Current issues in Parkinson's disease

Parkinson's disease remains a clinical diagnosis and a reminder of the UK brain bank criteria can help ensure that our clinical diagnoses maintain a reasonable level of specificity. DaTSCANs™ can be helpful where diagnostic uncertainty remains, particularly in distinguishing Parkinson's disease from drug induced parkinsonism, but are of no use in distinguishing from the Parkinson-plus disorders. New evidence is driving increasing numbers of Parkinson's disease specialists to recommend earlier treatment for Parkinson's disease; however, the choice of medication to initiate should still be tailored to the individual patient according to their disability.

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Many recent discoveries in the field of neurodegenerative disease have changed how we conduct our day-to-day practice. As always, we are expected to provide accurate diagnoses and optimum contemporary management that is tailored to the individual patient's medical, social, and psychological needs. This article will focus on current issues in Parkinson's disease of relevance on a daily basis for the practising clinician or specialist nurse.

Diagnostic uncertainty in PD

Since 2006, NICE has produced guidance for the management of Parkinson's disease in primary and secondary care. This guidance provides advice from the time of diagnosis through to palliative care.[1] Together with the National Service Framework for Long-term (Neurological) Conditions,[2] it provides the template for patient centered care for people with Parkinson's disease. It recommends that a specialist makes the diagnosis, and that treatment should be reviewed on an at least yearly basis.

Although a diagnosis of Parkinson's disease is straightforward in some patients, it can be very challenging in others—particularly, when an individual has comorbidity or does not have all of the typical symptoms and signs of the disease. Additionally, there is no doubt that Parkinson's disease not only presents with varying symptom predominance but also evolves in different ways. Some individuals will have a relatively benign, predominantly motor disease while others will develop multiple non-motor symptoms early on in the course of their disease. To aid clinical diagnosis, the UK brain bank criteria[3] (box 1) have been developed and they have been shown to have excellent specificity and sensitivity. But, nevertheless, they should be applied carefully to avoid erroneous diagnoses being made. Bradykinesia, which is the cornerstone of these criteria, can be assessed by asking the patient to perform finger taps, large hand movements, arm movements, or foot taps. Also, bradykinesia typically has a fatigable nature with both amplitude and frequency reducing with sustained movements.

Misdiagnosis of other forms of tremor as Parkinson's disease is a common pitfall. Patients with essential tremor usually have a dominant family history, a long duration of disease without developing other symptoms, and a beneficial response from alcohol. Cerebellar tremors should be distinguishable through the predominance of action tremor over rest or postural tremor. But, dystonic tremor, or Holmes'/ rubral tremor (present at rest, with posture and on actions) may be misdiagnosed as Parkinson's disease, especially among those with a marked tremor at rest. The presence of a head tremor or dystonia while writing can raise the alarm that the patient has dystonia rather than straightforward Parkinson's.

Where there is diagnostic uncertainty, despite application of clinical criteria, a DaTSCAN™ can be of use to increase diagnostic certainty and prevent long periods of unnecessary and sometimes very expensive treatments for Parkinson's disease. This neuro-imaging test requires the intravenous infusion of ioflupane radiolabelled with iodine.

It is not yet universally available throughout the UK, but its use and availability is likely to increase in the coming years and must therefore be used appropriately. A DaTSCAN™ will only evaluate the integrity of the nigrostriatal pathway and will not discriminate between

Box 1: UK Parkinson's Disease Society brain bank diagnostic criteria for Parkinson's disease

Step 1: Diagnosis of Parkinsonism

Bradykinesia and at least one of the following:

- Muscular rigidity
- 4–6 Hz resting tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2: Features tending to exclude Parkinson's disease as the cause of Parkinsonism

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- >1 affected relatives
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski's sign
- Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3: Features that support a diagnosis of Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent (70–100%) response to levodopa
- Severe levodopa-induced chorea
- Levodopa response for ≥5 years
- Clinical course of ≥10 years

Parkinson's disease and Parkinson-plus disorders, such as multiple system atrophy or progressive supranuclear palsy.[4] Patients diagnosed with Parkinson's disease but who are subsequently identified as "subjects without evidence of dopaminergic deficit" (SWEDDs) following a DaTSCAN™ frequently have dystonic tremor and retrospectively can be seen to have a distinctive thumb extension component to what otherwise looks like a typical Parkinson's disease rest tremor.[5] Another use of this scan is that it might be the only way to distinguish Parkinson's disease from drug-induced parkinsonism.

Which drug to start following diagnosis?

Treatment of Parkinson's disease needs to be tailored to the individual patient, and enthusiasts of protocols or restrictive guidelines need to take account of the range of factors that may influence treatment initiation. The choice of drug must take account of both the nature and extent of disability experienced by the patient due to specific symptoms, the ability of various drugs to relieve these symptoms, and the likelihood that the patient may develop acute or chronic side effects. Conventionally, recommendations have been that treatment should be introduced when a patient has

developed symptoms that have started to impact on their quality of life. However, there has recently been a move toward prescribing medication earlier following diagnosis of Parkinson's disease based on evidence from a number of trials that shows the advantages of an earlier initiation of drugs.

Undoubtably, levodopa has the greatest efficacy in the relief of the symptoms of Parkinson's disease. Aside from the usually mild nausea and postural hypotension when first introduced, it tends to be very well tolerated by patients of all ages. Particular concerns regarding the development of drug-induced dyskinesias have, however, led many Parkinson's disease specialists to delay the prescription of levodopa in favour of non-ergot dopamine agonists such as ropinirole, pramipexole, or rotigotine but with the expectation that supplemental levodopa will be required at some point in the future. These dopamine agonists have lower efficacy than levodopa, are more likely to lead to side effects such as sleepiness, dopa dysregulation (eg, gambling, hypersexuality or compulsive shopping), or cognitive dysfunction, but they do reduce the risk of developing drug-induced dyskinesias. Among patients with little or no evidence of impaired cognition who are expected to have many years of Parkinson's disease to deal with, non-ergot dopamine agonists have a very useful role. The MAO-B inhibitors, selegiline and rasagiline, slow the metabolism of dopamine. Studies show that they have modest therapeutic effects when used as monotherapy in early Parkinson's disease, are convenient in terms of their once daily prescription, and are generally well tolerated.

As yet, we do not have definitive proof that any agent has neuro-protective properties in humans, but earlier treatment seems to convey a long-term advantage in clinical outcomes. This may be due to prevention of secondary disability from falls, increased ability to engage in healthy behaviours, or indeed a neuro-protective effect. The TEMPO study[6] randomised drug-naive patients to either placebo or rasagiline. After six months, patients on placebo were switched to rasagiline. These delayed-start patients never caught up, in terms of observed improvements, with patients who had been given rasagiline straight away. Follow-up data that reviewed patients (all of whom are now on medication regimes considered to be optimum by their physicians) six years after treatment was initiated has now been published.[7] The manufacturers of rasagiline have published data from another trial in a larger group of patients with Parkinson's disease (the ADAGIO study)[8] that replicated TEMPO's results.

Further head-to-head studies need to compare the relative advantages of using different agents as monotherapy in early Parkinson's disease to identify whether equivalent early symptomatic benefits have equivalent long-term outcomes. Until that time, the option of using an MAO-B inhibitor as a first choice for Parkinson's disease patients with mild disease seems to be appropriate in terms of patient convenience (and thus compliance) while minimising the risk of adverse effects. Once a patient's symptoms have progressed beyond the therapeutic efficacy of the MAO-B inhibitors, then dopamine agonists or levodopa or both should be added as tolerated or required.

Options in advanced disease

Ultimately almost all patients with Parkinson's disease will require levodopa therapy. At widely varying times after introduction of levodopa (1-20 years), patients develop a fluctuating treatment response as well as disabling involuntary movements known as dyskinesias. There is evidence that these complications occur because of the pulsatile administration of the drug that cannot be buffered by the diminishing number of surviving dopaminergic cells, and this leads to non-physiological stimulation of the post synaptic dopamine receptors.[9]

Treatment of advance disease has shifted towards trying to provide continuous dopaminergic stimulation with either levodopa/COMT inhibitor combinations, or using polypharmacy to combine levodopa with long acting oral or transdermal dopamine agonists. Among patients with the complications of Parkinson's disease despite optimum oral drug therapy, continuous dopaminergic stimulation can be achieved with subcutaneous apomorphine pumps, and most recently by infusing levodopa directly into the jejunum. These latter therapies have been shown to be able to reverse the dyskinesias and fluctuations associated with chronic pulsatile levodopa treatment.

Deep-brain stimulation of the subthalamic nucleus (STN-DBS) has also been shown to improve quality of life among patients with advanced disease[10] and can be a very effective option in patients with motor impairments despite optimum medical therapy. There are ongoing trials to assess whether the use of DBS earlier in the illness has any advantage over medical treatment in the short and long term.[11] DBS does not have a chronological age limit, but

patients must be free from significant cognitive impairment and have healthy looking brains on MRI scan to minimise the likelihood of them developing complications from surgery. Among elderly patients suffering from severe dyskinesias, DBS of the internal pallidum (GPi) has possibly an even lower risk of causing adverse effects than STN-DBS and may be contemplated by experienced teams. While either GPi or STN DBS can improve the dopa responsive symptoms of Parkinson's disease, it will not improve patients beyond their best response to levodopa. The only exception to this rule is that of levodopa refractory tremor that can often be helped by thalamic or subthalamic DBS or by gamma knife thalamotomy among patients considered at high risk for surgery in view of age or comorbidity.

Non-motor symptoms

Non-motor symptoms affect 99% of patients with Parkinson's disease[12] and as the disease advances, these symptoms—particularly depression, and cognitive impairment—have the greatest impact on the quality of life of the patient.[13] There is trial-based evidence of the efficacy of rivastigmine in the treatment of cognitive impairment in Parkinson's disease.[14] Patients with hallucinations are in the greatest need of treatment as it seems that these patients will deteriorate most quickly if left untreated. Trials are also underway to assess whether memantine may be of additional use. Data suggest that specific subgroups of patients with Parkinson's disease (eg, those with a specific tau gene haplotype, individuals unable to generate lists, and those unable to copy intersecting pentagons) are at the greatest risk of going on to develop dementia.[15,16] But we do not have any evidence at the moment as to whether or not earlier intervention for these vulnerable subgroups would be beneficial. Depression can be treated with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors, which should used with caution among patients who are being treated with MAO-B inhibitors because adverse reactions (serotonergic syndrome) have been reported with combinations of these drugs.

Non-medical support and carer Issues

Parkinson's disease specialist nurses provide an invaluable knowledge and support base, which all patients should be able to access quickly and easily. They provide practical advice for patients and GPs while facilitating care with the local specialist services, and they often provide home visits and monitor the disease and adjust medication doses. Physiotherapy, occupational therapy, and speech therapy should be routinely offered to Parkinson's disease patients who have developed problems with mobility, activities of daily living, or speech despite a limited evidence base for their effectiveness. To help address this issue, the University of Birmingham (UK) is conducting a large randomised controlled trial into the effectiveness of physiotherapy and occupational therapy (clinical trial number ISRCTN 17452402). It is hoped that this trial will report in late 2013 and greatly increase the available evidence regarding these therapies.

The clinical diagnosis of Parkinson's disease not only impacts on an individual's life but also on those people providing care and support to that person. Carers often feel isolated and unsupported. On a national level, the Government has established the National Carers' Strategy.[17] This package includes an additional £255 million worth of funding for carers' support over the next 3 years. The package includes more respite care, GP training to recognise and support carers, and specific help for younger carers.

A large proportion of the help available outside of primary care is provided by the Parkinson's Disease Society. This is a registered charity that has been in existence for 40 years, providing care and support via 300 local branches to more than 30,000 members. They provide information and help to both patients and carers, and many of the support networks are organised at a local level. A Parkinson's disease information pack can be obtained through the Society Helpline: 0800 800 0303 or its website: www.parkinsons.org.uk.

Options on the horizon

All currently available medical and surgical therapies will only treat the symptoms of Parkinson's disease. Therefore, a huge number of studies have investigated agents (such as growth factors, gene therapies, and cell therapies) that may help protect or restore the degenerating brain cells. Open label trials in small numbers of patients have frequently produced exciting and positive results, but these have generally been followed by negative or adverse outcomes following double blind randomised controlled trials. This has occurred with Glial cell line Derived Neurotrophic factor (GDNF),[18] dopamine transplants using fetal cells,[19] retinal pigment cell (Spheramine) transplants,[20] and most

recently GDNF-Neurturin gene therapy.[21] Whether these negative outcomes relate to methodological differences in trial design, inclusion of inappropriate patient subgroups, or genuine absence of benefit remains controversial.[22,23] All these trials have considered overall mean changes in patient outcome, which can potentially miss important therapeutic gains among subgroups of patients.

Despite several disappointing results over the past 10 years, many growth factor, gene therapy and cell therapy options remain on the horizon, and treatments such as stem cells are frequently in the media and are well known to patients with Parkinson's disease. All professionals involved in the care of patients, therefore, need to be aware of these technologies. It is now possible to take a skin biopsy from a patient and expose the skin cells to a combination of factors, and thus re-programme them to become stem cells (iPS cells).[24] These cells are then capable of renewing themselves and differentiating into any cell type in the body including dopamine neurons.

Whether transplanting these cells in either an undifferentiated state, or differentiated into dopamine neurons will be able to achieve what fetal dopamine cells have thus far failed to do is unknown. There is much preclinical work left to do before clinical trials of stem cell transplantation can commence. These cells will, however, enable scientists to make cell models of Parkinson's disease that are exactly tailored to an individual patient and thus screen multiple novel pharmacological agents for beneficial effects in the lab before entering clinical trials. There is much to hope for.

Dr T Foltynie has received honoraria for speaking at meetings from GSK and Teva.

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