All that shakes isn't Parkinson's disease:

A guide to diagnosing Parkinsonism.

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Clinical Encounter 1: A case of the shakes

Mrs ET, a 60 year old, right handed woman, initially presented to her family doctor with a tremor in her dominant hand. This was causing her problems with a number of tasks such as sewing and drinking tea. She had been worrying about the possibility of Parkinson's disease as her mother who was diagnosed with the condition had a similar tremor. On examination her doctor found that Mrs ET had an animated facial expression and that the tremor was mainly postural, but with some overspill into rest. The doctor also felt that Mrs ET had a mild degree of 'cog-wheel' rigidity in the upper limbs. The doctor suspected a diagnosis of Parkinson's disease but referred Mrs ET on to the local neurologist for further management.

Following a thorough history and examination the neurologist felt that essential tremor was most likely in Mrs ET but decided to undertake a DaTSCAN SPECT image of Mrs ET's brain to assist with the diagnosis. This was reported as normal so supporting the diagnosis of an essential tremor. Treatment with propranolol was initiated.

The first thought that comes to mind when someone mentions Parkinson's disease is the characteristic 'pill rolling' tremor, yet it is actually bradykinesia (or slow movement) that is the defining feature of Parkinson's disease and other causes of Parkinsonism. In many instances a presumptive diagnosis of Parkinson's disease will be correct but in others the patient may have one of the many conditions that can masquerade as Parkinson's disease. Autopsy studies from Parkinsonian brain banks have revealed that even specialists may misdiagnose patients as having Parkinson's disease in up to 25% of cases.[1] Accurate diagnosis is largely based on the physician's clinical acumen as currently only neuropathological analysis of the brain can yield a definitive diagnosis. Misdiagnosing a patient and the subsequent use of inappropriate medication can have detrimental health and social implications. For example increasing the dose of a dopaminergic medication may lead to unnecessary adverse effects, while providing little or no additional benefit. With this review the authors hope to provide an aid to recognise and differentiate Parkinson's disease from some similar forms of movement disorder.

Idiopathic Parkinson's disease (IPD)

It is almost 200 years ago since James Parkinson, an English surgeon (1755-1824), provided the seminal description of the condition in his paper entitled *'The Shaking Palsy'*.[2] Approximately 1% of people over the age of 50 and 2.5% of those over 70 have IPD. It is a progressive neurodegenerative disorder clinically characterised by varying combinations of bradykinesia, resting tremor, rigidity and postural instability. Patients commonly present with either a mild asymmetrical resting tremor or an awareness of slowness - which may manifest as clumsiness during dextrous tasks. Some patients notice an insidious change in their handwriting which becomes smaller (micrographia). As the disorder develops, patients may adopt a characteristic flexed truncal posture and exhibit difficulty in initiating walking. A festinant gait

(festination is an involuntary tendency to take short accelerating steps when walking; it is as if the patient is continuously trying to catch up with their centre of gravity) is characteristic of Parkinson's patients, and there may be a notable loss of arm swing. Other clinical features include: loss of facial expression, delayed swallowing and a monotonous hypophonic voice. Intriguingly constipation, depression, sleep disturbance due to enactment of violent dreams and impaired sense of smell may all pre-date the motor symptoms of IPD by several years.

The 3-5 Hz tremor of IPD typically occurs at rest and commonly affects the upper limb in the form of pill-rolling movements of the thumbs and forefingers. The lower limb and jaw may also be affected and is the initial focus of tremor in some cases. Up to two thirds of patients will have a tremor at presentation but a minority will never show any tremor during the course of their illness. 'Lead-pipe' extrapyramidal rigidity also develops and when superimposed by a tremor may exhibit a cogwheel quality. This can be elicited by holding the patient's hand and feeling for resistance as the wrist and fingers are alternately flexed and extended. The combination of akinesia and rigidity may cause the greatest disability to the patient.

Depression and dementia are common neuropsychiatric manifestations of IPD and they occur more frequently than one would normally expect in people of a similar age3. Autonomic failure can occur but, as with postural instability and falls, it tends to be a late feature of the condition. Levodopa preparations represent the gold standard of IPD therapy. Indeed this treatment almost always leads to clinical improvement, and in instances when this does not occur the physician should be suspicious of an alternative diagnosis. To aid clinical diagnosis, clinical criteria have been formulated by the United Kingdom Parkinson's Disease Society Brain Bank[4].

The Common Differential Diagnoses

There are many conditions that can mimic IPD and in the absence of definitive diagnostic tests the importance of the clinical history and examination cannot be overstated. Below are some similar conditions and their clinical features that may help in differentiating the diagnosis.

Essential Tremor (ET)

ET is the most common movement disorder and is often misdiagnosed as Parkinson's disease, which can cause the patient unnecessary anxiety. The tremor is typically postural in nature and may be accentuated at the termination of movement. It is uncommonly seen at rest. The tremor may be symmetrical and can affect other body parts with advancing age such as the head in the form of a yes-yes (nodding) titubation, or vocal chords, neither of which are normally observed in Parkinson's disease. Patients may describe a family history of tremor and they may also report a beneficial effect of alcohol in diminishing their tremor. This frustrating and socially disabling condition may be treated with beta-blockers or a host of other agents, but often with limited success.

Factors which favour a diagnosis of ET include: (a) an action or postural tremor; (b) an early age of onset (c) a quick tremor of 6-9 Hz or greater; (d) a bilateral symmetrical tremor; (e) head, voice and trunk involvement; (f) absent or minimal bradykinesia and rigidity (g) a family history of tremor; (h) no response to levodopa. A DaTSCAN SPECT study is a form of imaging that measures the density of dopamine transporters in the brain and is helpful in discriminating IPD from ET in that the study is normal in the latter, whilst shows reduced striatal tracer uptake in the former (Figure.1).

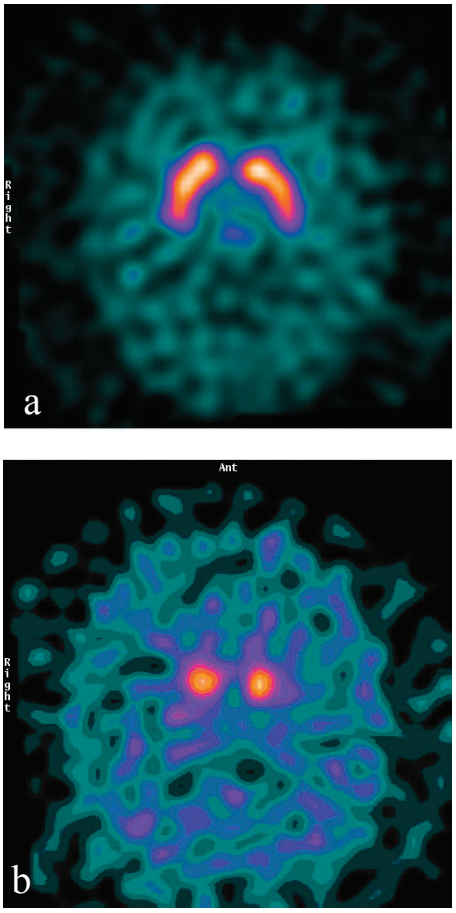

Figure 1 DaTSCAN SPECT Imaging study in (a) normal patient (b) patient with Parkinson's disease

Radiology images courtesy of Mr Ian Driver (Department of Medical Physics Newcastle General Hospital)

Vascular Parkinsonism (VP)

VP may be misdiagnosed as IPD. Infarcts within the basal ganglia can lead to Parkinsonism that mainly affects the lower limbs such that a patient may report that their legs are not working in synchronisation with the top half of their body. Consequently patients may adopt a short stepped and wide based gait, which is traditionally referred to as *marche à petits pas*. Gegenhalten rigidity (paratonic rigidity, where the patient resists the examiner's testing) may be identified but patients are recognised from those with IPD by the notable absence of tremor, akinesia and rigidity in the upper limbs.

An acute or sub-acute onset, together with a stepwise progression are also suggestive of vascular pathology. Patients are generally elderly with several vascular risk factors. Neuro-imaging may be useful in differentiating IPD from VP in that basal ganglia infarcts or frontal and periventricular white matter lesions are commonly found in VP. In contrast to IPD, levodopa has little or no impact on the patient's clinical outcome.

Drug Induced Parkinsonism (DIP)

Eliciting a complete drug history from a patient is of paramount importance when trying to elucidate the cause of Parkinsonism as several drugs can induce potentially reversible movement disorders. Common culprits include dopamine receptor antagonists, such as haloperidol or metoclopramide or any drug that depletes dopamine, such as reserpine or tetrabenazine. Patients with DIP may resemble those with IPD but symptoms will usually resolve upon cessation of the offending agent, although this may take several months. The patient should be made aware of this possibility.

Dementia with Lewy Bodies (DLB)

DLB is a neurodegenerative condition characterised clinically by a variable combination of dementia, neuropsychiatric features and Parkinsonism. Bradykinesia rather than tremor is often the predominant feature of the Parkinsonism. A psychiatric history is vital, as depression, hallucinations and fluctuating cognitive dysfunction are all notable features of the disorder. Although some patients may benefit from levodopa they are more prone to levodopa-induced psychosis.

Atypical Parkinsonism

Atypical Parkinsonism describes a group of Parkinsonian disorders with additional clinical features that are notably absent in

IPD. Progressive supranuclear palsy and multiple system atrophy are forms of atypical Parkinsonism and each affect approximately 5 per 100,000 of the population.

Progressive Supranuclear Palsy (PSP)

Also known as Steele-Richardson-Olszewski syndrome after the doctors that initially described it[5], this is a chronic neurodegenerative condition that may be difficult to diagnose as the early symptoms of the illness are often similar to those observed in IPD. Interestingly, a study showed that 6% of patients receiving a clinical diagnosis of IPD in fact had PSP at autopsy[1]. Progressive Parkinsonism and disturbances of gaze are two features which should alert to the possibility of PSP. Vertical supranuclear ophthalmoparesis is a classical sign, which is manifest by paralysis of vertical gaze, especially down gaze. Preserved range of eye movements when undertaking the occulocephalic (doll's eyes) manoeuvre will demonstrate the supranuclear component of this abnormality.

Early backward falls, prominent axial rigidity and pseudobulbar symptoms such as dysarthria, dysphagia and emotional lability would all favour a diagnosis of PSP. Over- activity of the frontalis muscles can lead to an 'astonished' facial expression. Patients with PSP also suffer from early cognitive decline and dementia may ensue. Typically patients do not respond well to levodopa or other dopaminergic agents[6].

Clinical Encounter 2: A Touch of Frost

Mrs MSA, a 57 year old right handed woman, presented to her family doctor when she began to have difficulties with dextrous tasks such as doing up buttons. Mrs MSA's akinetic-rigid disorder was subsequently diagnosed as Parkinson's disease and she was started on levodopa medications. This initially provided some mild benefit to Mrs MSA but after a year her condition had progressively worsened and she required the permanent use of a wheelchair for mobility. Mrs MSA was also experiencing dizziness when she stood up and nausea which the doctor attributed to side effects of the l-dopa.

Mrs MSA's poor response to l-dopa prompted her doctor to refer her to a local movement disorder specialist. The specialist became suspicious of an atypical form of Parkinsonism. He noticed that although it was a warm Spring day, Mrs MSA's hands appeared to be of a grey/ blue hue and felt very cold to the touch. On further questioning Mrs MSA reported that she was experiencing urinary urge incontinence. Such autonomic dysfunction prompted the specialist to revise the diagnosis to multiple system atrophy and Mrs MSA's medication was reviewed. The specialist recommended the patient contact the Sarah Matheson Trust, an organisation that could provide additional support.

Multiple System Atrophy (MSA)

As the name suggests, this is a disorder that affects several brain structures so that a patient may report or exhibit signs of extrapyramidal, pyramidal, cerebellar, or autonomic dysfunctions[7]. Up to 90% of patients develop Parkinsonism during their illness whereas a smaller proportion will exhibit cerebellar ataxia. Patients may have a symmetrical akinetic rigid form of Parkinsonism that progresses rapidly, and because of this the use of a wheel chair is often required after disease onset – something referred to in the clinic as the 'wheelchair sign'. Patients may report a tremor but this is more commonly postural and jerky in nature.

Features that may help to distinguish MSA from IPD include; (a) an early onset of postural hypotension, (b) bowel and bladder dysfunction, (c) abnormal sweating and temperature

regulation, (d) Pisa syndrome or axial dystonia, (e) cold dusky peripheries with poor vascular circulation, (f) excessive snoring, respiratory stridor, and sleep apnoea, (g) impotence. A small proportion of patients may derive a transient benefit from levodopa but more often the medication has little or no effect and can potentiate the condition by worsening postural hypotension.

Some Rarer Causes of Parkinsonism

The toxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) can produce an exact clinical mimic of IPD and this first came to light during the 80's when a small group of drug addicts in California displayed Parkinsonian features after using heroin contaminated with MPTP[8]. Cortical-basal ganglionic degeneration is a rare disorder characterised by asymmetric motor impairment. Patients may present with rigidity, myoclonus, dystonia, and apraxia. A potentially treatable condition is Wilson's disease, and this should be suspected particularly in the younger patient with a Parkinsonian movement disorder. Another condition, which may present as an akinetic-rigid disorder in the young patient is Huntington's disease, in which case it is referred to as the Westphal variant. In the early part of the last century the world experienced a pandemic of encephalitis lethargica. Many sufferers went on to develop post-encephalitic Parkinsonism, a particular group of whom were made famous by the Oliver Sacks novel and subsequent Hollywood movie entitled *Awakenings*[9].

Examining the patient with Parkinsonism

Some important features of the clinical examination, which should be considered when examining the patient with Parkinsonism (modified from Burn 2006[11]).

Observe the patient during the history for:
- Distribution of tremulous movements and dystonic postures;
- Facial animation & blink frequency;
- Breathing patterns and excessive sighing (suggestive of MSA and PSP).

Observe the patient's gait for:
- stance width, stride length;
- turning;
- dystonic posturing of the limbs;
- arm swing;
- postural reflexes (stand behind the patient and use the pull test);
- axial tone (turn the patient from side to side in vertical axis using shoulders).

Cognitive assessment
Assess tone – using reinforcement if necessary.
Power and coordination.
Assess bradykinesia by observing fine finger and rapid alternating movements
Observe the patient's handwriting
Assess eye movements (especially range and speed of fast eye movements).

Cardiovascular assessment:
- lying and standing blood pressures,
- cool dusky blue peripheries

Further Guidance

We may feel confident in recognising the shaking palsy, but remember; all that shakes is not IPD. The accurate diagnosis of Parkinsonism may be difficult and for this reason the current NICE guidelines[10] recommend that patients with suspected IPD should be referred untreated, to a movement disorder specialist. A regular review of the diagnosis and reconsideration in the light of atypical features is necessary to provide the patient with the most appropriate therapy. Communicating with and educating the patient about their specific form of movement disorder

can be of huge benefit, and contact with the appropriate charitable society associated with the condition can provide another avenue of support.

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