

## PARKINSON'S DISEASE IN THE ELDERLY

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### ABSTRACT

**Parkinson's disease (PD) is the second most common neurodegenerative disorder globally and its prevalence in Singapore is expected to increase exponentially with our ageing population. Diagnostic and management issues unique to the elderly population will be discussed broadly in this topic review.**

**Keywords: Parkinson's Disease (PD), diagnosis, management, elderly**

### INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide and the fastest growing one, with prevalence more than doubled from 1990 to 2015.<sup>1</sup> Prevalence and incidence rates vary according to geographical regions, and are slightly lower in the East.<sup>2</sup> A local community-based study showed a prevalence rate of 61.9 per 100,000 for those above 50 years of age, age-adjusted to WHO 2000 census. Rates increased exponentially with age, peaking in those aged 80 and beyond.<sup>3</sup> With the rapidly ageing population in Singapore, PD prevalence will continue to increase, making it imperative for the general practitioner to be familiar with this condition. The disease presentation, trajectory, and management, with emphasis on issues specific to the older population will be discussed.

#### 1. Pathophysiology, Phenotypes and Progression

PD is characterised pathologically by the presence of widespread cytoplasmic  $\alpha$ -synuclein aggregation in the form of Lewy bodies, and neuronal loss in the ventrolateral substantia nigra. Recent evidence suggests that  $\alpha$ -synuclein aggregates are propagated in a prion-like fashion, being released by affected neurons into the extracellular space and taken up by neighbouring neurons.<sup>4</sup>

The role of deranged intracellular homeostasis of  $\alpha$ -synuclein in PD is supported by genetic studies that link mutations in LRRK2 and GBA (the most common genetic risk factor for PD) to reduced lysosomal autophagy system function. The final common pathway to cellular death may be mediated by mitochondrial dysfunction and oxidative stress.<sup>5</sup>

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The loss of modulation of the substantia nigra pars compacta on the striatum, resulting in inhibition of the excitatory direct thalamo-cortico-basal ganglia pathways and facilitation of inhibitory indirect pathways, accounts for the motor symptoms of PD in a simplistic manner.

Clinical heterogeneity and lack of reliable biomarkers (for both diagnosis and prognosis) make it intuitive for clinicians studying PD to try and identify clinical phenotypes that help make sense of the disease course. Hoehn and Yahr observed in their seminal paper that 'patients whose chief complaint is tremor have a slightly better prognosis than those whose akinesia or rigidity is the main manifestation'. Categorisation of PD patients into 'tremor-predominant' and 'postural instability/ gait disorder (PIGD; later referred to as 'akinetic-rigid' in subsequent studies)' subtypes was first operationalised by Jankovic et al. in the DATATOP study.<sup>6</sup>

Criticism of this method of clinical subtyping include the arbitrary nature of the algorithms used to determine subtypes, resulting in patients being classified differently based on the algorithm used. A new method of determining clinical subtypes by using cluster analysis, a type of hypothesis-free analysis that removes the bias of choosing criteria based on experience, has gained popularity. A novel study applied non-motor symptoms including orthostatic hypotension, mild cognitive impairment and rapid eye-movement sleep behaviour disorder to the algorithm and defined a new 'diffuse/malignant' group of PD patients who had a rapid rate of progression.<sup>7</sup> Whether these are distinct clinical variants of PD or simply different stages of the same disease process is still a matter of ongoing debate. The merit of these studies is to bring attention to the fact that all physicians should screen PD patients for both motor and non-motor symptoms to help anticipate disease course and manage potential complications.

Studies comparing early-onset or intermediate-onset PD to late-onset PD (LOPD), have demonstrated decreased, similar and increased frequencies of tremor as presenting features in LOPD. Gait abnormalities were more common in LOPD but could have been confounded by existing comorbidities which are more prevalent in the older age groups.<sup>8</sup> A cross-sectional study of middle-aged and old-aged PD patients showed that for a similar disease duration, patients with LOPD had greater motor impairment (higher bradykinesia and rigidity scores but not tremor scores). The authors suggested that a more rapid disease progression or less aggressive medical treatment could account for this difference.<sup>9</sup>

## 2. Diagnosis

The diagnosis of PD can be made in the presence of bradykinesia accompanied by one of two other cardinal motor features of rest tremor or rigidity. While bradykinesia can affect the voice, face and gait, slowness of limb movements must be documented to establish a diagnosis of PD.<sup>10</sup> The latest clinical criteria proposed by the International Parkinson and Movement Disorder Society (MDS) introduced non-motor supportive criteria for the first time, namely olfactory loss and cardiac sympathetic denervation. Importantly, autonomic dysfunction and dementia are no longer absolute exclusion criteria, supported by study findings of mild cognitive impairment and autonomic dysfunction in incident or incipient PD populations.<sup>11,12</sup>

The accuracy of the clinical diagnosis of PD has not improved over the last 25 years in spite of advances made in the field of neuroimaging. A meta-analysis of clinic-pathologic studies showed a pooled diagnostic accuracy of 80.6 percent.<sup>13</sup> While structural magnetic resonance imaging is helpful for differentiating PD and atypical parkinsonism, demonstrating atrophy, iron deposition and increased signal changes in particular brain regions in atypical parkinsonism, these changes may not be apparent in early parkinsonian presentation. Radionuclide imaging of presynaptic dopaminergic function shows a typical pattern of asymmetric tracer uptake in the posterior striatum, but does not differentiate PD and atypical parkinsonism. Metabolic imaging (e.g. with<sup>18</sup> F-fluorodeoxyglucose) may be useful but lack of normative values and availability of techniques at most centres limit their potential.

The incidence rates of PD have been reported in several studies to decline in the eighth decade of life – this is at odds with the widely-accepted understanding of age as a risk factor of disease and may be due to under-diagnosis in this age group. Common musculoskeletal and neurological comorbidities in older patients contribute to tone, dexterity and balance difficulties that are challenging to distinguish from the motor features of PD. In addition, patients and their families often mistake early PD signs and symptoms for normal ageing.<sup>14</sup>

Conversely, while the clinical picture of PD has expanded vastly to include various non-motor features, it behoves the physician to exclude other possible aetiologies for each symptom. A good example would be constipation, for which an endoscopic evaluation to rule out malignancy may be appropriate before attribution to PD.

## 3. Management

PD affects multiple domains including motor, autonomic, psychological and cognitive functions.<sup>15</sup> The main aim of pharmacological therapy in PD is symptom control. As age has been found to be an independent risk factor for falls, cognitive impairment and visual hallucinations, I will focus on the management of these conditions.

### Management of motor symptoms including falls

It is common clinical practice to start older patients on levodopa mono therapy for fear of an increased risk of adverse effects

with a levodopa-sparing strategy.<sup>9,16</sup> This fear is not unfounded as many older patients have comorbidities that require polypharmacy –increasing the risk of drug interactions – and themselves may lower the threshold for side effects of anti-parkinsonian drugs (e.g. psychosis in a patient with pre-existing dementia or orthostatic hypotension in a patient with diabetic autonomic dysfunction). In addition, there are fewer concerns about levodopa-related motor complications like dyskinesia and fluctuations since these are more common in patients with a younger age of onset and longer disease duration.<sup>17</sup>

Gait and balance difficulties in PD increase with age. Falls in the elderly can lead to serious injuries, decreased mobility and loss of independence. They are also substantially costly.<sup>18</sup> The best predictor of a fall is history of a prior one. A comprehensive assessment to identify modifiable factors like orthostatic hypotension, presence of environmental hazards and wearing off of dopaminergic drug effects is important. Cueing strategies and assistive devices are mainstay therapies in fall prevention. In view of the findings of cholinergic neuronal loss in the pedunculopontine nucleus of PD patients with gait instability, cholinesterase inhibitors have been evaluated for falls reduction, with the latest MDS update on treatments for motor symptoms of PD concluding that rivastigmine is possibly useful.<sup>19</sup>

### Management of neuropsychiatric symptoms: cognitive impairment and psychosis

The gamut of neuropsychiatric symptoms in PD includes apathy, depression, anxiety, impulse control disorders, psychosis and dementia. This review focuses on cognitive impairment and psychosis, for which incidence rates increase with age and disease duration.<sup>11,20</sup>

The MDS diagnostic criteria for mild cognitive impairment (PD-MCI) allows for the cognitive decline to be reported by the patient, informant or observed by the clinician. Cognitive deficits must be demonstrated on testing and should not interfere significantly with functional independence. The preferred test for global cognition in PD is the Montreal Cognitive Assessment (MoCA). PD-MCI can be further subtyped into single domain and multiple domain involvement, via comprehensive neuropsychological testing that includes at least two tests for each of five cognitive domains (attention and working memory, executive function, language, memory and visuospatial function).<sup>21</sup>

The five-year prevalence of PD-MCI in an incident PD cohort has been reported to be >40 percent with annual progression rates to dementia of 12.1 percent in patients with baseline PD-MCI.<sup>11</sup> It is important for physicians to screen PD patients regularly for cognitive impairment. PD with dementia may be difficult to distinguish from dementia with Lewy bodies (DLB) or Alzheimer's dementia because of the overlap of clinical and pathological changes. Significantly, the revised MDS diagnostic criteria qualifies that PD can be diagnosed regardless of when dementia occurs in relation to parkinsonism onset, and in cases where parkinsonism subsequently develops in a patient with dementia, the diagnosis 'PD (DLB subtype)' is recommended.

The cholinesterase inhibitor, rivastigmine, is clinically useful for the treatment of dementia in PD while donepezil and galantamine are possibly useful, in the MDS-commissioned

update on treatment for non-motor symptoms of PD. There is insufficient evidence to support the use of cholinesterase inhibitors for non-dementiacognitive impairment.<sup>22</sup>

Psychosis in PD tends to develop later in the disease course, arising in the context of clear sensorium. Insight is usually retained but may be lost with progression. Visual hallucinations of people or animals, lasting from seconds to minutes, usually occur in the evenings when lighting is low. Auditory hallucinations, if they occur, tend to accompany visual hallucinations and compared to those in primary psychotic disorders, are less likely to be of a threatening nature. Presence and passage hallucinations described respectively as the sense of a presence in the room, behind or beside the patient and the sense of movement in the periphery, may be a prodromal symptom and is not usually reported by patients. Delusion commonly take the form of suspicions of spousal infidelity.<sup>20</sup>

Management starts with identifying and treating reversible factors like concomitant infections, electrolyte abnormalities, cerebrovascular event etc. The next step involves simplification of anti-parkinsonian drug regimens with the gradual removal of drugs in the preferred order of anticholinergics, selegiline, amantadine, dopamine agonists, catechol-O-methyltransferase inhibitors, and levodopa.

Clozapine is clinically useful for the treatment of psychosis but can only be prescribed by a psychiatrist in our local context and required specialized monitoring. Quetiapine, hence is the preferred anti-psychotic, but its use in demented person needs to be accompanied by a warning that there may be an increased risk of cardiovascular events and death. Pimavanserin, a selective serotonin 5-HT<sub>2A</sub> agonist, is useful for the short-term treatment of PD psychosis.<sup>22</sup>

#### Management of autonomic dysfunction: orthostatic hypotension

Orthostatic hypotension (OH) occurs in approximately 20 percent of those aged 65 and above, contributed, undoubtedly, by the presence of polypharmacy. This prevalence is even higher in PD patients, with rates of 30-50 percent, increasing with age and disease duration. Neurogenic hypotension occurs in Lewy-body disorders because of postganglionic sympathetic dysfunction, which results in cardiac denervation and impaired compensatory vasoconstriction upon standing.<sup>23</sup> Like cognitive impairment, OH significantly lowers quality of life (QoL) in PD patients and can occur early in disease.

The symptoms of OH, including tiredness and neck and shoulder discomfort (coat hanger pain), can be non-specific and easily missed. In one study, only 16 percent of PD patients with OH were symptomatic. Importantly, regardless of symptoms, OH was associated with greater health care utilisation and falls.<sup>24</sup>

The management of OH is complicated by the frequent coexistence of supine hypertension. *Espay et al* argue for the prioritization of OH over supine hypertension as OH poses risks for falls and cognitive impairment in the near/ immediate future while the purported risks of cardiovascular events with supine hypertension occur over decades.<sup>25</sup> The authors propose that the

American Geriatrics Society recommendation to accept supine hypertension in elderly (>80 years) patients without PD might also be appropriate for younger PD patients with coexistent OH and supine hypertension.

Nonpharmacological methods are attempted first. These include increasing water intake (often challenging for PD patients who have impaired gastric motility, urinary urgency and decreased mobility), using physical counter-maneuvres (e.g. leg crossing, squatting), sleeping with head of bed elevated, avoiding autonomic stressors (e.g. large meals, hot showers) and using abdominal binders or compression stockings.

Possibly useful pharmacotherapy for OH are fludrocortisone (often prescribed with potassium supplement), midodrine and droxidopa. Pyridostigmine, although not in the MDS guideline, is sometimes used with the potential additional benefit of improving constipation.

#### 4. Living life successfully with Parkinson's Disease

The adage that 'it takes a village to raise a child' may also be applied to the elderly PD patient, given the complexity of care. Given the sobering finding that PD patients have worse health-related QoL than patients with other chronic illnesses such as strokes, arthritis, diabetes, heart failure and coronary heart disease, there is no doubt that PD care has to improve.<sup>26</sup> Helping our PD patients live life successfully starts by understanding their perception of success and supporting the development of positive mindsets and acceptance of challenges, while at the same time, drawing on family support.<sup>27</sup> Patient-centred care may sound cliché but cannot be further emphasised – patients need to agree upon set goals of management before a fruitful therapeutic alliance is established. A crucial member of the 'village' is the caregiver whose burden and strain if not addressed, may inadvertently result in poorer patient outcomes and institutionalisation in the long run. Other aspects of care include access to specialised allied health care, regular physical activity, support groups and palliative care.<sup>26</sup>

#### 5. Conclusions

PD is a multifaceted disease with often overlooked non-motor symptoms that arguably impact QoL more substantially than motor symptoms. As our population ages, the general practitioner will increasingly encounter older PD patients in the community. Differences in illness presentation, response to medications and presence of comorbidities serve as unique challenges to management in this patient group, but can be overcome by a nuanced and careful approach.

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## LEARNING POINTS

- **The diagnosis of PD in the elderly is complicated by the presence of multiple age-related co-morbidities that may confound the clinical picture. Certain examination findings like the presence of a rest tremor or a supporting history of non-motor features (e.g. hyposmia, RBD), may be helpful to differentiate PD from these other co-morbidities.**
- **Cognitive impairment and autonomic dysfunction may be present from the onset of motor symptoms in PD and should be sought for specifically by the physician during each consult, as these non-motor symptoms often impact QoL and health outcomes negatively.**
- **The management of falls, cognitive impairment, psychosis and orthostatic hypotension (often markers of advanced disease) has to be a well-considered and coordinated approach consisting largely of non-pharmacological interventions – crucially, allied health care input – and a small amount of pharmacological therapy.**