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Parkinson's Disease – From Pathogenesis To Novel Therapeutic Approaches

Introduction

Parkinson's Disease (PD) ranks as the second most common neurodegenerative disorder (1). The main site affected is the substantia nigra pars compacta (SNpc) in the midbrain, which suffers a relentless degeneration of dopaminergic neurons of the nigrostriatal pathway, hence resulting in a lack of the neurotransmitter dopamine (DA) in the basal ganglia. Both genetic and environmental factors contribute to the aetiology of the disease (2). Few (10-15%) cases are familial and single gene mutations give rise to less than 5% of PD forms –monogenic (Mendelian inheritance) (3). The genes SNCA, LRRK2 and VPS35, are autosomal dominant, whereas Parkin, PINK1 and DJ-1 are autosomal recessive. Recently, glucocerebrosidase (GBA) gene mutations have been found to be a prime genetic risk factor for PD (4). In fact, heterozygous loss of function of GBA causes more than a five-fold increase in the probability of developing PD (5).

Apart from genetic predisposition, age is a major risk factor for PD. Its incidence climbs up with age to almost 100 per 100,000 person years, between 70 and 79 years (5). The median age of onset is 60 years (5). Substantial evidence shows that a 3:2 ratio of men to women exists (2). In contrast to familial PD, the aetiology of idiopathic PD is multifactorial, as it is the product of an interplay of components: multiple genes, environment and life style -caffeine, smoking and pesticides are among the most strongly associated with PD (3). Moreover, consumption of tea (rich source of polyphenolic compounds), is associated with neuroprotective and neurodegenerative effects in PD, although further studies are needed (6).

Pathophysiology

Since PD involves the extrapyramidal system, this means that the basal ganglia motor circuitry is disturbed (7,8). Since the SNpc projects onto the striatum, the subcortical motor circuitry suffers from loss of DA leading to the motor features accompanying PD.

However, cell degeneration also occurs in other catecholaminergic structures, such as the dorsal nuclei of the vagus and the locus coeruleus, thus explaining the non-motor features of PD (5). DA receptors exist as an excitatory type (D1) and as an inhibitory type (D2).

DA works by affecting motor activity. The basal ganglia are part of this system, namely: striatum substantia nigra pars reticulata (SNpr) and internal globus pallidus (GPi). These structures form part of bigger circuits including the thalamus and the cerebral cortex.
Essentially, two pathways exist: direct (D1) and indirect (D2). The SNpc modulates these pathways by projecting dopamine onto the striatum. DA excites D1 but inhibits D2, and since D2 is in itself inhibitory for (competing) movement, but D1 activates movement, the overall effect of DA is to favour (wanted) motor action. What happens in Parkinson's patients, is that since both pathways are being deprived of dopamine, D1 gets less excited and D2 has its normal inhibition decreased. The outcome is increased inhibitory GPi output, leaving the thalamus with less ability to activate the frontal cortex (9).
Lewy bodies (LB) in the substantia nigra (SN), first identified by Dr. Fritz Heinrich Levi over 100 years ago (10) are a histopathological hallmark of PD (11). These are mainly composed of α-synuclein (α-syn), a presynaptic protein expressed in the brain, which under oxidative stress aggregates. The mechanisms through which LB cause neuron degeneration in the SN are under intense study, and include mitochondrial dysfunction and/or release of pro-apoptotic molecules like cytochrome C (12).

Clinical Features

Although originally described by the English surgeon and apothecary James Parkinson in 1817 as a "shaking palsy" (13), Parkinson's patients experience both motor and non-motor symptoms (NMS). The early stage (around 4-6 years) of the disease comprises non-motor features (Table 1), presenting subtly, and may be easily mistaken as linked to normal aging (2). The crucial triad of motor symptoms are bradykinesia, tremor at rest and muscle rigidity; postural instability is also often a presenting feature. The clinical presentation of PD can vary appreciably between patients. Recognized motor subtypes include: 'postural instability and gait difficulty' (PIGD), 'tremor dominant' and 'indeterminate' (14, 15). A relationship between the patient's age at onset and the PD motor presentations may be present; patients older than 64 years are twice as likely to have tremor at onset compared with patients younger than 45 years (2).
The Unified Parkinson's Disease Rating Scale (UPDRS) is the trusted scale to assess the clinical status of PD patients. Prodromal or premotor symptoms can occur up to 10 years before diagnosis, including: hyposmia, constipation, rapid eye movement sleep behaviour disorder (RBD) and depression. This prodromal

Motor symptoms	Non-motor symptoms
Tremor	Hyposmia
Rigidity	Psychiatric symptoms: depression, anxiety, apathy, hallucinations, psychosis
Bradykinesia	Dementia/cognitive impairment
Postural instability	Sensory symptoms
Postural abnormalities	Genitourinary symptoms: urinary frequency, urgency, reduced libido, sexual dysfunction
Gait disturbances	Gastrointestinal symptoms: constipation, delayed stomach emptying
Alterations in blinking/eye movements	Dysphagia, sialorrhea, dysarthria, hypophonia
Hypomimia	Disturbances of sleep and wakefulness
Micrographia	Cardiovascular symptoms: blood pressure variations, dysrhythmias

Table 1. Motor and Non-motor symptoms of PD. (Adapted from Balestrino & Schapira, 2020).

stage allows identification of those with PD at its primitive stages, a necessity for early treatment (16). A web-based prodromal PD risk calculator which calculates the probability of prodromal PD, has recently become available (17).

Diagnosis

Central to PD diagnosis are a thorough patient's history and physical examination. Over time, the response to treatment and any development of motor fluctuations, must be assessed. Table 2 shows the criteria formalized by the UK Parkinson's Disease Society Brain Bank, with 90% diagnostic accuracy. Early-onset patients have more marked bradykinesia and rigidity, but are less likely to present with gait disturbance than those with late-onset PD (18). Forming an early diagnosis is tied to early identification of non-motor comorbidities, like depression, anosmia, sleep disorders, and their potential association with PD (19).

Imaging techniques, like magnetic resonance imaging (MRI), are useful only to exclude other neurological disorders. Normally, it is only when motor symptoms become prominent that PD is diagnosed, hence the idea of biomarkers may lead to a quicker and earlier diagnosis (2).

Presently, no clinically useful biomarker for PD diagnosis exists. Single-photon emission computed tomography (PET) can be used as dopaminergic imaging to display asymmetric and decreased uptake of striatal dopaminergic biomarkers (particularly in the posterior putamen), suggesting dopaminergic

1. **Bradykinesia and at least one of the following:**	✓ Rigidity ✓ Resting tremor (4-6Hz) ✓ Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
2. **Exclusion of other causes of parkinsonism**	
3. **At least three of the following supportive (prospective) features:** Unilateral onset, Persistent asymmetry primarily affecting the side of onset, Resting tremor (hand, leg or jaw; low frequency [4–5 Hz], asymmetric, disappears with action), Excellent response to levodopa (70%–100%), Progressive disorder, Severe levodopa-induced chorea (dyskinesias), Levodopa response for five years or more, Clinical course of 10 years or more	

Table 2. Criteria of the UK Parkinson's Disease Society Brain Bank for diagnosing Parkinson disease. (Adapted from Jankovic et al., 2008).

denervation (16). This type of imaging is effective in separating PD from other conditions with no dopaminergic denervation. In the future, 7-T MRI may be useful in assessing the anatomy of the SN (2).

Treatment

Unfortunately, current PD treatment is only symptomatic and primarily targets the dopaminergic pathway. Levodopa (L-dopa) is the cardinal rule for PD treatment –it is the most effectual drug for motor symptoms (20). Whether given in tablet form several times in a day or via duodenal infusion (in advanced disease patients), L-dopa provides a dramatic improvement in symptoms. However, L-dopa brings about peripheral dopaminergic side-effects (can be evaded by decarboxylase inhibitors) and other side-effects like confusion and hallucinations (21). It also causes motor fluctuations and dyskinesia.

These draw-backs may be due to the discontinuous stimulations of dopamine receptors in the striatum, rather than the prolonged dopamine supply (22). The severity of dopaminergic neurodegeneration, the L-dopa dose, low weight and female sex, are all factors linked to the origin of motor complications (23).

Recently, an extended-release carbidopa-levodopa formulation (IPX066) was approved, to decrease motor fluctuations (24). Other formulations like an inhaled formulation and a levodopa prodrug (XP21279) are being investigated (16).

Dopamine agonists trigger the striatal postsynaptic dopamine receptors. Compared to L-dopa, these drugs are less effective in improving the motor symptoms, but are not as likely to cause dyskinesia (16). Monoamine oxidase B (MAO-B) inhibitors reduce dopamine

metabolism and so, extend dopamine stimulation. Since L-dopa is metabolized by Catechol-O-methyl transferase (COMT) enzymes, COMT inhibitors are used as a supplement to L-dopa, since they prolong its half-life (25).

No disease-modifying therapies are available. Hence, the search for potential neuroprotective therapies continues in earnest. Targets for such therapies include: α-syn, calcium homeostasis, mitochondrial dysfunction, oxidative stress and autophagy. Short-interfering RNAs (siRNAs) can be used to decrease α-syn expression (26). Passive and active immunotherapies that target Syn are currently undergoing clinical trials (16). Studies indicate that caffeine and nicotine can affect α-syn aggregation and that isradipine (calcium channel blocker) and urate behave like antioxidants (16). However, isradipine did not show clinical effectiveness in a recent trial (27). The diphenylpyrazole compound, anle138b, has been found to have anti-aggregation effects on α-syn (28). In Tau pathology models (for Alzheimer's disease), anle138b, saved neuronal loss (29), and is undergoing clinical trials.

Drugs that target the GBA pathway are also under investigation (30). Enhancing autophagy can halt the degenerative process of PD, as evidenced in animal and in vitro models (31).

Conclusion

PD pathology is complex, involving an amalgam of genetics, epigenetics and environmental triggers. Despite countless investigations, PD remains incurable. Its complete aetiology is still unknown. Each case is heterogenous and depends on the individual. .

However, our current knowledge of PD is constantly being tested by new discoveries, and should be directed towards the development of biomarkers and disease-modifying measures, if we are to find a cure for this movement disorder, hopefully in the near future.

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