Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism

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In this review we discuss the epidemiological, clinical, and genetic characteristics of early-onset parkinsonism, defined as parkinsonism starting before age 40 (sometimes 50) years. Juvenile parkinsonism is very rare and is the result of various secondary or genetic causes. In patients with onset at or above age 21 years, secondary causes require exclusion but are rare; most cases with a fairly pure parkinsonian syndrome (eg, young-onset Parkinson’s disease; YOPD) are due to typical Lewy-body Parkinson’s disease or, less commonly, genetic causes. In comparison with patients with late-onset disease, most patients with YOPD progress more slowly in terms of motor features and have a longer disease course with preservation of cognitive function, but typically develop motor fluctuations and dyskinesias earlier. Patients with YOPD generally experience a greater effect in their lives than those with late onset, with poorer social adjustment, higher rates of depression, and lower quality of life. Management of YOPD must therefore aim to maintain occupational, social, and daily functioning, while delaying or ameliorating motor complications of treatment, providing psychological support, and, where possible, preventing psychiatric complications including depression.

Introduction

Early-onset parkinsonism refers to patients presenting with a parkinsonian syndrome with onset before age 40 years, although some authors include onset up to age 50 years. The incidence of early-onset parkinsonism in the USA is 0.8 per 100 000 per year in those aged 0–29 years, rising to 3.0 per 100 000 per year in those aged 30–49 years. However, because of the long disease course of Parkinson’s disease—particularly in those with early onset—of all patients with Parkinson’s disease 3–5% have onset before age 40 years; this is as high as 10% in Japan. Early-onset parkinsonism has been further subdivided into cases with onset before age 21 years (juvenile parkinsonism) and those with onset at or above age 21 years; within the latter group, patients with a primarily parkinsonian phenotype have usually been defined as having young-onset Parkinson’s disease (YOPD). Several clinical, pathological, and genetic findings give support to the arbitrary division between juvenile parkinsonism and YOPD: juvenile parkinsonism is very rare, at least in Western societies, is commonly familial, and most patients have atypical features and pathology. By contrast, YOPD has a rising incidence with increasing age, is less commonly familial, and both the clinical picture and the pathology, with the exception of some of the genetic forms, usually resemble that of older-onset Parkinson’s disease. Juvenile parkinsonism and YOPD will therefore be considered separately in this review (panel).

Juvenile parkinsonism

Although juvenile parkinsonism is rare, it seems to be more common in Japan than elsewhere; this may be related to historically high rates of consanguinity in the Japanese population as the disorder is commonly familial and the proportion of patients with a genetic disorder in juvenile parkinsonism is high. In those patients with a pure parkinsonian syndrome without additional features, most cases are due to mutations in the parkin gene. The main differential diagnoses are Wilson’s disease and dopa-responsive dystonia. Young-onset Huntington’s disease may present with a parkinsonian phenotype (the Westphal variant) and is an important diagnostic consideration especially in the presence of an autosomal dominant pedigree. In patients with additional non-parkinsonian neurological features, Wilson’s disease and dopa-responsive dystonia must be considered alongside a wide range of other genetic, metabolic, toxic, and structural causes that should be excluded with appropriate investigations (many of these causes have been extensively reviewed by Paviour and colleagues). Some of the more important differential diagnoses and relevant diagnostic tests that might need consideration in juvenile parkinsonism are shown in the table.

Panel: Definitions used in this review

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>Parkinson’s disease at any age</td>
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<tr>
<td>Early-onset parkinsonism</td>
<td>All causes of parkinsonism starting below age 40 years; however, some studies use age 50 years as the cut off</td>
</tr>
<tr>
<td>Juvenile parkinsonism</td>
<td>Subset of early-onset parkinsonism presenting below age 21 years</td>
</tr>
<tr>
<td>YOPD</td>
<td>Subset of early-onset parkinsonism, with onset at or above age 21 years, and a clinical phenotype resembling “typical” Parkinson’s disease. Most patients will have Lewy-body Parkinson’s disease (particularly with increasing onset age) or, more rarely, a genetic form of parkinsonism.</td>
</tr>
</tbody>
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http://neurology.thelancet.com Vol 5 April 2006
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**Important, potentially treatable causes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Investigations</th>
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</thead>
<tbody>
<tr>
<td>Wilson’s disease</td>
<td>Copper, caeruloplasmin in serum, 24-h copper excretion, Kayser-Fleischer rings, liver biopsy</td>
</tr>
<tr>
<td>Dopa-responsive dystonia-parkinsonism</td>
<td>Phenylalanine loading test, dopamine transporter single-photon emission CT, fluoroethoxy PET</td>
</tr>
<tr>
<td>Drug-induced parkinsonism</td>
<td>History of neuroleptic medication, antiretines, calcium-channel blockers, and others, dopamine transporter single-photon emission CT</td>
</tr>
<tr>
<td>Structural lesions (stroke, space-occupying lesions, central extrapontine myelinolysis)</td>
<td>Brain MRI of basal ganglia, supratentorium, and posterior fossa</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Brain CT/MRI</td>
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**Genetic causes**

- PARK1, 2, 6, 7, 8
- Huntington’s disease (Westphal variant)
- Spinoocerebellar ataxia (especially spinoocerebellar ataxia types 2 and 3)
- Neuroacanthocytosis
- Rapid onset dystonia-parkinsonism
- X-linked dystonia-parkinsonism (Lubag)
- Leigh’s and other mitochondrial diseases
- Niemann Pick type C
- Juvenile neuronal ceroid lipofuscinosus
- Gaucher’s disease
- Hallervorden-Spatz syndrome/pantothenate kinase-associated neurodegeneration and HARP
- Neuroendometriopathy
- Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)
- Cerebrotendinous xanthomatosis

**Other**

- Carbon monoxide poisoning and other toxins
- Systemic lupus erythematosus
- Fahr’s syndrome
- Infectious/postinfectious causes
- Primary neurodegenerative
  - Idiopathic Parkinson’s disease
  - Multiple system atrophy

**Table: Important causes of early-onset parkinsonism and relevant investigations**

**YPD**

Although the differential diagnosis of a patient with early-onset parkinsonism starting at or after age 21 years is similar to that for juvenile parkinsonism (table), secondary parkinsonism is much less common in this age group and becomes increasingly rare with increasing age at onset. Nevertheless, Wilson’s disease, dopa-responsive dystonia, drug-induced parkinsonism, and structural causes must be excluded in any young patient presenting with parkinsonism—even in the absence of other neurological features—and various other diagnoses might need consideration depending on the clinical phenotype (table).

In patients with early-onset parkinsonism with onset at or after age 21 years and a typical Parkinson’s disease phenotype (YPD), the likelihood of a family history of Parkinson’s disease is increased compared with both the general population and patients with late-onset Parkinson’s disease, although the percentage with affected family members differs between studies.**26** Despite increasing evidence that late-onset Parkinson’s disease may also have a substantial familial component, available evidence still suggests that hereditary components play a greater part in the origin of YOPD than of older-onset Parkinson’s disease.**20–25** About 50% of patients with YOPD and a positive family history have parkin mutations. In isolated cases of early-onset Parkinson’s disease, about 80% of those with onset before age 20 years will harbour a parkin mutation, but in patients with onset over age 30 years this figure is reduced to around 3%. Some cases of apparently idiopathic YOPD may also be due to either very rare and atypical genetic abnormalities, or as yet unidentified genetic defects. Different genetic diseases might have different phenotypic presentations in certain ethnic groups: spinoocerebellar ataxia type 2 can present with a pure parkinsonian phenotype, particularly in Asian populations; and spinoocerebellar ataxia type 3 should be considered in African patients presenting with familial Parkinson’s disease. However, even though other genetic mutations can cause YOPD, most patients will not have an identifiable genetic cause.

On the other hand, patients with YOPD are less likely than their older counterparts to have other degenerative diseases or substantial vascular disease as a cause of their parkinsonism. Thus, progressive supranuclear palsy, multiple system atrophy,**26** and corticobasal degeneration,**27** are important potential mimics of idiopathic Parkinson’s disease in people over age 50 years, but are very rare in those under age 50 years: symptom onset under age 30 years is an exclusion criterion for a diagnosis of multiple system atrophy;**28** no patients with pathologically confirmed progressive supranuclear palsy had disease onset before age 40 years; and no patients with pathologically confirmed corticobasal degeneration had onset before age 45 years.**29**

**Clinical features**

The clinical features of YOPD are generally similar to those of classic, older onset Parkinson’s disease. However, there are several characteristics that seem to cluster together in young-onset presentations of the disease, and data-driven approaches have confirmed a degree of
phenotypic homogeneity in YOPD.25,26 Patients with YOPD tend to have slower disease progression than those with later onset,26,27 particularly with regard to falls and freezing; similarly YOPD is found to be associated with less cognitive decline, at least until a more advanced age.7 By contrast, more patients with YOPD have earlier motor complications, such as dyskinesias, dystonia (which is commonly painful), and motor fluctuations; dyskinesias can become violent and disabling and motor fluctuations unpredictable and severe.7,28

The onset of YOPD can be unusual: dystonia is common at onset, and there can even be paroxysmal exercise-induced dystonia, with later development of parkinsonism.29 Despite slower progression of motor features and later development of cognitive impairment, mortality in YOPD is at least two times that of the normal population,7 and may be worse than in older-onset cases,30 although there are no direct comparative epidemiological studies. Mean survival in patients with YOPD is around 20 years with large variability from 10 years to 40 years.7

**Imaging studies and pathology**

The results of structural imaging in YOPD are typically normal; functional imaging with PET or single photon emission CT generally reveals similar findings to those in classic Parkinson’s disease with presynaptic dysfunction of nigrostriatal dopaminergic neurons,31,32 although this may be particularly severe in some of the genetic forms. In patients with Parkinson’s disease that cannot be clinically distinguished from drug-induced parkinsonism or dopa-responsive dystonia, the results of dopamine-transporter imaging, which are normal in the latter two conditions, can be a useful diagnostic aid.33 (figure). In contrast with juvenile parkinsonism, pathological studies show that most patients with YOPD have classic Parkinson’s disease pathology, although the degree of nigral-cell loss seems to be greater in young-onset patients than in patients with late onset.16

**Monogenetically inherited early-onset parkinsonism**

Several genetic mutations cause early-onset parkinsonism;34 in particular, mutations in the parkin (PARK2) gene cause a substantial proportion of juvenile parkinsonism and YOPD, particularly if the parkinsonism is relatively “pure”, and if there is positive family history. Several other genes cause Parkinson’s disease (reviewed by Healy and colleagues34 and Gasser35), particularly early-onset parkinsonism, and new loci are still being identified.

**Alpha-synuclein gene (SNCA; PARK1)**

An autosomal dominantly inherited mutation in the α-synuclein gene on chromosome 4q was first identified in a large family from the village of Contursi in southern Italy (PARK1).36 The clinical phenotype associated with this mutation is similar to that of classic Parkinson’s disease, apart from early onset (on average in the fourth decade). However, atypical features—including prominent dementia, hypoventilation, and severe autonomic disturbances—have also been described.37 The results of PET imaging reveal a pattern of dopamine deficiency, with preserved dopamine D2-receptor-binding, indistinguishable from older-onset Parkinson’s disease,38 and pathological changes are typical, albeit more widespread,37 with Lewy-body deposition at postmortem.16 Two other mutations of the α-synuclein
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Disability and appears greater than may be expected on the PET abnormalities does not correlate with clinical dopaminergic dysfunction.\textsuperscript{32,52} The severity of fluorodopa expression is found in Japan,\textsuperscript{47} but has subsequently been shown in several other populations.\textsuperscript{42,43} Some mutations in the chromosome 4q region have been associated with a phenotype overlapping with diffuse Lewy-body disease.\textsuperscript{4} Aside from these mutations’ scientific importance, particularly because α-synuclein is a major component of Lewy bodies,\textsuperscript{8} these mutations are rare and are not usually considered in the differential diagnosis of YOPD.

Parkin gene (PARK2)
The most common monogenic cause of early-onset parkinsonism is due to mutations in the parkin gene on chromosome 6q.\textsuperscript{4,10} The disease is autosomal recessive, and numerous mutations in parkin have been described to date.\textsuperscript{14,44} PARK2-regulated YOPD was initially reported in Japan,\textsuperscript{6} but has subsequently been shown in several other ethnic groups.\textsuperscript{4} About half of all patients with familial Parkinson’s disease with onset before age 45 years and a family history compatible with autosomal recessive inheritance have mutations in the parkin gene, and it causes about 10–20\% of apparently sporadic cases with onset before age 45 years.\textsuperscript{24,45} Disease onset is before age 40 years in most cases, although later onset may occur.\textsuperscript{10,12} An inheritance pattern suggesting autosomal dominant inheritance has also been reported in rare cases.\textsuperscript{15}

Clinically, patients with parkin mutations have a good response to anticholinergics and are very sensitive to small doses of levodopa; small doses can cause severe dyskinesia and occasional psychosis.\textsuperscript{12} Patients with these mutations show slow disease progression but may have early fluctuations and dyskinesias that may be atypical. Other features include early instability, freezing, festination or retropulsion, autonomic dysfunction, brisk reflexes, and sleep benefit.\textsuperscript{32,34} Dystonia is a common feature, and may be present at onset.\textsuperscript{12} Cognitive impairment is usually rare, although patients can have a high rate of psychiatric disturbance, including anxiety, psychosis, obsessive-compulsive disorder, and early behavioural disturbances.\textsuperscript{35} However, none of these features is specific to parkin-related disease and they can all be seen in other early-onset forms of Parkinson’s disease. Olfactory function is reduced in typical Parkinson’s disease,\textsuperscript{13} but is preserved in parkin-related Parkinson’s disease and may be a useful diagnostic discriminator.\textsuperscript{35,36} As the initial features can include dystonia, sleep benefit, and hyper-reflexia, parkin-related YOPD may resemble dopa-responsive dystonia. However, in parkin-related disease, motor fluctuations and dyskinesias appear rapidly, and the results of fluorodopa-PET reveal similar findings to those in typical Parkinson’s disease, with presynaptic dopaminergic dysfunction.\textsuperscript{32,34} The severity of fluorodopa-PET abnormalities does not correlate with clinical disability and appears greater than may be expected on the basis of clinical disease severity.\textsuperscript{37} Lewy bodies have been found in association with compound heterozygous parkin mutations.\textsuperscript{32,56} Otherwise, the typical pathology in parkin-related disease is severe neuronal loss and gliosis without Lewy bodies in the substantia nigra pars compacta and locus coeruleus.\textsuperscript{16} These findings have contributed to the ongoing debate as to whether the presence of Lewy bodies is needed for the diagnosis of Parkinson’s disease.\textsuperscript{52}

**PINK1 gene (PARK6)**
Mutations in the PINK1 gene, located on the short arm of chromosome 1 and encoding a mitochondrially located protein, cause autosomal recessive YOPD.\textsuperscript{27} Onset occurs at age 30–50 years, and the phenotype is again similar to parkin-related disease: focal dystonia and sleep benefit are less common but still present in a few patients.\textsuperscript{46} Dementia has been reported in early-onset cases with deletions in PINK1.\textsuperscript{33} PINK1 mutations seem to cause relatively few cases of YOPD but may be the second most common cause of autosomal recessive familial Parkinson’s disease after parkin.\textsuperscript{13,27} Whether heterozygous mutations in PINK1 (or in parkin or DJ-1) simply indicate carrier frequency in the general population\textsuperscript{9} or whether they are related to later-onset Parkinson’s disease, possibly through increasing susceptibility, is unclear.\textsuperscript{30,33} The pathology associated with PINK1 is unknown, but the results of PET imaging in both DJ-1 and PINK-related Parkinson’s disease show a more uniform pattern of striatal dopaminergic terminal dysfunction than is seen in classic Parkinson’s disease, greater dopaminergic dysfunction than expected in relation to clinical severity, and only mild dysfunction in asymptomatic carriers.\textsuperscript{38}

**LRRK2 gene (PARK8)**
The recent discovery that mutations in the leucine-rich repeat kinase 2 (LRRK2) gene coding for the protein dardarin\textsuperscript{39} can cause autosomal dominant Parkinson’s disease\textsuperscript{40,41} has led to a flurry of further papers.\textsuperscript{42–44} Mutations in LRRK2 can account for 5–6\% of familial\textsuperscript{36} and 1–2\% of apparently sporadic cases of PD.\textsuperscript{45} The clinical features and epidemiology of LRRK2-related Parkinson’s disease continue to be elucidated, but mutations are present in various populations.\textsuperscript{37,41} Most
patients have onset above age 50 years,\textsuperscript{7,75} and penetrance seems to be age related.\textsuperscript{81} Nonetheless, several cases of YOPD are associated with \textit{LRRK2} mutations, including a recent report of a mutation in a 28-year old with apparently sporadic disease.\textsuperscript{84}

The phenotype associated with \textit{LRRK2} mutations seems to be typical for Parkinson’s disease, with asymmetrical tremor, rigidity, and bradykinesia, and good response to levodopa.\textsuperscript{7,76} PET imaging shows maximum reduction of presynaptic dopamine synthesis in the putamen, similar to that in idiopathic Parkinson’s disease.\textsuperscript{7,81} However, pathology is highly variable, and can include typical Lewy-body pathology in the brainstem, more widespread Lewy-body deposition as seen in diffuse Lewy-body disease, neurofibrillary tangles similar to progressive supranuclear palsy, and neuropathological findings with none of these other features but pure nigrostriatal cell loss.\textsuperscript{7} These mutations may prove invaluable for our understanding of the mechanism of neurodegeneration in Parkinson’s disease, not only because they link several pathological patterns even within a single family, but also because they are found in patients with typical later-onset pathologically confirmed Parkinson’s disease.\textsuperscript{84}

**Management**

**Diagnosis**

Investigations in YOPD must be guided by clinical presentation and presence or absence of a family history. In those with additional neurological features, detailed investigation is needed to exclude secondary causes of parkinsonism. However, even in patients with apparently typical Parkinson’s disease, Wilson’s disease, dopa-responsive dystonia, structural abnormalities, and drug-induced parkinsonism should be considered and excluded where appropriate. Thus, in all patients, a history of neuroleptic or antiemetic drug use should be sought, and measurement of serum copper, caeruloplasmin, urinary 24 h copper excretion, assessment for Kayser-Fleischer rings, and brain MRI should be considered. In suspected cases of dopa-responsive dystonia, normal results on dopamine transporter scan,\textsuperscript{85} an abnormal phenylalanine concentration,\textsuperscript{86} or exquisite responsiveness to a trial of anticholinergic drugs can support the diagnosis; in such cases treatment with anticholinergics might be preferable to a trial of levodopa because of the risk of inducing early-motor complications in those who turn out to have YOPD. Genetic testing for dopa-responsive dystonia is offered by some centres, although not all patients with the disorder will have identifiable mutations in the GTP cyclohydrolase I (\textit{GTP-CHI}) gene.\textsuperscript{87} In patients with pure parkinsonism and juvenile onset, parkin-related disease is the most probable diagnosis. However, testing for this gene in most countries is only possible on a research basis. Deciding when to offer genetic testing for affected patients might not be straightforward, particularly given the potential implications for other family members.\textsuperscript{88} In such cases, referral to a specialist centre should be considered.

**Medication**

The decisions as to when to start drug treatment and which drugs to use in patients with YOPD depend on several factors, including disease severity, functional disability, comorbidity, personal expectations, employment status, and psychosocial handicap. Because patients face a lifetime of a usually slowly progressive disease, and as motor complications begin early in these patients, management should be tailored to the individual whilst specifically aiming to delay and minimise the effect of motor complications. For this reason, the use of levodopa is usually deferred for as long as possible and the dose kept at the lowest clinically effective level.\textsuperscript{81} Alternative treatment options with non-dopaminergic drugs include inhibitors of monoamine oxidase B (selegiline hydrochloride or rasagiline mesilate), amantadine hydrochloride, or, where tremor is a particular problem, anticholinergics—although use of the latter might be restricted by cognitive side-effects.\textsuperscript{89–91}

When dopaminergic therapy is necessary, dopamine agonists are usually started before levodopa in YOPD because they delay the onset of dyskinesias compared with levodopa.\textsuperscript{75,81} There is an ongoing debate as to whether these drugs have additional neuroprotective effects.\textsuperscript{90} In common with all dopaminergic drugs, dopamine agonists can be associated with sudden sleep attacks\textsuperscript{90} which is of particular importance in young patients who work, are looking after young children, or who drive; accordingly patients should be counselled about such risks before therapy is started. Pulmonary and cardiac valve fibrosis are serious although rare side-effects particularly associated with pergolide mesilate and other ergot-containing dopamine agonists and can develop many years after initiation of treatment.\textsuperscript{91} Care should be taken to follow the manufacturer’s advice regarding screening for complications should these drugs be initiated, particularly in YOPD when treatment can continue for years.

Once other pharmacological and non-pharmacological measures are no longer sufficient to improve disability, fear of inducing extrapyramidal side-effects should not delay initiation of therapy with levodopa (combined with a peripheral decarboxylase inhibitor), which improves health-related quality of life in Parkinson’s disease.\textsuperscript{92} Whether early addition of entacapone, a reversible inhibitor of catechol-O-methyltransferase, to levodopa results in delay if motor complications is under investigation.

If and when motor complications develop, the addition and manipulation of doses of levodopa, dopamine agonists,\textsuperscript{93} and inhibitors of catechol-O-methyltransferase\textsuperscript{94} and monoamine oxidase B inhibitors\textsuperscript{95} can all be helpful in improving these complications and the
resulting disability. Controlled-release levodopa given at night can help nocturnal and early morning akinesia,\textsuperscript{5,11} and amantadine hydrochloride may help dyskinesias.\textsuperscript{103} However, when manipulations of oral antiparkinsonian drugs are exhausted, patients with YOPD with no cognitive impairment or other contraindications, may be good candidates for continuous apomorphine infusions\textsuperscript{5,10} or stereotactic surgery, including deep brain stimulation.\textsuperscript{16} Botulinum-toxin injections may help patients with dystonia. Apomorphine and surgical treatment options depend on the patient’s symptoms, functional disability, age, cognitive, psychiatric, and general medical status, as well as personal expectations and circumstances. Early involvement of a Parkinson’s disease specialist nurse and, where appropriate, referral to a specialist centre should be considered.

Even though treatment of motor dysfunction in YOPD is often the major challenge in many patients, there is increasing awareness of the burden of other non-motor symptoms including depression, anxiety, psychosis, sleep disturbance, fatigue, hypersalivation, constipation, urinary and sexual dysfunction, postural hypotension, pain, dysarthria, and dysphagia.\textsuperscript{107} These complications can be appropriately addressed in neurology clinics, but for many patients, referral to other medical and allied specialists may be appropriate.

**Psychosocial impact**

Although many features of Parkinson’s disease are no different in younger and older patients—ie, physical pain, immobility, and increasing dependence—the overall effect of the disorder in patients with young onset disease differs from that in older patients.\textsuperscript{108} Patients with young onset disease are more likely to become unemployed or to have to retire early because of their disability, and experience more family and marital problems. Patients with YOPD perceive greater stigmatisation, have higher depression scores, and they rate their quality of life as worse, on average, than patients with older onset who have similar disease severity.\textsuperscript{108} Even though more severe treatment-related motor complications and other disease characteristics could account for some of these differences, it is likely that social and psychosocial factors including role expectations probably contribute to greater impairment of quality of life in young patients.\textsuperscript{108} The effect of patients’ disease on their partners and children should be considered,\textsuperscript{106,118} and counselling\textsuperscript{106} of the whole family or cognitive behavioural therapy\textsuperscript{106} may be useful to address these particular difficulties. Where possible the involvement of an experienced Parkinson’s disease specialist nurse is invaluable.

Particular psychosocial issues that can affect patients with YOPD are those of pregnancy and employment. Pregnancy in patients with Parkinson’s disease is rare, but parkinsonism may temporarily or permanently worsen during pregnancy.\textsuperscript{119} Antiparkinsonian drugs are usually well tolerated in pregnancy with the exception of amantadine hydrochloride, which can induce obstetric complications.\textsuperscript{1} There is limited formal evidence as to the safety of dopamine agonists in pregnancy, although there are anecdotal reports of successful pregnancies on combinations of levodopa and cabergoline.\textsuperscript{104} Formal trials in pregnant women are clearly difficult to do, leading to calls for a database of pregnancy in Parkinson’s disease.\textsuperscript{114}

Employment is another important issue for patients and their families, not only because of financial implications but also because of the effect on role functioning, social contacts, and self-esteem. Although gainful employment can commonly be maintained for years, more patients with YOPD have to retire early (on average about 5 years after onset\textsuperscript{119}) than patients with older-onset Parkinson’s disease.\textsuperscript{109} However, there is considerable variability in time to loss of employment, indicating that information and support can influence the decision to leave work.

**Driving**

Many patients with YOPD will still be driving at the time of diagnosis, and this has implications for safety on the road, as well as choice of treatment. Cessation of driving can have particular implications for patients with YOPD not only in terms of loss of independence, but also in relating to self-esteem, and to employment. It is difficult for patients or clinicians to judge the safety of driving in Parkinson’s disease,\textsuperscript{115} but diagnosis on its own does not usually lead to withdrawal of a driving licence. However, there can be impairment of driving safety even in the absence of cognitive impairment, and so patients should be instructed to inform driving authorities and their driving insurer when a diagnosis of Parkinson’s disease is made.\textsuperscript{116} Specific warnings about somnolence and sleep attacks must be given before dopaminergic treatment is started, particularly with dopamine agonists but also with levodopa preparations.\textsuperscript{118} Reduction of dose or withdrawal of the offending medication leads to resolution of these side-effects in most cases.

**Conclusion**

Although alternative and potentially treatable causes of juvenile parkinsonism and YOPD need to be excluded, and some patients, particularly if there is a positive family
history, have an underlying genetic cause, most patients with YOPD have idiopathic Lewy-body Parkinson’s disease. The overall course of the disease in these patients is slower than in those who are older at onset, and particular attention needs to be paid to problems associated with longer disease duration, higher rate of motor complications, and the greater psychosocial impact in YOPD.

Acknowledgments
We acknowledge the department of Nuclear Medicine at the Royal Free Hospital, London, UK for the images.

Authors’ contributions
Both authors contributed to the writing of this review.

Conflicts of interest
We have no conflicts of interest.

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