarely severe. Urinary hesitancy may reflect IPD or prostatism, but urgency and incontinence are usually caused by bladder instability. Increased sweating "seborrhoea" and facial flushing are late disease features. Dopaminergic agents are ineffective and worsen hypotension. Anticholinergic drugs such as tolterodine worsen constipation but can help bladder instability. Constipation may respond to senna laxatives or lactulose.

Cognition and mood
Frank dementia is unusual at presentation though slowness with executive functions such as sorting, fluency, and problem solving can be evident. Later, significant dementia occurs in 25% of patients—probably reflecting cortical Lewy body involvement or associated Alzheimer's changes. The dementia associated with cortical Lewy body disease is said to be more frequently manifest as fluctuating confusion, visual hallucinations, and paranoid delusions than Alzheimer's disease, but mixed pathology is frequent at postmortem examination. Dopaminergic and anticholinergic agents are ineffective and indeed may cause or exacerbate confusion, hallucinations, and psychosis. Anticholinesterase inhibitors such as rivastigmine may be helpful, particularly from a behavioural as well as a cognitive point of view.

Mild apathy and frustration are common at disease onset and a majority of IPD patients are mildly depressed, though severe depression requiring antidepressant treatment is less common. Panic attacks and anxiety can be presenting features of IPD.

Pathology
IPD is generally accepted to be pathologically characterised by Lewy body degeneration targeting the substantia nigra, other pigmented brain stem nuclei, the dorsal nucleus of the vagus, the nucleus basalis, and cortical association areas. Lewy bodies are eosinophilic intraneuronal inclusions with a characteristic halo which contain degenerating neurofilaments that

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Table 2 Lewy body syndromes

- Parkinson's disease
- Dementia
- Isolated tremor
- Segmental dystonia
- Autonomic failure
- Supranuclear gaze palsies

stain positive for the heat shock protein ubiquitin and also α synuclein. A problem in regarding IPD and Lewy body disease as synonymous is that brainstem and diffuse Lewy body disease can cause a variety of syndromes, dementia being the most common (table 2). Approximately 5% of brainstem Lewy body parkinsonian cases, confirmed postmortem, do not show levodopa response in life and 20% have only a poor response. Given this, a levodopa challenge is not a reliable discriminator of this pathology. To confuse the situation further, *parkin* gene mutations cause young onset levodopa responsive parkinsonism in the absence of any Lewy body formation. Additionally, occasional Lewy bodies have been found as mixed pathology in a number of other cortical and subcortical degenerations, including atypical parkinsonian syndromes.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA) includes within its spectrum striatonigral degeneration, olivopontocerebellar atrophy, and isolated autonomic failure. The majority of MSA patients present with parkinsonism and, like IPD, this manifests as asymmetrical limb rigidity and bradykinesia with complaints of stiffness, muscular aching, and hand clumsiness. Rest tremor is seen in MSA but is far less frequent than in IPD.

Limb ataxia can be present in MSA, particularly in later stages, and is evident as past pointing on finger–nose testing. This is never a feature of IPD. While IPD patients often have postural and action tremors, the presence of an intention tremor where amplitude increases with acceleration is a distinguishing feature of MSA. Whereas IPD peaks in the seventh decade, MSA tends to present during the sixth decade and is more rapidly progressive.

Gait disturbance with falls, bulbar involvement, and clinically significant orthostatic hypotension when free from medication are all seen early in MSA, in contrast to IPD, and should immediately raise suspicions of an atypical parkinsonian syndrome. Bulbar involvement can lead to stridor, particularly at night, and sleep apnoea is common. Severe apnoeic attacks and hypoventilation can become severe

enough to warrant a tracheostomy. Dysphagia and regurgitation may require percutaneous endoscopic gastrostomy (PEG) feeding. Poverty of palatal movement leads to nasal escape and a spastic dysarthria along with hypophonia.

Impotence at presentation is frequent (in women, lack of sexual stimulation—anorgasmia) and both sexes may respond well to sildenafil. Intracavernosal papaveretum injections may also transiently help impotence. Urinary urgency and incontinence occur early and may be helped by anticholinergic agents. In time, however, a penile sheath or catheterisation is required.

Extraocular smooth pursuit movements are hypometric to pursuit with saccadic intrusion but, unlike IPD, may also show sustained nystagmus. Square wave jerks may also be evident on central fixation. Voluntary saccades are usually full but occasionally supranuclear gaze problems have been noted (see below).

Hyperreflexia can be found in all parkinsonian syndromes but a positive Babinski response is only seen in MSA and not IPD (associated cervical myelopathy or vascular disease can cause pyramidal signs in IPD).

MSA patients adopt a flexed posture that can be extreme, patients becoming bent double with their chins on their chest. This is rarely seen in IPD patients unless they are end stage and have been withdrawn from medication. Limb dystonia can also be a feature of MSA.

While frontal executive problems are found in MSA, frank dementia is rare, as are the hallucinations, confusion, and psychosis associated with cortical Lewy body disease.

It is frequently stated that MSA patients show a poor levodopa response. This, however, is by no means invariable—in one series of pathologically proven striatonigral degeneration cases 50% maintained a good levodopa response until death and so this cannot be used to exclude the diagnosis. High doses of levodopa are always worth trying, though unfortunately levodopa tends to exacerbate orthostatic hypotension and MSA patients seem to be more frequently nauseated by this agent than IPD cases. Levodopa induced dyskinesias are rare but occasionally atypical isolated facial dyskinesias can be seen. Amantadine can be beneficial where dopaminergic agents either do not help or are poorly tolerated.

Management of orthostatic hypotension associated with MSA consists initially of taking simple measures such as reducing dopaminergic medication where possible, having the patient wear elastic tights (avoiding rucking of the leggings which can cause restricted venous return), and raising the head of the bed by 10°. Nocturnal polyuria can be controlled with nasal desmopressin (DDAVP) though hyponatraemia can
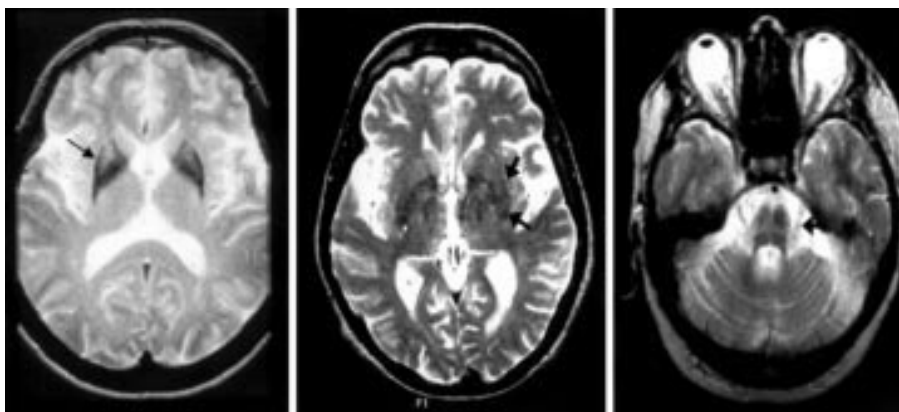
Figure 1 Left: reduced lateral putamen signal in multiple system atrophy (MSA) on T2 weighted magnetic resonance imaging (MRI) probably reflecting iron deposition. Centre: increased lateral putamen signal in MSA on T2 weighted MRI probably reflecting gliosis. Right: if concomitant pontocerebellar degeneration is also present the lateral as well as longitudinal pontine fibres become evident as high signal on T2 MRI manifesting as the "hot cross bun" sign.

Abbreviations

CBD: corticobasal degeneration
EMG: electromyelogram
IPD: idiopathic Parkinson's disease
MIBG: metaiodobenzylguanadine
MRI: magnetic resonance imaging
MSA: multiple system atrophy
NAA: N-acetyl aspartate
OKN: opticokinetic nystagmus
PEG: percutaneous endoscopic gastrostomy
PET: positron emission tomography
PSP: progressive supranuclear palsy
SPECT: single photon emission computed tomography

become a complication. If these measures fail fludrocortisone or a sympathomimetic agent such as midodrine can be used.

Pathology

The pathology in MSA is distinct from that in IPD, targeting the striatum, substantia nigra, brainstem nuclei, dentate nuclei of the cerebellum, intermediolateral columns of the spinal cord, and Onuf's spinal nucleus, which innervates the urethral and anal sphincters. Argyrophilic neuronal and glial cytoplasmic inclusions that stain positive for α synuclein are pathognomonic but are also occasionally seen in progressive supranuclear palsy and corticobasal degeneration. Lewy bodies are not a feature.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP), also known as Steele-Richardson-Olszewski syndrome after those who first characterised its pathology, presents as a symmetrical rather than asymmetrical akinetic–rigid syndrome—in contrast to IPD and MSA. It also initially targets the trunk and neck rather than the limbs, causing early postural and gait instability with falls and a dystonic posture where the trunk is flexed but the neck extended. Any elderly patient with truncal or neck rigidity either in the absence of or with only mild limb involvement and impaired postural reflexes should be suspected of having PSP. Later, limb rigidity and bradykinesia develop in a symmetrical fashion but rest tremor is uncommon. Limb ataxia can be seen in PSP but is far less common than in MSA. Hyperreflexia and extensor plantars are a frequent finding, but the presence of associated cervical spondylosis can complicate the interpretation of such signs.

Voluntary gaze problems are pathognomonic but may be a late feature or even absent. An early clue is a complaint of difficulty with reading because of problems scanning the printed text. Asking the patient to look up and down voluntarily, or left and right, in the absence of a target often reveals impaired volitional saccades when ocular smooth pursuit movements are still preserved. Failure of voluntary down or lateral gaze corrects when the patient's eyes are centrally fixated and their head passively tilted backwards or rotated, confirming a supranuclear gaze problem. Reflex saccades to a target become impaired at a later stage as do pursuit eye movements. Given this, isolated testing of pursuit ocular movements in suspected PSP cases is likely to miss a supranuclear gaze problem. As the disease develops pursuit ocular movements become hypometric and show saccadic intrusion. Later nystagmus and frank oculoparesis may occur causing the patient to complain of diplopia. Square wave jerks on central fixation become
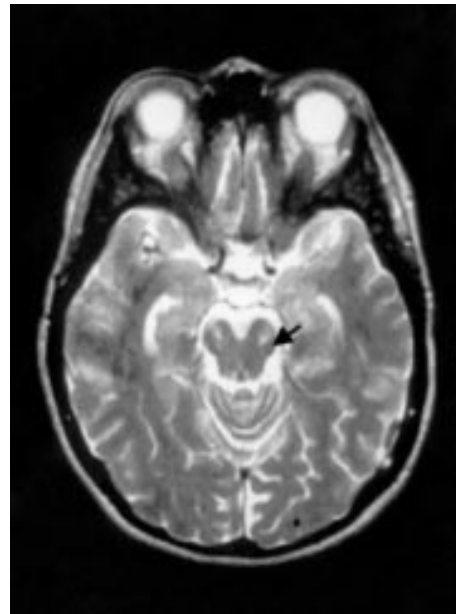
Figure 2 Magnetic resonance image showing midbrain atrophy in progressive supranuclear palsy.

evident. In PSP the optokinetic reflex is lost early with a sustained deviation of the eyes rather than saccades occurring on viewing a striped rotating drum. The combination of neck extension and a downgaze palsy predisposes PSP patients to falls, particularly when descending stairs. Eyelid retraction can give rise to a characteristic staring expression.

While IPD cases can show isolated impairments of voluntary upgaze and convergence, as can elderly normals, these are generally partial and isolated. A sustained gaze deviation to opticokinetic nystagmus (OKN) is never a feature of IPD.

Early bulbar involvement with a nasal spastic dysarthria and hypophonia is the norm and dysphagia follows later. Feeding with thickened fluids can overcome oesophageal hypomotility to a degree, but if choking attacks develop a PEG may well be required in end stage disease.

Impaired cardiovascular reflexes with orthostatic hypotension are not a predominant feature of PSP unless high doses of levodopa are being employed. Urinary urgency, urge incontinence, and constipation, however, are frequently present. The former may respond to anticholinergic agents.

Impairment of frontal executive functions is frequent in PSP, and dementia, often of a frontal type, is common in later disease leading to memory impairment, expressive dysphasia, and limb apraxia. In practice, the presence of severe dysarthria and hypophonia can make dysphasia difficult to characterise while severe rigidity and bradykinesia can mask apraxia. Limb apraxia is generally symmetrical and patients show difficulties imitating postures (ideomotor apraxia) and pantomiming patterns of limb movements (ideational apraxia) even allowing for slowness—this is not seen in uncomplicated IPD though can be seen if superadded dementia is present due to cortical involvement. Eyelid opening apraxia can occasionally be present, patients taking seconds or even minutes to open their eyes volitionally after eye closure. Personality changes are common in PSP and emotional lability can cause patients to oscillate inappropriately between episodes of laughing and crying. In end stage disease grasp and pout reflexes can be elicited.
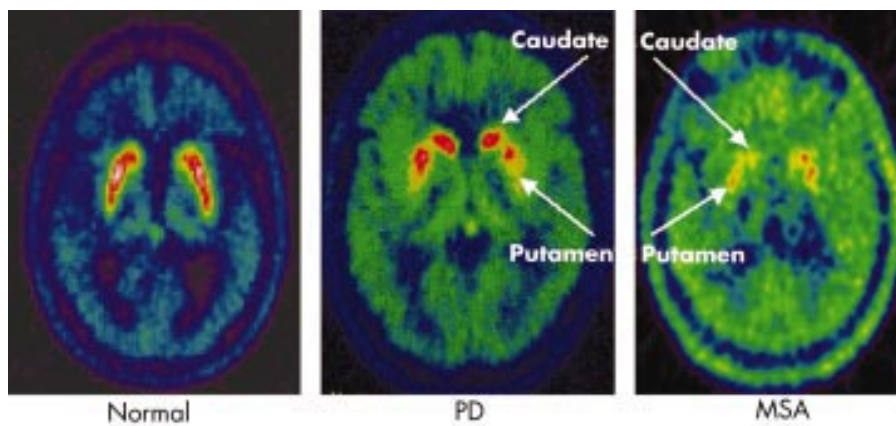
Figure 3 ¹⁸F-dopa positron emission tomography (PET) in a normal subject, a patient with idiopathic Parkinson's disease (PD), and a patient with multiple system atrophy (MSA). The idiopathic PD case shows relative sparing of caudate dopamine storage compared with the MSA case. Picture courtesy of Alex Gerhard.

A poor levodopa response is usual though high doses can be beneficial initially. As with MSA, amantadine can be useful where levodopa is ineffective or poorly tolerated.

Pathology
This targets the pallidum (rather than the striatum), the substantia nigra compacta, and reticulata, peri-aqueductal grey matter, oculomotor, vestibular, and cerebellar dentate nuclei, and the superior colliculi. Cortical involvement, particularly superior frontal areas, is present but to a lesser extent. Globose tau positive neurofibrillary tangles are found as neuronal inclusions. Occasionally mixed pathology can be found with Alzheimer changes, and Lewy bodies also present.

CORTICOBASAL DEGENERATION
Corticobasal degeneration (CBD) is strikingly asymmetrical in its presentation, mimicking IPD and MSA but contrasting with PSP. Typically the patient becomes aware of a clumsy stiff limb but, unlike IPD and MSA, there is striking apraxia and the patient complains that the limb does not behave itself or follow orders, and that it feels as if it belongs to somebody else. Cortical sensory loss with simultagnosia and dysgraphaesthesia is frequent, the patient having problems recognising objects in their pockets by tactile impressions, though crude light touch and pin prick sensation remain preserved. In extreme cases the patient may develop an alien limb—that is, the arm may involuntarily perform apparently purposeful movements. Typical examples are the affected arm comes across and interferes with actions of the less affected arm or grasps onto railings or door handles. An alien limb should not be confused with simple involuntary limb elevation which often reflects impaired cortical sensory processing rather than aberrant higher motor control.

Other features of CBD include limb myoclonus that may be stimulus sensitive, asymmetric postural limb tremor, and intense limb muscular aching which is far more severe than that seen in IPD. Limb dystonia can result in ulceration of the palm caused by involuntary finger flexion. Severe bulbar problems—dysphagia and dysarthria—occur early and, while supranuclear gaze difficulties have been described, they are less common. Patients may develop pyramidal signs such as extensor plantar responses.

Dementia is usually a late feature of CBD, but an early frontal dementia mimicking Pick's disease can occasionally be seen. Dysphasia occurs early and frequently, and the patient may become anarthric making cognition difficult to assess. Frontal release signs can occasionally be seen.

Although the cerebellar dentate nuclei are targeted by the pathology, it is rare to see frank ataxia in CBD. Dysautonomia is also not a feature of this disorder.

A poor levodopa response is invariable in this disorder and amantadine, in my experience, is also usually ineffective. Treatment is essentially supportive.

Pathology
This consists of asymmetrical degeneration of posterior frontal, inferior parietal, and superior temporal cortices, the thalamus, substantia nigra, and cerebellar dentate nuclei. Swollen, achromatic, tau positive neurones (Pick cells) are characteristic in the absence of argyrophilic Pick bodies. Other pathologies can mimic the clinical syndrome of CBD which has been reported in association with diffuse Lewy body disease, PSP, Pick's disease, prion disease, and multifocal leucoencephalopathy.

INVESTIGATIONS OF PARKINSONISM
Standard laboratory investigations (blood haematology, blood and urine biochemistry, cerebrospinal fluid) are all normal in IPD, MSA, PSP, and CBD.

Electrophysiology can be supportive in certain situations. If there is doubt concerning the frequency and amplitude of a tremor, a surface electromyelogram (EMG) recording can help clarify this. MSA patients may have degeneration of Onuf's nucleus which can be detected as polyphasic potentials with a prolonged latency on urethral or anal sphincter EMG. False negatives are common, however, and conversely one can see such polyphasic delayed potentials in occasional normals and IPD cases, particularly if they have prostatic hypertrophy or have had prostatic surgery.

Eye movement recordings can also be helpful in confirming hypometric saccades, supranuclear gaze problems, square wave jerks, and abnormal OKN, though it is uncommon for these to be detected in the absence of any clinical suspicion.

Formal assessment of cardiovascular reflexes can be helpful in characterising the nature of the lesion when dysautonomia is present. Pulse and blood pressure responses to tilting, mental arithmetic, cold stimulation, and a Valsalva manoeuvre help define sympathetic and parasympathetic involvement.

Structural imaging
Magnetic resonance imaging (MRI) can be helpful in a number of ways (table 3). Firstly, structural lesions can be excluded. Basal ganglia tumours, haemorrhage, small vessel disease, calcification, and hydrocephalus have all been associated with parkinsonism. There is still debate concerning

Table 3 Magnetic resonance imaging findings in parkinsonian syndromes

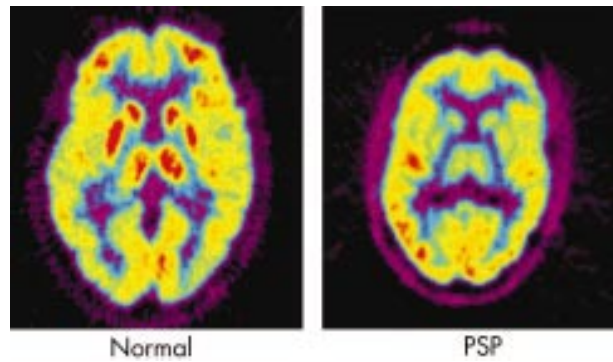|		
IPD	Nigra	Patchy signal loss
MSA	Putamen	Low posterior T2 signal
		Lateral slit-like hyperintensity
	Pons	Increased tegmental signal
		"Hot cross bun"
	Cerebellum	Atrophy
PSP	Midbrain	Atrophy
	3rd ventricle	Dilatation
CBD	Cortex	Asymmetrical atrophy

CBD, corticobasal degeneration; IPD, idiopathic Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.
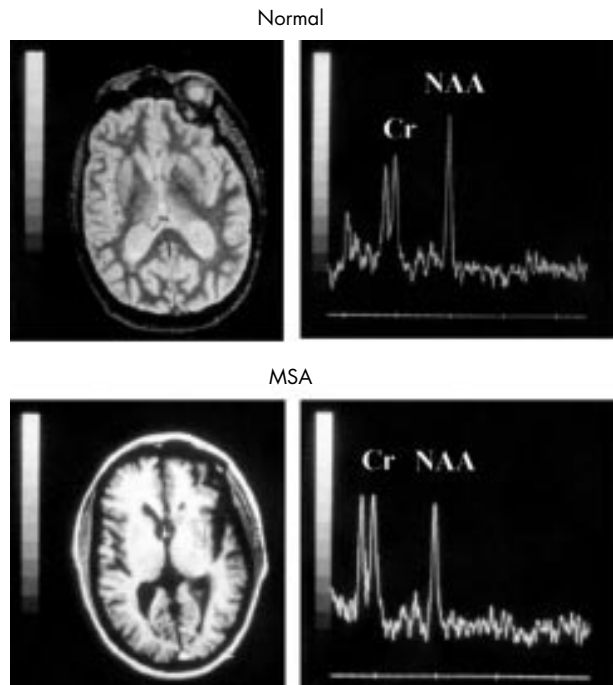

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Figure 4 ^{18}F-FDG PET in a normal subject and a patient with progressive supranuclear palsy (PSP). The PSP image shows low striatal and frontal glucose metabolism. Picture courtesy of Paola Piccini.

whether vascular parkinsonism is a distinct entity. Clinically it is said to be characterised by lower body parkinsonism, gait apraxia, and a poor levodopa response, but at postmortem examination mixed pathology is frequently found.

Secondly, high field T2 weighted MRI may show altered nigral signal in IPD but the striatum and pallidum should appear normal. In striatonigral degeneration/MSA the putamen characteristically shows reduced signal running up the lateral extent caused by iron deposition (fig 1, left panel) and this may be covered by a rim of increased signal caused by gliosis (fig 1, centre panel). If concomitant pontocerebellar degeneration is also present the lateral as well as longitudinal pontine fibres become evident as high signal on T2 MRI manifesting as the "hot cross bun sign" (fig 1, right panel). Cerebellar and pontine atrophy may also be present with increased signal evident in the cerebellar peduncles. PSP patients do not show the striatal changes of MSA but may show third ventricular widening and midbrain atrophy (fig 2). In CBD MRI can usefully exclude multi-infarct disease and multifocal leucoencephalopathy, and asymmetric hemispheric atrophy may be present.

While the above MRI findings can be helpful, they tend to be most evident in well established disease by which time the diagnosis is generally becoming relatively clear.

Functional imaging

This is of limited availability but potentially very informative (table 4). ^{18}F-dopa positron emission tomography (PET), FP-CIT single photon emission computed tomography (SPECT), and β-CIT SPECT are all sensitive means of detecting dopamine terminal dysfunction in parkinsonism, and can be useful in discriminating essential and parkinsonian tremors where diagnostic difficulty exists. Quantitative analysis is more sensitive than visual inspection. While these modalities discriminate dopamine terminal dysfunction from normal, they are unable to separate atypical from typical parkinsonism reliably. Having said that, atypical PD cases tend to show a

Table 4 Functional imaging and parkinsonian syndromes

IPD	Striatum	Asymmetrical low F-dopa, FP-CIT, beta-CIT
		Uptake (putamen < caudate)
		Normal putamen FDG and D2
		Normal ^{1}H-MRS NAA:Cr ratio
MSA	Striatum	Asymmetrical low F-dopa, FP-CIT, beta-CIT
		Uptake (putamen < caudate)
		Asymmetrical low putamen FDG and D2
		Low ^{1}H-MRS NAA:Cr ratio
	Cerebellum	Low FDG
PSP	Striatum	Symmetrical low F-dopa, FP-CIT, β-CIT
		Uptake (putamen = caudate)
		Symmetrical low putamen and caudate FDG and D2
		Low ^{1}H-MRS NAA:Cr ratio
	Frontal	Low FDG (posterior < inferior)
CBD	Striatum	Asymmetrical low F-dopa, FP-CIT, β-CIT
		Uptake (putamen = caudate)
		Low putamen and caudate FDG and D2
		Low ^{1}H-MRS NAA:Cr ratio
	Thalamic	Asymmetrical low FDG
	Cortical	Asymmetrical low FDG inferior parietal and posterior frontal

Normal

MSA

Figure 5 Lentiform nucleus proton magnetic resonance spectroscopy in a normal subject and in a patient with multiple system atrophy (MSA). The MSA images show a relative reduction in NAA signal. Picture courtesy of Michelle Hu.

Table 5 Clinical discriminators of parkinsonian syndromes

	Essential tremor	IPD	MSA	PSP	CBD
Tremor	Symmetrical; post 4–8 Hz; arms, head, voice; no latency	Asymmetrical; post 4–8 Hz, rest 3–5 Hz; arms and legs, jaw, eyelids; latency to onset	Asymmetrical; post 4–8 Hz, rest 3–5 Hz; arms or legs; latency	Uncommon	Asymmetrical; postural, with stimulus sensitive myoclonus
Rigidity	Occasional cogwheel	Asymmetrical; limb	Asymmetrical; limb	Symmetrical; axial >limb	Asymmetrical; limb
Finger movements	Slow but fixed amplitude	Progressive slowing with decreasing amplitude	Progressive slowing with decreased amplitude	Spared early	Early apraxia—hand can become useless
Facies	Normal	Early loss of expression and blinking. Late blepharoclonus	Early loss of expression; facial dyskinesias	Lid retraction; staring; eye opening apraxia	Early loss of expression; orobuccal apraxia
Dysautonomia	None	Early impotence, late OH, bladder, constipation	Early OH, bladder, impotence, constipation	Early impotence, bladder, OH rare	Early impotence, bladder, OH rare
Bulbar	None	Late dysarthria; hypophonia	Early dysarthria, dysphagia; night stridor	Early dysarthria, dysphagia	Early dysarthria, dysphagia
Gait and posture	Normal	Late falls; retropulsion; festination, flexed posture	Early falls, flexed posture; antecollis ++	Early falls, retrocollis	Early falls
Eye movements	Normal	Hypometric	Nystagmus, hypometric	Eye deviation to OKN, SGP	Occasional SGP
Ataxia	None	None	Frequent	Rare	Rare
Apraxia	None	None	None	End stage limb; eye opening	Limb, alien phenomena

OH, orthostatic hypotension; OKN, opticokinetic nystagmus; SGP, supranuclear gaze palsy.

more uniform pattern of caudate and putamen dysfunction, whereas there is a putamen emphasis in IPD (fig 3).

In IPD striatal metabolism and dopamine D2 receptor binding are spared whereas they are impaired in atypical syndromes. ^{18}FDG PET shows reduced striatal glucose metabolism in 80–100% of cases suspected of having atypical PD (fig 4), though cannot reliably discriminate striatonigral degeneration/MSA from PSP and CBD. Features supporting PSP rather than MSA include a greater caudate and frontal emphasis, while CBD patients characteristically show very asymmetrical patterns of glucose hypometabolism targeting inferior parietal, thalamus, and striatum. Atypical syndromes may also show loss of striatal D2 receptor binding which can be detected with ^{11}C-raclopride PET, ^{123}I-IBZM SPECT, and ^{123}I-epidipride SPECT. The general impression is that striatal glucose metabolism is a more sensitive indicator of striatal degeneration than loss of D2 receptor binding, but both can be helpful. Proton magnetic resonance spectroscopy can also detect striatal dysfunction evidenced as a reduction in N-acetyl aspartate: (NAA) creatine peak ratio (fig 5). Reports vary concerning how sensitive a discriminator this modality is but, if a reduced NAA signal is present, it can be helpful in supporting a diagnosis of atypical parkinsonism.

Finally cardiac MIBG (metaiodobenzylguanadine) scanning may be helpful in discriminating MSA from IPD. MIBG is taken up by sympathetic terminals and the cardiac signal is severely reduced in IPD but relatively spared in MSA.

CONCLUSIONS
Table 5 details clinical pointers helpful in discriminating atypical from typical parkinsonian syndromes.

KEY REFERENCES
1 **Litvan I**, Agid Y, Goetz C, *et al.* Accuracy of the clinical diagnosis of corticobasal degeneration: a clinicopathological study. *Neurology* 1997;**48**:119–25.
2 **Litvan I**. Diagnosis and management of progressive supranuclear palsy. *Semin Neurol* 2001;**21**:41–8.
3 **Gilman S**, Low PA, Quinn N, *et al.* Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999;**163**:94–8.
4 **Litvan I**, Booth V, Wenning GK, *et al.* Retrospective application of a set of clinical diagnostic criteria for the diagnosis of multiple system atrophy. *J Neural Transm* 1998;**105**:217–27.
5 **Riley DE**, Lang AE, Lewis A, *et al.* Cortical-basal ganglionic degeneration. *Neurology* 1990;**40**:1203–12.
6 **Maher ER**, Lees AJ. The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology* 1986;**36**:1005–8.
7 **Savoiardo M**, Girotti F, Strada L, *et al.* Magnetic resonance imaging in progressive supranuclear palsy and other parkinsonian disorders. *J Neural Transm* 1994;(suppl 42):93–110.
8 **Brooks DJ**. Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease. *J Neurol* 2000;**247**(suppl 2):11–18.

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