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Parkinsonism and tremor disorders.
A clinical approach

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Abstract: Differentiation of idiopathic Parkinson's disease from other causes of Parkinsonism, such as Multiple System Atrophy, Progressive Supranuclar Palsy and Vascular Parkinsonism can be difficult. Clinicopathological studies suggest that the clinical diagnosis of idiopathic Parkinson's disease is 76% reliable. Also, clinical differentiation of tremor prominent Parkinsonism from Essential Tremor or Drug induced Parkinsonism may be problematic, especially in the early stages of the disease. Since these disorders are obviously different in clinical progress, it is important for the clinician to address the patient's and family's concerns about prognosis from a firm diagnostic footing. In this article the clinical features of the common and important causes of Parkinsonism and tremor disorders are reviewed and a practical approach is suggested.

Key Words: Idiopathic Parkinson's Disease, Multiple System Atrophy, Progressive Supranuclar Palsy, Vascular Parkinsonism, Essential Tremor, Drug induced Parkinsonism.

Introduction

James Parkinson first described Parkinson's disease in 1817 in his famous Essay on the "Shaking Palsy" [1]. Since then there have been huge developments and changes in the understanding of the pathophysiology, clinical features and treatment of the disease, which carries his name. However, the diagnosis is still a clinical one and there are no biological markers to diagnose this condition. In the majority of patients the diagnosis of idiopathic Parkinson's disease seems straightforward. However, many patients with Parkinsonism and tremor disorders exhibit a diagnostic challenge particularly in the early stage of the illness. Clinico-pathological studies have shown that 24% of patients with a clinical diagnosis of idiopathic Parkinson's disease (made by a neurologist or geriatrician) do not fulfil pathological criteria and have an alternative diagnosis [2,3]. Multiple system atrophy, progressive supranuclar palsy and vascular disease are the main pathological diagnoses in such cases. The bias introduced by these pathological studies when compared to a clinical setting is in the absence of essential tremor and drug induced Parkinsonism.

Why is it important to differentiation between idiopathic Parkinson's disease and other causes of Parkinsonism and tremor disorders especially in the early stages? Firstly, there are differences in clinical progress and survival from the more benign essential tremor through idiopathic Parkinson's disease to multiple system atrophy or progressive supranuclar palsy. Therefore, it is appropriate for the clinician to address the patient's and family's concern about prognosis and provide accurate prognostic information. Secondly, introduction and amendment of drug therapy is tailored to the patients' condition and progress, e.g. patients suspected to have idiopathic Parkinson's disease in whom a revised diagnosis of essential tremor is reached, can have levodopa withdrawal. Finally, an accurate diagnosis would help in understanding the aetiology and pathophysiology of different causes of Parkinsonism and tremor disorders, and define accurately a patient cohort for clinical research studies.

In this article the clinical features of idiopathic Parkinson 's disease (PD), Multiple System Atrophy (MSA), Progressive Supranuclar Palsy (PSP) and Vascular Parkinsonism (VP) as well as Essential Tremor (ET) and Drug Induced Parkinsonism (DIP) will be discussed.

Definition and classification of parkinsonism: Parkinsonism is a clinical syndrome characterised by bradykinesia: slowness of movement, hypokinesia: reduced movement, akinesia: loss of movement, rigidity: increased resistance to passive extension and flexion, tremor: mainly resting.

Parkinsonism may be classified as:

1. Idiopathic Parkinson's disease, of unknown aetiology.

2. Parkinsonism as part of other neurodegenerative disorders, such as MSA, PSP.

3. Parkinsonism with identifiable causes, such as VP and DIP.

Idiopathic Parkinson's Disease (PD): Idiopathic Parkinson's disease consists of Parkinsonism characterised pathologically by neuronal loss with Lewy bodies in the substantia nigra. Lewy bodies, which are eosinophilic intracytoplasmic inclusions first described by F H Lewy in 1914, are not specific for PD. Other conditions such as MSA, PSP, and Lewy body dementia were shown to have Lewy bodies. Also, Lewy bodies can be found as an incidental finding in elderly patients without clinical features of PD, which probably represent pre-clinical or early stages of PD [4-7].

Idiopathic Parkinson 's disease is the common cause of parkinsonism, with an annual incidence of 20.5 per 100 000 of the population and prevalence 164 per 100 000 [8-10]. The prevalence of the disease increases with age from 47 per 100 000 for ages 40-49 years, to 832 per 100 000 for 70-79 years [10]. The mean age at onset PD is between 55-65 years, with a slight

male predominance of 60%, and mean age of death is 75.5 years [10-12].

The majority of patients with Parkinson's disease have no family history of Parkinsonism. However, some patients with positive family history could have the familial form of Parkinsonism especially patients with young onset disease. Several genetic variants have been identified such as the parkin gene in both autosomal recessive and dominant forms. Some of these cases do not have Lewy bodies. Over the next few years the understanding of the genetics of Parkinsonism would modify our views about the aetiology of PD [13,14].

Patients usually present with non-specific pains and aches, stiffness, changes in the handwriting, or general slowing down. Examination usually shows loss of arm swing, tendency to drag a leg, difficulty with hand movements, loss of facial expression, reduced voice volume, lead-pipe rigidity or cog-wheel rigidity if tremor is superimposed and tremor mainly at rest. The onset is asymmetric in 72% of the patients. Tremor is the presenting features in 70% of patients but 42% have tremor only without bradykinesia or rigidity and 11% have tremor dominant disease hence the name Benign Tremulous Parkinson's disease, which has a better prognosis than the akinetic rigid presentation. In the late stages of PD patients develop speech and swallowing difficulties. Also, falls, gait problems, autonomic dysfunction and dementia (up to 40%) are late features. Almost every patient with PD responds to levodopa therapy [11].

Table 1: Summary of clinical features of idiopathic PD

- Three Subtypes: Tremor dominant (26%),
- Akinetic-rigid (38%) and - Mixed type (36%).
- Bradykinesia and tremor and/or rigidity.
- Unilateral onset with persistent asymmetry affecting the side of the onset most (Hemi-parkinsonism).
- Arms are more involved than legs.
- Excellent response to levodopa.

Multiple System Atrophy (MSA)

MSA is a sporadic, adult onset, neurodegenerative disease. It is a clinico-pathological entity, which can present with any combination of Parkinsonism, cerebellar and/or pyramidal signs and autonomic dysfunction. Pathologically, it is characterised by cell loss and gliosis and α-synuclein positive oligodendroglial cytoplasmic inclusions in a selection of brain structures such as: substantia nigra, striatum, locus coeruleus, pontine nuclei, cerebellar purkinje cells, inferior olives, and Onuf's nucleus in the spinal cord [15-18].

Shy and Drager described in 1960 a neurological syndrome associated with orthostatic hypotension [19]. In 1969, Graham and Oppenheimer introduced the term MSA, [20] but it has since become a title, which covers a wide range of different degenerative conditions [15].

The following subtypes of MSA have been defined in a clinico-pathological study: [21].
(i) Shy-Drager syndrome, in which autonomic failure predominates.
(ii) Striatonigral degeneration, in which Parkinsonism predominates.
(iii) Olivopontocerebellar atrophy, in which cerebellar features predominate.

However, Oertel and Quinn [22] argue against using the term Shy-Drager syndrome because autonomic dysfunction is almost universal in MSA. [21] They define MSA subtypes as follows:
(i) Striatonigral degeneration (MSA-parkinsonian type or MSA-P).
(ii) Sporadic olivopontocerebellar atrophy (MSA-cerebellar type or MSA-C).

There are no definite incidence figures for this disorder and it has been postulated that MSA contributes between 3.6 and 22% of incident cases of parkinsonism [15, 16,19-24]. MSA-P is 2 to 4 times more common than MSA-C. MSA is slightly more common in male patients, with a mean age of onset of 54 years, mean age at death of 60 years and mean duration of illness of 6-9 years [23,24].

Autonomic dysfunction is usually present in almost all patients and impotence is the most common feature in males. Postural faintness, urinary incontinence and/or urinary retention are other features. Half of the cases have cerebellar signs, mainly gait ataxia, and pyramidal signs can be demonstrated in 50% of MSA patients. Parkinsonism occurs in the majority of cases, with akinesia as the more common feature, rest tremor in less than half of cases and classical pill-rolling tremor seen only in 10% of patients. Other features included stridor and muscular contractions while dementia is rarely a feature of MSA. Only a third of patients show some response to levodopa, which is usually unsustainable [23,24].

Table 2- Summary of clinical features of MSA

- Two Subtypes: MSA-P and MSA-C.
- Mainly symmetrical bradykinesia and rigidity.
- Features of autonomic dysfunction.
- Cerebellar signs and pyramidal signs.
- Stridor, and muscular contractions.
- Dementia is rare.
- Poor response to levodopa

Progressive Supranuclear Palsy (PSP) or Steele-Richardson-Olszweski Syndrome

In 1964 Steele, Richardson and Olszewski described the clinical and pathological features of nine patients with a progressive disorder of vertical gaze, axial rigidity, dysarthria, pseudobulbar palsy and mild dementia, which they called progressive supranuclear palsy [25]. Pathologically PSP is characterised by the presence of neurofibrillary tangles and neuropil threads and tufted astrocytes within the following areas: pallidum, subthalamic nucleus, substantia nigra, midbrain and pontine reticular formation. These distinctive histopathological inclusions are made up of insoluble aggregation of tau phosphoprotein. Tau-positive glial inclusions are a pathological feature of PSP [26].

PSP is under-diagnosed, making accurate epidemiological data difficult to obtain. Several studies showed a prevalence between 1.39 to 6.5 per 100 000 [27,28]. Annual incidence of 3.1 to 4.0 cases per million has been estimated in one study [27].

PSP is a sporadic disorder, but familial cases have been described [29, 30]. It is slightly more common in males and usually presents in the seventh decade. Postural instability and falling are the presenting features in more than 50% of patients, and dysarthria in one third. Visual disturbances in the form of diplopia, blurred vision, burning eyes, and light sensitivity are the initial symptoms in around 15% of patients. Cognitive or behavioural changes generally follow [31-33]. Other clinical features include; bilateral bradykinesia, axial rigidity, speech changes (dysphonic, palilalia, ataxic and unintelligible speech), frontal lobe symptoms, personality changes, dysphagia and neck dystonia [34]. Vertical downward palsy is the single most important clinical feature of PSP. Although upward gaze and convergence become impaired, this also occurs in other basal ganglia disorders and in old age [31]. The oculocephalic manoeuvre remains intact (except in very advanced stages), and it is this characteristic that makes the disorder supranuclear [35, 36]. Other ocular manifestations include supranuclear ophthalmoplegia, absent Bell's phenomenon, impaired pupillary light reflexes, lid retraction, a markedly reduced blink rate, frontalis muscle overactivity, blepharospasm, and apraxia of eye opening or closure [31, 37]. These changes give the patient a fixed, staring, and astonished expression [31]. Although the presence of down-gaze palsy is an essential finding to secure the diagnosis of PSP, there are a few pathologically proven cases reported who had not developed such abnormality during life [34,37].

Table 3: Summary of clinical features of PSP

- Postural instability and falls.
- Symmetrical bradykinesia and rigidity.
- Cognitive or behavioural.
- Dysarthria and speech changes.
- Vertical downward palsy with intact oculocephalic manoeuvre.
- Poor response to levodopa

Vascular Parkinsonism (VP)

The concept of VP was introduced when Critchley in 1929 described 5 types of clinical presentations of what was termed arteriosclerotic Parkinsonism [38]. Rigidity, fixed faces and short-stepping gait were the main clinical signs. Pseudo-bulbar, dementia, incontinence, pyramidal or cerebellar signs were considered as additional features. After several clinical studies in the 1960's and 1970's showed no relation between arteriosclerosis and PD, Critchley in 1981 renamed the condition arteriosclerotic pseudo- parkinsonism [39-42]. With the development of CT and MRI the concept of VP was revived, but there are no generally accepted clinical criteria to diagnose this condition [43-45].

Several clinical features have been described relating brain vascular lesions to Parkinsonism. An insidious onset of parkinsonism, at times indistinguishable from PD, including a response to levodopa, due to brain vascular infarcts has been described [3,12,44-47]. On the other hand, two patients presented with acute onset Parkinsonism, due to vascular lesions in the basal ganglia, and recovery without anti-parkinsonian drugs had been reported [48,49].

Lower body Parkinsonism (LBP) is another term used to describe patients with VP and it represents a group of patients, probably hypertensive, who usually have gait difficulty, symmetrical rigidity, absent tremor, and no or some response to levodopa therapy [50-52].

The association of ischaemic stroke and vascular risk factors was addressed in two studies, where the incidence of ischaemic stroke among PD patients was lower than controls in one study but an association was found in another [53-54]. Thus PD may co-exist with cerebrovascular disease, but there may be a lower probability of a chance association because of the risk factor profiles for each disease. Post-mortem studies provide definite evidence that PD patients may also have cerebrovascular disease, and that patients with parkinsonism may have cerebrovascular disease but no pathological features of PD [3]. The clearest clinical description of Parkinsonism in association with cerebrovascular disease is that of LBP. However, upper body signs and symptoms are not excluded in such patients, and a vascular aetiology for patients with less than pure lower body features appears possible.

Finally, a small subset of patients may be unfortunate enough to have predominately upper body features from PD and lower body features from VP.

Table 4: Summary of clinical features of VP

- Gait difficulty, symmetrical rigidity, absent tremor (lower body Parkinsonism).
- An insidious onset of parkinsonism indistinguishable from PD.
- Acute onset parkinsonism, due to vascular lesions in the basal ganglia.
- Modest or poor response to levodopa. Occasionally good response.

Essential Tremor (ET)

Essential tremor is the most common movement disorder, with a worldwide prevalence estimated at between 4 and 39 per 1000. The annual incidence is about 23 per 100 000 population [55, 56]. A bimodal distribution with peaks in the second and fifth decades has been reported with men and women equally affected, [57,58] but other studies indicate an onset usually around 45 years with an earlier onset in familial cases [59]. Penetrance is usually complete by the age of 65 years, and no evidence of the disease skipping a generation was found in studying 20 kindreds, thereby indicating autosomal dominant inheritance [58]. However, no responsible gene has yet been identified [60].

Typically the tremor is postural and therefore occurring while voluntarily maintaining position against gravity and mainly involving hands and forearm, starting intermittently and progressing to become permanent, rarely remitting and usually worsened by emotion [61]. Tremor of the head, voice, tongue, and legs may follow [57,58]. ET is different from parkinsonian tremor, which is mainly resting and therefore occurs in muscles, which are completely supported against gravity [62, 63]. Although this description implies a clear separation of the tremor types, there is often a degree of overlap making ET one of the conditions which is most commonly misdiagnosed as PD, especially with less experienced physicians [64]. It is important to remember, "No single type of tremor can be pathognomonic of a particular disorder" [63].

There is conflicting evidence from the literature about the association between ET and PD, several studies showing no evidences of an association [56,58,59,64-66] and others suggesting otherwise [57,67,68]. There are no specific pathological features of ET [69, 70].

It is commonly stated that 30 to 50% of ET patients have an affected relative, [64, 71] however, reviewing all service-based and community-based published studies of familial aggregation in ET found that a range of 17-100% of patients reported affected relatives, clearly suggesting variation in data collection techniques [72]. Also, ET is sometimes described as benign, and although it does not affect life expectancy, it

can impair physical function such as the ability to eat, drink, and write and can be a social embarrassment [73,74]. Up to 15% of patients take early retirement as a result of the disability caused by the tremor [75].

As many as 50-66% of ET patients report an improvement in their tremor after consuming alcohol [57,58,76,77]. Although this was also reported in one study for parkinsonian tremor, [78] it was not reproduced in another study [79].

Treatment is mainly with beta-blockers particularly propranolol up to a dose of 320mg daily [61]. Primidone can have a beneficial effect but the majority of patients do not tolerate it [80].

Table 5: Summary of clinical features of ET

- Mainly postural tremor but an overlap with resting tremor can be seen.
- No rigidity or bradykinesia.
- Positive family history.
- Improvement with alcohol.
- Treatment mainly with beta blockers particularly propranolol

Drug Induced Parkinsonism (DIP

DIP is the most frequent neuroleptic induced side effect. Both Phenothiazines and non-phenothiazines can induce parkinsonism in 10-15% of psychotic patients treated with these drugs [81,82]. Anti-emetic drugs such as prochlorperazine and metoclopramide can cause Parkinsonism [83-85]. Other drugs such as sodium valproate, tetrabenazine and calcium-channel blockers such as cinnarizine are also reported to cause DIP [86-88]. DIP unmasked PD can be difficult to distinguished from pure DIP, especially that DIP could take some months if not years to reverse on withdrawal of the offending drug [89]. Stopping the offending drug is obviously the treatment of choice in DIP however; this could be difficult especially with neuroleptic drugs. Anticholinergic, amantadine and pyridoxine may help in reducing the parkinsonian symptoms in patients with DIP [90,91]

Table 6- Summary of clinical features of DIT

- Neuroleptic drugs are the most frequent cause of DIP.
- If possible the offending drug should be stopped.
- Parkinsonism can take a long time to resolve after stopping the offending drugs.
- Anticholinergic amantadine and pyridoxine could help.

Summary

Parkinsonism and tremor disorders could represent a diagnostic challenge. However, a good clinical assessment usually helps in reaching a final diagnosis but sometimes the patient needs

to be assessed several times before a clear diagnosis emerges due to lack of diagnostic investigation.

The clinicians should be alert to the unusual symptoms and signs such as: a) Absent or poor response to levodopa, b) Rapid disease progression, c) Autonomic failure, d) Early falls, e) Cerebellar and/or pyramidal signs, f) Supranuclear palsy, g) Lower body Parkinsonism, h) Early dementia.

I suggest the following practical approaches to patients presenting with parkinsonism and/or tremor:

1) Confirm that the patient has parkinsonian features, 2) Always think of essential tremor when tremor is the prominent feature and there is no gait problem nor difficulty to rise from a low chair, 3) Ask about drug history, 4) Ask about symptoms of autonomic dysfunction, 5) Ask about early falls, 6) Check for pyramidal and cerebellar signs, 7) Measure the blood pressure, supine and erect, 8) Check eye movements, 9) Check the Mini-mental test, 10) If not sure whether the patient has PD or other diseases (MSA, PSP, VP) try L-dopa.

With being alert to the unusual features and following a systemic approach the likelihood of getting the diagnosis right is high although this may take some time.

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