

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease first characterised by James Parkinson in 1817. It is clinically defined as a movement disorder, but is often accompanied by cognitive decline (Wüllner et al., 2007; Park and Stacy, 2009;). Motor dysfunction in PD is caused by the selective degeneration of dopaminergic neurons in the substantia nigra (SN). Clinical characteristics include resting tremor, slowness of movement (bradykinesia). Loss of movement (akinesia) and postural instability may also develop as pathology progresses (Reichmann, 2010). A loss of olfaction (hyposmia) often precedes motor dysfunction (Politis et al., 2010). Other non-motor symptoms can develop in late stage disease and include dementia, hallucinations, sleep disturbances, autonomic dysfunction and depression (Park and Stacy, 2009). These symptoms associate with proteinaceous intraneural inclusions called Lewy bodies (Valls-Solé and Valdeoriola, 2002).

The extent of Lewy body pathology correlates with PD development, initially affecting brainstem and subcortical nuclei and then progressing into the neocortex (Braak et al., 2006). The primary site of pathology differentiates PD from Dementia with Lewy bodies (DLB), as the later is associated with early development of Lewy bodies in the cortex. The involvement of these lesions in neurodegeneration remains unclear, despite strong correlations between their presence and clinical disease progression.

Age is the greatest risk factor associated with PD (Fahn, 2010). PD affects approximately 2% of the male population and 1.3% of females over 60 years of

age. The incidence increases exponentially past this age to affect up to 5% of the total population over 85 years (Rao et al., 2006). Females are less susceptible owing to the neuroprotective properties of oestrogen. This female sex hormone stimulates the production of brain-derived neurotrophic factor (BDNF), which facilitates differentiation and survival of dopaminergic neurons. BDNF levels are reportedly decreased within the substantia nigra in PD patients (Howells et al., 2000).

The underlying cause of PD and DLB is often attributed to an 'interplay between genetic and environmental factors' although 90% of cases have no known genetic cause. It is thought that behavioural factors, specifically high consumption of iron, manganese, lutein, cholesterol and saturated fats, as well as incidences of head trauma, contribute to idiopathic disease pathogenesis (Powers et al., 2009). However, these risk factors do not consistently correlate with disease across independent studies and in most incidences the evidence for environmental contributors is weak (Hardy, 2006). Discrepancies within the segregation of PD among identical twins suggest that environmental factors do contribute to disease pathogenesis (Tanner et al., 1999). However, these findings are equally representative of a self-propagating disease such as a prion disease. A 'prion-like phenomenon' is currently proposed as an alternative hypothesis for the pathogenesis of neurodegenerative conditions associated with protein aggregation, including PD and DLB (Goedert et al., 2010).

Clinical manifestations of PD have been linked to exposure to the common pesticides rotenone and paraquat (McCormack, 2002). These agents cause

toxicity through induction of mitochondrial and cytosolic free-radical production, respectively. Administration of either paraquat or rotenone directly into the Nigrostriatal Dopaminergic Pathway of rodents causes selective degeneration of nigrostriatal dopaminergic neurons (Pan-Montojo et al., 2010). Rotenone toxicity is also linked to the formation of intracellular inclusions which biochemically resemble Lewy bodies (Betarbet et al., 2000).

There is a strong correlation between familial PD and symptomatic onset prior to the age of fifty years (Fahn, 2010). Multiple mutations in two distinct genes (*SNCA* and *LRRK2*) cause dominant Mendelian inheritance of PD. These familial cases are characterised by both neurodegeneration and Lewy body pathology (Shulman et al., 2011). Mutations to three genes (*PRKN*; *PINK1* and *DJ-1*) are associated with recessive inheritance of PD or Parkinsonism, although the occurrence of Lewy body pathology in these conditions is variable (Shulman et al., 2011). There is a disproportionately high incidence of glucocerebrosidase gene (*GBA*) mutations in sporadic PD patients. It remains undetermined whether these incidences represent a strong susceptibility locus or a Mendelian inheritance pattern with incomplete penetration (Shulman et al., 2011). Other susceptibility loci are found within the *MAPT* gene, encoding the microtubule associated tau protein (Pankratz et al., 2009).

Current therapies can aid in controlling the motor symptoms of PD but do not reverse cell loss or prevent further degeneration. Dopamine replacement therapy (levodopa) is the first line of drug treatment for PD patients (Poewe et al., 2010). However, the symptomatic benefits of levodopa decrease over time

and fluctuations in motor response occur in the majority of patients after three to five years of treatment. The severity of these fluctuations correlates with the duration of therapy (Abbruzzese, 2008). Levodopa is often used concomitantly with second line therapies such as monoamine oxidase-B inhibitors, dopamine receptor agonists and catechol-*o*-methyl transferase inhibitors. These agents act to augment the effects of levodopa.

Non-pharmacological therapies are recognised as potential methods in PD treatment. Deep brain stimulation of the subthalamic nucleus is a well established technique of improving motor function (Kopell et al., 2006), although, its use is appropriate for just 5-10% of people with PD due to the strict patient criteria (Pereira and Aziz, 2006). Foetal mesencephalic graft transplantation is an alternative therapy, which offers potential restoration of the Nigrostriatal Dopaminergic Pathway and reversal of motor symptoms. Recent clinical trials indicate that these grafts can improve motor function (Olanow et al., 2009), although the success of these grafts is limited and post-mortem analysis indicates Lewy body pathology in dopaminergic neurons of the graft tissue (Li et al., 2010). Further development of this technique is hindered by current legal and ethical limitations. Gene therapy is also undergoing clinical trial in PD patients and some vectors show early indications of success (Marks et al., 2010).

Further investigations of the underlying genetics, cellular mechanisms and differential vulnerability that defines Parkinson's disease is essential for the

development of new therapeutics targeted at curing or slowing onset of this devastating disease.

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