CASE FOUR

Short case number: 3_22_4
Category: Neurology
Discipline: Medicine
Setting: General Practice
Topic: Parkinson's disease, hereditary ataxias and motor neurone disease

Case

Ken Kwa aged 59 years, presents with increasing tremor in his right hand. He has increasing difficulty with fine motor movements and his balance appears to have deteriorated although he has not actually fallen. He comments that recently the tremor seems to have begun in his right leg as well.

Questions

1. What further history & examination would you undertake?
2. What investigations would you order?
3. What are the presenting symptoms and physical abnormalities of Parkinson's Disease?
4. Outline the management of Parkinson's Disease in terms of drug therapy, surgery, and allied health therapy (physiotherapy/speech therapy).
5. List some common akinetic rigid syndromes that may be confused for Parkinson's Disease.
6. In a table summarise the key features of the hereditary ataxias.
7. In a table, summarise the key features of Motor neurone disease
8. Outline the management and prognosis of motor neurone disease.

Suggested reading:

- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014. Chapter 26.

ANSWERS

1. What further history & examination would you undertake?

The history includes onset of tremor, with the most common initial finding in PD being an asymmetric resting tremor in an upper extremity. History also needs to focus on other symptoms including clumsiness, bradykinesia, rigidity, and gait difficulty. Other symptoms to be sought include fatigue, depression, constipation, sleep problems, muscle stiffness, difficulty swallowing and drooling. Symptoms of autonomic dysfunction may develop and include constipation, sweating abnormalities, sexual dysfunction, and seborrheic dermatitis.
Other features to be sought in the history include mediations, past history of illicit drug use, a family history of similar problems, recent travel or surgery.

Physical examination must include examination for the absence or presence of the three main signs of PD which are resting tremor, rigidity, and bradykinesia. This is because 2 out of 3 are required to make the clinical diagnosis. Postural instability is the fourth sign, but this tends to develop later in the disease.
The characteristic PD tremor is present and most prominent with the limb at rest. The frequency of the tremor is 3-5 Hz and it is usually described as “pill rolling”.
Rigidity refers to an increased resistance to passive movement of a joint. This is described as either “cogwheeling” or “leadpipe ‘.
Badykinesia refers to slowness of movement. There are numerous stigmata of bradykinesia and include micrographia, blank facial expression, reduced blinking rate and soft speech.

2. What investigations would you order?

The diagnosis is made clinically, as there is no diagnostic test for Parkinson's disease. Sometimes it is necessary to investigate patients to exclude other causes of parkinsonism if there are any unusual features.
Patients presenting before the age of 50 are usually tested for Wilson's disease, and imaging (CT or MRI) of the head may be needed if there are any features suggestive of pyramidal, cerebellar or autonomic involvement, or the diagnosis is otherwise in doubt.

3. What are the presenting symptoms and physical abnormalities of Parkinson's Disease?

General
Expressionless face
Greasy skin
Soft, rapid, indistinct speech
Flexed posture
Impaired postural reflexes

Gait
Slow to start walking
Shortened stride
Rapid, small steps, tendency to run (festination)
Reduced arm swing
Impaired balance on turning

Tremor
Resting 4-6 Hz
Usually first in fingers/thumb
Coarse, complex movements, flexion/extension of fingers
Abduction/adduction of thumb
Supination/pronation of forearm
May affect arms, legs, feet, jaw, tongue
Intermittent, present at rest and when distracted
Diminished on action

Tremor
Postural 8-10Hz
Less obvious, faster, finer amplitude
Present on action or posture, persists with movement

Rigidity
Cogwheel type, mostly upper limbs
Plastic (leadpipe) type, mostly legs

Bradykinesia
Slowness in initiating or repeating movements
Impaired fine movements, especially of fingers

4. Outline the management of Parkinson's Disease in terms of drug therapy, surgery, and allied health therapy (physiotherapy/speech therapy).

Drug therapy

- Levodapa
  Although the number of dopamine-releasing terminals in the striatum is diminished in Parkinson's disease, remaining neurons can be driven to produce more dopamine by administering its precursor, levodopa. If levodopa is administered orally, more than 90% is decarboxylated to dopamine peripherally in the gastrointestinal tract and blood vessels, and only a small proportion reaches the

brain. This peripheral conversion of levodopa is responsible for the high incidence of side-effects if used alone. The problem is largely overcome by giving a decarboxylase inhibitor that does not cross the blood-brain barrier along with the levodopa. Two peripheral decarboxylase inhibitors, carbidopa and benserazide, are available as combination preparations with levodopa, as Sinemet and Madopar.
The initiation of levodopa therapy should be delayed until there is significant disability, since there is concern regarding long-term side-effects. With this in mind, some authorities suggest that it is advisable to initiate treatment with a dopamine agonist (see below) or a slow-release preparation of levodopa in order to minimise or delay the onset of long-term side-effects, particularly in patients who develop the disease before age 70. Levodopa is particularly effective at improving bradykinesia and rigidity. Tremor is also helped but rather unpredictably. The initial dose is 50 mg 8- or 12-hourly, increased if necessary. The total levodopa dose may be increased to over 1000 mg/day, but should be kept as low as possible. Side-effects include postural hypotension, nausea and vomiting, which may be offset by the use of a peripheral dopamine antagonist such as domperidone. Other dose-related side-effects are involuntary movements, particularly orofacial dyskinesias, limb and axial dystonias, and occasionally depression, hallucinations and delusions.
Late deterioration despite levodopa therapy occurs after 3-5 years in one-third to one-half of patients. Usually this manifests as fluctuation in response. The simplest form of this is end-of-dose deterioration due to progression of the disease and loss of capacity to store dopamine. More complex fluctuations present as sudden, unpredictable changes in response, in which periods of severe parkinsonism alternate with dyskinesia and agitation (the 'on-off' phenomenon). End-of-dose deterioration can often be improved by dividing the levodopa into smaller but more frequent doses, or by converting to a slow-release preparation. The 'on-off' phenomenon is difficult to treat, but sometimes subcutaneous injections of apomorphine (a dopamine agonist) are helpful to 'rescue' the patient rapidly from an 'off' period.
Involuntary movements (dyskinesia) may occur as a peak-dose phenomenon, or as a biphasic phenomenon (occurring during both the build-up and wearing-off phases). Management is difficult, but again involves modifying the way levodopa is administered to obtain constant levels in the brain, and the use of alternative drugs, particularly dopamine agonists.

- Anticholinergic medications
  These have a useful effect on tremor and rigidity, but do not help bradykinesia. They can be prescribed early in the disease before bradykinesia is a problem, but should be avoided in elderly patients in whom they cause confusion and hallucinations. Other side-effects include dry mouth, blurred vision, difficulty with micturition and constipation. Many anticholinergics are available- for example, trihexyphenidyl (benzhexol; 1-4 mg 8-hourly) and orphenadrine (50-100 mg 8-hourly).
- Amantadine
  This has a mild, usually short-lived effect on bradykinesia, but may be used early in the disease before more potent treatment is needed. Amantadine can be particularly useful in controlling the dyskinesias produced by dopaminergic treatment later in the disease. The dose is 100 mg 8- or 12-hourly. Side-effects include livedo reticularis, peripheral oedema, confusion and seizures.
- Selegiline
  Selegiline has a mild therapeutic effect in its own right. Evidence that it slows the progression of the disease is highly controversial. There has been some doubt as to its safety, but this is also controversial and the subject of ongoing research. The usual dose is 5-10 mg in the morning.
- COMT (catechol-O-methyl-transferase) inhibitors
  Entacapone (200 mg with each dose of levodopa) prolongs the effects of each dose and reduces motor fluctuations when used with levodopa. This allows the levodopa dose to be reduced and given less frequently.
- Dopamine receptor agonists
  An increasing number of these drugs are becoming available. They all have slightly different activity at the various dopamine receptors in the brain. Apomorphine given alone causes marked vomiting and

has to be administered parenterally. The vomiting can be overcome by the concomitant use of domperidone, and parenteral administration achieved through continuous subcutaneous infusion from a portable pump, or direct injection as needed. This requires considerable nursing support but, used correctly, can be very useful.

- Surgery
  Stereotactic thalamotomy can be used to treat tremor, though this is needed relatively infrequently because of the medical treatments available. Other stereotactic lesions are currently undergoing evaluation, in particular pallidotomy to help in the management of drug-induced dyskinesia. The implantation of foetal mid-brain cells into the basal ganglia to enhance dopaminergic activity remains experimental.
- Physiotherapy and speech therapy
  Patients at all stages of Parkinson's disease benefit from physiotherapy, which helps reduce rigidity and corrects abnormal posture. Speech therapy may help in cases where dysarthria and dysphonia interfere with communication.

5. List some common akinetic rigid syndromes that may be confused for Parkinson's Disease.

Multiple systems atrophy (MSA)
This is a sporadic condition seen in middle-aged and elderly patients. Features of parkinsonism, often without tremor, are combined with varying degrees of autonomic failure, cerebellar involvement and pyramidal tract dysfunction. The combination of parkinsonism with autonomic failure was called the Shy-Drager syndrome, but this term is declining in use. Degeneration is more widespread than in idiopathic Parkinson's disease, and the disappointing response to levodopa and other anti-parkinsonian drugs is probably because of degeneration of post-synaptic neurons in the basal ganglia. Autonomic features include postural hypotension, sphincter disturbance and sometimes respiratory stridor; diagnosis is often assisted by performing tests of autonomic function. Management of postural hypotension includes physical measures such as head-up sleeping position and compression stockings, and drugs such as fludrocortisone and midodrine. Falls are much more common than in idiopathic Parkinson's disease, and life expectancy is considerably reduced.
Progressive supranuclear palsy
Like MSA, this sporadic condition presents in middle-aged patients, and is due to more widespread degeneration in the brain than is seen in idiopathic Parkinson's disease. The clinical features include parkinsonism, though with rigidity in extension rather than flexion, and tremor is usually minimal. In addition, there must be a supranuclear paralysis of eye movements, usually down gaze, for the diagnosis to be made. Other features include pyramidal signs and cognitive impairment.
Other kinetic-rigid syndromes
There are many conditions which can rarely manifest as parkinsonian syndromes, including other degenerative diseases (e.g. Huntington's disease, Wilson's disease) and infective diseases (e.g. syphilis). Drug-induced parkinsonism is much more common (particularly with neuroleptic agents and anti-emetics). These conditions should always be borne in mind in the differential diagnosis. In particular there are several specific degenerative conditions that can mimic idiopathic Parkinson's disease, particularly in the early stages. These conditions are relatively uncommon, but about 10% of those thought to have idiopathic Parkinson's disease have one of these variants. The variants are notable in causing a more rapid clinical deterioration than idiopathic Parkinson's disease and in being more resistant to treatment with dopaminergic medication.

6. In a table summarise the key features of the hereditary ataxias.

Type	Inheritance	Onset	Clinical features
Friedreich's ataxia	Autosomal recessive	8-16 years	Ataxia, nystagmus, dysarthria, spasticity, areflexia, proprioceptive impairment, diabetes mellitus, optic atrophy, cardiac abnormalities. Usually chairbound by age 20
Ataxia telangiectasia	Autosomal recessive	childhood	Progressive ataxia, athetosis, telangiectasia on conjunctivae, impaired DNA repair, immune deficiency, tendency to malignancies
Abetalipoproteinaemia	Autosomal recessive	childhood	Steatorrhoea, sensorimotor neuropathy, retinitis pigmentosa, malabsorption of vitamins A, D, E, K, cardiomyopathy
Spinocerebellar ataxia types 1-21	Autosomal dominant	Childhood to middle age	Progressive ataxia, some types have associated retinitis pigmentosa, pyramidal tract abnormalities, peripheral neuropathy and cognitive deficits
Dentato-rubro-pallido-luysian atrophy (DRPLA)	Autosomal dominant	Childhood to middle age	Children present with myoclonic epilepsy and progressive ataxia; adults have progressive ataxia with psychiatric features, dementia and choreoathetosis
Episodic ataxias (types 1-4)	Autosomal dominant	Childhood and early adulthood	Brief episodes of ataxia, sometimes induced by stress or startle. Some develop progressive fixed ataxia

7. In a table, summarise the key features of Motor neurone disease

Onset Usually after the age of 50 years Very uncommon before the age of 30 years Affects males more commonly than females Symptoms Limb muscle weakness, cramps, occasionally fasciculation Disturbance of speech/swallowing (dysarthria/dysphagia) Signs Wasting and fasciculation of muscles Weakness of muscles of limbs, tongue, face and palate Pyramidal tract involvement causes spasticity, exaggerated tendon reflexes, extensor plantar responses External ocular muscles and sphincters usually remain intact No objective sensory deficit No intellectual impairment in most cases Course Symptoms often begin focally in one part and spread gradually but relentlessly to become widespread

8. Outline the management and prognosis of motor neurone disease.

The glutamate antagonist, riluzole, has recently been shown to have a small effect in prolonging life expectancy by about two months. It is not clear at which stage of the illness this prolongation occurs, and therefore it may not be particularly helpful. Other agents such as nerve growth factor show promise. Psychological and physical support, with help from occupational and speech therapists and physiotherapists, are essential to maintain the patient's quality of life. Mechanical aids such as splints, walking aids, wheelchairs and communication devices all help to reduce handicap. Feeding by percutaneous gastrostomy may be necessary if bulbar palsy is marked. Sometimes non-invasive ventilatory support may help distress from weak respiratory muscles although maintenance ventilation is usually not requested. Relief of distress in the terminal stages usually requires the use of opiates and sedative drugs.

Motor neuron disease is progressive; the mean time from diagnosis to death is 1 year, with most patients dying within 3-5 years of the onset of symptoms. Younger patients and those with early bulbar symptoms tend to show a more rapid course. Death is usually from respiratory infection and failure, and the complications of immobility.