Learning objectives

1- Illustrate Parkinson's disease and Parkinson-plus syndromes.

2- Clinical clues to diagnose Parkinson-plus syndromes.

3- Review the contribution of DatScan in imaging of Parkinson-plus syndromes.
Background

Parkinson disease (Parkinson’s disease, PD) is a progressive neurodegenerative disorder associated with a loss of dopaminergic nigrostriatal neurons. It is named after James Parkinson, the English physician who described the shaking palsy in 1817.

The major neuropathologic findings in Parkinson disease are a loss of pigmented dopaminergic neurons in the substantia nigra and the presence of Lewy bodies. The loss of dopaminergic neurons occurs most prominently in the ventral lateral substantia nigra. Approximately 60-80% of dopaminergic neurons are lost before the motor signs of Parkinson disease emerge.

Lewy bodies are concentric, eosinophilic, cytoplasmic inclusions with peripheral halos and dense cores. The presence of Lewy bodies within pigmented neurons of the substantia nigra is characteristic, but not pathognomonic, of idiopathic Parkinson disease. Lewy bodies also are found in the cortex, intermediolateral column of the spinal cord, and other areas. Lewy bodies are not specific to Parkinson disease, as they are found in some cases of atypical parkinsonism, Hallervorden-Spatz disease, and other disorders.

Recent studies demonstrate that Lewy-body pathology in Parkinson disease actually begins in the olfactory bulb and lower brainstem (fig.1).[1]

These early stages are associated with premotor symptoms such as loss of sense of smell and rapid eye movement (REM) sleep behaviour disorder (RBD).[2]

The pathology ascends up the brainstem to later involve the midbrain and nigrostriatal dopaminergic neurons. This stage correlates with onset of the motor phase of the disease and patients may exhibit bradykinesia, rigidity, and tremor. The pathology continues to ascend late in the disease to affect the cortex and patients may then exhibit cognitive dysfunction and dementia.

The basal ganglia motor circuit modulates cortical output necessary for normal movement (fig.2).

Signals from the cerebral cortex are processed through the basal ganglia-thalamocortical motor circuit and return to the same area via a feedback pathway. Output from the motor circuit is directed through the internal segment of the globus pallidus (GPI) and the substantia nigra pars reticulata (SNr). This inhibitory output is directed to the thalamocortical pathway and suppresses movement.
Two pathways exist within the basal ganglia circuit; they are referred to as the direct and indirect pathways. In the direct pathway, outflow from the striatum directly inhibits GPi and SNr. The indirect pathway comprises inhibitory connections between the striatum and the external segment of the globus pallidus (GPe) and the GPe and the subthalamic nucleus (STN). The subthalamic nucleus exerts an excitatory influence on the GPi and SNr. The GPi/SNr sends inhibitory output to the ventral lateral (VL) nucleus of the thalamus. Striatal neurons containing D1 receptors constitute the direct pathway and project to the GPi/SNr. Striatal neurons containing D2 receptors are part of the indirect pathway and project to the GPe. Dopamine is released from nigrostriatal (SNc) neurons to activate the direct pathway and inhibit the indirect pathway. In Parkinson disease, decreased striatal dopamine causes increased inhibitory output from the GPi/SNr. This increased inhibition of the thalamocortical pathway suppresses movement. Via the direct pathway, decreased striatal dopamine stimulation causes decreased inhibition of the GPi/SNr. Via the indirect pathway, decreased dopamine inhibition causes increased inhibition of the GPe, resulting in disinhibition of the STN. Increased STN output increases GPi/SNr inhibitory output to the thalamus.

Frequency

The incidence has been estimated to be 12 cases per 100,000 population per year. Estimates of Parkinson disease and associated syndromes prevalence is approximately 110 per 100,000 population.[3]

Mortality/Morbidity

In a community-based study of 230 patients with Parkinson disease, median survival from motor onset was 15.8 years. Independent predictors of mortality were age at onset, chronological age, psychotic symptoms, and dementia.[4]

Sex

Parkinson disease is about 1.5 times more common in men than in women.

Age

The incidence and prevalence of Parkinson disease increase with age. The average age of onset is approximately 60 years. Onset in persons younger than 40 years is relatively uncommon.

Causes

Most cases of idiopathic Parkinson disease are believed to be due to a combination of genetic and environmental factors.
• Environmental risk factors include use of pesticides, living in a rural environment, consumption of well water, exposure to herbicides, and proximity to industrial plants or quarries.
• Several individuals have been identified who developed parkinsonism after self-injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). [5]
• The oxidation hypothesis suggests that free radical damage, resulting from dopamine’s oxidative metabolism, plays a role in the development or progression of Parkinson disease.
• The role of genetic factors has been studied in twins.
• The identification of a few large families with apparent familial Parkinson disease sparked further interest in the genetics of the disease.
• A recent hypothesis suggests that Parkinson disease is caused by abnormalities of the proteosome system, which is responsible for clearing abnormal proteins.
• Several homozygous deletions in a gene dubbed parkin (PARK2), which is located on chromosome 6, have been found to cause autosomal-recessive juvenile parkinsonism (AR-JP). This form of parkinsonism differs pathologically from Parkinson disease in that no Lewy bodies are found in the substantia nigra.
• Several other gene abnormalities have been identified in families with Parkinson disease and these are designated PARK3-PARK12.
• It has been estimated that all currently known genetic causes of Parkinson disease account for less than 5% of Parkinson disease cases.

Parkinson-Plus Syndromes

Several primary neurodegenerative disorders have parkinsonian features, such as bradykinesia, rigidity, tremor, and gait disturbances, in common. These neurologic conditions are associated with complex clinical presentations that reflect degeneration in various neuronal systems in addition to the nigrostriatal degeneration seen in idiopathic Parkinson disease (PD). As they share common Parkinsonian features, the disorders have been collectively named Parkinson-plus syndromes.

Patients with Parkinson-plus syndromes typically have a worse prognosis than those with Parkinson disease, and Parkinson-plus syndrome responds poorly to the standard anti-Parkinson treatments. An adequate response to treatment in a patient with Parkinsonian symptoms may indicate that a Parkinson-plus syndrome is developing, and searching for the signs and symptoms of degeneration in other neuronal systems is important.

Clinical clues suggestive of Parkinson-plus syndromes include the following:

• Lack of response to levodopa/carbidopa or dopamine agonists in the early stages of the disease
• Early onset of dementia
• Early onset of postural instability
• Early onset of hallucinations or psychosis in the untreated state or with low doses of levodopa/carbidopa or dopamine agonists
• Ocular signs, such as impaired vertical gaze, blinking on saccade, square-wave jerks, nystagmus, blepharospasm, and apraxia of eyelid opening or closure
• Pyramidal tract signs not explained by previous stroke or spinal cord lesions
• Autonomic symptoms such as postural hypotension and incontinence early in the course of the disease
• Prominent motor apraxia
• Alien-limb phenomenon
• Marked symmetry of signs in early stages of the disease
• Truncal symptoms more prominent than appendicular symptoms
• Absence of structural aetiology such as normal pressure hydrocephalus (NPH)

[A]-Multiple System Atrophy

Dejerine and Thomas first used the term olivopontocerebellar atrophy (OPCA) in 1900 when they described 2 patients with a degenerative disorder leading to progressive cerebellar dysfunction and parkinsonism. In 1960, Shy and Drager described a neurologic syndrome (Shy-Drager syndrome [SDS]) of orthostatic hypotension with Parkinsonian features. This was followed by the report in 1961 by Adams, Eecken, and Bogaert of 3 patients with striatonigral degeneration (SND) with atrophy of the caudate nucleus and putamen. In 1969, Graham and Oppenheimer noted that the clinical and pathologic findings of OPCA, SND, and SDS overlapped significantly. They advanced the term multiple system atrophy (MSA) to describe these disorders.

Further work by Bannister and Oppenheimer in 1972 confirmed the coexistence of these 3 entities in both clinical and pathological terms. However, the discovery of glial cytoplasmic inclusions as the pathological hallmark by Papp (1989) and Nakazato (1990) led to the ultimate acceptance of this disorder as a separate clinicopathological entity.

MSA is a progressive, idiopathic, degenerative process beginning in adulthood. The cardinal features include various degrees of parkinsonism, autonomic failure, cerebellar dysfunction, and, pyramidal signs that are poorly responsive to levodopa or dopamine agonists. Glial cytoplasmic inclusions (GCIs) and a neuronal multisystem degeneration are the pathologic hallmarks of this clinically variable disorder.

Patients with idiopathic PD are distinguished from patients with MSA by the lack of autonomic and cerebellar features as well as by their response to levodopa/carbidopa.

[B]-Progressive Supranuclear Palsy
Progressive supranuclear palsy (PSP) was first described in 1963 by J Clifford Richardson as a syndrome that included a combination of supranuclear gaze palsy, postural instability, progressive axial rigidity, bulbar palsy, and mild dementia. Subsequently, Olszewski and Steele described the pathology of this syndrome, so the condition is also referred to as Steele-Richardson-Olszewski syndrome. No strong genetic component is known in this idiopathic condition. However, some rare familial clusters have been reported.

The disease usually begins when patients are in their 50s to mid 60s. PSP is associated with neuronal loss, gliosis, and neurofibrillary tangles in the pretectal area, substantia nigra, subthalamic nucleus, globus pallidus, superior colliculus, and substantia innominata. Degeneration of multiple neurotransmitter systems leads to a more diffuse disorder than idiopathic Parkinson Disease. The cholinergic and adrenergic systems are involved in addition to the dopaminergic system. Tau-positive glial inclusions are a consistent pathologic finding. Coiled bodies, which are small round cells of oligodendrocytic origin found in white matter, are also seen in a widespread distribution.

Patients with PSP tend to have progressive deterioration, with a 9.7-year median survival from the onset of symptoms. Gait difficulties occur early, and patients require assistance within 3 years. Confinement to bed or a wheelchair is typically necessary within 8 years. Eventual death usually follows a severe fall, pulmonary embolus, or aspiration pneumonia.

[C]-Diffuse Lewy Body Disease

Diffuse Lewy body disease (DLBD) is a progressive neurodegenerative disorder characterized by the presence of Parkinsonian symptoms and neuropsychiatric disturbances commonly accompanied by dementia. Progressive dementia is often the first and predominant symptom. Of note, longitudinal studies of patients with Parkinson disease show that 78% meet the criteria for dementia in the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R), after a decade of motor symptoms as opposed to the 25-30% estimate from cross-sectional studies.[8]

No familial disposition for DLBD has been reported. Some have proposed that DLBD represents an extended form of PD. However, other authors view this as a clinically distinct entity.

The common thread to DLBD and PD is the presence of Lewy bodies. In PD, they are mainly observed in the substantia nigra. In contrast, in DLBD they are scattered throughout the cerebral cortex and also are seen in the nigra and other subcortical regions. In contrast to Alzheimer disease, cortical atrophy is not prominent. Two distinct forms of the condition have been described. The pure form occurs with Lewy bodies in the cortical and subcortical structures, whereas the common form has Lewy bodies accompanied by plaques and tangles.

[D]-Corticobasalganglionic Degeneration
CBGD is characterized by frontoparietal cortical atrophy in addition to degeneration within the extrapyramidal system. The disease tends to occur in those aged 60-80 years, with a mean age of onset of 63 years. CBGD is a rare syndrome with an estimated incidence of 0.02-0.92 per 100,000 population per year.

The substantia nigra is depigmented. However, Lewy bodies and diffuse neuronal loss are conspicuously absent. Neuropathologic diagnostic criteria include tau-immunoreactive lesions in neurons, glia, and cell processes.

PSP and MSA may initially be confused with CBGD. However, the true diagnosis becomes clear as the apraxia and dystonia develop. CBGD usually progresses to severe disability and death within 10 years.

Magnetic resonance imaging (MRI) and computed tomography (CT) scan are unremarkable in Parkinsonism.

There are a number of clinical diagnostic criteria used for the diagnosis of neurodegenerative disorders such as the UK PD Society Brain Bank, Quinn criteria for MSA and NINDS-Society for PSP.

The apomorphine test or a trial of levodopa is occasionally used to clarify the diagnosis, although caution is required in its interpretation due to the common occurrence of false-negative results [9]. Other disease states that demonstrate one or more features of parkinsonism (e.g. benign essential tremor, drug-induced parkinsonism, and frontal lobe gait apraxia d usually caused by cerebrovascular disease) are often mistakenly diagnosed as PD. Hence, the accuracy of diagnosis is variable, with one study on 402 community-based cases revealing misdiagnosis in approximately 26%. In this group, the final diagnoses included essential tremor, gait apraxia and early dementia.[10]

A histopathological study demonstrated that the strict application of clinical criteria was associated with Parkinson's pathology in 93%, but a further 32% of pathologically proven cases did not fulfil this stringent criteria [11]. In addition, these findings were based on the last clinical assessment prior to death and would therefore represent an advanced form of the disease. Retrospective studies based on case notes noted the mean time of ‘diagnostic phase’ from symptom onset to clinical diagnosis to be of the order of 1.6 years, with a significant minority not receiving a final clinical diagnosis for at least 5 years [12,13]. Consequently, although the predictive value of a clinical diagnosis is high, there is a significant minority of patients in whom the diagnosis remains unclear for a considerable time. It therefore begs the question as to whether imaging the dopaminergic system can provide a useful adjunct in the clinical work-up.

Dopamine exerts its effects through the activation of the dopamine receptors, which are present both pre- and postsynaptically at synapses. These receptors play a primary role in modulating locomotor function and are an important target for dopaminergic
medication. At least five different subtypes of these receptors have now been described, but broadly they fall into two classes: D1 type (D1,D5) and D2 type (D2,D3,D4). The highest concentration of D1 and D2 receptors are in the striatum.

The dopamine transporter, or reuptake site, is a Na/Cl dependent presynaptic protein located on membrane of dopaminergic neurone terminals, which project from the substantia nigra to the striatum. Its function is to actively reuptake dopamine from the synaptic cleft after the termination of its interaction with dopamine receptors on post synaptic neurone, therefore controlling dopamine levels [14]. (fig.3)

Pathologically, Parkinsonism is characterized by severe degeneration of dopaminergic neurons in substantia nigra, leading to a marked decrease in dopamine transporter.

Positron emission Tomography (PET) and Single-photon emission computed tomography (SPECT) studies use tracers for presynaptic dopaminergic nerve terminals to image dopamine transporters and allow visualizing and quantifying dopaminergic neurons in vivo and, therefore, offer the possibility to monitor progressive nerve cell loss in PD patients [15].

However, PET is expensive and is available only in major research centers, and is not therefore accessible to clinical practice. SPECT on the other hand is less expensive, more available, and its tracers have a longer half-life.

A class of cocaine analogues has been developed and is available for SPECT. These include [123 I] ioflupane (also referred to as 123 I- FP-CIT, DaTSCAN, General Electric Healthcare Chalfont St, Giles, UK).
Images for this section:

Fig. 0: Stages in the development of Parkinson disease-related pathology.

Fig. 0: Schematic illustration of the basal ganglia-thalamo-cortical "motor" circuit and its neurotransmitters.

**Fig. 0:** Schematic illustrating the dopaminergic synapse forming the rationale behind the development of the DaTScan. Tyrosine is the precursor for dopamine production. Dopamine acts at several dopamine receptors (D1A, D2-4). The dopamine transporter serves as a regulator of synaptic dopamine concentration.

Procedures and Methods of [123 I] ioflupane (123 I- FP-CIT, DaTSCAN) imaging

Before the study, patients are required to stop the following drugs: amphetamine, benztropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline. Thyroid blocking is necessary using either: Lugol's solution (0.1 ml in milk, water or food) three times a day on the day before the examination, the day of, and the day after the examination, or oral potassium iodide 120 mg, 1-4 h pre-injection and 12-24 h postinjection.

Pregnancy is a contraindication to the study, as is a history of hypersensitivity to iodine.

A slow intravenous injection of 111-185 MBq [123I]ioflupane is administered, and images are acquired 3-6 h after injection using a dual head gamma camera fitted with low-energy high-resolution collimators. A headrest is used and lights are dimmed during acquisition, to reduce patient movement. One hundred and twenty projections are acquired over 360° with a frame time of 35 s on a 128x128 matrix with a zoom factor of 1.2. Step and shoot mode is used, with the camera heads at a constant radius tailored to the individual patient. Images are reconstructed on a workstation using filtered back projection with a Butterworth filter (cut-off 0.47 cycles/cm; power 10). Soft-copy images are interpreted using visual assessment of striatal uptake.

Image interpretation

Following intravenous injection of [123 I] ioflupane to healthy individuals, the uptake in the corpus striatum will appear as two mirror image commas (fig.1).

In PD patients, there will be reduced tracer uptake in putamen leaving visualization of only the caudate nucleus (fig.2).

In PSP patients, there is more symmetrical putamen reduced uptake, than PD, MSA and CBD. Also there is a more of uniform degree of dopamine transporter loss in the caudate and putamen [16]. (fig.3)
Also there is similar caudate and putamen loss in PSP and CBD patients, while the caudate nuclei are spared in PD and MSA.

In MSA, there is more impairment of the nigrostriatal dopaminergic projections to the caudate nucleus than patients with PD. However the putamen to caudate nucleus ratio in both PD and MSA, is not clear enough to make a distinction in individual cases on the basis of the results of imaging of nigrostriatal pathway alone[17].

And so consequently, imaging of the striatal presynaptic terminal status is not able to reliably differentiate PD from Parkinson-plus syndromes.

**Studies assessing the role of [123 I] ioflupane (123 I- FP-CIT, DaTSCAN) imaging in suspected Parkinsonism:**

In a phase III study, 97% of the 158 patients who fulfilled the UK Parkinson's Disease Society Brain Bank criteria for a clinical diagnosis of PD had an abnormal scan. Thee other 4 patients with suspected PD and had normal scans may have creditable alternative diagnosis.[18]

Another study more reflective of clinical practice was undertaken in 33 patients with uncertainty of clinical diagnosis at presentation. All patients who had an abnormal scan were classified clinically as having PD at 2-4 years follow up whereas 22 of the 24 normal scans were not associated with a final clinical diagnosis of PD, with overall concordance of between image findings at presentation and subsequent clinical diagnosis was 94% [19]. The two discrepant scans were in patients with MSA and juvenile onset PD.

In the European Multi-center phase IV trial demonstrated that the scan changed the initial clinical diagnosis in 52% of 118 patients studied and altered therapeutic management in 46% of cases [20].

In a study on Seventeen patients with a presumptive diagnosis of PD. two patients on neuroleptic medication exhibited features of PD; one had an abnormal scintigraphic examination that confirmed PD, the other had a negative examination, confirming drug-induced parkinsonism. Of the other cases, the results of 10 examinations were compatible with PD. Five were reported as being normal, the final diagnoses in this group included: cerebrovascular disease (CVD); early Alzheimer's; provisional clinical diagnosis of generalized movement disorder; and possible Wilson's disease. One patient was felt to have a parkinsonian syndrome despite the normal result (this patient had a positive apomorphine test).[21]
Which Patients with suspected Parkinsonism should be imaged?

According to the Parkinson’s disease society, 5-25% of patients with suspected Parkinsonism may require [123 I] ioflupane imaging.

Recommendation of Parkinson’s disease society for which patients to image:

- Atypical tremor
- Equivocal bradykinesia
- Equivocal response to trial of treatment.
- Co-morbidity e.g. arthritis, cognitive impairment, cerebrovascular disease.
- Unexpected severe Parkinsonian features in response to neuroleptic treatment.
- Degree of functional impairment in patients with ambiguous signs.
- Patient anxiety of uncertain diagnosis.
**Fig. 0:** Normal appearance of DaTSCAN with a "comma-shaped" caudate and putamen as indicated above.

Fig. 0

Fig. 0

Conclusion

SPECT imaging using markers of presynaptic dopaminergic function in the central nervous system provides a unique method of differentiating Parkinsonian patients with presynaptic loss of dopaminergic cells from patients suffering from genetic dopamine synthesis abnormalities as well as from patients with post-synaptic parkinsonism due to lack of dopamine receptors. This technique is also quite helpful to early discriminate true Parkinsonism from non-dopaminergic parkinsonism (e.g. essential tremors and psychogenic Parkinsonism) and to monitor progression of disease. The recent widespread availability of FP-CIT (DaTSCAN) ligand brings us a breakthrough in the diagnostic difficulties in differentiating various parkinsonian syndromes. It is our hope that further studies are performed to define the role of imaging in differentiating PD from Parkinson-plus syndromes.
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References


