An ABC of Parkinson's disease: a review of Parkinson's disease and its proposed aetiological theories

Rachel Skelly

Rachel is a second-year student at Lancaster Medical School.

INTRODUCTION

Parkinson's disease (PD) is a degenerative neurological condition affecting 127,000 people in the UK. PD bears the name of James Parkinson, who published 'An Essay on the shaking Palsy' in 1817, establishing PD as a medical condition. The aetiology of PD remains unknown, but a number of theories have been suggested. Idiopathic PD is driven by a decrease in the levels of dopamine in the brain. This is associated with the death of nerve cells in the pars compacta area of the substantia nigra region of the basal ganglia, which is responsible for the synthesis and secretion of dopamine. PD is diagnosed clinically with its distinctive triad of motor symptoms: tremor; rigidity (stiffness of muscle) and bradykinesia (slowness of movement), which typically manifest when 70% of associated nerve cells in the brain have been lost.⁽¹⁾ Postural instability is another core symptom and is tested on clinical examination, although it is not always present in the early stages of PD.

Medications work to restore the level of dopamine in the body or intensify the effects of the dopamine produced by dopaminergic cells in the substantia nigra. Levodopa, dopamine agonists and monamine oxidase type b (MAO-B) inhibitors can be used as a first-choice medication in the treatment for PD symptom control, but can cause motor complications such as dyskinesia and on/off fluctuations.⁽²⁾ Other medications, such as anticholinergics and glutamate antagonist, can be used as an adjunct therapy or later in the disease progression, but there is limited evidence for their effects on symptoms and their associated side effects.⁽²⁾ Anticholinergics are avoided in the elderly due to a high prevalence of side effects.

SIGNS, SYMPTOMS AND DIAGNOSIS OF PD

Parkinsonian symptoms develop gradually, randomly, and are varied amongst patients. Typically, Parkinsonian patients suffer a triad of motor symptoms: tremor; bradykinesia and rigidity caused by dopamine depletion. Initially, a tremor is unilateral affecting one hand or foot at rest, but as the disease progresses a tremor can manifest bilaterally, often affecting the limbs. Tremors tend to improve on application, which is often referred to as 'improving on intention', but can be emphasised by stress or heightened emotion.⁽¹⁾ Classically, with PD, a 'pill-rolling' tremor is observed, where the thumb continually moves along the palmar aspect of the fingers. PD is commonly associated with a tremor, but up to 30% of patients avoid the manifestation of a tremor completely.⁽¹⁾ Bradykinesia is defined as slowness of movement and difficulty to initiate movement, whereas rigidity refers to the stiffness within the muscles, which can make it difficult for patients to turn around or roll over in bed. Muscular rigidity is responsible for the reduced, mask-like, facial expression commonly seen in patients with PD.

Cogwheel rigidity is caused by jerkiness in the muscles on forced movement and lead-pipe rigidity may be palpated on passive movement, which is commonly associated with abnormalities of the basal ganglia. Postural instability and a festinating gait are also frequently seen in PD patients.^(2,3) Often, patients suffer with constipation or dysuria that is thought to be due to a malfunction of the autonomic nervous system.

Motor	Non-motor
Rest tremor	Sleep/fatigue
Bradykinesia	Depression
Rigidity	Apathy
Postural instability	Anxiety
Festinating gait	Pain
Micrographia	Cognitive impairment
Difficulties with speech	Autonomic dysfunction
Posture	Sensory symptoms

Table 1 Some of the motor and non-motor symptoms associated with PD

The diagnosis is clinical. There are no investigations which can clearly diagnose PD. Some use of scans, for example Single Photon Emission Computed Tomography (SPECT), can be considered to differentiate between an essential tremor and one of Parkinsonism, that cannot be distinguished clinically.⁽²⁾ PD can be difficult to differentiate from other degenerative disorders, such as multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies and non-degenerative disorders, including essential tremor and drug-induced Parkinsonism.^(3,4)

PATHOLOGY OF PD

The key pathological finding in PD is loss of pigmentation in the pars compacta region of the substantia nigra. This is due to a decrease in the number of neuromelanin-containing dopaminergic neurons. This disrupts the projection of neurons into the striatum and, therefore, interrupting the nigrostriatal pathway, which is involved in movement and balance. The majority of PD symptoms are due to this pathology. Also, the presence of cytoplasmic inclusions containing α -synuclein are another key pathological finding known as Lewy bodies.

A 2003 study proposed six stages of brain pathology seen in PD (see table 2).⁽⁵⁾ Stages one to three relate to the pre-symptomatic stages of PD, and stages four to six describe the pathologies relating to PD symptoms.

Men are 1.5 times more likely than women to develop PD. Similarly, hospital and community studies have shown PD is less common amongst the Afro-Caribbean population, but all

Stage	Description of each stage
1	Involvement confined to the medulla oblongata
2	Medulla and pontine tegmentum
3	Stage 2 plus midbrain, in particular the pars compacta of the substantia nigra
4	Stage 3 plus basal proencephalon and mesocortex
5	Stage 4 plus lesions in high-order sensory association areas of the neocortex and prefrontal neocortex
6	Stage 5 plus premotor areas
Table 2 Stages of brain pathology in PD (proposed by ⁽⁵⁾)	

ethnicities are affected to an extent.⁽⁶⁾ It has been established that PD is a degenerative disease, therefore incidence and prevalence of PD increase with age and the rate of both has increased significantly due to an increase in life expectancy of the population.

DISCUSSION: THEORIES OF AETIOLOGY

There is limited evidence available for what could cause PD, but a number of biological, environmental and environmental-genetic interaction theories have been proposed.⁽⁷⁾ The aetiology of neuronal degeneration is unknown, but several hypotheses have been rationalised for the pathogenesis of PD: oxidative stress, defective mitochondrial energy metabolism, apoptosis, excitotoxin and xenobiotic-related cell death and protein misfolding.⁽⁸⁾

This review will go on to investigate some of the aetiological evidence for PD including:

- biological causes
 - ageing
 - genetics
- environmental causes
 - lifestyle: diet and smoking
 - exposure to chemicals/toxins, eg pesticides and well-water consumption

Ageing

Ultimately, cell degeneration occurs with age. Life expectancy increases proportionately with the risk of PD, suggesting if the entire population lived to over 120 years old they would all develop PD.⁽⁹⁾ It has been suggested that ageing cells are associated with the production of more free radicals, which have the ability to damage neuronal cells and induce early apoptosis. Free radicals react with a cell by removing an electron to make a molecule which can alter cell structure or make a cell dysfunctional.⁽⁹⁾

Genetics

Family members passing away before the onset of PD symptoms can complicate genetic research into the cause of PD. This disguises familial patterns, and up to 25% of cases diagnosed as idiopathic PD are in fact a type of Parkinsonism. Through studying Mendelian and non-Mendelian disease pathways, recent advances have found a number of gene mutations that could be plausible explanations. SNCA (α -synuclein) was the first autosomal dominant gene identified for causing PD. Three coding mutations were recognised (A53T, A30P and E46K) which can increase the formation of synuclein, thus suggesting an early stage of disease.⁽¹⁰⁾ Also, copy variants on the SNCA locus can influence transcription,

but is not sufficient alone in causing disease.⁽¹⁰⁾ Other research has found dominant gene mutations on the LRRK2 (Leucine-rich repeat kinase 2) loci, which codes for a protein dardarin responsible for aiding the transmission of signals in the body.⁽¹¹⁾ Therefore, α -synuclein and LRRK2 mutations have been recognised as significant risk factors for PD.⁽¹¹⁾

A study in 1998 compared the brain pathology of three known PD patients compared to three matched healthy controls.⁽¹²⁾ They found that the three PD cases had an accumulation of the α -synuclein mutation in subcortical and cortical Lewy bodies, but there was an absence of plaques and neurofibrillary tangles compared to the three controls where no brain pathology was identified. This is suggestive that the accumulation of α -synuclein mutants in Lewy bodies could be the cause of PD.⁽¹²⁾ On the other hand, the previously mentioned 2003 study proposed PD originates in the periphery, outside of the central nervous system.⁽⁵⁾ Further research is required in this field, but researchers have suggested a preclinical marker may be detectable and could be used to prevent the development of idiopathic PD.⁽¹³⁾

Moreover, a 1983 study compared monozygotic and dizygotic twins.⁽¹⁴⁾ It was found that the concordance rate for Parkinsonism remained unchanged amongst the twins compared to the general incidence of disease, concluding genetics are not the main aetiological factor.

However, a 1992 study conducted a further comparison of twins, with one twin previously being diagnosed with PD.⁽¹⁵⁾ Following analysis of 18-fluorodopa PET scans it was found that the unaffected twin had abnormally low 18-fluorodopa uptake compared to the affected twin. Further scans revealed worsening of the defect highlighting advancing deterioration. The PET findings concluded a 45% concordance rate amongst monozygotic twins and a 29% concordance rate amongst dizygotic twins, highlighting a genetic contribution to PD is credible.

Lifestyle: diet and smoking

A longitudinal study recently published findings after a 22-year follow-up of 6,715 individuals, aged 50-79 years and who showed no signs of PD.⁽¹⁶⁾ All subjects completed an initial health examination recording their leisure-time physical activity, smoking and alcohol consumption. Follow-up revealed an incidence of 101 participants. Initially, body mass index (BMI) did not carry an associated risk with PD, yet after excluding the 15-year follow-up mark, a higher BMI indicated an increased risk of PD. Similarly, subjects who engage in more physical activity have showed a lower risk of PD than participants who did not exercise at all. PD appeared to be less common in current smokers compared to individuals who have never smoked, suggesting smoking may be a protective factor. However, smoking has many other detrimental effects on health, so this is questionable. On the other hand, individuals with a moderate amount of alcohol consumption showed an elevated risk of developing PD compared to patients who do not consume alcohol at all. This study highlights lifestyle can impact the development of PD and such factors can be used to predict the incidence of PD.

Moreover, research has found vitamin D deficiency is common amongst PD patients. New evidence has revealed vitamin D is involved in brain development, neuroprotection and regulating brain function.⁽¹⁷⁾ The mechanism and cause of neuronal death is unknown, yet it has been proposed that vitamin D may have

neurotropic and protective effects at a cellular level.⁽¹⁷⁾ This would provide protection for the dopamine system and by modifying gene expression motor symptoms can be limited.⁽¹⁷⁾

Chemical exposure

In 1976, a chemistry graduate, Barry Kidston, artificially synthesised MPPP (1,3-dimethyl-4-phenyl-4-propionoxypiperidine) and injected the chemical into his body. The product was found to contain an impurity of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). MPTP's active, neurotoxic metabolite is MPP⁺ (1-methyl-4-phenylpyridinium) that can accumulate in the matrix of the mitochondria reducing the effects of complex I and inhibiting oxidative phosphorylation.⁽¹⁸⁾ Three days later, he began eliciting Parkinsonian symptoms and survived 18 months before an overdose of cocaine took his life. Autopsy confirmed destruction of dopaminergic neurons in the substantia nigra, in keeping with idiopathic PD.⁽¹⁹⁾ Therefore, it is considered that MPTP is selectively toxic towards cells in the substantia nigra.⁽¹⁹⁾

In 1982, a second case of MPPP synthesis occurred and was sold publicly as synthetic heroin. Batches were studied and contamination with MPTP was confirmed. Some cases were fatal. Parkinsonian symptoms had a rapid onset and at post mortem permanent changes had occurred in the substantia nigra, indicating the anatomical location for the disease process of PD.⁽²⁰⁾ Drug-induced Parkinsonism has been identified as a side effect of some drugs, eg neuroleptic drugs metoclopramide and prochlorperazine, as well as typical antipsychotics such as haloperidol.

Also, an association between PD and exposure to organophosphates has been proposed, although specific pesticides and herbicides (eg Rotenone) increasing the risk of PD are yet to be found.⁽²¹⁾ It has been identified that a component of pesticides (MPTP) is linked to increased risk of PD.⁽¹⁸⁾ A longitudinal, case-control study estimated the exposure of 119 people (357 PD cases and 752 population controls) to 36 commonly used organophosphate pesticides (OP). Through evaluating exposure to each OP separately, it was found that there was an increased risk of developing PD and exposure-response patterns were observed.⁽²¹⁾ However, the majority of participants were exposed to a combination of OPs that generated similar results. Therefore, functionalities and toxicities were assumed to be similar and OPs were indistinguishable.⁽²¹⁾ Further studies into low-dose ambient exposure of OPs would be advantageous in order to determine neurotoxicity mechanisms and be reflective of real life exposure.⁽²¹⁾

Ninety percent of oxygen that enters a cell is used in oxidative phosphorylation to produce ATP, which is crucial for neuronal activity and survival. All aerobic organisms can produce free radicals as a by-product of oxygen reduction during oxidative phosphorylation. Accumulation of oxygen and nitrogen free radicals induces oxidative stress and they can cause damage to vital cell components.⁽²²⁾ Through monitoring biomarkers, including reactive oxygen species and reactive nitrogen species, inconclusive evidence has found mitochondrial damage, disrupted mitochondrial respiration and oxidative stress plays a role in the disease process of various neurodegenerative disorders.⁽²²⁾

Furthermore, studies have highlighted a higher incidence of PD in farmers and people who drink water from wells.⁽²³⁾ A case-

control study assessed pesticide exposure and well-water consumption in 250 PD cases and 388 healthy control subjects matched on age and sex.⁽²⁴⁾ Significant increased odd ratios were found from life-long well-water consumption compared to well-water consumption at some point in the subject's life. This suggests well-water consumption has a cumulative effect on the development of PD.⁽²⁴⁾ Similarly, a study conducted in Spain studied 384 (128 PD patients and 256 age, sex controls) residents in an urban area.⁽²⁵⁾ It was found that exposure to well water may be a likely factor leading to the pathogenesis of PD. However, only prolonged exposure of over 30 years showed significant differences between the study groups. It was also found that well-water consumption was not associated with increased disability or earlier onset of disease. These studies highlight PD can occur nationwide, but although this evidence states an association between well-water consumption and the development of PD, the constituents of well water are unknown. This suggests further research would be beneficial to distinguish the components of well water and what constituent is responsible for the degeneration of neuronal cells, as the water could have been contaminated.

TREATMENT

The aim of pharmacological management is to reduce the symptoms associated with PD.⁽³⁾ The mainstay of treatment for PD is levodopa therapy, a precursor of catecholamines, eg dopamine. Dopamine cannot be given directly due to its inability to diffuse across the blood-brain barrier in order to enter the brain, thus being ineffective. Levodopa is decarboxylated in the extracerebral tissue to form dopamine. Dopaminergic neurons and their pathways are part of the brain's 'response selector' mechanism. Over activity of these pathways leads to dyskinesia (involuntary movements) and 'off' periods.⁽²⁶⁾ Levodopa comes in a preparation combined with either benserazide or carbidopa (an extracerebral dopa-decarboxylase inhibitor), which aids the transportation of levodopa into the required parts of the brain. Levodopa has been used since the 1960s and is considered the most effective treatment for PD symptoms.⁽²⁶⁾

Dopamine agonists are used to directly stimulate nerve cells, much like dopamine. Although they are effective in attenuating symptoms of PD, they can cause a number of side effects, including the inability to control impulsive or compulsive behaviours, like gambling, hypersexuality, compulsive eating and compulsive shopping. In those suffering with addiction, there is an increase in dopamine levels, and dopamine-based medications have the potential to artificially induce this.⁽²⁷⁾ Moreover, MAO-B inhibitors may be sufficient for the management of symptoms in early PD, as they work by blocking the enzyme monoamine oxidase type B, which is responsible for inhibiting the catabolism of dopamine in the brain and, therefore, prolonging its effects. There is evidence to suggest that taking an MAO-B inhibitor earlier on in PD can delay the requirement of levodopa, but this evidence is inconclusive. Likewise, taking an MAO-B inhibitor as an adjunct to levodopa can prolong the effects of levodopa, which is effective for patients suffering with the 'wearing-off' of medication. However, strengthening the effects of levodopa can have implications by fortifying the potential side effects, including nausea and dyskinesia. Similarly, COMT inhibitors are commonly used as an adjunct of levodopa to prolong its effects and to prevent 'end-of-dose deterioration'. In some cases, COMT inhibitors

can lead to a lower dose of levodopa being required. Stalevo is an example of one of the medications containing the combination of levodopa, carbidopa and a COMT inhibitor.

Moreover, there is little evidence-base for the use of glutamate antagonists in PD, but anecdotal evidence has suggested improvements in muscle stiffness and tremor with its use, its mechanism of action perhaps modifying the chemical imbalance within the brain. Previously, anticholinergics were used to block the action of acetylcholine at neuromuscular junctions, but these are now being replaced by levodopa therapy due to their side effects. Elderly patients tend not to tolerate anticholinergics well, and they have been found to induce memory impairment, disorientation, dysuria and constipation, which can already pose an issue in PD. If levodopa therapy fails, anticholinergics may be used in some younger patients to treat tremor. Many medications for PD are known to cause postural hypotension. In order to combat this, domperidone, an anti-emetic, is prescribed that is secondarily used to prevent postural hypotension.

Surgical intervention is another management option, but is often reserved for advanced PD. A stereotactic thalamotomy can be performed to treat a tremor, but this is infrequently practised due to the substantial medications available. Moreover, in order to treat drug-induced dyskinesia, stimulating electrodes can be implanted into the globus pallidus region of the brain. There is ongoing, experimental research into the implantation of foetal mid-brain cells into the basal ganglia in order to augment dopaminergic activity.⁽²⁸⁾ Throughout PD, patients may suffer with dysphagia, dysarthria and dysphonia, which can affect eating and communication. Speech and language specialists can advise and attempt to help patients combat this. Likewise, physiotherapy can be beneficial to reduce rigidity and help to maintain a good posture.⁽²⁸⁾ Similarly, occupational therapists can supply PD patients with aids to assist independent living.

MORTALITY AND PROGNOSIS

It is believed PD doesn't significantly affect a patient's life expectancy, but can leave the patient more vulnerable to infection and generally poorer health.

CONCLUSION

PD is a progressive neurological condition affecting movement that has an average age of onset of 60-65 years old, but is more prevalent with age. The cause of idiopathic PD remains unknown, but there are a number of proposed theories, which this review has explored. Research has shown there is a potential genetic link in PD, following analysis of familial patterns and twins studies. Inconclusive evidence has suggested in rare cases exposure to welding fumes and some metals causes Parkinsonism or hastens the onset of PD. Further research into this area would be advantageous to develop a more comprehensive explanation.

Paradoxically, the negative correlation between Parkinson's disease and smoking is a challenge to those charged with public health.

REFERENCES

1. McCall B, Findley L. Parkinson's – answers at your fingertips. London. Class Publishing. 2010
2. National Institute of Health and Clinical Excellence. Parkinson's disease: diagnosis and management in primary and secondary care. 2011 (Accessed 21/03/2014) Available from: <http://www.nice.org.uk/CG035>
3. Scottish Intercollegiate Guidelines Network. Diagnosis and Pharmacological Management of Parkinson's Disease. 2014 (Accessed 25/03/2014) Available from: <http://www.sign.ac.uk/guidelines/fulltext/113/index.html>
4. Rajput A, Rozdilsky B. Accuracy of clinical diagnosis in parkinsonism – a prospective study. Can J Neurol Sc 1991;18(3):275-8
5. Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology relating to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-211
6. Ma C, Su L, Xie J, Long J, Wu P, Gu L. The prevalence and incidence of Parkinson's disease in China: a systematic review and meta-analysis. J Neural Transm 2014;121(2):123-34
7. Tsuboi Y. Environmental-genetic interactions in the pathogenesis of Parkinson's disease. Exp Neurobiol 2012;21(3):123-8
8. Wirdefeldt K, Adami H, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol 2011;26(1):1-58
9. Lieberman A, Williams F, Imke S, et al. Parkinson's Disease – The Complete Guide for Patients and Caregivers. Simon and Schuster. 1993
10. Lubbe S, Morris HR. Recent advances in Parkinson's disease genetics. J Neurol 2014;261(2):259-66
11. Martin I, Dawson V, Dawson T. Recent Advances in the Genetics of Parkinson's Disease. Annu Rev Genomics Hum Genet 2011;12:301-25
12. Takeda A, Mallory M, Sundsmo M, Honer W, Hansen L, Masliah E. Abnormal accumulation of NACP/ α -synuclein in neurodegenerative disorders. Am J Pathol 1998;152:367-372
13. Ludolph A. Comment: Braak staging in clinical practice? Neurology 2014;82(10):862
14. Ward CD, Duvoisin RC, Ince SE, et al. Parkinson's disease in 65 pairs of twins and in a set of quadruplets. Neurology 1983;33:815-24
15. Burn DJ, Mark MH, Playford ED, et al. Parkinson's disease in twins studied with 18F-dopa and positron emission tomography. Neurology 1992;42:1894-900
16. Sääksjärvi K, Knekt P, Männistö S, et al. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity. Eur J Epidemiol 2014:1-8

17. Liu Y, Li Y, Tang Y, et al. Vitamin D: Preventive and Therapeutic Potential in Parkinson's disease. *Curr Drug Metab* 2013;14(9):989-93
18. Langston J, Ballard P, Tetrud J, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983;219:979-80
19. Fahn S. Book Review - The Case of the Frozen Addicts: How the Solution of an Extraordinary Medical Mystery Spawned a Revolution in the Understanding and Treatment of Parkinson's Disease. *New Engl J Med* 1996;335(26):2002-3
20. Parkinson's organisation. MPTP and Drug-Induced Parkinson's. 2007 (Accessed 01/04/2014)
Available from: www.parkinsons.org.au
21. Wang A, Cockburn M, Ly T, Bronstein J, Ritz B. The association between ambient exposure to organophosphates and Parkinson's disease risk. *Occup Environ Med* 2014;71(4):275-81
22. Ramalingam M, Kim S. Reactive oxygen/nitrogen species and their functional correlations in neurodegenerative stress. *J Neural Transm* 2012;119(8):891-910
23. Tugwell C. Parkinson's Disease in Focus. Pharmaceutical Press. 2008
24. Firestone J, Smith-Weller T, Franklin G, Swanson P, Longstreth W, Checkoway H. Pesticides and risk of parkinson disease: a population-based case-control study. *Arch Neurol* 2005;62(1):91-5
25. Jiménez-Jiménez F, Mateo D, Giménez-Roldán S. Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. *Mov Disord* 1992;7(2):149-52
26. Royal Pharmaceutical Society. British National Formulary 62. BMJ Group and Pharmaceutical Press. 2011
27. Kelley B, Duker A, Chiu P. Dopamine agonists and pathologic behaviors. *Parkinsons Dis* 2012;2012:1-5
28. Colledge N, Walker B, Ralston S. Davidson's Principles & Practice of Medicine. 21st ed. Churchill Livingstone. 2010

FURTHER READING

Parkinson's UK. What is Parkinson's? 2010 (Accessed 16/03/2014)
Available from: <http://www.parkinsons.org.uk/content/about-parkinsons>