

PARKINSON'S DISEASE

– clinical features, pathophysiology and genetics

By NAHEED L. KHAN, MA, MB, BCHIR, MRCP, and THOMAS BRITTON, MD, FRCP

Parkinson's disease is a relatively common neurodegenerative disease, which mainly affects the elderly.

The first part of this month's special feature looks at clinical symptoms, the genetic basis of Parkinson's disease, and diagnostic issues, including distinguishing the idiopathic illness from other conditions producing parkinsonism

Transmission electron micrograph of a section through a Lewy body: finding Lewy bodies in the substantia nigra is indicative of Parkinson's disease

LYSIA FORNO/SPL

After being questioned in connection with an alleged plot to murder King George III, James Parkinson, surgeon and apothecary, focused his attentions on medicine. He first described the clinical features of the condition that now bears his name in a monograph entitled "An essay on the shaking palsy" in 1817. Subsequently, Parkinson's disease was associated with the histopathological finding of Lewy bodies within the substantia nigra and degeneration of dopaminergic nigrostriatal neurones. Degeneration of dopaminergic neurones results in dopamine deficiency within the basal ganglia and produces a levodopa-responsive syndrome, with the clinical triad of bradykinesia, rigidity and tremor (parkinsonism).

Although Parkinson's disease was once considered a single disease entity, it is now recognised that many disease states can pro-

duce parkinsonism. Clinically it is often difficult to distinguish between idiopathic (Lewy body) Parkinson's disease and the other forms of parkinsonism, with up to 25 per cent of cases being misdiagnosed. Recent advances in immunohistochemistry and genetics have greatly improved our understanding of the causes and pathogenesis of parkinsonism, and have also led to a re-evaluation of our concept of neurodegenerative diseases. Future work is likely to lead to better clinical diagnostic tests for Parkinson's disease and parkinsonism and to improved treatments.

CLINICAL FEATURES

Motor features Parkinson's disease is primarily a disorder of voluntary movement. Typically the patient will complain of a gradual "slowing up". Further enquiry may elicit a history of a shuffling gait, difficulty turning over in bed and progressively smaller handwriting. Other presenting symptoms may include a gradual softening of the voice and difficulty using an arm particularly for tasks that require rapid alternating move-

ments such as polishing or cleaning. Around 70 per cent of patients with parkinsonism also have tremor, which is typically a resting tremor, occurring at times when the arms or legs are relaxed and the patient is attending to something else – for example, when sitting watching television. Falls may occur, although typically only later in the course of the disease.

Clinical examination reveals the combination of bradykinesia (slowness of movement) and rigidity (which is the sense of resistance felt when the clinician attempts to impose passive movements on a joint – see Figure 1, p10). Slowness of movement may best be appreciated by asking the patient rapidly to open and close their hands or to tap their feet. Paucity of facial expression and a monotonous soft voice may also be present. The gait is typically shuffling and associated with reduced arm swing. A resting tremor, usually at a frequency of around 3Hz, may be evident, disappearing on voluntary movement of the limb. In the upper limb the resting tremor often has a "pill-rolling" appearance, the description referring to a previous era when tablets were

Dr Khan is a specialist neurological registrar and Dr Britton is a consultant neurologist at King's College Hospital, London

Figure 1: Assessing rigidity in a patient with Parkinson's disease

made by hand using the thumb and fingers to roll the medicine into a round pill. Lower jaw tremor is also commonly seen in patients with parkinsonism. In more advanced cases, the postural reflexes may be impaired and the patient may have difficulty getting out of a chair or on to the examination couch.

Non-motor features Although Parkinson's disease is primarily a motor disorder, it is often complicated by cognitive and neuropsychiatric problems and careful examination often reveals abnormalities in other parts of the nervous system, including the visual, olfactory, somatosensory and autonomic systems. Failure to appreciate these non-motor problems is often the cause of distress to patients.

For most patients with Parkinson's disease, the cognitive deficits are generally mild and subtle. However, up to 25 per cent of patients with parkinsonism will develop dementia over four years. Dementia occurs more commonly in patients with atypical parkinsonian syndromes, such as progressive supranuclear palsy (PSP) or corticobasal ganglionic degeneration (CBGD).

The reported prevalence of depression in Parkinson's disease varies widely, some studies noting only 4 per cent prevalence, while others have found a 70 per cent rate. Differences in the diagnostic criteria used to identify depression and the difficulties in distinguishing depressive symptoms from the neuro-behavioural symptoms of Parkinson's disease probably account for most of this variation. Whatever the true rate, there is no doubt that the condition causes considerable frustration to the majority of patients.

Sleep is also commonly affected, with many patients complaining of insomnia, restless legs and nightmares. REM (rapid eye movement) sleep behaviour disorder is a specific sleep condition that has been linked

to Parkinson's disease and other neurodegenerative disorders associated with alpha-synuclein in the brain, including multiple system atrophy (MSA) and dementia with Lewy bodies (DLB).

Patients have an impaired sense of smell and subtle visual impairments of colour discrimination and contrast sensitivity, even in the early stages of their disease. The visual deficits have been attributed to degeneration of dopamine-containing cells in the retina. Difficulties with chewing and swallowing can also present early in the course of Parkinson's disease, and up to one third of patients may regard such difficulties as a major problem. Video-fluoroscopy demonstrates silent aspiration in up to 20 per cent of asymptomatic patients and up to 36 per cent of symptomatic patients. Such swallowing difficulties, along with respiratory muscles abnormalities, are likely to contribute to the excess mortality from pneumonia seen.

Patients often complain of pain in their limbs, which is usually linked to the severity of their motor symptoms. In addition, however, subtle (sub-clinical) sensory abnormalities have been reported, including impairment of joint position sense. The autonomic abnormalities associated with Parkinson's disease include various cardiovascular disorders, impaired sweating, gastrointestinal dysfunction and bladder disturbance. Of these, gastrointestinal dysfunction probably warrants more attention than clinicians usually give it. Bowel problems may affect up to 80 per cent of patients and treatment of bowel disturbance (especially constipation) often improves parkinsonism without the need to alter or increase dopaminergic medication. The presence of autonomic symptoms in a patient with parkinsonism is often the first indicator that alerts the physician to the possibility of an alternative diagnosis. For example, symptomatic postural hypotension occurring within the first year after disease onset is generally indicative of MSA.

— DIAGNOSIS

The diagnosis of Parkinson's disease can only properly be made at post-mortem, by the finding of Lewy bodies in the substantia nigra. There is currently no clinical diagnostic test. In the early 1990s two clinico-pathological studies suggested that the accuracy of the clinical diagnosis of idiopathic Parkinson's disease was about 75 per cent. In other words, 25 per cent of patients with a clinical diagnosis of Parkinson's disease would turn out to have a different condition at post-mortem.

A more recent survey suggests that the clinical diagnostic accuracy is better than this, although some 10 per cent of patients with idiopathic Parkinson's disease were still misclassified and approximately 20 per cent of patients with MSA or PSP misdiagnosed.¹

Diagnosing Parkinson's disease accurately during life is complicated because it can result from a variety of causes. One of the more common causes of parkinsonism in clinical practice is neuroleptic medication. Other neurodegenerative conditions that can produce parkinsonism, include MSA, PSP, CBGD and dementias with parkinsonism linked to chromosome 17 (FTDP-17).

Imaging techniques can, however, be useful diagnostic tools. For example, standard CT (computerised tomography) or MR (magnetic resonance) brain imaging is generally normal in patients with Parkinson's disease, but is commonly undertaken to exclude hydrocephalus as a cause. More detailed MR imaging may help distinguish MSA from idiopathic Parkinson's disease, particularly if atrophy of the brain stem or putamen (part of the striatum) is seen. Atrophy within the brainstem may give rise to the so-called "hot cross bun sign" on the scan.

Nuclear medicine studies (ie, ¹⁸F-Fluorodopa PET [positron emission tomography]) or studies using dopamine-transporter binding ligand (ie, SPECT studies [single photon emission computerising topography]) offer a means of assessing the dopaminergic system *in vivo* and can be useful in the diagnosis of difficult parkinsonian syndromes. These scans are only available in specialist centres. An assessment of sympathetic innervation using ¹²³I-metaiodo-benzylguanidine cardiac scintigraphy may also have a future role in the diagnostic process. The procedure can be used to distinguish between idiopathic Parkinson's disease (where autonomic dysfunction is predominantly caused by post-ganglionic damage) and MSA (where autonomic dysfunction is primarily caused by degeneration of pre-ganglionic and central autonomic neurones).

Other conditions that require consideration include DLB (a progressive dementing illness with significant fluctuations in cognition, visual hallucinations and/or parkinsonism, with the extrapyramidal motor signs appearing not more than one year before the dementia) and PDD (Parkinson's disease with dementia, where dementia complicates Parkinson's disease after years of an otherwise typical course). Similarly vascular parkinsonism also remains a contentious issue. A recent review² noted that, in comparison with patients with idiopathic parkinson's disease, patients with vascular parkinsonism were generally older and more likely to present with gait difficulty and were also less likely to respond to treatment with levodopa.

— PROGNOSIS

Patients often ask how rapidly their disease is likely to progress. One of the difficulties in providing an answer in the clinic is the fact that up to 25 per cent of patients confidently diagnosed in life as

having Parkinson's disease may turn out to have a different condition at post mortem (see p10).

In general, patients with parkinsonism that is not due to Parkinson's disease have a worse prognosis. Muller and colleagues³ have recently confirmed this by reviewing the case notes of 81 pathologically confirmed patients with various types of parkinsonism. Disease progression in patients with idiopathic Parkinson's disease was significantly slower than in patients with MSA, PSP, DLB or CBDG. Furthermore, no patient with Parkinson's disease developed mid-stage disease (ie, Hoehn and Yahr stage III) within one year of the onset of motor symptoms, whereas 72 per cent of those with other types of parkinsonism did. The median latency to reach end-stage disease (ie, Hoehn and Yahr stage V) was 15 years in patients with Parkinson's disease, compared with five years for atypical parkinsonism.

PATHOPHYSIOLOGY

Pathology The pathological hallmark of Parkinson's disease is the Lewy body, an eosinophilic intra-cytoplasmic inclusion, typically located within the pigmented brain stem nuclei. Lewy bodies can, however, be seen more widely throughout the

brain and cerebral cortex, particularly in patients with dementia.⁴ Three types of "Lewy body disease" are now recognised: brain stem predominant Lewy body disease (as typically found in idiopathic Parkinson's disease), limbic (or transitional) Lewy body disease, and neocortical Lewy body disease. The presence of cortical Lewy bodies is often (but not invariably) associated with dementia. Lewy bodies are also found in central and peripheral autonomic nuclei (producing the autonomic features of Parkinson's disease). The ability to detect Lewy bodies in post-mortem brain tissue has been greatly enhanced by the availability of antibodies to ubiquitin and more recently to alpha-synuclein.

Neurophysiology The currently favoured model of the neuronal pathways involved in abnormal motor function in Parkinson's disease is shown in Figure 2. Briefly, dopamine deficiency in the substantia nigra causes overactivity of the globus pallidus interna (GPi) by direct and indirect pathways, resulting in excessive inhibition of the thalamus, which in turn reduces cortical stimulation.

Recent research suggests that the pedunculopontine nucleus (PPN), an upper brainstem nucleus, is also involved. The PPN, like the thalamus, is excessively inhibited

by overactivity of the GPi. Inhibition of the PPN reduces neuronal input into the lower brainstem, cerebellar and spinal motor centres. In animal studies, lesions of the PPN cause akinesia.

The fact that patients with Parkinson's disease move more slowly than normal must imply some abnormality in the way that their muscles are activated. However, identifying these abnormalities at a single motor unit level has proved problematic. In many ways, single motor unit activity is remarkably normal.

Slight changes in motor unit activity do occur, including a tendency for motor unit firing to be modulated at around 10Hz. Other studies have suggested that there is a subtle change in the spectral analysis of motor unit firing: in normal subjects, a tonic contraction is associated with a small peak at about 20Hz and again at about 40Hz (Piper frequency) on the spectral analysis of the EMG (electromyography). In patients with Parkinson's disease, these peaks are absent, but can be restored with dopaminergic treatment.

Neurochemistry Several lines of evidence suggest that oxidative stress is important in the pathogenesis of Parkinson's disease. The substantia nigra contains increased levels of iron, which is a catalytic agent for the pro-

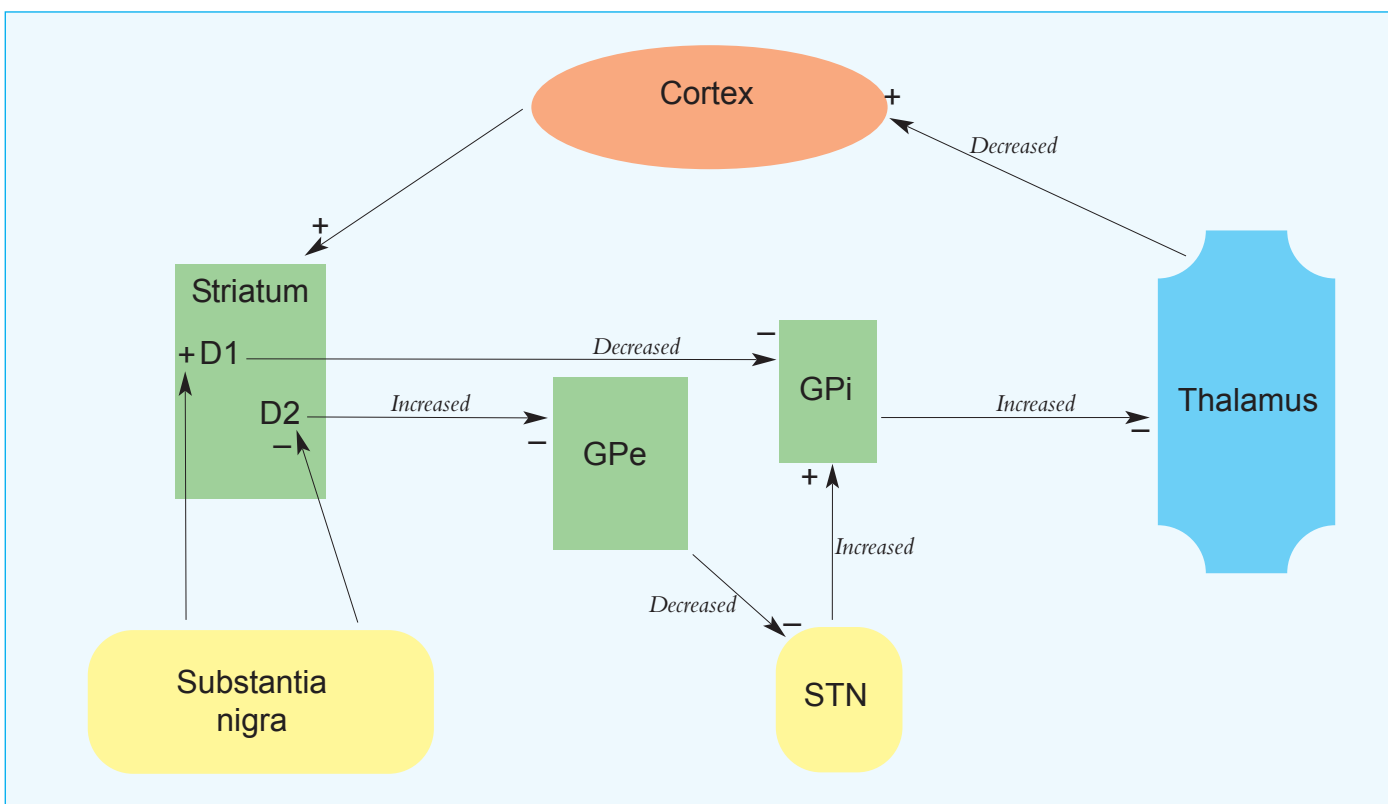


Figure 2. Diagram of the neuronal pathways potentially involved in Parkinson's disease. "GPe" means globus pallidus externa, "GPi" means globus pallidus interna, "STN" means subthalamic nucleus, "+" means an excitatory projection on a neuronal pathway, "-" means an inhibitory projection on a neuronal pathway, "increased" and "decreased" indicate the putative changes in activity in a dopamine-deficient state. The structures shown in green and yellow are included in the basal ganglia. Dopamine deficiency in the substantia nigra stimulates D1 receptors and inhibits D2 receptors in the striatum. This causes overactivity of the GPi by (a) directly reducing the otherwise inhibitory effect of D1-receptor activation and (b) indirectly increasing GPi stimulation from the STN. Overactivity of GPi results in excessive inhibition of the thalamus, reducing excitatory input to the cortex. Overactivity of the GPi is also believed to cause excessive inhibition of the pedunculopontine nucleus (not shown), a structure that also influences movement. See text for further details.

Panel 1: Genes in familial Parkinsonism

Gene/locus	Location	Inheritance	Age onset	Clinical features	Pathology
SNCA synuclein	4q21.3-q22	Dominant	Late	Rapid progression, tremor uncommon	Lewy bodies
PARK2 "parkin"	6q25-q27	Recessive	Early/juvenile	Slow progression; dystonia or dyskinesia	No Lewy bodies*
PARK3	2p13	Dominant	Late	Cognitive decline	Lewy bodies
PARK4	4p15	Dominant	Late	Postural tremor; dementia and weight loss	Lewy bodies
UCHL1	4p14	Dominant	Late	Similar to idiopathic Parkinson's disease	No pathology
PARK6	1p36-p35	Recessive	Early	Slow progression; tremor at rest	No Lewy bodies
PARK7 DJ-1	1p36	Recessive	Early	Focal dystonia, psychiatric symptoms	No pathology
PARK8	12p11-p13	Dominant	Late	Similar to idiopathic Parkinson's disease	Lewy bodies in some
PARK9	1p36	Recessive	Juvenile	Spasticity/dementia; abnormal eye movements	No pathology
PARK10	1p32	Non-mendelian	Late	Similar to idiopathic Parkinson's disease	No pathology

*Except in one case. "Non-mendelian" means that inheritance is not simply dominant or recessive

duction of hydroxyl radicals, as well as increased manganese superoxide dismutase activity. Levels of the reduced form of glutathione are decreased in the midbrain. There is also evidence of increased oxidative damage to lipids, proteins and DNA as well as oxidation of catecholamines.

Impaired protein clearance or the overwhelming production of abnormal proteins (eg, mutant alpha-synuclein) may play a role in the degeneration of dopamine-containing neurones. The ubiquitin-proteasome system (UPS) is the main biochemical pathway responsible for the degradation of normal and abnormal intracellular proteins. Ubiquitination (which involves a number of proteins, including parkin, the protein associated with autosomal recessive juvenile parkinsonism [ARJP]) marks proteins for proteolysis by proteasomes that are found in the cytoplasm, endoplasmic reticulum, peri-nuclear region and nucleus of eukaryotic cells. Failure of the UPS to degrade unwanted proteins could be a common factor underlying protein accumulation or Lewy body formation in both sporadic and familial Parkinson's disease.

GENETICS

Twin studies Twin studies are used to provide information about the relative contributions of genetic and environmental factors to disease. If genetic factors are important, the concordance rate (ie, rate of co-occurrence of the disease in both twins) for twins who are genetically identical will be greater than that for non-identical twins. If genetic factors are unimportant, then the concordance rates for monozygotic and dizygotic twins should be equal. Unfortunately the results from such studies in patients with parkinsonism have been contradictory.

The study by Tanner and colleagues,⁵ the largest twin study of Parkinson's disease to date, analysed nearly 20,000 white male twins enrolled in the National Academy of Sciences/National Research Council

World War II Veteran Twins Registry. Of 268 twins with suspected Parkinsonism and 250 presumed unaffected twin brothers, complete information was subsequently obtained on 161 twin pairs. The concordance rate for monozygotic twins was similar to that for dizygotic twins suggesting that genetic factors do not play a major role in causing parkinsonism. However, in 16 twin pairs with a diagnosis of parkinsonism before the age of 50, there was a significant increase in the monozygotic concordance rate, suggesting that genetic factors are important in younger patients.

The application of twin studies to a late-onset illness such as Parkinson's disease poses problems because of the difficulty in identifying subclinical cases. To overcome this, Piccini and colleagues⁶ used ¹⁸F-fluorodopa positron emission tomography to study dopaminergic function in twin pairs over a period of seven years. At baseline, the concordance rate for subclinical dopaminergic dysfunction was higher in the 18 monozygotic than in 16 dizygotic twin pairs (55 per cent and 18 per cent respectively). Twelve of the monozygotic twins and nine of the dizygotic twins were evaluated a second time, seven years later. Over the seven year period, the asymptomatic monozygotic co-twins all showed progressive loss of dopaminergic function and four developed clinical Parkinson's disease. None of the dizygotic twin pairs developed Parkinson's disease. After seven years, the combined concordance levels of subclinical dopaminergic dysfunction and clinical Parkinson's disease were 75 per cent in the 12 monozygotic and 22 per cent in the nine dizygotic twin pairs, the results being consistent with a substantial role for inheritance in Parkinson's disease.

Monogenic forms of parkinsonism The use of modern genetic techniques and, in particular, positional cloning in families with autosomal dominant and recessive parkinsonism⁷ has led to the identification of several disease-causing loci and mutations

in five genes (Panel 1). PARK2, which causes ARJP, appears to be one of the more common causes of genetically determined parkinsonism and may also account for up to 15 per cent of apparently sporadic young onset (less than 40 years) parkinsonism.

The PARK8 gene is as yet undefined but may be a significant cause of late onset familial Parkinson's disease. Other genetic loci associated with parkinsonism include spinocerebellar atrophy 2 (SCA2), SCA3, dopa-responsive dystonia (DRD), and FTDP-17.

Susceptibility genes An alternative tool for identifying disease-causing genes uses linkage disequilibrium in population-based studies using large numbers of unrelated Parkinson's disease cases and matched controls. A logical choice of candidate genes for association studies would include those involved in known biochemical pathways that could be implicated in Parkinson's disease pathogenesis (eg, dopamine transport or metabolism, synaptic plasticity and function, and mitochondrial and cytoskeletal function). As yet, no specific gene polymorphism has been unequivocally associated with Parkinson's disease.

EPIDEMIOLOGY

Prevalence and age distribution Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease, affecting 2 per cent of the population over the age of 65, the prevalence increasing with age. It occurs in all races and there appears to be little variation in prevalence rates among different European countries. Some studies have suggested that Chinese populations have a lower prevalence than Western ones, and African populations have been reported to have a higher frequency.

Case-controlled studies suggest that Parkinson's disease is associated with an increased mortality (despite the introduction of levodopa therapy). Although case-control

studies may overestimate mortality, because only patients with more advanced parkinsonism are likely to come to medical attention, increased mortality rates are still seen in population based cohort studies where the risk of death associated with Parkinson's disease was approximately twice normal, being slightly higher for men than women.⁸

Environmental risk factors The mechanism underlying the selective neuronal loss and Lewy body formation remains undefined. However, most cases of Parkinson's disease are believed to be "complex traits" attributable to a combination of one or more susceptibility genes interacting with one or several environmental factors.

Environmental factors have included living in a rural environment, farming, drinking well water, exposure to pesticides, diets high in animal fats or carbohydrates, and low consumption of foods rich in the

anti-oxidant vitamins C and E. Of these putative risk factors, exposure to pesticides is the one that has shown the most consistent association. Furthermore, rats chronically exposed to rotenone, an organic pesticide, develop the anatomical, neurochemical, behavioural and, significantly, neuropathological features similar to those of Parkinson's disease.

Some drug-addicts exposed to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, an impurity formed during the processing of narcotics) in the 1980s developed parkinsonism indistinguishable from idiopathic Parkinson's disease but without Lewy body pathology. However, not all exposed individuals developed parkinsonism suggesting that some additional (perhaps genetic) factor protected them from MPTP.

Cigarette smokers are at reduced risk of developing Parkinson's disease, but whether this represents a biological effect on the underlying disease process or

merely a confounding or selection bias remains uncertain. The risk of developing Parkinson's disease in an individual who has ever smoked is approximately half that of life-long non-smokers. Biological hypotheses to explain this effect have focused largely on nicotine, including induction of detoxifying enzymes, inhibition of bio-activating enzymes and trophic factor stimulation, but none has been proven. Others have argued that smoking is part of a "pre-parkinsonian" personality that may be inherited.

Encephalitis lethargica or von Economo's encephalitis was first described in 1917 and was a cause of significant morbidity and mortality during the years 1918 to 1925. The initial symptoms included headache, fever, coma, delirium, lethargy, and psychiatric symptoms. The mortality rate was up to 40 per cent. Those patients who initially recovered subsequently developed profound chronic parkinsonism. The epidemic was

temporally associated with an influenza pandemic, leading to the suggestion that the influenza virus was the cause of the encephalitis itself. However, a recent study⁹ was unable to identify influenza RNA in archival brain tissue from acute encephalitis lethargica cases.

CONCLUSIONS

Parkinsonism is primarily a movement disorder characterised by slowness of movement, rigidity and resting tremor. The condition can no longer be considered a single disease entity.

Immunohistochemistry and genetic studies have revolutionised our understanding of Parkinson's disease and parkinsonism and have revealed previously unsuspected links between several neurodegenerative disorders. New methods of classifying neurodegenerative diseases will be necessary as a result.

REFERENCES

1. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002; 125:861–70.
2. Winikates J, Jankovic J. Clinical correlates of vascular Parkinsonism. *Archives of Neurology* 1999;56:98–102.
3. Muller J, Wenning GK, Jellinger K, McKee A, Poewe W, Litvan I. Progression of Hoehn and Yahr stages Parkinson's Disease: a clinicopathologic study. *Neurology* 2000;55:888–91.
4. Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology – Later-developing dementia and loss of the levodopa response. *Archives of Neurology* 2002; 59:102–12.
5. Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, Langston JW. Parkinson Disease in Twins: an etiological study. *Journal of the American Medical Association* 1999;281:341–46.
6. Piccini P, Burn DJ, Ceravolo R, Maraganore D, Brooks DJ. The role of inheritance in sporadic Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. *Annals of Neurology* 1999; 45: 577–82.
7. Dekker MJC, Bonifati V, van Duijn CM. Parkinson's disease: piecing together a genetic jigsaw. *Brain* 2003;126:1722–33.
8. Berger K, Breteler MMB, Helmer C, Inzitari D, Fratiglioni L, Trenkwalder C et al. Prognosis with Parkinson's in Europe: a collaborative study of population-based cohorts. *Neurology* 2000;54(Suppl): S24–S27.
9. McCall S, Henry JM, Reid AH, Taubenberger JK. Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in post encephalitic parkinsonian cases. *Journal of Neuropathology and Experimental Neurology* 2001;60:696–704.