Idiopathic Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease, affecting four million people worldwide (Nussbaum et al. 2003). PD is an irreversible, progressive neurodegenerative disorder, characterized clinically by four major symptoms: resting tremor, bradykinesia, postural instability and rigidity. These motor symptoms do not typically develop until 50-60% of nigral neurons have been lost and 80-85% of the dopamine content of the striatum has been depleted (Marsden, 1996).

In addition to the severe motor deficits associated with Parkinson’s disease, a variety of cognitive and emotional impairments also may manifest during disease course (Rodriguez-Oroz et al. 2009). In a study of newly diagnosed PD patients, 24% of patients exhibited cognitive dysfunction, compared to 4% of controls (Muslimovic et al. 2005). Braak and colleagues (2005) reported that one-third of patients with sporadic PD at stage 3 of the Braak neuropathological staging already showed significant cognitive decline, even though alpha-synuclein aggregations are not yet present in the cortex during this early pathological stage. This number rose to two-thirds of the cohort at stage 4, was greater than 90% at stage 5 and reached 100% at stage 6 (Braak et al. 2005). Population-based longitudinal studies have suggested that some degree of cognitive impairment is present in 80% of patients within 12 to 20 years after motor symptom emergence (Aarsland et al. 2001; Hely et al. 2008).

Studies have suggested that cognitive symptoms may be more important than motor abnormalities in determining the quality of life of patients and caregivers.
Aarsland et al. 1999; Martinez-Martin, 2011). Interestingly, studies suggest that non-motor symptoms may pre-date the emergence of motor abnormalities by several years, and, thus, may serve as an early clue to Parkinson’s disease (Hubble et al. 1993). This may allow for the detection and treatment of the disease at earlier stages, before the loss of nigral neurons becomes catastrophic, which may lead, ultimately, to the development of more effective treatments. Thus, research into the basis of the cognitive symptoms of PD is critical.

Cognitive deficits in PD range from mild cognitive impairment, mainly in the domains of executive functioning and visuospatial functioning, to dementia (Mulsimovic et al. 2005; Rodriguez-Oroz et al. 2009). In a recent review of the scientific literature, Kudlicka and colleagues (2011) found deficits in PD patients across a broad range of executive functions, including cognitive flexibility, set switching, response inhibition, selective attention/working memory and concept formation. Visuospatial attention and executive function appear to deteriorate in parallel with the degeneration of motor function in PD (Owen, 2004). Van Spaendonck and colleagues (1996) reported that deficits in cognitive shifting were consistently and significantly correlated with motor symptom severity. While deficits in attention and executive functioning are often more pronounced in parkinsonian patients with cognitive dysfunction than in AD patients, memory impairments tend to be less severe in PD (Park and Stacy, 2009).

In addition to those that experience mild cognitive impairment, another subset of patients with PD qualify for a diagnosis of Parkinson’s Disease with dementia (PD-D). Although prevalence rates of Parkinson’s disease with dementia (PD-D) vary widely across different studies, dementia is estimated to occur in approximately 30% of PD patients (Riedel et al. 2008; Aarsland and Kurz, 2010). Compared to non-PD
patients, parkinsonian patients have a six-fold increased risk for developing dementia (Aarsland et al. 2001). In a prospective population based study, Aarsland and colleagues (2003) found that 78% of patients with PD developed dementia after eight years of follow-up, a prevalence that was nearly three times that of the non-PD group.

In Parkinson’s disease with dementia, symptoms primarily consist of impairments in attention, executive, and visuospatial functions, particularly in processing speed (Emre, 2003; Park and Stacy, 2009). Memory may also be impaired, particularly working memory capacity, and some studies indicate that long-term memory may be impaired as well (Wilson et al. 1980; Pillon et al. 1996). Along with these cognitive impairments, patients with PD-D also exhibit behavioural features, such as hallucinations, delusions, apathy, excessive daytime sleepiness, and personality and mood changes (Poewe et al. 2008).

The treatment of cognitive impairment in PD is difficult for neurologists. Treatment with both L-dopa and dopamine agonists, two of the most common treatment strategies for PD, has failed to produce significant improvements in cognition (Kulisevsky et al. 2000; Brusa et al. 2005). Cholinesterase inhibitors used for the treatment of Alzheimer’s have been shown to lead to some improvement in cognition for Parkinson’s patients (Aarsland et al. 2002; Emre et al. 2004). Unfortunately, there is a fear that these drugs may worsen parkinsonian motor impairment, potentially limiting the use of these drugs (Leroi et al. 2004; Ravina et al. 2005). New treatment strategies are needed.

One such treatment might be the use of adenosine A\textsubscript{2A} receptor antagonists. In recent years, adenosine A\textsubscript{2A} receptor antagonists have gained popularity as a potential non-dopaminergic antiparkinsonian treatment, and the first commercially
available of these drugs, istradefylline, has been approved for use as an adjunctive treatment for PD in Japan (Dungo and Deeks, 2013). In addition to reversing motor symptoms, there is a growing body of recent evidence suggesting that adenosine A_{2A} antagonists may also have utility in treating cognitive dysfunction (Shen and Chen, 2009; Wei et al. 2011). This could provide a novel and effective treatment strategy for this debilitating symptom of PD.

In conclusion, cognitive impairments are a severe, debilitating, and prevalent source of non-motor dysfunction in Parkinson’s disease. Ranging from relative minor cognitive impairments in executive or visuospatial function to subcortical dementia, these cognitive deficits present with varying degrees of severity in patients. In fact, even at the end stages of the disease, approximately 20% of patients are free from any measureable cognitive impairment. To date, it remains to be seen why some parkinsonian patients are more at risk for the development of cognitive impairment than others, although findings from recent epidemiological studies are beginning to clarify this issue, providing insight into potential risk factors. Given the significant decreases in quality of life of the patient and increases in caretaker burden associated with cognitive deficits in PD, the development of novel and effective treatment strategies for this debilitating symptom is of utmost importance and should be a significant research focus in the coming years.

References:


