Idiopathic parkinsons disease: epidemiology, diagnosis and management

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SUMMARY. Since the introduction of levodopa therapy for idiopathic parkinsons disease over 20 years ago, there has been an awakening of research interest in this chronic neurodegenerative disorder. This paper describes current understanding of the role of genetic and environmental factors in the aetiology of idiopathic parkinsons disease and problems associated with both diagnosis and management. It briefly outlines both pharmacological and non-pharmacological options for treatment. Despite an increasing armoury of available treatments, the optimum management for this condition remains controversial.

Keywords: parkinsons disease; epidemiology; diagnosis; management of disease; drug therapy.

Introduction

THE prevalence of idiopathic parkinsons disease is estimated to be 160 per 100 000 of the population.[1] In a health authority of 250 000 individuals there will be around 400 people suffering from this disease. On an average general practitioner's list of 2500 patients, one could expect to find three or four patients with parkinsons disease.[2] However, the prevalence increases markedly with age, being extremely rare in those under the age of 45 years and being present in up to 2% of individuals over the age of 85 years.[1] Thus, the age structure of the practice population will determine the total number of cases. With the progressive ageing of the population and the decline in cardiovascular mortality, chronic neurodegenerative disorders, such as idiopathic parkinsons disease and dementia, will have a greater impact on future health service provision.[3]

Epidemiology

Relationship between genetic and environmental factors

It is generally believed that genes do not have a predominant role in the aetiology of idiopathic parkinsons disease.[4] This evidence is derived from twin and family studies, although it remains controversial[5] (Tables 1 and 2).

Despite the small sample sizes of the twin studies, the findings are remarkably consistent and do not suggest a genetic role, as concordance rates (the proportion of twin pairs where both twins are affected by the disease) are no greater for monozygotic than dizygotic twins (Table 1). The high concordance rates in the study by Vierrege and colleagues[9] reflect the authors' biased method of twin ascertainment through relevant charities and colleagues. This method would be expected to over-ascertain concordant pairs. More recent research comparing positron emission tomography scans has suggested that subclinical abnormalities in the substantia nigra might be more common in monozygotic than dizygotic twins and than expected from clinical studies,[13] although this fails to explain why only one twin develops clinical disease.

Patients with idiopathic parkinsons disease are often concerned about the risk of their children developing the disease. Family studies suggest that the risk of a secondary case within the immediate family is no greater than for a control population (Table 2). However, there are rare but well documented cases of familial aggregation (clustering of the disease in families),[14] and early-onset cases (under the age of 40 years) appear to be more likely than late-onset cases to have another affected family member.[15] Although the exact role of genetic factors in sporadic disease is unclear, family studies suggest that inheritance may follow an autosomal dominant pattern with reduced penetrance.[16]

More recently, there has been much interest in a possible interaction between genes and the environment. Several groups have demonstrated that a mutant gene for debrisoquine hydroxylation appears more commonly in patients with idiopathic parkinsons disease than in healthy controls.[17,18] Individuals with this mutant gene metabolize debrisoquine more slowly and therefore may be more susceptible to any potentially harmful environmental neurotoxin. Other abnormalities have also been demonstrated such as the poor conjugation of paracetamol with sulphate and sulphoxidation of carbocysteine.[19]

Another approach to understanding the roles of genes and the environment is to study migrants and to compare their risk with that of their host and country of origin. One study has compared the prevalence of idiopathic parkinsons disease in a bi-racial community in Mississippi in the United States of America[20] and Nigeria,[21] using standardized, population-based case ascertain-

Table 1. Concordance rate of idiopathic parkinsons disease (IPD) in twin studies.

First author, date	Concordance rate of IPD (%) in Monozygotic twins	Dizygotic twins
Ward, 1983[6]	1/43 (*2.3*)	1/19 (*5.3*)
Marsden, 1986[7]	1/11 (*9.1*)	1/11 (*9.1*)
Martilla, 1988[8]	0/18 (*0*)	1/14 (*7.1*)
Vieregge, 1992[9]	3/9 (*33.3*)	3/12 (*25.0*)
Total	5/81 (*6.2*)	6/56 (*10.7*)

Table 2. Prevalence of idiopathic parkinsons disease (IPD) in family studies.[a]

First author, date	Prevalence of secondary cases of IPD (%) in IPD family	Control family
Martilla, 1976[10]	16/429 (*3.7*)	11/443 (*2.5*)
Martin, 1976[11]	16/488 (*3.3*)	7/450 (*1.6*)
Roy, 1983[12,b]	19/648 (*2.9*)	2/466 (*0.4*)
Duvoisin, 1986[4]	4/146 (*2.7*)	3/145 (*2.1*)

[a]Number of cases in immediate family or siblings. [b]Study reported the number of secondary cases in 50 selected IPD subjects with a known family history. If all clinic cases are included the rate of secondary cases is no different from controls (0.4%).

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ment methods screening all households. The study found no difference in the prevalence of idiopathic parkinsons disease in white or black subjects in Mississippi, but far fewer cases in Nigeria than would have been expected from the rates among black Americans. The authors concluded that black migration to the USA had resulted in an increased risk of idiopathic parkinsons disease in this group as a result of environmental factors.[21]

Possible environmental factors

There have been many suggested environmental factors. These can be broadly divided into three groups (infective, neurotoxic and lifestyle), although some lifestyle factors could act through either an infective or neurotoxic route.

Infective factors. Infective factors comprise encephalitis lethargica, intrauterine influenza, herpes simplex, Japanese B encephalitis and coxsackie. The encephalitis lethargica global epidemic between 1918 and 1926 resulted in the distinct entity of postencephalitic parkinsonism. It has been argued that subclinical infection might also result in 'idiopathic' disease (the encephalitis lethargica hypothesis).[22] Some weak evidence exists that cohorts of individuals exposed to the epidemic may have a greater risk of developing idiopathic parkinsons disease.[22-24] However, long-term data from Minnesota in the USA suggest that the incidence in this population has remained remarkably similar over time and does not support the hypothesis.[25] There is a possibility that a different viral exposure may result in partial damage to the substantia nigra, which only appears much later after further age-related degeneration (the two-stage hypothesis[26]). Most sero-epidemiologic studies (population-based prevalence estimates of sero-positivity) have, however, failed to find any differences in antibody titres for a wide variety of viruses between cases with idiopathic parkinsons disease and controls.[27,28] This does not exclude an infective hypothesis, as age at infection or genetic susceptibility, rather than infection itself, may be a more important determinant. If idiopathic parkinsons disease was a rare sequel of a common infection then one would not expect to find differences in viral antibody titres.

Neurotoxic factors. The neurotoxic factors comprise manganese, a meperidine analogue 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), carbon disulphide, carbon monoxide, mercury, pesticides such as paraquat, and well-water. Several occupation-related exposures have been associated with idiopathic parkinsons disease, for example, to manganese. However, these exposures are in general rare and could not account for the vast majority of cases. The serendipitous discovery of a group of drug addicts with a parkinsonian syndrome led to the detection of the neurotoxic meperidine analogue MPTP.[29] Scientists noted the chemical similarity between this neurotoxin, which is rarely found in the environment, and paraquat, a more plausible candidate for a common neurotoxin.[30,31] An ecological study from Canada supported the idea by demonstrating increased disease prevalence in rural areas with the highest usage rates of pesticides.[32] Some case studies,[33-35] but not all,[36] have also supported the potential role of pesticides.

A neurotoxic hypothesis would predict a greater risk of this disease for manual than for non-manual occupations as a result of exposure to any potential toxin. Mortality data from England and Wales support this hypothesis to some degree,[23] but are limited because of differences in certification and case fatality. Other studies, however, do not find a difference between social class,[33,37] occupational groups[38] or years of education,[39-41] which is a good proxy indicator of social class. These observations appear to conflict with any hypothesis of exposure to toxins associated with manual work having a greater risk.

Consumption of well-water has also been noted to be associated with an increased risk of idiopathic parkinsons disease.[36,42,43] Well-water could act as a source of transmission for pesticides, organic and inorganic compounds or even an infectious agent. However, it is unclear whether well-water is simply a marker for growing up in a rural habitat.[36]

Lifestyle factors. Several studies have consistently noted an increased risk of idiopathic parkinsons disease with rural habitat, in particular with early-onset cases.[42,44] This finding is difficult to interpret, as a rural lifestyle can affect exposure to toxins and infections and can even influence diet. Increased consumption of raw vegetables[33] and decreased consumption of dietary vitamin E has been noted in some studies;[45] antoxidants could protect the substantia nigra from oxidative free radical damage.[46]

Studies have noted that a past history of a head injury is more frequently reported in cases of idiopathic parkinsons disease than in control subjects.[41] This probably reflects recall bias. Patients with the disease are more likely to recall a head injury because, from a lay perspective, such an event would be consistent as an explanation for their neurological disorder. Researchers have tried to minimize this bias by only studying serious injuries, for example loss of consciousness, and still show an effect.[41] It is unclear, however, why a non-specific injury should result in such localized damage restricted to the substantia nigra.

The observation that idiopathic parkinsons disease is associated with not smoking cigarettes has been noted since the 1950s.[47,48] These findings have been shown consistently for both cohort and case-control studies[49,50] and show a dose-response effect. Current smokers have the lowest risk, with former smokers having an intermediate risk as compared with those who have never smoked.[51] This observation has led some to speculate that smoking is protective and that people over 60 years of age should take up smoking to reduce their risk of developing idiopathic parkinsons disease or alzheimers disease, another disease with the same association.[52] The interpretation of these findings is, however, complex. Smoking may protect the substantia nigra from oxidative damage. Hydrazine, a compound present in tobacco smoke has been shown to protect dopaminergic nigrostriatal neurones in mice from damage by MPTP.[53] However, smokers with idiopathic parkinsons disease do not present at an older age and show the same spectrum of disease severity.

One possible explanation is that smokers who would have developed idiopathic parkinsons disease die at a younger age from cardiovascular disease. Smokers who selectively survive and live to an older age are genetically less susceptible to neuronal degeneration.[54] Smokers would then appear to be artefactually protected from idiopathic parkinsons disease, that is, smoking is not actually protective but a proxy marker of subjects who are genetically less susceptible to idiopathic parkinsons disease. This hypothesis, however, is invalid as the protective effect is still found in monozygotic twins discordant for idiopathic parkinsons disease where the twin with parkinsons disease is more likely to be a non-smoker and the other twin a smoker, and early-onset cases where the selective mortality from smoking would be weak.[55]

Another explanation is related to premorbid personality. The largest study of twins found the affected twin to be quieter and less dominant than the other twin.[56] Similar differences in personality are found between smokers and non-smokers with the former exhibiting more type A behaviour.[57] It is possible that personality determines whether an individual takes up smoking and is related to other exposures that determine the development of idiopathic parkinsons disease. For example, an extrovert is more likely to be a smoker and to be involved in sport, with risk of head injury.[58] Alternatively, a more introverted personality may reflect a very early manifestation of the disease. It still

remains unclear as to when the degenerative disease process actually begins and some have postulated a latency period of up to 40 years before clinical onset.[59]

Diagnosis

The diagnosis of a parkinsonian syndrome depends on a constellation of signs and symptoms: a slow tremor (4–6 Hz frequency), bradykinesia, muscle rigidity and impaired postural reflexes. In advanced idiopathic parkinsons disease these signs, combined with a stooped posture, impassive facies and small stepped shuffling gait, produce a characteristic clinical picture. Initially, however, symptoms and signs may be unilateral, or at least asymmetrical, and generalized involvement may take many years.[60] Tremor at rest is present in up to 80% of patients and is the commonest presenting complaint but is rarely the first symptom. At the opposite end of the disease spectrum are patients with an akinetic-rigid syndrome. Typical tremor is usually regarded as strong evidence of idiopathic parkinsons disease and its absence should raise suspicion of an alternative pathology.

The diagnostic difficulties of idiopathic parkinsons disease, both for the general practitioner and the specialist, may arise in its early stages and in distinguishing it from other parkinsonian syndromes. Early disease, with its insidious onset and probable long preclinical period[59,61] may be a diagnostic puzzle because vague complaints often antedate signs and some complaints appear to be unrelated to the motor system. Depression, a common feature of idiopathic parkinsons disease, can precede the diagnosis by many years.[62-64] Sensory symptoms of dysaesthesiae, burning and pain, which plague 40% of patients, may occur months to years before the diagnosis.[65] Other non-motor complaints include seborrhoeic dermatitis, constipation (possibly due to the involvment of the autonomic ganglia[66]) and loss of sense of smell.[67] Tremor, a subjective feeling of stiffness and impaired function of the limb in the absence of muscle weakness are often intermittent. Patients' presenting complaints may be influenced by their occupation.[68] The footballer Ray Kennedy was aware of difficulties with his performance on the pitch well before there was any evidence of disease identifiable by a clinician. Positron emission tomography may show a reduced striatal uptake of fluorodopa at least 18 months before the first signs,[69] but the method is too costly for routine clinical use.

Differential diagnosis

The major diagnostic challenge for neurologists is to differentiate idiopathic parkinsons disease from a heterogeneous group of other parkinsonian syndromes (Figure 1).

A positive response to an acute challenge with levodopa or subcutaneous apomorphine strongly supports the diagnosis of idiopathic parkinsons disease but some patients with other parkinsonian syndromes may also show a positive response. Certain clinical features such as early symmetrical signs should raise a suspicion of an alternative pathology. Pyramidal and sometimes cerebellar signs, profound orthostatic hypotension and an upright posture suggest multiple system atrophy.[70] Gaze palsies, especially downwards, early unexplained falls, and pseudobulbar signs are suggestive of progressive supranuclear palsy. Dementia in parkinsonian patients is not uncommon; its reported prevalence ranges from 15%[71] to 41%.[72] However, early or severe dementia is unlikely to be due to idiopathic parkinsons disease. Such patients usually have other pathologies such as alzheimers disease or diffuse Lewy body disease.[73,74] The recommended diagnostic criteria used by the United Kingdom Parkinsons Disease Society Brain Bank for idiopathic parkinsons disease are summarized in Figure 2.[75]

Common conditions which may cause confusion for doctors not specializing in movement disorders are benign essential tremor and parkinsonism secondary to small vessel disease. Benign essential tremor is slightly faster than parkinsonian tremor, absent at rest and triggered by sustained posture, best seen with the patient holding the arms outstretched.[76] A similar postural and/or action tremor can be seen in some parkinsonian patients, but rest tremor is never seen in benign essential tremor. Head tremor often coexists and has a characteristic 'yes-yes' pattern. Other features of parkinsonism are absent, in particular bradykinesia. Essential tremor responds to beta-blockers and alcohol. A family history may often be elicited and autosomal dominance is

1. **Idiopathic parkinsons disease**
2. **Secondary (symptomatic) parkinsonism**
   - Postencephalitic
   - Drug induced (eg, antipsychotics, metoclopramide)
   - Arteriosclerotic (small vessel disease of the brain)
   - Toxic (eg, manganese, carbon monoxide, MPTP)
   - Wilsons disease
   - Post-traumatic
   - Neoplastic
   - Normal pressure hydrocephalus
3. **Parkinsonism in neural system degeneration**
   - Multiple system atrophy
     - Striatonigral degeneration
     - Shy–Drager syndrome
     - Olivopontocerebellar atrophy
   - Progressive supranuclear palsy (Steele–Richardson–Olszewski)
   - Alzheimers disease
   - Pallidonigral and corticobasal degenerations
   - Diffuse Lewy body disease

Figure 1. *Clinical classification of parkinsonian syndromes.*

Step 1. Diagnosis of a parkinsonian syndrome

Bradykinesia and at least one of the following:
- Muscular rigidity
- Rest tremor (4–6 Hz)
- Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction

Step 2. Exclusion criteria

History of:
- Cerebrovascular disease with stepwise progression
- Repeated head injury
- Antipsychotic or dopamine-depleting drugs
- Definite encephalitis and/or oculogyric crises on no drug treatment

More than one affected relative
Sustained remission
Negative response to large doses of levodopa (if malabsorption excluded)
Strictly unilateral features after three years
Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis
Exposure to known neurotoxin

Step 3. Supportive criteria

Unilateral onset
Excellent response to levodopa
Rest tremor present
Progressive disorder
Persistent asymmetry affecting side of onset most
Severe levodopa-induced chorea
Levodopa response for five years plus
Clinical course of 10 years plus

Figure 2. *United Kingdom Parkinsons Disease Society Brain Bank clinical diagnostic criteria.*[75]

the mode of inheritance in familial cases.[76] A parkinsonian syndrome caused by cerebrovascular disease should be considered in an individual with vascular risk factors, history of strokes or transient ischaemic attacks, and stepwise (rather than slowly progressive) deterioration. Often, gait is disproportionally affected with start hesitation, freezing, and shuffling. Additional clues may be provided by the presence of pyramidal signs and poor response to levodopa. Magnetic resonance imaging shows multiple ischaemic lesions in the white matter and basal ganglia.

How valid is a clinical diagnosis?

The validity of a clinical diagnosis of idiopathic parkinsons disease can only be determined by comparing pre-mortem diagnosis with post-mortem pathological confirmation. This has been done for a series of 100 cases of idiopathic parkinsons disease recruited by the UK Parkinsons Disease Society Brain Bank.[75] All cases were diagnosed by a consultant neurologist, usually with an interest in this disorder, or a consultant geriatrician. The results show that the positive predictive value of an expert diagnosis is around 76%. The most frequent misdiagnoses were progressive supranuclear palsy (6%) and multiple system atrophy (5%). If stricter diagnostic criteria were used (Figure 2), this improved the predictive value to 82%. A later analysis of data also showed that restricting cases to those with no atypical features, an asymmetrical onset and no other possible cause increased the predictive value to 88%.[77]

Prevalence studies include patients from multiple sources who have been diagnosed by a wide range of clinicians. They provide perhaps a more typical picture of the rate of erroneous diagnoses, but rely on clinical rather than pathological validation and therefore are an underestimate of the true error rate. In a study from Aberdeen, 15% of cases with possible idiopathic parkinsons disease were excluded after examination.[1] Most had benign essential tremor, dementia or cerebrovascular disease. Other studies also suggest that benign essential tremor is the most common misdiagnosis by general physicians.[78,79] If the results from both the post-mortem and prevalence studies are combined, it is likely that from a sample of 100 possible cases of idiopathic parkinsons disease, only 65 cases would be confirmed at post-mortem.

Treatment and management

All drugs used for treating idiopathic parkinsons disease are symptomatically effective but none can prevent disease progression.

Levodopa

More than 20 years after its discovery, levodopa combined with a peripheral dopa-decarboxylase inhibitor (benserazide or carbidopa) remains the most effective symptomatic drug. However, its long-term use is marred by involuntary movements, dystonias, motor fluctuations and neuropsychiatric side effects.[80] These adverse reactions reflect more the disease progression than levodopa toxicity per se.[81] The motor fluctuations begin as an end-of-dose deterioration ('wearing off') and evolve into sudden and unpredictable swings of motor performance known as the 'on–off' phenomenon.[82] 'On–off' swings occur with falls of plasma levodopa level and can be abolished by maintaining the drug level continuously above the effective threshold.[83]

Levodopa preparations are available as Madopar® (Roche), containing four parts levodopa to one part benserazide, and Sinemet® (Du Pont), containing four parts levodopa or 10 parts levodopa to one part carbidopa. Their efficacy is similar. The daily levodopa requirements range from 150 mg to as much as 1500 mg, increasing with disease progression. Initially, three or four doses per day produce a sustained benefit, but with the onset of motor fluctuations the duration of each dose decreases and dose failures occur, requiring more frequent administration. The risk of neuropsychiatric complications and dyskinesias is dose-dependent. The current recommendation is to avoid, if possible, high doses of levodopa and add a dopamine agonist, such as bromocriptine, if the daily requirement exceeds 400–600 mg.

Controlled-release preparations of Madopar and Sinemet provide a slow, sustained release of levodopa for up to eight hours. They are useful in the management of milder forms of motor fluctuations[84,85] and can be effective in newly diagnosed patients.[86] A bedtime dose of a controlled-release drug often relieves nocturnal 'off' symptoms. Owing to reduced levodopa bioavailability a dose of a controlled-release preparation should be 30% to 50% higher than an effective dose of standard drug.[82,87] Individual response to controlled-release preparations varies greatly and some patients find their response too erratic. An additional dose of a standard levodopa preparation may be needed first thing in the morning.

Dopamine agonists

Dopamine agonists act directly on dopamine receptors. Oral agonists available in the UK are pergolide, bromocriptine and lysuride. Their efficacy appears similar,[88-90] but pergolide may be preferred because of its longer half-life and better tolerability. The issue when to introduce dopamine agonists has been a subject of debate. The advocates of agonist monotherapy in early idiopathic parkinsons disease argue that this approach delays motor fluctuations and reduces dyskinesia.[91] However, inadequate therapeutic response and early side effects such as nausea and orthostatic hypotension often hamper its use, and after a mean of 2.3 years[92] levodopa has to be added anyway. In the UK parkinsons disease research group study, bromocriptine alone was less effective than levodopa, but it was also associated with fewer motor fluctuations and dyskinesias; the rate of disease progression was similar with both agents.[93] A delay in onset of motor fluctuations and reduced dyskinesia have also been reported with early combined therapy consisting of low-dose levodopa and a dopamine agonist,[91,94-96] but these results have been criticized on methodological grounds.[97,98] It appears that at present the advantages of early agonist therapy, alone or in combination with levodopa, remain disputable. Many neurologists believe, and we share this view, that oral dopamine agonists should be introduced when control of symptoms with levodopa begins to fail owing to motor fluctuations.

Apomorphine, a potent dopamine D_1 and D_2 receptor agonist, has to be administered subcutaneously or intranasally, and benefit from a single dose lasts for about 60 minutes. The advantage of apomorphine is its quick (within 10 minutes) and reliable action. Self-administered injection can be used as a rescue at the first warning of forthcoming 'off'.[99] In advanced cases a continuous subcutaneous infusion of apomorphine via a portable pump significantly reduces 'on–off' swings.[100] Apart from dose-dependent dopaminergic overstimulation, the main side effects are local cutaneous reactions.

Monoamine oxidase B inhibitors

Selegiline at a dose of 10 mg per day selectively inhibits monoamine oxidase B, the main enzyme that degrades dopamine in human striatum.There is little doubt that selegiline added to levodopa in advanced idiopathic parkinsons disease has a mild to moderate symptomatic benefit[101,102] and this is consistent with increased availability of dopamine following monoamine oxidase B inhibition. The controversy has arisen around its role in early idiopathic parkinsons disease. The observation that selegiline monotherapy reduces progression of disabilities and delays need for levodopa in newly diagnosed patients[103,104] has been ascribed

to its neuroprotective action. It was proposed that selegiline could decrease generation of neurotoxic free radicals generated during dopamine metabolism, and the above results were interpreted within the framework of oxidative stress theory.[105] However, a large study failed to obtain firm evidence for the neuroprotective effect of selegiline[106] and at present its action is thought to be predominantly, if not totally, symptomatic.[93,107,108]

Antimuscarinics and amantadine

Antimuscarinics, such as benzhexol and benztropine, act at the muscarinic receptors correcting a relative cholinergic dominance in the striatum caused by dopamine deficiency.[109] These drugs have a relatively weak antiparkinsonian action, especially on bradykinesia and rigidity, but can be a useful adjuvant to levodopa to control tremor. The incidence of confusion and hallucinations is high, especially in elderly patients and patients with dementia. The peripheral side effects include impaired visual accommodation, dry mouth, constipation and urinary retention. Amantadine was once thought to combine the properties of an antimuscarinic drug and a weak dopamine agonist but more recent evidence suggests that it is a glutamic agonist.[110] Its use is limited to mild disease.

It is important to be wary of potential interactions between antiparkinsonian medications and other drugs, especially in elderly patients. Common drugs that worsen parkinsonism and should therefore be avoided are antipsychotics, metoclopramide, and some calcium antagonists such as cinnarizine. A survey of the medication used for 101 community-based parkinsonian patients in Dunedin, New Zealand demonstrated that 8% were simultaneously on phenothiazines, which would exacerbate their symptoms, and 17% were taking benzodiazepines.[111] The prescription of benzodiazepines is worrying in view of their association with falls and gait disturbances. Younger patients, not surprisingly, were more likely to be under the care of a specialist than were older patients.

Which treatment should be used first?

There are no firm guidelines as to which drug should be used first and, indeed, this may not be critical.[93] On balance, selegiline appears to be an appropriate first choice in mild cases. It provides mild symptomatic relief for up to the first 6–24 months and it may have additional, if unproven, neuroprotective effects. As the disease progresses to a level where significant functional handicaps have occurred, levodopa should be started, either alone or in combination. The concern that levodopa may accelerate degeneration of the nigral neurones by enhancing free radicals formation[112,113] remains unproven[81,114-117] and the drug should not be withheld from patients with increasing disabilities. This is supported by the evidence that levodopa treatment initiated early in the course of the disease increases life expectancy.[118]Although initial therapy with dopamine agonists reduces the risk of later complications, their symptomatic effect is less spectacular than that of levodopa and may dissatisfy many patients.

Management of dyskinesias

Dyskinesias can occur at peak plasma levodopa concentrations, throughout the 'on' period, or accompany a sudden increase or fall in the drug level (biphasic pattern).[119] The peak dose dyskinesia and intradose dyskinesia, which occurs about one hour after levodopa administration, can be diminished by reducing the dose. However, this may result in suboptimal motor response and in many patients the beneficial effects of levodopa cannot be dissected from the involuntary movements.[120] It is a common experience that patients prefer being dyskinetic to being 'off'. Reducing the levodopa dose with substitution by a dopamine agonist may occasionally be helpful. Continuous apomorphine infusion via a pump is effective and in some cases may be used as monotherapy.[121]

The biphasic dyskinesias are generally more difficult to manage. The fluctuations in the degree of dopaminergic stimulation should be avoided and these patients often fare better with higher, but less frequent, doses of levodopa. The end-of-dose dyskinesia sequence is sometimes extremely severe and violent; a subcutaneous dose of apomorphine at its onset may help the patient through the worst phase. In our experience from a specialist movement disorder clinic, biphasic dyskinesias generally fail to respond to a continuous apomorphine infusion. Tetrabenazine, buspirone, lithium and sulpiride have been tried with limited success but in desperate cases thalamotomy or pallidotomy (as discussed later) is probably the only effective treatment.[121]

Non-pharmacological management

With the advent of levodopa, the days of stereotactic surgery in idiopathic parkinsons disease seemed to be over. Ventrolateral thalamotomy remained an effective option in severe tremor, but it did not improve bradykinesia, the most disabling feature of the disease. However, novel stereotactic procedures may emerge as a therapy of choice, especially when drug treatment fails because of side effects. The posteroventral pallidotomy has been reported to improve all main parkinsonian disabilities, including bradykinesia and rigidity, and to decrease the requirement for levodopa. Most importantly, the dystonias and drug-induced dyskinesias may be appreciably improved.[122] Preliminary reports are impressive, but further studies, based on a more thorough pre- and post-operative assessment of patients, are awaited.

Another novel approach is to stimulate electrically the specific structures within the basal ganglia which are known to be pathologically hyperactive in dopamine deficiency states.[123] This is analogous to using a pacing wire to stimulate cardiac tissue. Thalamic stimulation can extinguish both parkinsonian and essential tremor. The subthalamic nucleus is probably a better target and the first results of its electrical stimulation are encouraging.

Implantation of dopaminergic neurones is still experimental and no final consensus has been reached as to when, where and what should be grafted. In animal models of idiopathic parkinsons disease, grafts of fetal nigral neurones into the striatum survive for long periods and, by acting as biological mini-pumps, restore dopaminergic neurotransmission to a functionally important degree.[124] The first approach tested in humans was to graft autologous adrenal medulla into the striatum or lateral ventricle, but the improvement was inconsistent and transient.[125] The limited autopsy data suggest poor survival of adrenal grafts.

Transplantation of fresh or cryopreserved fetal nigral neurones into the putamen is more promising but is associated with difficult ethical and political issues. Its efficacy is hard to evaluate because of the small number of properly documented cases. Convincing improvement paralleled by increased fluorodopa uptake on positron emission tomography scanning has been reported in two cases of idiopathic parkinsons disease[126,127] and in two patients with MPTP-induced parkinsonism.[128] Other studies have now also reported improvement after grafting[129,130] but more consistent and rigorous research protocols are needed to explore all advantages and limitations of neurotransplantation in idiopathic parkinsons disease.

Other forms of therapy

There is little good-quality research on the benefits of other treatments such as physiotherapy, speech or occupational therapy.

Studies are difficult to interpret owing to the small numbers of patients involved and inadequate objective measures of improvement. Furthermore, benefits may be short-lived. As Godwin-Austen states, 'any review of this subject founders on unsupported assertion and unscientific methodology... on the other hand there are dangers to the patient from too rigorous and nihilistic an attitude'.[131] Some studies suggest that physiotherapy may be of some benefit[132,133] while others do not.[134] Speech therapy appears to be used rarely, despite the large proportion of patients with some speech impairment (in one survey only 3% of 460 patients had received any speech therapy[135]). Some improvement in both comprehension and rhythm after therapy has been observed[136] lasting in one study up to six months.[137] An occupational therapy survey in Glasgow noted considerable underprovision of aids among a selected sample of moderately disabled patients. Particular need was noted for bath and feeding aids. Seventy six per cent of patients previously seen by an occupational therapist still required further aids. A subsequent follow up at 10 months found a high proportion of these aids to be considered valuable. Simple measures to counter negative aspects of the environment should also be considered, for example, removing uneven rugs and placing chairs on non-slippery surfaces. Useful advice and help for patients can be provided by the Parkinsons Disease Society.

Who should manage patients with parkinsons disease?

Ideally all patients suspected of having idiopathic parkinsons disease should be diagnosed by a neurologist or consultant geriatrician prior to the initiation of therapy. Obviously this approach will be limited by the availability of local specialist services. The initial choice of therapy may not be essential but sooner or later the patient will need treatment with levodopa. The first few years of treatment are usually regarded as a 'honeymoon' period with a stable response to therapy and few side effects. The onset of dyskinesias, motor fluctuations or neuropsychiatric complications signals progression towards a brittle phase, where control of symptoms becomes increasingly complicated.

There are at least three different management options: general practitioner care (primary management by the general practitioner with referral to a specialist for accurate diagnosis and as and when problems occur); shared care (primary management by the general practitioner with regular annual review by a specialist); and specialist care (primary management by a specialist with the general practitioner managing other aspects of health care).

There is no empirical evidence to suggest whether any of these different approaches is superior as regards mortality, morbidity or quality of life. The relative knowledge and enthusiasm of the general practitioner as well as the availability of specialist services will play major roles in determining the most suitable approach. General practitioner care allows the general practitioners to help the patient and the family come to terms, over time, with the difficulties of living with a chronic progressive disorder. This is a challenge for both the patient, the family and the doctor. Ironically, doctors are given more help and support to cope with terminally ill patients, where there is at least a definite endpoint in sight, than with those suffering with a chronic progressive disorder. A useful insight to the attitudes of both patients and doctors is provided by Ruth Pinder, whose qualitative research demonstrates the varying needs of patients and the different strategies used by general practitioners in dealing with their patients.[138]

In some areas, a specialist nurse in parkinsons disease has been employed to help manage patients at home on apomorphine pumps. These nurses are also able to coordinate other aspects of care, similar to diabetic liaison nurses. A large randomized controlled trial is currently underway to measure the benefits of this intervention on a national scale.

Conclusion

There appears to be an exciting future ahead in both our understanding and management of idiopathic parkinsons disease. Despite the many new developments in therapy, many aspects of management remain controversial. Future studies will hopefully provide empirical evidence to rationalize current treatment and management strategies. Early diagnosis may remain difficult until either simple diagnostic tests or biological markers are developed. This will be particularly important if future therapies can arrest or retard disease progression and disability. The condition even of patients with severe disease may be improved if some of the current experimental treatments live up to their promise.

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