**5th World Parkinson Congress**

**4 - 7 June, Kyoto, Japan**

**Notes on Sessions attended by Dr Hagop Bessos**

1. History of Levodopa and Dopamine Agonists: Benefits and Myths

Stanley Fahn MD, Columbia University, New York

2. Can We Predict And Therefore Minimise Falls in PD?

Lynn Rochester PhD, Newcastle University

3. Can We Predict Falls ?

Colleen Canning PhD, Australia

4. Factors that Contribute to Falls

Anat Mirelman PhD, Tel Aviv

5. What is apathy?

Kathy Dujardin PhD, Lille University Medical Centre, France

6. Managing Peripheral Problems in PD

Dr Lim Shen-Yang, Division of Neurology, University of Malaya

Hagop’s impressions from the presentations are summarised below.

**1. History of Levodopa and Dopamine Agonists: Benefits and Myths: Stanley Fahn MD, Columbia University, New York**

Dr Fahn reviewed the history of Levodopa and dopamine agonists and then discussed the benefits of Levodopa and some common myths linked to its use. The lecture covered a number of issues previously addressed by Dr Breen and Dr Davenport during our local ERIG meetings. It was interesting to hear another leader in the PD field sharing similar perspectives on Levodopa and the use of agonists.

Synopsis

Effective high dose L-dopa treatment began 52 years ago and remains the most potent and important treatment for PD. Dr Fahn discussed the development of treatment for PD over decades and mentioned the common side effects of agonists over Levodopa, such as excessive daytime sleepiness; hallucinations and issues related to impulse control disorders.

As PD progresses, new symptoms can appear that are unresponsive to Levodopa - such as flexed posture, loss of balance, freezing of gait. Some patients have used the emergence of these symptoms as the main reason to delay initiating Levodopa therapy. This delay is unnecessary because Levodopa remains effective: it is the progression of the disease that is the problem and not the Levodopa. Another myth is that Sinemet (Levodopa) lasts only for a few years, losing its effectiveness after 5 years. The truth is that Levodopa is our most effective drug and fear of Levodopa or "Dopa phobia" is unnecessary. At some point, all people with PD will require it to provide a decent quality of life. Dr Fahn suggested that some patients wait too long because of this phobia, resulting in impaired quality of life and marked dependency on others. The biggest concern would appear to be the development of motor complications (fluctuations and dyskinesias), however some patients never get these complications. And for those who do, many fluctuations and dyskinesias are mild and tolerable. Severe motor complications can be ameliorated with Deep Brain Stimulation or with continuous intestinal infusion of Levodopa or with apomorphine subcutaneous infusions.

Dr Fahn suggested that patients older than 70 years should not start treatment with a dopamine agonist instead of Levodopa as older people generally have poor tolerance to the agonist compared to Levodopa and have more hallucinations and confusion. Also, the prime reason for starting an agonist is to delay motor fluctuations but these are less common in the elderly population, so Dr Fahn tends to avoid dopamine agonists in patients with cognitive decline, which is predominantly the elderly population.

**2. Can We Predict And Therefore Minimise Falls in PD?: Lynn Rochester PhD, Newcastle University**

Dr Rochester discussed the significant issue of falls in PD patients and reviewed strategies to prevent or minimise them. A considerable amount of discussion was focused on prediction methodologies as the disease progresses through various stages. There were important take-home messages for patients and professionals in working together to identify the best approach for each person to minimise the risk of falling.

Synopsis

PD is associated with increased risk of injurious falls up to 10 years before diagnosis. 60% of PD patients will suffer from single falls and 39% from recurrent falls. Consequences can be severe such as hip fracture or head injuries. 31 primary/secondary risk factors for falls were age associated, with the strongest predictor being a previous fall. These risk factors include axial rigidity, cognitive impairment, disease severity, dyskinesias, postural instability, shuffling and slow gait. With later manifestation of the disease such as gait, balance, and mobility problems it makes it hard to target interventions. A simple clinical tool comprising a brief questionnaire may, however, be used to predict falls. Questions include whether the patient has fallen in the last twelve months; experienced freezing of gait over the past month; or how long the patient takes to walk in a restricted area. Data collected from this simple clinical tool could indicate the probability of falls. Levodopa was mentioned as being a double-edged sword for balance and gait in people with PD.

A clear message from Dr Rochester was that minimising falls requires a personalised approach, including observational data from family or friends to focus on the areas of greatest difficulty. For example, people with PD tend to explore their environment less when walking and their balance may be worse when distracted. Simple steps such as putting down a cup before answering or stopping doing two things at once (multitasking) may help. PD patients often do not prioritise visual information, possibly leading to gait impairment and falls risk. This can be improved by paying attention to visual scanning and by cues/environmental modification. Risk of falls could be improved by early referral to address gait and postural control; exercise and delaying the first fall; better education regarding falls risk and addressing community/home-based risk separately.

In summary, falls include multiple risk factors that change with the stage of disease: risk management should be focused according to disease stage and patient age; patients should be encouraged to engage with challenging gait and balance exercises early on for a preventative approach; and increase supervision of exercise with increased disease severity.

**3. Can We Predict Falls?: Colleen Canning PhD, Australia**

Dr Canning described the common elements that lead to falls in PD including changes in muscle strength; freezing of gait and how changes in cognition impact on gait. There was some cross over between the data presented by Drs Canning and Rochester in terms of risk prediction methodologies and outcomes. However there was some variation in statistics regarding the percentage of PD patients that have falls and or recurrent falls by a factor of 20%.

Synopsis

Dr Canning focused on a specific predictive modelling tool for recurrent falls over a 6 month, 12 month, and 36 month period. Specific PD related risk factors included: axial rigidity, cognitive (frontal) impairment, disease severity, dual tasking, dyskinesias, fall history, freezing of gait, functional neurosurgery, higher total doses of Levodopa, use of dopamine agonists including anti-cholinergic, postural abnormalities, postural instability, shuffling, slow mobility, and urinary incontinence. The predictive clinical tool indicated that up to 70% of people will fall each year and over 60% will fall recurrently. There was no real difference in the range of factors assessed by the predictor tool but there were higher numbers of falls predicted than described by Dr Rochester in her talk.

The key take home message was that levels of falls can be accurately predicted and this may lead people with PD to seek appropriate and timely assessment and intervention thus preventing injurious falls and or frequency of falls. The information may also be helpful to professionals when considering how best to support patients.

**4. Factors that Contribute to Falls: Anat Mirelman PhD, Tel Aviv**

Dr Mirelman reviewed the evidence that rating scales or other factors can predict who will fall. There was considerable cross-over in the information presented across all the sessions on falls.

Synopsis

For older people, falls are the leading cause of fatal injury and the most common cause of non-fatal trauma related hospital admissions among older adults. In Europe, fractures from falls account for more disability adjusted life years than all common cancers, with the exception of lung cancer. The estimated cost per patient in Europe is 1,961 €. Annual projected costs of falls related injuries worldwide by 2050 is 130 billion€. Approximately 38 % - 68% of PD patients experience falls as a serious complication of gait disturbances. Risk was once again described as related to intrinsic changes in motor, sensory and cognitive functions. The most common risk factor was small shuffling steps and increased gait variability. Freezing of gait also increases the risk of falls.

Dr Mirelman provided evidence of the impact of dual tasking and cognitive function as measured on healthy adults and PD patients. It showed the negative impact of dual tasking on the gait of PD patients as well as the effect on stride length and walking speed. Cognitive dysfunction affects the risk of falling. Depression, for example, is common in PD, with prevalence of 32% - 45%. Depression has been associated with increased risk of falls in older adults and patients with PD and psychotropic use was confirmed as an independent risk factor for falls.

Patients with PD are often prescribed multiple medications and previous studies have shown that polypharmacy is associated with greater risk of falling. ACE-inhibitors have been associated with orthostatic hypotension (low blood pressure) in older population. However ACE-inhibitors have been shown to slow age-related declines in muscle strength and improve exercise capacity. They have been shown, along with angiotensin II receptor blockers to exert direct neuroprotective effects in experimental models of PD.

**5. What is apathy?: Kathy Dujardin PhD, Lille University Medical Centre, France**

Dr Dujardin discussed the history of apathy and how to recognise and better assess and treat it. She described diagnostic criteria for determining whether or not the patient has apathy or another clinical condition, often confused with apathy. Correct diagnosis is important to ensure the patient receives appropriate clinical treatment.

Synopsis

A clinical case was presented - Mr V a 69 year old retired production manager had PD for 2 years and was taking 800 mg/day Levodopa-Carbidopa. The neurologist requested a neuropsychiatric examination as the patient's wife was concerned that he was significantly less active than before, although Mr V had no specific complaint and did not feel sad or tired. It was clear from the patient's responses to the clinician's questions that Mr V lacked motivation and spontaneity in his daily life which his wife found difficult to deal with. During other clinical investigations and using the Montreal Cognitive Assessment scale, it was clear that Mr V did not have depression, anxiety disorder, insomnia, sleep apnea syndrome or any other sleep disorder. His anti-parkinsonian treatment was well-balanced and he had no anti-psychotic treatment. Mr V therefore had Apathy syndrome.

Apathy was described as a poverty of awareness, interest, concern, or emotion. After World War I apathy had medical connotations related to numbness and indifference associated with combat - related stress. By the end of the 20th century apathy was related to symptoms of several disorders and is a topic of recent research. Clinically, apathy refers to a set of cognitive, behavioral and emotional features such as reduced interest; lack of initiative and participation; and lack of perseverance. There is no consensus on the definition of apathy and there is an overlap between the clinical manifestations of apathy and those of other disorders such as depression, anhedonia (lack of pleasure), cognitive decline, and personality traits.

There are diagnostic criteria that clinicians can use to assess patients for apathy. According to the 2018 Apathy diagnostic criteria, patients must fulfil a number of criteria such as a quantitative reduction of goal directed activity either in behavioural, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning. For example, reduced activity at home or work, making less effort or needing to be prompted to perform activities. Less persistence in maintaining an activity or conversation or finding solutions to problems. Less interest in or reaction to news or in doing new things. Less spontaneity with a reduced emotional reaction to positive or negative events. Less empathy to the emotions or feelings of others or concern about the impact of their actions or feelings on others. Less verbal or physical reactions that reveal their emotional state. Less interested in their own health and wellbeing or personal image. Less initiative in proposing social or leisure activities to family or friends or participation in social or leisure activities suggested by people around them. Less interest in family members or getting out to meet people. Less likely to initiate a conversation or early withdrawal from it. These changes may be reported by the patients or by observation of others. A number of criteria must be present for at least four weeks and present most of the time.

Apathy and depression are not the same but may be linked. Depression is prevalent in 30% - 35% of PD patients and apathy is one of the main symptoms of depression. Both syndromes may coexist but there are differences between and depression. Apathy includes indifference, low intellectual curiosity, low productivity, and poor persistence whereas depression includes sadness, guilt feelings, deprecation, hopelessness, suicidal feeling, pessimism, insomnia, loss of appetite.

Apathy and fatigue are also correlated. The prevalence of fatigue in PD patients is 33% to 70%. In relation to cognitive impairment, severity of apathy is negatively correlated to cognitive status. Apathetic patients have poorer performance in executive functions. An 18 month study of 20 patients with apathy and 20 without showed higher cognitive decline in patients with apathy and a higher rate of conversion to dementia, implying that apathy is a predictive factor for dementia in PD.

In summary, apathy is a frequent neuropsychiatric disorder in PD and is related to cognitive impairment. It is a source of significant disability in PD and can overlap with depression, fatigue and anhedonia (reduced pleasure) and have a negative impact on quality of life for the patient and care givers. Unfortunately, there is limited knowledge of the underlying mechanisms of apathy and the overlaps with other conditions and therefore treatments are poorly developed. Early detection is needed and the severity of symptoms must be assessed to determine the best clinical treatment.

**6. Managing Peripheral Problems in PD: Prof Lim Shen-Yang MD, Division of Neurology, University of Malaya**

Professor Shen-Yang critically appraised the evidence that PD starts outside of the brain and then spreads to involve it. He listed a number of common non-motor symptoms and discussed treatment options. He suggested that there is now a much better appreciation of the clinical importance of a range of "peripheral" problems to people living with PD. This improved understanding of the underlying pathophysiology of such problems has led to an increasing array of effective treatments. However, to date, few large randomised control trials have been conducted for these problems in PD and this is an area for ongoing and future work.

Synopsis

Professor Shen-Yang gave a case study to illustrate the challenges of developing an effective treatment plan for a PD patient. He described a 65 year old lady with PD for 25 years who had many non-motor symptoms associated with PD such as: the urge to urinate frequently; excessive sweating; bloated abdomen; constipation and hallucinations. She had received deep brain stimulation and was independent for mobility and personal care and some housework. Professor Shen-Yang then described in more detail the common non motor symptoms and the complexities involved in managing the symptoms and the difficulty in getting the balance of treatments right.

Orthostatic hypotension (drop in blood pressure when one stands up). Around 30% - 40% of PD patients have neurogenic orthostatic hypotension. Only 33% - 50% (and only 25% of those with severe orthostatic hypotension) describe having symptoms. Even if it does not cause giddiness, orthostatic hypotension can have important clinical effects, including poorer function and risk of falls (which are the most frequent reason for hospitalisation in PD patients). One study indicated a 10 year survival rate of 74% versus 93% in PD patients with, versus those without orthostatic hypotension, leading some investigators to argue that patients should be screened for orthostatic hypotension, regardless of symptoms. So far, however, a theoretical long term benefit of treating non symptomatic orthostatic hypotension has not been demonstrated.

In relation to cognition, patients were assessed on a tilt table in supine, upright and then supine position again. A reversible decline in cognition was noted in patients in the upright position (e.g. verbal fluency). Many with orthostatic hypotension however were asymptomatic. This may be a potential therapeutic target for cognitive decline in PD although it remains unknown whether aggressive management of orthostatic hypotension can alter cognition. Dr Shen-Yang discussed some medications that may improve orthostatic hypotension and reduce falls although long term effects are currently unclear and awaiting further study.

Gastroparesis (delayed emptying of stomach). Symptoms associated with gastroparesis include nausea, early satiety, bloating, heartburn, vomiting, abdominal pain ("dyspepsia" symptoms) and weight loss. Gastroparesis also interferes with the effectiveness of oral PD medications. A number of suggestions were made to improve symptoms such as small but frequent low-fat meals and referral to a dietitian to correct malnutrition, if present. Professor Shen-Yang discussed the use of Domperidone and L-Dopa and the timing of medications around meal times. For example, he suggested that patients may be able to improve L-dopa action by taking it on an empty stomach (i.e. 30 mins prior to, or 2 hours after, meals) and consider protein restriction/re-distribution by having their main meal in the evening. L-dopa can also be crushed and taken with a carbonated drink (or dissolved with Vitamin C) in order to speed up drug absorption. If possible, patients should take their next dose of L-dopa while still ON, as gastric emptying is delayed further in the OFF state).

Constipation. This is generally defined as less than 3 bowel movements per week and may be due to slow colonic transit or an outlet obstruction. Further investigations should be carried out (colonoscopy/barium enema) to exclude organic obstruction. The patients' family history of colorectal or other cancers should be reviewed to rule out any major clinical problems. Prof Shen-Yang discussed a range of medications that can exacerbate constipation (e.g. opioids, anticholinergics, tricyclic anti-depressants, antihistamines, calcium channel antagonists, diuretics, and non-steroidal anti-inflammatory drugs) and suggested they should be replaced if possible. An association between dopaminergic medications and constipation remains debatable. Double blind placebo controlled randomised controlled trials (n=120) showed that fermented milk containing multiple probiotic strains and probiotic strains resulted in improved constipation. Laxatives are a common approach in the management of constipation. Although lactulose syrup may contain small amounts of absorbable sugars, this has rarely been reported to worsen glycemic control in diabetic patients. The suggestion that chronic use of stimulant laxatives may cause long-term problems (e.g., damage to the intestinal smooth muscle is poorly documented. More recent work suggests that stimulant laxatives used at recommended doses are unlikely to be harmful to the colon.

Urinary dysfunction. Overactive bladder or detrusor hyperreflexia is the major cause of urinary symptoms associated with PD. The resulting "irritative" symptoms that include nocturia (waking during the night), frequency, urgency and incontinence, compounds the bladder disorder. Professor Shen-Yang explained that it is crucial to treat any urinary tract infections and ensure there is no constipation/faecal impaction that can cause either irritation or obstruction in the lower urinary tract. Behavioural strategies were discussed such as bedside urinals; timed voids, e.g. 3 - 4 hourly during waking hours, even if there is no urge to urinate; and pelvic floor exercises that may reduce incontinence episodes. It was suggested that some PD dopaminergic medications may have an unpredictable effect on bladder function. There were ongoing trials into medications that improved the number urinary incontinence episodes but there was no data in PD. Finally, electrical stimulation of the posterior tibial nerve was recently reported to be beneficial in PD patients.

Sexual dysfunction. Impaired sexual function in PD occurs in both men and women. Erectile dysfunction develops in the majority of men with PD. A recent large study involving 1,132 men with recent onset PD (diagnosed within the past 3.5 years; mean age 67 years) reported erectile dysfunction in 56.1% of patients. Sexual issues commonly experienced by women include reduced libido, difficulties in reaching orgasm and vaginal dryness. Impaired sexual function in patients with PD may not arise solely from the neurodegenerative process affecting the autonomic nervous system. Psychological issues (lowered self-esteem, depression, anxiety, cognitive impairment, apathy, couple relationship problems), impaired mobility, fatigue, and pain may also contribute to sexual dysfunction. Frustration is sometimes further compounded when patients experience an increase in sexual urge or even hypersexuality due to treatment with dopamine agonists. Management of sexual dysfunction often needs to be multifaceted and may need to include the partner. Pharmacological treatment of erectile dysfunction include Sildenafil (Viagra®) which has the best evidence, in clinical use since 1998, and is the most commonly used agent. The starting dose is 50 mg (dose range 25 - 100 mg). No studies of treatment of sexual dysfunction in women with PD have been reported.

In summary, it is important to address aggravating factors in peripheral problems in PD; consider lifestyle and other non-pharmacological strategies; review medication treatments (physicians need to bear in mind that drugs for autonomic problems may treat one symptom while potentially worsening another at the same time e.g. anticholinergics for overactive bladder may aggravate constipation); and consider the effects of deep brain stimulation.