THE BARE ESSENTIALS

Parkinson's disease

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Parkinson's disease is a progressive neurodegenerative disorder characterised by slowness of initiation of, and a progressive reduction in, the speed and amplitude of sequential movements (ie, motor decrement or decay), with muscular rigidity and a coarse slow pill rolling rest tremor. The pathological signature most frequently associated with this clinical picture is severe loss of pigmented neurons in the ventrolateral tier of the pars compacta of the substantia nigra with the presence of distinctive α synuclein immunoreactive inclusions in surviving nigral neurons (Lewy bodies).

EPIDEMIOLOGY

In the UK:

- prevalence about 1/800, annual incidence 1/8000
- 1% of people over the age of 65 years are affected
- a general practitioner will have three to four patients at any one time
- median age of onset is 60 years, with a slight male preponderance
- disease onset to death is about 15 years, twice the number of observed to expected deaths (standardised mortality ratio 2:1).

The disorder is no respecter of race or creed Literary and historical precedents to Parkinson's seminal description suggest it is unlikely to be a post-industrial disease. In common with other neurodegenerative diseases, increasing age is the major risk factor although 15% of cases present before the age of 45 years and the incidence may decrease somewhat in the ninth decade of life. Genetic factors are now considered to significantly increase risk.

Habitual non-cigarette smokers are twice as likely to develop the illness as smokers and there may also be a mildly increased risk to men who do not take any caffeine, perhaps related to dopamine's role in reward pathways, rather than due to a protective effect of nicotine or coffee. Loose associations with rural living, middle age, obesity and lack of exercise, well water ingestion and pesticide exposure have also been reported. Environmental toxins such as 1-methyl-4 phenyl 1,2,3,6 tetrahydropyridine, manganese, cyanide and toluene can produce a similar but not identical clinical picture.

MAKING THE DIAGNOSIS

The diagnosis of parkinsonism hinges on the presence of bradykinesia (akinesia and hypokinesia are often used synonymously with bradykinesia). This may be apparent as soon as a patient enters the consulting room but in other cases early diagnosis depends on scrupulous history taking and a detailed neurological examination. A coarse pill rolling rest tremor, muscular rigidity and postural abnormalities are commonly associated physical signs which support the diagnosis. Parkinson's disease is the commonest cause of bradykinesia but there is a long list of secondary and Parkinson-plus syndromes (table 1). Symptoms come on so insidiously that patients and their family may understandably attribute the early subtle changes to chronic fatigue, depression or ageing, even when a change in demeanour, posture and speed of movement is immediately evident to strangers.

Bradykinesia is responsible for the common presenting complaints of difficulty fastening buttons, cleaning teeth, deterioration in handwriting, increased number of typing errors, weakness of one leg, and reduction in volume and slowing of speech. To elicit bradykinesia, a series of distinct motor tasks should be carried out, making each movement as large and as fast as possible, and continued for about 20 s:

- touch each finger onto the thumb in turn
- tap the index finger on to the thumb
- carry out piano playing movements
- tap the foot on the floor.

The characteristic abnormalities of delayed initiation of movement, associated with a progressive motor decrement on repetition, may occur only with one of these tasks. The patient should then be asked to write four lines of long hand in the case notes. It is common for the script in Parkinson's disease to slope upwards and the writing is crabbed and becomes progressively smaller and smaller. Semiquantitative tapping and pegboard tests may also be helpful.

Slowness and awkwardness in at least one of these tasks strongly suggests parkinsonism but pyramidal and cerebellar lesions and the slowness associated with severe retarded depression and obsessive–compulsive disorder need to be distinguished. Bradykinesia can also be extremely difficult to elicit in a limb affected by severe tremor; a helpful supporting feature here is that patients with Parkinson's disease often hold their hand in

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Table 1 Causes of parkinsonism

- Common
  - Parkinson's disease
  - Iatrogenic
    - Prochlorperazine
    - Metaclopramide
    - Antipsychotics
    - Several calcium channel blockers
    - Amiodarone
    - Sodium valproate
    - Ciclosporin
    - Cytosine arabinoside
    - Lithium
    - Chloroquine
    - Cephaloridine
  - Progressive supranuclear palsy-parkinsonism
  - Multiple system atrophy-parkinsonism
  - Dementia with Lewy bodies
  - Diffuse subcortical white matter ischaemia
  - Lower half parkinsonism with marked gait apraxia
  - Acute vascular parkinsonism
- Uncommon
  - Autosomal recessive young onset parkinsonism
  - Infectious and postinfectious
    - HIV
    - Japanese B
    - Coxsackie B
    - Mycoplasma pneumoniae
    - Neurocysticercosis
    - Tuberculosis
    - Epstein–Barr
    - Poststreptococcal
  - Tumours in the basal ganglia and frontal lobes
  - Normal pressure hydrocephalus
  - Toxins
    - Chronic manganism
    - Heroin pyrolysate
    - Solvents
    - Methanol
    - Cyanide
    - n-Hexane
    - Organophosphates
  - Metabolic and endocrine
    - Carbon monoxide
    - Extrapontine myelinolysis
    - Uraemia with diabetic ketoacidosis
  - Hallervorden–Spatz syndrome and other neurodegenerative disorders associated with brain iron accumulation
  - Head trauma
    - Post-traumatic encephalopathy
    - Chronic subdural and extradural haematoma
  - Hemiparkinsonism/hemiatrophy
  - Familial idiopathic basal ganglia calcification

a fixed cataleptic attitude after completing each motor task rather than resuming a normal relaxed posture.

Tremor. A slow coarse pill rolling rest tremor of one hand or leg is the commonest neurological presenting symptom of Parkinson's disease but is insufficient alone to make the diagnosis without the presence of bradykinesia. Holmes tremor, severe essential tremor and dystonic and neuropathic tremors all may have a prominent rest component, while a postural and kinetic tremor is not infrequent in Parkinson's disease. Although most patients with Parkinson's disease have a tremor at some stage of their disease, it can be very mild and unobtrusive, while in others it can be severe, continuous, disabling and involve all four limbs, the lips and the jaw.

There are some rare cases of familial alcohol responsive essential tremor which after decades of stability evolve gradually into full blown Parkinson's disease. Some are erroneously given the label benign tremulous Parkinson's disease.

Rigidity. Muscular stiffness with aching discomfort may be an early complaint. Uniform resistance to passive stretch in a relaxed patient at the elbow, shoulder, knee or neck (ie, lead pipe rigidity) is the third cardinal sign of parkinsonism. A ratchety jerky resistance may also be elicited at the wrist (cogwheel phenomenon) and is a supportive finding. In contrast, spasticity is revealed by initial increased resistance to stretch followed by a sudden give way (clasp knife rigidity) and gegenhalten (an opposing voluntary resistance).

The importance of the history

The patient should be given ample time to describe the evolution and nature of their complaints. Wherever possible, a family member should be present and asked to contribute additional information once the history has been taken from the patient.

Specific questions may be necessary to determine the patient's ability to execute dextrous activities rapidly and adroitly:

- Difficulties doing up buttons, problems with stirring and wiping, and awkwardness in getting small objects out of bags and pockets are some of the common early complaints.
- Patients often blame faulty equipment for their difficulties such as the 'worn out towel', 'blunt knife', 'dripping wash cloth', 'the faulty car accelerator' or the 'defective keyboard'.
- Problems with clothes include the 'floppy sleeve', the 'narrow pocket', the' shrinking gloves' and the 'lop-sided belt'.

In patients who complain of a quivering hand it is particularly instructive to ask directly whether in hindsight any subtle changes in movement, posture or behaviour might have preceded the tremor.

Many patients also volunteer a specific trigger for their symptoms, such as a period of prolonged stress or an accident or operation.

Patients should be asked about parkinsonism, tremor and other neurodegenerative disorders in first degree relatives. If there is more than one affected relative or the patient presents before the age of 40 years, then the chance of a monogenetic form of parkinsonism is increased.

Any medications or herbal remedies?

A careful medication history, including enquiry about herbal remedies and health food intake

(kava kava, betel nut and snake root), may reveal a medication induced cause. Sodium valproate and some calcium channel blockers, including high doses of cinnarizine (Stugeron), are potentially rare reversible causes of parkinsonism and should be added to the list of iatrogenic causes which include prochlorperazine (Stemetil) for vertigo, metaclopramide (Maxolon) for dyspepsia, and proprietary combinations of nortryptiline and trifluoperazine for irritable bowel syndrome. Withdrawal of these drugs does not always lead to resolution of symptoms because they may have been responsible for revealing underlying Parkinson's disease.

THE PRODROMAL PHASE

Once the diagnosis of Parkinson's disease has been made, about a quarter of patients will describe a constellation of non-specific symptoms, which with hindsight may have been early manifestations of the disease:

- A severe depressive illness can usher in the motor symptoms although a misinterpretation of the early signs of akinesia as depression is a catch.
- Profound fatigue and slight poverty of thought and mental inflexibility are striking in some instances.
- Autonomic symptoms including a defective thermostat (profound drenching sweats in cold weather), disturbances of colonic mobility and dribbling of saliva onto the pillow at night are also well recognised, as is erectile failure.
- Frozen shoulder and chronic low back pain are common rheumatological presentations, probably as a consequence of immobility and postural abnormalities.
- Idiopathic REM sleep behaviour disorder (nightmares, shouting out and thrashing violently about in sleep and falling out of bed) may be a prodromal syndrome but is not specific. A bed partner needs to be interviewed about sleep patterns to evaluate the severity of this disturbance.
- Hyposmia may be a harbinger of Parkinson's disease. Formal testing of smell with either the University of Pennsylvania smell tests kit or Sniffin Sticks pens is needed to detect it. This seems to be much more common in Parkinson's disease than the other parkinsonian syndromes and essential tremor, so although not specific may help in distinguishing Parkinson's disease.

Many of these symptoms have been considered 'pre-motor' and support Braak's hypothesis that the disease begins in the peripheral autonomic system, olfactory bulb and the dorsal nucleus of the vagus and then spreads rostrally up the brainstem by a prion-like mechanism before finally invading the cerebral cortex. However, the detection of subtle motor abnormalities preceding the clinical diagnosis by over a decade in some observant young onset patients (eg, Ray Kennedy the England, Arsenal and Liverpool football player) suggests caution in assuming that autonomic and olfactory signs really do occur first. The disease process, however, almost certainly begins many years before the emergence of bradykinesia, rigidity and rest tremor.

Incidental diagnosis

- The distinctive hang dog habitus and sad slightly anxious expression can lead to diagnosis at routine medical checkups, or during the pre- or postoperative assessments for a minor surgical procedure.
- Self-referral for aches and pains to a physiotherapist or masseuse may lead to the detection of severe rigidity and subsequent neurological referral.
- Some patients and their families have already accurately diagnosed the condition by the time of the first referral, either by surfing the web or because a family member, close friend or colleague had similar symptoms.

Box 1 Some unusual motor presenting symptoms

- Clawing up of one foot during long distance running
- Swimming in circles
- The 'Rolex sign' (lack of arm swing leading to repeated technical failure of a self winding watch)
- Abnormal stillness when seated
- Poor timing leading to faulty dance steps
- Brief resting tremor of one hand only after yawning
- Unexplained episodes of gait festination and propulsion

Further points for attention during the examination

- Examination of eye movements is essential. Particular attention should be paid to any slowing (suggestive of progressive supranuclear palsy (PSP)) or delay in initiation (suggestive of corticobasal degeneration) of vertical saccadic movements, or the presence of horizontal square wave jerks or gaze evoked nystagmus (suggestive of multiple system atrophy (MSA)).
- A nasal slightly whining speech suggests MSA while patients with PSP have a very slow drawling growling component to their speaking.
- Virtually absent spontaneous blinking and apraxia of eyelid opening also suggest PSP-parkinsonism (PSP-P), the clinical subtype of PSP which may masquerade as Parkinson's disease.

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- Babinski signs in the absence of cervical spondylotic myelopathy or a past stroke should make one consider PSP, MSA or a genetic pallidopyramidal syndrome such as Hallervorden–Spatz syndrome or one of the other rare neurodegenerative disorders associated with brain iron accumulation (PLA2G6 neuroaxonal dystrophy and Kufor–Rakeb syndrome).
- Lying and standing blood pressure taken after 2 min is important because asymptomatic orthostatic hypotension (fall of standing blood pressure by 20 mm Hg or more) may increase the risk of syncope on starting dopaminergic medication. Autonomic failure is not incompatible with a diagnosis of Parkinson's disease but syncope preceding motor symptoms raises the possibility of MSA-parkinsonism (MSA-P).
- Tremor at rest in the arms should be looked for with both hands resting lightly on the knees in the sitting position, and also during finger movements with the contralateral hand which can bring out a latent tremor.
- Tremor of the hands may also be unmasked during walking, whereas tremor of the legs may be seen on sitting or lying.
- A delayed emergent tremor on holding the hands outstretched (with a latent interval of a few seconds before the tremor appears) is said to be helpful in distinguishing Parkinson's disease from essential tremor (in the latter the tremor is present immediately the arms are held out).
- Some patients can run better than they can walk, and ride a bicycle without difficulty, even when they have a shuffling gait and marked freezing.
- To explore cognitive function, general questions about the patient's ability to manage their finances, the timing and dosing of their medication, use mechanical equipment competently and their capacity to cope in social situations should be asked. If early dementia is suspected, then a Mini-Mental Score (<26) or the Addenbrooke's cognitive estimate ACE-R (<83) are useful. Patients with Parkinson's disease dementia have particular difficulties with executive and visuospatial tasks; visual hallucinations, delirium and daytime somnolence are common accompaniments.
- If dementia is present within the first year of the illness or actually precedes motor symptoms, then the term dementia with Lewy bodies is used rather than Parkinson's disease with dementia (although the underlying pathogenesis of these two clinical entities may be identical).

THE TELLING OF THE DIAGNOSIS

This must be unhurried, truthful and provide real hope. Patients need to be reassured that Parkinson's disease is treatable and no longer a death sentence. Optimistic examples of what can be achieved are helpful and young patients particularly may benefit from being put in touch with an articulate and positive patient of similar age who is doing well, either via the Parkinson's Disease Society, Cure Parkinson's Trust, or after prior consent.

CONFIRMING THE DIAGNOSIS

There are no mandatory laboratory or imaging investigations in the workup of parkinsonism; the diagnosis can be made with confidence in most cases on clinical grounds alone.

Most patients with Parkinson's disease have a sustained excellent response to dopaminergic therapy but in the early stages of disease it may be difficult to convincingly demonstrate improvement. A baseline Unified Parkinson's Disease Rating Scale parts 2 and 3 repeated again at 3 months may be useful in determining whether dopaminergic responsiveness has actually occurred. If doubt remains, the dose of medication should be doubled and a further review carried out after a month. If there is still no tangible subjective benefit on 750 mg/day levodopa or less than a 2 point change on the Unified Parkinson's Disease Rating Scale then a formal acute levodopa challenge using 250 mg dispersible levodopa/benserazide should be carried out using finger tapping and timed walking tests at baseline and then again at 1 and 2 h. Before this challenge, all antiparkinsonian medication should be stopped overnight and if the patient has experienced nausea or dizziness on long term levodopa, domperidone 30 mg three times daily should be given for 24 h.

In patients with a predominantly bradykinetic–rigid syndrome who have failed to improve with dopaminergic treatment, an MR brain scan should be ordered looking for changes suggestive of:

- MSA (pontine and cerebellar atrophy, pontine hot cross bun sign and hypointense lesions with hyperintense rim in the putamen on axial T2 sequences).
- PSP (midbrain and superior cerebellar peduncle atrophy).
- Vascular parkinsonism (severe subcortical white matter ischaemia and striatocapsular infarcts).
- Rarer causes of secondary parkinsonism (paramagnetic signals in the basal ganglia).

In predominantly tremulous patients, a dopamine transporter single photon emission computed tomography (DAT) scan may be helpful; absence of nigrostriatal dopaminergic degeneration effectively excludes Parkinson's disease but there are problems of standardisation and interpretation.

RARITIES NOT TO BE MISSED

There are a small group of rare causes of atypical and secondary parkinsonism where MRI and other investigations may provide the diagnosis.

- The most important are supratentorial meningiomas and communicating hydrocephalus because both are potentially surgically remediable.
- The eye of the tiger sign on MRI (T2 weighted star sequence imaging shows areas of hyperintensity surrounded by a larger area of hyperintensity in the medial globus pallidus) may point to Hallervorden–Spatz syndrome (PANK-2 mutation).
- The middle cerebellar peduncle sign on MRI (increased T2 signal in the white matter of the middle cerebellar peduncle) in a patient with tremor, ataxia and parkinsonism points to the fragile X premutation, particularly if the patient is male and there is a family history of mental retardation in a grandchild.
- Wilson's disease can present with parkinsonism in adolescence or young adult life but this is much rarer than either the dystonic or pseudosclerotic forms. These cases usually have associated neuropsychiatric problems, a Kayser–Fleischer ring visible with a hand lens on the back of the cornea, and a poor or absent response to levodopa. The diagnosis is confirmed by a very low serum caeruloplasmin and if doubt remains by a 24 h urinary copper collection, MR brain scan and liver biopsy to measure copper levels.
- Dopa responsive dystonia may sometimes have parkinsonian features and presents in young adults as well as in children. There are a number of different mutations of enzymes involved in catecholamine metabolism, including GTP cyclohydrolase, tyrosine hydroxylase and sepiapterin reductase. Useful investigations include a DAT scan, oral phenylalanine loading test, blood and spinal fluid pterin levels, and genetic testing.
- Ephedrone toxicity should be considered in young Eastern European men who present with the subacute onset of bradykinesia, severe dysarthria, a cock-like walk due to dystonia and severe postural instability with falls backwards. The repeated chronic intravenous use of methcathinone (Ephedrone) a psychostimulant prepared illicitly from the nasal decongestant pseudoephedrine (Sudafed), potassium permanganate and vinegar leads to the clinical and radiological changes of chronic manganism and has become a significant public health hazard in the former Eastern bloc. Diagnosis is supported by: hyperintense signals on T1 MR sequences in the pallidum, nigra reticularis and subthalamic nucleus with lesser involvement in the putamen and dentate nucleus; measurement of blood and pubic hair manganese; normal DAT scan; and admission of ephedrone abuse. Discontinuation of use does not always lead to improvement even when the scan appearances improve; there is an unfavourable prognosis for full recovery. Although methcathinone is used as a 'legal high' in the UK as a designer drug known on the street as miaou-miaou, it is not normally prepared with permanganate.

MANAGEMENT

Although the dopamine miracle of 40 years ago has proved to be something of a false dawn, levodopa remains the most significant and important landmark in the therapeutics of neurodegenerative disease. An illness that once led to severe physical handicap and a markedly reduced life expectancy can now be adequately controlled for more than 20 years in many patients. There has, however, been an increasing recognition that although bradykinesia, rigidity, tremor and postural instability are responsible for a great deal of physical handicap, associated symptoms such as depression, pain, insomnia and constipation may also contribute to a reduced quality of life. Fortunately, symptomatic treatments are available for many of these non-motor symptoms (table 2) and their effective management is an important part of good clinical practice.

Somewhat disappointingly, levodopa in combination with a peripheral dopa decarboxylase inhibitor (carbidopa or benserazide) remains the best symptomatic therapy and almost all patients will receive the drug at some stage of their illness. A number of prospective studies have shown there is no long term advantage in delaying levodopa, by starting treatment with an oral dopamine agonist or a selective monoamine oxidase inhibitor. Concern about daytime somnolence, ankle oedema and impulse control disorders (pathological gambling, hypersexuality, compulsive shopping, hoarding, binge eating and reckless generosity) with the dopamine agonists has swung the pendulum back towards early levodopa, even in young onset patients (table 3).

The initial maintenance dose of levodopa should start with 50 mg three times daily and not exceed 600 mg/day if the risk of long term adverse effects, particularly dyskinesias and behavioural disorders, is to be minimised. Levodopa sparing agents, including dopamine agonists (ropinirole, pramipexole tablets and rotigotine transdermal patches), selective type B monoamine oxidase inhibitors (selegiline, rasagiline) and catechol-O-methyl transferase (COMT) inhibitors (entacapone and tolcapone) can all be combined with levodopa and help to reduce end of dose deterioration and the on–off syndrome (capricious psychomotor fluctuations occurring several times a day). Combination of lower doses of levodopa with these adjuvant therapies also reduces the risk of severe disabling peak dose choreoathetosis. Amantidine may also be helpful in attenuating drug induced involuntary movements in some but not all cases, and anticholinergic drugs still have a role for off period dystonia in young onset patients.

The current trend is to start symptomatic therapy in most patients within a year of diagnosis

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in the hope that this will aid neuro-adaption and help compensate for progressive nigrostriatal denervation. In patients with mild motor disability, rasagiline is a reasonable and popular choice although claims that it is neuroprotective or disease modifying are not justified on the available evidence. In addition to early drug treatment, skilled physical therapy and programmed exercise are of great importance. Parkinson's disease nurse specialists have improved the overall care and support for UK patients; they should be involved early but always work closely with a neurologist for best results.

In patients with refractory motor fluctuations three highly effective treatment options are now available.

- The cheapest, safest and least invasive is waking day subcutaneous apomorphine administered from a small pump attached to a needle inserted each morning under the skin of the abdominal wall.
- Another approach is intrajejunal continuous administration of a soluble dopa gel through a gastrojejunostomy, which in the UK at least is restricted to apomorphine pump failures.
- Finally, bilateral deep brain stimulation of the subthalamic nucleus markedly reduces off periods and permits, on average, a 50% reduction in oral medication resulting in abolition of dyskinesias in many cases.

It is unclear whether any one of these approaches has major advantages over either of the others, and most specialist centres now offer all three. It seems reasonable to offer apomorphine as firstline treatment for the time being and then consider one of the other options as secondline approaches.

Once the terminal phase of the illness ensues, palliative care becomes more and more important and drug treatment should be simplified. The cause of death in many patients with Parkinson's disease remains obscure but a terminal chest infection often as a consequence of aspiration or pulmonary embolism is the commonest explanation.

Table 2 Treatment of the autonomic and psychological symptoms in Parkinson's disease

Insomnia: take nocturnal dose of dopaminergic drug, sleep hygiene, clonazepam, low dose amitryptiline
Depression: noradrenergic reuptake inhibitors, amitryptiline and nortryptiline
Rapid eye movement behaviour disorders: clonazepam, melatonin (available in North America)
Fatigue: amantidine, selegiline
Daytime sleepiness: modafinil
Psychosis/hallucinations: reduce antiparkinsonian drugs, antipsychotics (clozapine, quetiapine, aripiprazole), cholinomimetics
Constipation: osmotic laxatives (macrogol), faecal softeners
Urinary urgency: bladder stabilisers (trospium, tolterodine), desmopressin for nocturia
Impotence: sildefanil, tadalafil, vardenafil
Pain due to dystonia or rigidity: clonazepam, anticholinergics (in young onset cases), avoid opioids
Restless legs: dopamine agonists
Orthostatic hypotension: increase water and salt intake, fludrocortisone, ephedrine or midodrine
Drooling: 0.5% atropine eye drops sublingually, botulinum toxin injections into salivary glands
Excessive sweating: propantheline, propranolol, topical aluminium creams
Dry eyes, tearing: hypomellose eye drops

Table 3 Orally active antiparkinsonian drugs

In descending order of efficacy:

- Levodopa in combination with a dopa decarboxylase inhibitor (madopar, sinemet); available formulations include immediate release, dispersible madopar and controlled release (madopar and sinemet CR)—dose range 150–2000 mg/day
- Levodopa in combination with a dopa decarboxylase inhibitor and a peripheral COMT inhibitor (entacapone), available in 50, 75, 100, 125, 150 and 200 mg strengths
- Dopamine agonists: pramipexole (0.75–4 mg/day), ropinirole (3–24 mg/day) and rotigotine transdermal patch (2–16 mm/24 h). Ropinirole (RequipXL) and pramipexole (Mirapexin MR) are now available as long acting formulations (ergoline dopamine agonists cabergoline, pergolide and bromocriptine now rarely used because of the risk of pleuropulmonary and restrictive cardiac valvular problems)
- Selective type B monoamine oxidase inhibitors: selegiline 5–10 mg/day also available as a sublingual lyphilised formulation 1.25 mg (Zelapar), and rasagiline (Azilect), 1 mg daily
- Amantidine HCl 100–400 mg/day
- Anticholinergic drugs: trihexiphenidyl (Artane) 1–6 mg/day, orphenadrine (Disipal), 50–300 mg/day

THE QUESTIONS PEOPLE WITH PARKINSON'S DISEASE ASK

Will I end up in a wheelchair?

One can be reasonably reassuring about this unless the diagnosis has to be revised later to PSP-P or MSA-P although in the late stages after more than 10 years of Parkinson's disease some elderly patients are chair bound as a result of frequent and persistent falls, and a few have syncope on standing due to postural hypotension which is usually due to associated autonomic failure aggravated by dopaminergic therapy.

Heterogeneity is a feature of all the common neurodegenerative diseases but Parkinson's disease is perhaps the most diverse in its clinical features making it almost impossible to predict the trajectory of an individual case at the outset. Bad prognostic signs are early bulbar and postural abnormalities, and a poor response to dopaminergic drugs but these should make one question the accuracy of the diagnosis.

How long does the treatment work for?

Many patients have read that antiparkinsonian medication has a finite period of usefulness and causes serious adverse effects. As a result they are often reluctant to start treatment in the early stages of the illness. The fear of drug induced involuntary movements with levodopa has now been partially replaced by worries about impulse control disorders with the dopamine agonists. Response to medication lessens with time requiring an increase in dopaminergic drugs while the eventual emergence of delirium and dementia may require the reduction or discontinuation of these drugs and the introduction of cholinomimetics, memantine and low dose antipsychotics. Furthermore, falls due to freezing seem to be at

Further reading

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Useful addresses

- Parkinson's disease Society of the United Kingdom. Registered Office: 215 Vauxhall Bridge Road, London SW1V 1EJ; Tel 020 7931 8080; www. parkinsons.org.uk
- Cure Parkinson's Trust The Vestry, 1, St Clement's Court, London, EC4N 7HB; Tel 020 7929 7656 or 07867 978662; cptinfo@cureparkinsons.org.uk

least partially refractory to drug therapy or surgical approaches. Despite these caveats, antiparkinsonian drugs continue to provide functional benefit and symptom relief for more than 10 years in most cases.

Will I become demented?

There is increasing evidence that elderly patients with Parkinson's disease have a six-fold increased risk of dementia and about 40% of patients over 70 years old have significant cognitive impairment. Visual hallucinations may be a harbinger in some cases and are also now considered an integral component of the terminal phase of the illness although the pathological substrate for both hallucinations and dementia is unknown.

What are the risks for my children?

In a patient presenting over the age of 60 years with no known family history of Parkinson's disease there is very little increased risk for their children.

Autosomal recessive parkinsonism due to the parkin mutation may affect up to 25% of cases of young onset parkinsonism. If an elder sibling is also affected, the risk of carrying the gene may be even higher. These cases run a benign course, may have a more restricted lesion limited to the substantia nigra and can often be predicted from the clinical history and examination (early onset, very slow progression, no anosmia, presentation in the legs, often with rest tremor).

LRRK-2 is an autosomal dominant gene with incomplete penetrance (the G2019S mutation has a 30–80% expression by the age of 80 years). It is a very common susceptibility gene among North African Arabs (30% of cases) and in Jews (10% cases), and in sporadic cases in the UK may be found in about 1% of cases. In patients with one parent or another first degree relative affected, the likelihood of carrying the LRRK-2 gene may be as high as 5%.

What can I do to minimise the handicap of Parkinson's disease?

There is increasing evidence that exercise, particularly in the early phases of the illness, can be beneficial and should be encouraged. A positive outlook towards the disease and vigorous treatment of any comorbidities are important. A healthy diet with plenty of fruit and roughage is to be recommended. Co-enzyme Q10 is unproven but harmless.

CONCLUSIONS

- Despite the diverse presentation and natural history, Parkinson's disease is a distinct clinicopathological entity which can be diagnosed with a high level of accuracy by neurologists.
- Genetic susceptibility seems to be very important in some races as a risk factor for the development of Parkinson's disease.
- Dementia occurs in at least 40% of cases by the terminal phase and the histopathological findings are indistinguishable from dementia with Lewy bodies.
- Symptomatic medical and surgical treatment significantly improves quality of life, reduces handicap and improves life expectancy.

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