

The diagnosis of Parkinson's disease

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The correct diagnosis of Parkinson's disease is important for prognostic and therapeutic reasons and is essential for clinical research. Investigations of the diagnostic accuracy for the disease and other forms of parkinsonism in community-based samples of patients taking antiparkinsonian medication confirmed a diagnosis of parkinsonism in only 74% of patients and clinically probable Parkinson's disease in 53% of patients. Clinicopathological studies based on brain bank material from the UK and Canada have shown that clinicians diagnose the disease incorrectly in about 25% of patients. In these studies, the most common reasons for misdiagnosis were presence of essential tremor, vascular parkinsonism, and atypical parkinsonian syndromes. Infrequent diagnostic errors included Alzheimer's disease, dementia with Lewy bodies, and drug-induced parkinsonism. Increasing knowledge of the heterogeneous clinical presentation of the various parkinsonisms has resulted in improved diagnostic accuracy of the various parkinsonian syndromes in specialised movement-disorder units. Also genetic testing and various other ancillary tests, such as olfactory testing, MRI, and dopamine-transporter single-photon-emission computed-tomography imaging, help with clinical diagnostic decisions.

Introduction

Parkinson's disease is a progressive neurological disorder characterised by tremor, rigidity, and slowness of movements, and is associated with progressive neuronal loss of the substantia nigra and other brain structures. Non-motor features, such as dementia and dysautonomia, occur frequently, especially in advanced stages of disease. Parkinson's disease is not regarded as a single disease entity and the term does not necessarily mean the same for all clinicians and researchers. Some use the term as a strictly clinical diagnosis and might accept different pathological substrates underlying the syndrome. Others will use the term only for those cases of idiopathic parkinsonism associated with Lewy body inclusions in the nigra cells and in cells in other brain regions. Here we use the term Parkinson's disease to refer to a clinical condition—progressive parkinsonism of undetermined cause without features suggestive of an alternative diagnosis responding to dopaminergic treatment—associated with depletion of brainstem neurons and with Lewy body inclusions in some of the remaining nerve cells.^{1,2}

Although a diagnosis of Parkinson's disease, as defined above, can be a straightforward clinical exercise in patients with typical presentations of cardinal signs and excellent response to levodopa treatment, the differential diagnosis versus other forms of parkinsonism can be challenging, especially early in the disease when signs and symptoms of different forms of parkinsonism have greater overlap. Error rates in clinicopathological series have been as high as 24% even though most of the patients in these studies had been treated by movement-disorder specialists.³ Two studies draw attention to the difficulties in the diagnosis of the disease in the early stages. In a prospective clinicopathological study, Rajput and colleagues⁴ showed that initial clinical diagnosis within 5 years of disease onset was correct in 65% of cases. After a mean duration of 12 years, the final diagnosis of

Parkinson's disease by the clinician was confirmed at autopsy in 76% of cases. Similarly, among 800 patients in the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson Disease⁵ study with mild early parkinsonism judged to have Parkinson's disease, 8.9% were later reported to have an alternative diagnosis on the basis of multifactorial, clinical diagnostic criteria.

With the use of standard clinical criteria, such as the UK Parkinson's disease brain bank criteria, accuracy of a clinical diagnosis of the disease can be improved significantly; however, up to 10% of patients diagnosed with the disease in life will still have to be reclassified at post-mortem examination.⁶ Diagnostic specificity and sensitivity of these criteria have been estimated as 98.6% and 91.1%, respectively.⁷ Diagnostic sensitivity and specificity of criteria used to diagnose atypical parkinsonian disorders, such as multisystem atrophy or progressive supranuclear palsy, are significantly lower than those used for Parkinson's disease.⁷⁻⁹

Population-based studies have shown that at least 15% of patients with a diagnosis of Parkinson's disease in the population do not fulfil strict clinical criteria for the disease, and about 20% of patients with Parkinson's disease who have already come to medical attention have not been diagnosed with the disease.¹⁰ In clinicopathological studies the most common misdiagnoses relate to other forms of degenerative parkinsonism, such as progressive supranuclear palsy, multisystem atrophy, or corticobasal degeneration.⁷ Clinically based studies have shown that other common errors include essential tremor, drug-induced parkinsonism, and vascular parkinsonism.¹¹ Additionally, there is ongoing debate on the distinction between Parkinson's disease with dementia and dementia with Lewy bodies.^{12,13} Here we review published work on the clinical differential diagnosis of the various parkinsonian syndromes and critically assess the role of ancillary tests in the diagnostic work-up of patients with parkinsonism.

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Clinical differential diagnosis

Essential tremor

Essential tremor is a monosymptomatic disorder characterised by the presence of bilateral, largely symmetrical, postural or kinetic tremor that affects the hands and forearms and is visible and persistent.¹⁴ Bradykinesia, rigidity, and postural instability are not part of the illness, but around 20% of patients with essential tremor are misdiagnosed with Parkinson's disease and vice versa.¹⁵ Postural tremor in essential tremor is apparent immediately as the arms are outstretched, whereas a re-emergent tremor that appears when outstretching the arms after some latency is more characteristic of Parkinson's disease.¹⁶ Particularly difficult diagnostic situations arise when an otherwise typical case of essential tremor is associated with rest tremor (10% of cases) or when the tremor is unilateral, which can occur during the first years of essential tremor.^{17,18} The presence of head tremor, voice tremor, and sensitivity to alcohol strongly favour essential tremor.¹⁹ A family history of a similar tremor could also be indicative of essential tremor because it is an autosomal dominant disorder in many cases. Classic rest tremor, predominantly unilateral tremor, leg tremor, concomitant rigidity, and sensitivity to levodopa strongly favour a diagnosis of Parkinson's disease.

Some patients have a resting and postural tremor without overt signs of bradykinesia or rigidity, but there is evidence on PET that these patients have a dopaminergic deficit. Patients with monosymptomatic tremor at rest are deemed to have monosymptomatic Parkinson's disease if tremor has been present for at least 2 years.²⁰

Vascular parkinsonism

Vascular parkinsonism, defined as parkinsonism occurring in patients with cerebrovascular disease,²¹ is a controversial entity. Diagnosis of the disorder requires exclusion of Lewy body disease or other neurodegenerative forms of parkinsonism, which can be difficult on clinical grounds alone.²² Furthermore, basal ganglia infarcts are not commonly associated with clinical signs of parkinsonism,²³ and a follow-up study of 11 patients with striatocapsular infarcts identified only one case of contralateral parkinsonism.²⁴ Conversely, vascular pathology is common in degenerative Lewy body parkinsonism.²⁵ Vascular parkinsonism is characterised by widespread bilateral deep lacunar white matter infarcts and typically causes a parkinsonian gait disorder with wide-based small stepped gait and freezing (lower body parkinsonism).²⁶⁻²⁸ Onset is usually gradual with stepwise progression, but basal ganglia infarcts affecting the putamen or putamino-pallido-thalamic pathways or the substantia nigra can give rise to acute onset of contralateral parkinsonism.²⁹⁻³¹ MRI studies and a clinicopathological study have confirmed that vascular lesions tend to localise in these two sites in cases of

vascular parkinsonism.²²⁻³² Multiple lacunar infarcts that interrupt thalamocortical outflow seem to be the most common type of vascular lesion and can cause progressive parkinsonism that is responsive to levodopa in about 50% of cases.²²⁻³³

Dementia with Lewy bodies

Dementia with Lewy bodies is currently regarded as the second most common type of degenerative dementia after Alzheimer's disease.¹³ According to published consensus criteria it is clinically defined as a progressive dementia syndrome with prominent attentional and visuospatial deficits, marked fluctuations in attention and cognition, visual hallucinations, and parkinsonism.³⁴ Neuropathology shows widespread neocortical and limbic Lewy body degeneration in addition to brainstem Lewy body disease.¹³ Up to 40% of patients with idiopathic Parkinson's disease will also develop dementia according to population-based studies.³⁵⁻³⁷ Clinical studies have not identified consistent clinical differences between patients with Parkinson's disease dementia and dementia with Lewy bodies, including fluctuations in attention and cognition.³⁸ Neuroleptic sensitivity with substantial motor worsening and changes in mental status has also been claimed as a distinctive feature of dementia with Lewy bodies,³⁹ but differences in tolerability of neuroleptic treatment between patients with this disorder and those with Parkinson's disease have never been established. Consistent with clinical overlap, neuropathological findings in patients fulfilling clinical criteria for either disease also seem indistinguishable, apart from a more pronounced temporal lobe Lewy body formation in dementia with Lewy bodies.⁴⁰ Although this characteristic has been suggested to separate the two disorders on the basis of dementia onset relative to parkinsonism, and to restrict the term Parkinson's disease dementia to patients in whom dementia begins at least 12 months after the motor manifestations of the disease,¹³ the two forms of dementia are probably two clinical manifestations within a spectrum of Lewy body diseases. This notion is also lent support by recent genetic findings, where triplication of the α -synuclein gene was associated with a clinical phenotype of Parkinson's disease dementia or dementia with Lewy bodies, whereas duplication of the same gene caused Parkinson's disease without dementia.⁴¹⁻⁴⁴

Progressive supranuclear palsy

Progressive supranuclear palsy, also known as Steel-Richardson-Olszewski syndrome, is a multisystem degenerative disorder that can be easily differentiated from Parkinson's disease when a patient presents with the typical clinical picture of supranuclear gaze palsy, including predominantly vertical gaze, parkinsonism, pseudobulbar palsy, and prominent frontal lobe syndrome.^{45,46} However, progressive supranuclear palsy

can be confused with Parkinson's disease in the early stages before gaze abnormalities appear, in patients without gaze palsy, or when full-blown parkinsonism dominates the clinical picture.⁴⁷ Clinicopathological⁴⁸ and epidemiological⁴⁹ studies highlight the frequent diagnostic confusion with Parkinson's disease. In progressive supranuclear palsy, axial (neck and trunk) symptoms predominate and rest tremor is uncommon. Bradykinesia is symmetrical and can be severe. Postural instability and falls commonly occur in the first year of disease.⁵⁰ Gait is more broad based and unsteady, unlike the typical small stepped shuffling gait with propulsion of Parkinson's disease. Several diagnostic criteria for progressive supranuclear palsy have been published. The most commonly used for research are those formulated by the US National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy.⁴⁶ According to these criteria for probable progressive supranuclear palsy, vertical supranuclear palsy and prominent postural instability with falls have to occur within the first year of disease onset. Retrospective analysis of these criteria indicate that they have better specificity, sensitivity, and positive predictive value than other criteria.⁵¹

Although usually sporadic, familial cases of progressive supranuclear palsy have been described.⁵² The disorder rarely improves with dopaminergic treatment,⁵³ although those patients presenting with prominent parkinsonism (so-called progressive supranuclear palsy parkinsonism) may respond favourably to levodopa.⁵⁴ Neuropathological studies of the disorder show presence of abundant tau-positive neurofibrillary tangles in subcortical and brainstem structures.⁵⁵

Multisystem atrophy

Multisystem atrophy is a sporadic multisystem degeneration associated with α -synuclein deposits in the CNS (oligodendrocytic inclusions), but not Lewy bodies or neuritis, apart from in a few patients (<10%).⁵⁶ The disorder can present as a predominantly or exclusively cerebellar (olivoponto cerebellar atrophy) or parkinsonian (striatonigral degeneration) form associated with variable degrees of autonomic failure.^{57,58} The parkinsonian variant of multisystem atrophy, currently referred to as MSA-p, can be very difficult to differentiate from Parkinson's disease. MSA-p affects a slightly younger age group than does Parkinson's disease, but the peak of onset is still in the sixth decade. The disorder can be reliably diagnosed only if prominent signs of autonomic failure, such as impotence or postural hypotension, develop early in the course of the disease or a clear cerebellar syndrome is present. Besides dysautonomia, other clinical characteristics can help differentiate MSA-p from Parkinson's disease: nocturnal stridor, rapid course, early instability and falls, stimulus sensitive myoclonus, pyramidal tract signs,

severe dysarthria, and insufficient or only transient response to levodopa.^{59,60} Parkinsonism in MSA-p can respond well to levodopa at onset and dyskinesia and motor fluctuations may occur with this treatment.⁶¹ Dyskinesia, however, are frequently restricted to the orofacial and cervical musculature.

Corticobasal degeneration

Corticobasal degeneration is a rare tauopathy that shares clinical and biological characteristics with progressive supranuclear palsy. The disorder can present clinically as unilateral parkinsonism, but also with any of a variety of asymmetrical cortical degeneration syndromes, which include primary progressive aphasia, frontal lobe dementia, and progressive apraxia.⁶² Most patients with corticobasal degeneration present in the sixth decade with an unilateral jerky tremulous akinetic rigid extremity held in a fixed dystonic posture. Limb kinetic apraxia is also common, but difficult to distinguish from clumsiness accompanying bradykinesia, rigidity, and dystonia. Alien limb phenomenon develops in about 50% of patients and cortical sensory deficits are also common.⁶³ Pronounced asymmetry of limb involvement is a hallmark of the classic disorder, but typical parkinsonian type rest tremor is not a common feature.⁶⁴ On examination at presentation most patients do not have significant global cognitive deterioration or dysphasia; however, dementia often develops in late disease stages and can even be the presenting feature in a few patients.⁶⁵ Motor symptoms rarely respond to levodopa,⁶⁶ and the disorder progresses relentlessly to become bilateral and produces severe disability within 2–7 years. Supranuclear ophthalmoplegia is not uncommon in advanced stages of the disease.⁶²

Other secondary parkinsonisms

Other parkinsonian syndromes are encountered in clinical practice and can be difficult to differentiate from Parkinson's disease. The most common one is drug-induced parkinsonism. Various antidopaminergic drugs can induce parkinsonism; the most common being the antipsychotics and the antiemetics.⁶⁷ The presence of orofacial dyskinesias or akathisia (movement disorders associated with chronic neuroleptics) is helpful for diagnosis.^{68,69} Symptoms and signs of drug-induced parkinsonism can be identical to those of Parkinson's disease, including asymmetric presentation with rest tremor. The diagnosis of drug-induced parkinsonism is especially difficult in patients in whom a drug history is unclear, in those taking small amounts of antidopaminergic drugs, and in those in whom withdrawal of the offending drugs is not followed by regression of parkinsonism, which suggests that Parkinson's disease might underlie the drug-induced state.⁷⁰ Panel 1 shows other parkinsonisms that have to be considered in the differential diagnosis of Parkinson's disease. For some of these disorders,

biological tests exist that allow for precise diagnosis, such as Huntington's disease (rigid form), Wilson's disease or spinocerebellar ataxia mutations (SCA-2, SCA-3, and SCA-17), and frontotemporal dementia with

parkinsonism linked to chromosome 17. In others, no such possibility exists, but neuroimaging can be helpful—eg, in cases of parkinsonism associated with communicating hydrocephalus or a subdural haematoma. Some of these syndromes—eg, psychogenic or drug-induced parkinsonism—can co-exist with Parkinson's disease.

Panel 1: Secondary parkinsonism

Infectious

Encephalitis lethargica and other viral infections (eg, AIDS, PML)
Prion disease
Neurosyphilis
Toxoplasmosis

Toxic

Carbon monoxide
Cyanide
Carbon disulphide
MPTP
Manganese
Solvents

Drug induced

Dopamine-receptor blockers
Classic neuroleptics (eg, phenothiazines, butyrophenones)
Atypical antipsychotics (eg, risperidone, olanzapine)
Dopamine-depleting drugs (eg, tetrabenazine)
Other drugs (eg, valproic acid, calcium channel blockers)

Brain tumours

Supratentorial and brainstem tumours
Arteriovenous malformations

Cranial trauma

Striatal variant of dementia pugilistica
Chronic subdural haematoma
Mid-brain trauma
Vascular lesions

Metabolic

Hypoxia
Hypoparathyroidism
Familial basal ganglia calcification
Extrapontine myelinolysis
Chronic liver failure
Wilson's disease

Miscellaneous

Huntington's disease
SCA mutations
FTDP-17
Neuroacanthocytosis
Dentatorubropallidal-luysian atrophy
Normal pressure hydrocephalus
Haemiatrophy-hemiparkinson syndrome
Psychogenic

PML=progressive multifocal leucoencephalopathy; MPTP=1-methyl-4-pnenyl-4-propionoxypiperidine; FTDP-17=frontotemporal dementia with parkinsonism linked to chromosome 17.

Ancillary tests in the differential diagnosis of Parkinson's disease

Although some core clinical characteristics differ between the various forms of degenerative parkinsonism, there is broad clinical overlap (table 1).⁷¹⁻⁷⁵ Error rates in clinicopathological studies draw attention to the need for additional diagnostic tests to solidify differential diagnostic accuracy. These tests include genetic testing, challenge tests of dopaminergic responsiveness, neurophysiological studies and autonomic function testing, tests of olfactory function, and neuroimaging. Most of these techniques have been used for diagnosis in established Parkinson's disease versus other forms of degenerative parkinsonism and their respective sensitivities and specificities in diagnosis of early disease have not been defined. Furthermore, clinical diagnoses were not confirmed post-mortem in most of the studies that assessed the diagnostic potential of ancillary tests. Studies have also begun to assess the potential of some tests to identify individuals at risk of the disease.

Genetic testing

Parkinson's disease is still regarded as a sporadic neurodegenerative disorder, characterised by the loss of midbrain dopamine neurons and presence of Lewy body inclusions. The disease is thought to result from a complex interaction between multiple predisposing genes and environmental effects, although these interactions are still poorly understood. An increasing number of loci linked to familial parkinsonism have been found (*PARK1-PARK11*). Of these, seven genes have been identified, four causing autosomal dominant parkinsonism (α -synuclein, *UCHL1*, *NURR1*, *LRRK2*) and three causing autosomal recessive disease (*DJ1*, *PINK1*, *parkin*).⁷⁶ Although extremely important for insights into the molecular pathogenesis of the disease, genetic testing for these mutations is so far of little clinical relevance. Genetic testing for parkin mutations can be offered in young-onset cases of levodopa-responsive disease. However, the chance of identifying parkin mutations is less than 5% in sporadic cases with onset at younger than 45 years.⁷⁷ This probability is much greater in those with onset at younger than 30 years and in those with an affected sibling.⁷⁷ Confirmation of this recessive form of disease might be helpful in genetic counselling because it renders transmission to the subsequent generation very unlikely. Genetic testing for α -synuclein gene

multiplications is rarely warranted in patients with autosomal-dominant pedigrees. Duplications seem to cause a classic phenotype, whereas more progressive disease, including dementia with Lewy bodies, occurs in cases with triplications.^{41–43} Overall, however, α -synuclein gene multiplication is not a common cause of Parkinson's disease or dementia with Lewy bodies.⁷⁸ Most recently the gene that causes another form of autosomal dominant Parkinson's disease *PARK8* has been identified: different point mutations in the gene encoding a leucine-rich repeat kinase (*LRRK2*) have been found in several families with autosomal dominant parkinsonism.^{79,80} Mutations in the *LRRK2* gene have subsequently been identified in 5–6% of patients with autosomal-dominant disease,^{81,82} and screening for a single common *LRRK2* mutation yielded positive results in 1.6% of patients with apparently sporadic disease.⁸³ These most recent figures suggest that screening for *LRRK2* mutations could become important in the diagnostic work-up and counselling of patients with Parkinson's disease. Currently, access to molecular genetic testing for the two most common mutations (*parkin* [*PARK2*], *LRRK2* [*PARK8*]) is still restricted to research centres and costs are high.

Drug challenge tests

Dopaminergic responsiveness has been proposed as a key prospective supporting feature in established clinical criteria for Parkinson's disease.⁵ Barker and colleagues⁸⁴ were first to suggest that responsiveness of parkinsonism to acute apomorphine challenges would differentiate between idiopathic Parkinson's disease and atypical parkinsonian disorders, such as multisystem atrophy and progressive supranuclear palsy. This notion was subsequently confirmed by several studies^{85–87} and acute levodopa challenge tests have yielded similar results.^{88,89} Overall positive and negative predictive values of acute dopaminergic challenge tests are suboptimum and the negative predictive value in de-novo patients is only between 40% and 60%.^{87,88} On the other hand, around 20% of patients with the parkinsonian variant of multiple system atrophy may initially show a good or marked response to levodopa, and levodopa responsiveness has also been reported for vascular parkinsonism.^{90,91} Patients with progressive supranuclear palsy who present with prominent parkinsonism may respond favourably to levodopa preparations.⁵⁴ Although an excellent and sustained response to levodopa treatment is supportive of a diagnosis of Parkinson's disease, negative results of an acute challenge test in de-novo cases are of little diagnostic value and should not discourage a rigorous trial of adequately dosed oral levodopa before concluding a non-responsiveness (>1000 mg/dL for at least 2 months). A review showed similar diagnostic accuracy of chronic dopaminergic therapy and acute challenge tests.⁹²

	PD ⁷¹	DLB ⁷²	MSA ⁷³	PSP ⁷⁴	CBD ⁷⁵
Dementia		+			
Apraxia					+
Akinesia	+	+	+	+	+
Rigidity	+	+	+	+	+
Tremor	+	+			
Gait disorder		+	+	+	+
Falls		+		+	+
Dysarthria		+	+	+	+
Dysphagia		+		+	
Gaze palsy				+	
Autonomic failure		+			

PD=Parkinson's disease; DLB=dementia with Lewy bodies; MSA=multisystem atrophy; PSP=progressive supranuclear palsy; CBD=corticobasal degeneration. + denotes features present in more than 70% of patients in post-mortem series.

Table 1: Frequency of clinical characteristics in parkinsonian disorders

Clinical neurophysiology

Clinical neurophysiological findings, including electroencephalography, somatosensory evoked potentials, anal sphincter-electromyography, or acoustic startle responses, are usually normal in patients with Parkinson's disease. Neurophysiological tests, such as measurements of long latency-reflex times, Bereitschaftspotential studies, and intracortical inhibition studied with transcranial magnetic stimulation have, however, yielded abnormal findings indicative of subcorticomotor or corticomotor loop dysfunction.^{93–95} Some neurophysiological abnormalities have been suggested as differential diagnostic markers for atypical parkinsonian disorders, such as abnormalities of sympathetic skin response and heart-rate variability in multisystem atrophy,⁹⁶ abnormal startle responses⁹⁷ and pathological sphincter-electromyography^{98,99} in multisystem atrophy and progressive supranuclear palsy, cortical myoclonus in corticobasal degeneration,¹⁰⁰ and slowing versus delayed initiation of saccades in progressive supranuclear palsy versus corticobasal degeneration.¹⁰¹ None of these seems to be highly specific for any particular form of degenerative parkinsonism and clinical neurophysiology is of little value in diagnosing parkinsonism in routine clinical practice.

Autonomic function testing

Autonomic failure is a key diagnostic feature of multisystem atrophy and an essential part of current diagnostic criteria.⁵⁸ Cardiovascular reflex testing and urodynamic function studies have been used to differentiate the parkinsonian variant of multisystem atrophy from Parkinson's disease. A study showed drops in blood pressure of more than 30 mm Hg systolic or more than 15 mm Hg diastolic with head-up tilt in about 50% of patients with multisystem atrophy versus 20% of patients with Parkinson's disease.¹⁰² Therefore, the presence of orthostatic hypotension does not distinguish between Parkinson's disease and multisystem atrophy, although orthostatic drops in blood pressure are greater and clinically significant orthostatic hypotension occurs

earlier in the course of disease in multisystem atrophy than in Parkinson's disease.¹⁰³ Urodynamic studies show characteristic patterns of dysfunction in multisystem atrophy, including detrusor hyper-reflexia and abnormal urethral sphincter function, but similar findings may be seen in later stages of Parkinson's disease.^{103,104} When patients with parkinsonism and symptoms of dysautonomia were studied, none of the routinely used autonomic function tests was able to discriminate between multisystem atrophy and Parkinson's disease.¹⁰⁵ By contrast with these disorders, patients with progressive supranuclear palsy usually show normal results with tests of autonomic function.¹⁰⁶ Overall, the importance of autonomic-function testing in the early differential diagnosis of de-novo patients with Parkinson's disease versus multisystem atrophy or progressive supranuclear palsy is not established.

Olfactory testing

Various studies have unequivocally established olfactory dysfunction as an early clinical sign in Parkinson's disease, which affects 90% of patients.¹⁰⁷ Olfactory dysfunction is a less frequent finding in the parkinsonian variant of multisystem atrophy, is also mild in patients with progressive supranuclear palsy,^{107,108} and has been shown to be largely intact in vascular parkinsonism.³³ Although almost universal in Parkinson's disease, hyposmia does not seem to occur in patients with young-onset parkinsonism who carry mutations in the parkin gene,¹⁰⁹ which raises the issue of specificity of hyposmia to Lewy body disorders or synucleinopathies. A study of olfactory function in 361 first-degree relatives of patients with Parkinson's disease identified 40 individuals with strictly defined hyposmia on the basis of impaired odour detection, discrimination, and identification. These clinically asymptomatic individuals, as well as 38 normosmic controls, were followed up with clinical examination and dopamine-transporter (DAT) single-photon-emission computed tomography (SPECT) imaging over 2 years when 10% of the hyposmic patients with reduced DAT binding at baseline developed clinical Parkinson's disease. The remaining hyposmic people showed a significantly increased decline of DAT binding during follow-up compared with none of the normosmic controls.¹¹⁰ Most of the previous studies of olfaction in parkinsonian disorders have used the University of Pennsylvania smell identification test, but Sniffin Sticks have been used to demonstrate reduced olfaction thresholds and discrimination in patients with Parkinson's disease.¹¹¹ The smell identification test has the advantage of self-administration by patients, but is more costly than its European counterpart and includes some odours that are not suitable for testing olfaction outside the USA. Despite the different methods used, these results draw attention to the potential of olfactory function testing as a screening tool for people at risk for the disease.

Imaging

Structural brain imaging with cranial CT is normal in uncomplicated Parkinson's disease. There may be age-associated abnormal changes, such as mild-to-moderate degrees of cortical and subcortical atrophy or signs of cerebrovascular disease with lacunar white matter lesions. These latter pathologies may raise diagnostic issues when they are deemed substantial enough to cause vascular parkinsonism or when parkinsonian signs have developed contralaterally to a basal ganglia infarct.^{25,26,112} Cranial CT is useful also in detection of normal pressure hydrocephalus in patients with so-called lower body parkinsonism who present with small stepped gait, freezing, and instability, but has limited sensitivity to detect cerebellar or pontine atrophy in multisystem atrophy, midbrain atrophy in progressive supranuclear palsy, or asymmetrical parietal cortical atrophy in corticobasal degeneration.

MRI has substantially greater differential diagnostic potential in degenerative parkinsonian disorders. Although signal void in the substantia nigra with high-field MRI has been reported in Parkinson's disease, no specific MRI marker for the disease has been identified.¹¹³ The true value of MRI in parkinsonian disorders is in differentiation of Parkinson's disease and atypical parkinsonism. Several structural MRI changes have been described for multisystem atrophy, progressive supranuclear palsy, or corticobasal degeneration (panel 2) and some of these changes have high specificity and positive predictive values. However, sensitivity is generally only around 60–80% or less.^{113–119} Sensitivity to detect changes of striatal signal intensity in the parkinsonian variant of multisystem atrophy can be increased above 80% with 3–5 mm slice thickness.¹²⁰ Complete separation of idiopathic Parkinson's disease from multisystem atrophy and progressive supranuclear palsy has been achieved with sophisticated techniques of MR volumetry, but this approach is not widely applicable.¹²¹ MR spectroscopy has revealed decreased N-acetyl-aspartate to creatinine ratios in the striatum of patients with parkinsonism compared with controls. This reduction may be greater in multisystem atrophy than in idiopathic Parkinson's disease, but there is substantial overlap.^{122–124} More recently, diffusion-weighted MRI has been used to differentiate between the disorders on the basis of changes of diffusivity of water molecules along fibre tracts, which were postulated to occur with striatal pathology in atypical parkinsonian disorders but not in the intact striatum of Parkinson's disease.^{125,126} Initial studies have yielded close to 100% sensitivity and specificity for differentiation of these disorders on the basis of increases in regional diffusion coefficients in the putamen. Three-dimensional diffusivity measurements with tensor MRI could further enhance this type of differentiation and diffusion-weighted MRI could prove a valuable routine parameter in the early differentiation between Parkinson's disease and other types of degenerative parkinsonism.

Panel 2: Routine MRI findings in degenerative parkinsonism

Parkinson's disease

Substantia nigra signal void on high-field MRI

Multisystem atrophy

Infratentorial pathology

Medullary and pontine atrophy

Cerebellar and dentate atrophy

Hyperintensity of middle cerebellar peduncle, cerebellum, inferior olives, pontine fibres (hot-cross bun sign)

Dilated fourth ventricle

Supratentorial pathology

Putaminal atrophy and/or hypointensity

Putaminal lateral hyperintensity (slit sign)

Progressive supranuclear palsy

Dilated 3rd ventricle

Midbrain atrophy

Globus pallidus hyperintensity

Nucleus ruber hyperintensity

Frontal cortical atrophy

Temporal cortical atrophy

Corticobasal degeneration

Asymmetric parietal cortical atrophy

SPECT

Iodine-123 labelled 3-iodo-6-methoxybenzamide (IBZM) was the first SPECT tracer to be used for diagnostic purpose in Parkinson's disease. IBZM binds to D2-dopamine receptors in the striatum. Brücke and colleagues¹²⁷ were first to show that striatal IBZM binding is low in parkinsonian disorders with striatal pathology compared with that in Parkinson's disease. Reduced D2-receptor binding with IBZM-SPECT in multisystem atrophy or progressive supranuclear palsy was subsequently confirmed in numerous studies and some authors have established correlations between results of dopaminergic drug challenge tests and IBZM binding using SPECT.^{128–130} The limitation of diagnosing Parkinson's disease with IBZM-SPECT is the large overlap in postsynaptic D2-receptor binding between patients with the disease and those with multisystem atrophy or progressive supranuclear palsy. A comparative study of diffusion-weighted MRI and IBZM-SPECT has found greater differentiation with diffusion-weighted MRI.¹³¹

Presynaptic dopaminergic terminal SPECT ligands have been introduced into clinical practice. The two commonly used tracers are tropane derivatives— β -CIT and FP-CIT (DaTSCAN)—which bind to the DAT protein of nigrostriatal nerve endings. Several studies have shown asymmetrical reductions in striatal DAT binding with SPECT, even in very early stages of disease.^{132–134} DAT-SPECT has therefore been proposed as a sensitive

early diagnostic marker for Parkinson's disease with differential diagnostic potential for non-parkinsonian tremor disorders, drug-induced parkinsonism, psychogenic parkinsonism, or vascular parkinsonism.^{135–138} The technique might also improve diagnostic accuracy in clinically uncertain parkinsonian syndromes.¹³⁹ DAT-SPECT imaging has also been used as a surrogate marker for disease progression since striatal tracer binding has been shown to be correlated with severity and duration of disease.¹⁴⁰ Although specificity of abnormal DAT-SPECT is high for differentiation of Parkinson's disease from essential tremor, secondary parkinsonism, or psychogenic parkinsonism there is still an unresolved issue about sensitivity. About 10% of clinically diagnosed patients with de-novo Parkinson's disease may have normal DAT binding with available SPECT tracers and whether this is due to limitations of sensitivity or lack of clinical diagnostic accuracy is unclear.^{141,142} DAT-SPECT cannot differentiate between nigrostriatal denervation due to Parkinson's disease and multisystem atrophy, progressive supranuclear palsy, or corticobasal degeneration, although progression of loss of tracer binding over time may be faster in the latter group of disorders.¹⁴¹ However, a study that used voxel-based statistical parametric mapping techniques was able to differentiate Parkinson's disease from multisystem atrophy with greater than 90% specificity on the basis of DAT-SPECT imaging.¹⁴³ SPECT investigation of sympathetic cardiac innervation with iodine-123 labelled meta-iodobenzylguanidine (MIBG) could be another useful test for early differential diagnosis of parkinsonism. Available studies have consistently shown loss of tracer binding in patients with Parkinson's disease, indicating postganglionic sympathetic cardiac denervation, which contrasts with the finding of preserved cardiac binding of MIBG in patients with multisystem atrophy or progressive supranuclear palsy.^{144,145} Overall, published reports indicate that cardiac MIBG-SPECT can accurately discriminate Parkinson's disease from multisystem atrophy with more than 90% sensitivity and specificity.¹⁴⁶ A study has raised some caution, however, by showing normal MIBG-binding in early stages of Parkinson's disease.¹⁴⁷

PET

Asymmetrically reduced putaminal uptake of the presynaptic dopaminergic PET ligand fluorine-18-labelled-dopa (18F-dopa) has been established as a characteristic finding in patients with Parkinson's disease. Reductions in putaminal Ki-values of 18F-dopa uptake have been correlated with disease duration and severity^{148,149} and have been used as surrogate markers for disease progression in recent intervention studies.¹⁵⁰ 18F-dopa PET has been able to identify preclinical nigrostriatal terminal dysfunction in first-degree relatives of patients, some of whom developed disease during follow up.^{151,152} However, up to 10% of individuals

with a clinical diagnosis of Parkinson's disease might have normal 18F-dopa PET findings and, similar to DAT-SPECT, whether this suggests imperfect sensitivity or clinical diagnostic errors is unclear.¹⁵⁰ Patterns of striatal 18F-dopa uptake differ between Parkinson's disease and multisystem atrophy or progressive supranuclear palsy, but 18F-dopa PET has little potential to differentiate between these parkinsonian disorders.^{153,154} This caveat also applies to PET studies of striatal D2-receptor function with carbon-11-labelled raclopride, a specific ligand for dopamine-D2-receptors.¹⁵⁵ 18-fluorodeoxyglucose (FDG) PET is able to detect striatal hypometabolism, thereby distinguishing multisystem atrophy and progressive supranuclear palsy from Parkinson's disease.^{156,157} Overall, restricted availability and high costs do not allow the use of PET in the routine clinical work-up of patients with parkinsonism.

Midbrain sonography

Transcranial B-mode-doppler-sonography can be used to visualise brain parenchyma.¹⁵⁸ Becker and colleagues¹⁵⁹ were first to describe hyperechogenicity of the substantia nigra with transcranial ultrasound midbrain imaging in patients with Parkinson's disease compared with controls.¹⁵⁹ Various studies have since confirmed that more than 90% of patients with a clinical diagnosis of Parkinson's disease will show hyperechogenicity of the substantia nigra.^{160,161} Around 9% of healthy controls also show significant hyperechogenicity in the parkinsonian range and a proportion of these individuals have been shown to exhibit subtle deficits in motor tests and reduced putaminal 18F-dopa uptake with PET compared with those without substantia nigra-hyperechogenicity.¹⁶² One study showed that almost 50% of first-degree relatives of patients with a clinical diagnosis of idiopathic Parkinson's disease also show hyperechogenicity of the substantia nigra and this finding

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE (up to July, 2005) and references from relevant articles. Other papers for inclusion were identified from the personal files of the authors, from previous reviews of the subject, either by these authors or by other authors, and from our editorial board duties on neurology journals. Only articles in the English language were reviewed.

correlated with impaired performance on some motor tests and reduced 18F-dopa uptake with PET.¹⁶³ Additionally, hyperechogenicity of the substantia nigra has been suggested as a differential diagnostic marker.¹⁶⁴ Taken together, these findings suggest that transcranial ultrasound examinations of the midbrain could be an easy accessible and non-expensive tool to lend support to a clinical diagnosis of Parkinson's disease. Further studies are needed to establish its role as a screening instrument to identify individuals at risk of the disease.

Conclusion

A correct diagnosis of Parkinson's disease is a prerequisite for patient counselling and therapeutic management. Despite all recent advances in imaging and genetics of parkinsonian disorders the diagnosis of Parkinson's disease remains a primarily clinical exercise. However, clinical diagnostic uncertainty is high at initial presentation and up to 30% of patients initially diagnosed as having the disease are clinically reclassified, even in specialised units.¹⁰ Imaging studies that used DAT-SPECT or diffusion-weighted MRI could improve differential diagnosis of parkinsonism, but cost-effectiveness remains to be established. Genetic testing is useful in only a few cases and only LRRK2 mutations seem to be a potentially reliable genetic screening target in patients with sporadic late-onset disease. Table 2 summarises the role of ancillary studies in the diagnosis of Parkinson's disease. The future challenge in diagnosis of the disease, however, lies in the definition of screening tools for individuals at risk and the development of preventive therapies.

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Authors' contributions

All three authors contributed similarly to the manuscript. ET was the primary author in the section on clinical differential diagnosis of parkinsonism and WP and GW of the section ancillary tests in the differential diagnosis of Parkinson's disease. All three critically reviewed the entire manuscript.

Conflicts of interest

We have no conflicts of interest.

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	Early (preclinical) diagnosis	Differential diagnosis	Availability	Cost
Drug challenge	–	++	Broad	Low
Olfactory testing	?	?	Broad	Low
Clinical neurophysiology	–	+	Restricted	Medium
Autonomic function testing	+	+	Restricted	Medium
Ultrasound	?	?	Broad	Low
CT	–	+	Broad	Medium
MRI	–	++	Restricted	Medium
SPECT				
DAT	++	+	Broad	Medium
IBZM	–	+	Broad	Medium
PET				
¹⁸ F-dopa	+	+	Restricted	High
¹⁸ FDG	–	+	Restricted	High
¹¹ C-raclopride	–	+	Restricted	High

– not useful; + limited usefulness or research use; ++ role in routine practice; ? further studies needed to verify. Cost: low = <€ 100 per test; medium = € 100–1000 per test; high = >€ 1000 per test.

Table 2: Role of ancillary studies in the diagnosis of Parkinson's disease

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