INTRODUCTION AND RATIONALE

Parkinson's disease (PD) is a neuro-degenerative disorder characterized by cardinal features including resting tremor, rigidity, bradykinesia, and postural difficulties which arise primarily from the loss of dopamine producing neurons and subsequent dysfunction of the basal ganglia-thalamo-cortical pathway ***(Konczak et al., 2009).***

The pathologic hallmark of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), resulting in depletion of striatal dopamine ***(McNaught & Olanow, 2006).*** This neurotransmitter regulates excitatory and inhibitory outflow of the basal ganglia ***(Simuni, 2007).*** A degenerative process in dopaminergic neurons from the substantia nigra (SN) midbrain nucleus is the basic origin underlying a set of symptoms developed in patients with Parkinson's disease ***(Andrade & Ferraz, 2003).***

The causes of most cases of PD are unknown. However, epidemiologic studies indicate that a number of factors may increase the risk of developing PD suggesting that environmental factors play an important role in development of the illness ***(Tanner, 2003).*** These include exposure to pesticides, herbicides, and industrial chemicals, wood pulp mills, farming, and living in a rural environment. Approximately 5% of patients with clinical features of PD have clear familial etiology. Therefore, genetic factors clearly contribute to the pathogenesis of PD ***(Hatano et al., 2009).***

Postural instability (PI) is a disabling disorder, which is associated with sudden falls, progressive loss of independence

and immobility ***(Grimbergen et al., 2004).*** It usually occurs at the later stages of the disease and, unlike gait disorders, responds poorly to medication. Marked alteration of gait is common in advanced PD ***(Stolze et al., 2005; Baltadjieva et al., 2006).*** Falls often have dramatic consequences, such as traumas and fractures. The high risk of fractures was demonstrated in a large case control study ***(Vestergaard et al., 2007)***

To date, management concepts in PD are still diverse. Despite gains made in the field of pharmacotherapy and deep brain stimulation, dopaminergic medications may produce a limited improvement in PI ***(Bloem et al., 1994; Visser et al., 2008).*** Thus, physiotherapy is the most commonly used procedure as an adjunct to drug therapy to treat PD movement disorders ***(Deane et al., 2001).*** At the moment, there is no uniformity of approaches for physiotherapy in PD. Rehabilitation for PD covers a number of different treatment techniques, largely centered on active exercises and re-education of mobility ***(Morris, 2000).***

Gene therapy represents a new hope to PD patients. It relies on transporting small pieces of genetic material, or DNA, into the targeted brain cells ***(Christine et al., 2009).*** The aim is to increase dopamine production in specific regions of the brain ***(Denyer & Douglas, 2012).*** It remains to be seen whether new concepts in management would substitute other traditional management protocols.

This study has been conducted in order to document vestibular &/or balance dysfunction, if any, in PD. It also aimed to explore the value of physiotherapy as an adjunct to medical treatment in controlling such dysfunction in patients with PD.

AIMS OF THE WORK

1- To assess the vestibular & balance functions in patients with Parkinson's disease.

2- To measure the effect of therapy in controlling vestibular dysfunction in Parkinson's disease.

Chapter One

PARKINSON'S DISEASE

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by cardinal features including resting tremor, rigidity, bradykinesia, and postural difficulties which arise primarily from the loss of dopamine producing neurons and subsequent dysfunction of the basal ganglia-thalamo-cortical pathway ***(Konczak et al., 2009).***

Patients with PD have difficulties in performing various motor tasks, such as walking, writing and speaking. Furthermore, PD leads to abnormalities in two main components of postural control: orientation (maintaining a normal postural arrangement and alignment) and stabilization (maintaining equilibrium) ***(Vaugoyeau & Azulay, 2010).***

Incidence

The mean age of onset of PD is approximately 60 years. It usually occurs in people over the age of 50 years, but can sometimes present in younger adults ***(Jankovic, 2008).*** Prevalence dramatically increases with age, from 290 per 100,000 for people aged 55 to 64 years to 2,940 per 100,000 for people aged over 85 years. Males are more likely to have PD than females ***(Access Economics, 2007).***

Epidemiology

PD is the second most common neurodegenerative illness (after Alzheimer's disease), and both incidence and prevalence rates increase with aging. As life expectancy of the general population rises, both the occurrence and prevalence of PD are likely to increase dramatically ***(Dorsey et al., 2007)***. During the final decades of the last century, data suggested ~1 in every 200 persons aged 60–69 had PD in the United States (US) and Western Europe. For people in their 70's, this increased to ~1 person with PD in every 100 people, and for people in their 80's, ~1 in every 35 had PD ***(Marras & Tanner, 2002).***

Disease prevalence estimates vary from country to country around the world. Both genetic predisposition and environmental factors may play a role. Caucasians in Europe appear to have the highest prevalence ***(Simuni, 2007).***

Etiology

The causes of most cases of PD are unknown. In the majority of populations, men are more likely to develop PD ***(Burn et al., 2007).***

Epidemiologic studies indicate that a number of factors may increase the risk of developing PD suggesting that environmental factors play an important role in development of the illness ***(Tanner, 2003).*** These include exposure to

pesticides, herbicides, and industrial chemicals, wood pulp mills, farming, and living in a rural environment.

Cigarette smoking, caffeine use, and high normal plasma urate levels are associated with lower risk of PD ***(Hernan et al., 2002).***Recently, ***Braak and Coworkers*** proposed the "***Dual Hit"*** theory, which postulated an unknown pathogen accesses the brain through two pathways, the nose and the gut ***(Hawkes et al., 2007).***

Approximately 5% of patients with clinical features of PD have clear familial etiology. Therefore, genetic factors clearly contribute to the pathogenesis of PD. Over the last decade, more than 16 loci and 11 causative genes have been identified. Recent studies revealed that PD-associated genes play an important roles in cellular functions, such as mitochondrial functions, autophagy-lysosomal pathway and membrane trafficking ***(Hatano et al., 2009).***

A. Environmental factors and PD

I- methyl-4phenyl-1, 2, 3, 6-tetrahydro-pyridine (MPTP)

This chemical agent is highly lypophilic, therefore it quickly crosses the blood-brain barrier and converts to (1-methyl-4-phenyl-2-3-dihydropyridinium) ion (MPP+), which is the active toxic compound, via monoamine oxidase B within non dopaminergic cells, such as glial cells and serotonergic neurons. MPP+ is transported into dopamine neurons by the

dopamine transporter, and therefore exhibits selective toxicity to dopaminergic neurons. Furthermore, MPP+ accumulates in mitochondria, inhibits the mitochondrial electron transport chain component complex I ***(Przedborski & Vila, 2003).***

II - Pesticides

Paraquat, which is a member of a chemical class known as bipyridyl derivatives, is one of the most commonly used pesticides, and leads to oxidative and nitrative stress ***(Berry et al., 2010).*** Recent studies revealed that exposure to a combination of paraquat and maneb, which is also widely used as an agricultural pesticide, exacerbate dopaminergic degeneration in the rodent model and cause an increased incidence of PD in humans ***(Costello et al., 2009).***

III - Caffeine, Smoking

Smokers and coffee drinkers have been associated with a lower risk of PD Several epidemiological studies showed that cigarette smokers had 60% lower risk for the development of PD than people without a history of smoking ***(Hernan et al., 2002).*** Several studies revealed that cigarette smoking inhibited monoamine oxidase (MAO) activity and nicotine stimulated dopamine release. As a result, cigarette smoking may suppress free radical generation via MAO-B-associated metabolism of dopamine, and be able to protect against dopaminergic cell death ***(Miller et al., 2007).***

IV- Disease process and dual hit theory

The pathological findings suggest that the neuronal degeneration in PD may extend from peripheral systems, such as olfactory and autonomic systems to cortices ***(Hawkes, et al., 2007).*** The dorsal motor nucleus of the glosso-pharyngeal and vagal nerves and the anterior olfactory nucleus were initially affected, and subsequently the substantia nigra and locus coeruleus became involved. Cortical areas showed less vulnerability and then gradually becoming affected ***(Braak et al., 2003).***

B - Genetic factors and PD

I- α-synuclein

The functions of **α**-synuclein under normal physiological conditions remain unknown. However, several studies have shown that **α**-synuclein associates with synaptic vesicles and modulate neurotransmitter release ***(Jensen et al., 1998 & Li et al., 2004).***

Aggregation of ***α*** -synuclein is thought to be a key event in dopaminergic neuronal cell death in both SNCA-linked and sporadic PD ***(Lee &Trojanowski 2006).*** ***α***-synuclein A53T mutation was isolated from an autosomal dominant PD case.

Cases of sporadic PD and A53T-associated patients displayed similar clinical phenotypes ***(Spira et al., 2001),*** multiplication of SNCA has also been identified to cause autosomal dominant familial PD ***(Ibanez et al., 2004, Chartier-Harlin et al., 2004, Nishioka et al., 2006, Ahn et al., 2008).***

II- LRRK2

LRRK2 mutations were identified as the causative gene for PARK8-linked familial PD ***(Zimprich et al., 2004).*** Some screening studies reported that LRRK2 mutations were identified not only in familial PD but also in sporadic PD. Since then, LRRK2 mutations seem to be the most frequent cause of autosomal dominantly-inherited familial PD ***(Lesage et al., 2006, Ozelius et al., 2006).***

C- Aging

The number of dopaminergic terminals appears to decrease with age, this takes place with a different temporal and spatial pattern than occurs in PD The loss of substantia nigra (SN) neurons in aging is linear and predominantly in the dorsal tier of the substantia nigra pars compacta (SNpc), whereas in PD it is exponential and predominantly in the lateral ventral tier ***(Scherman et al., 1999).***

Stages of Parkinson's disease

Stage I:

Unilateral involvement only, usually with minimal or no functional impairment, the patient has tremor, rigidity, slowness and difficulty of movement, or poor condition in the arm and/or legs/ on one side of the body. Occasionally one side of the face is involved, producing an asymmetry of expression that may look very like the effects of a mild stroke or Bell's palsy. This stage of Parkinson's is often missed entirely.

Stage II:

Bilateral or midline involvement, without impairment of balance similar symptoms and signs of stage I are noticed months or years later on the opposite side of the body, or other signs appear in "midline" called "Axial" signs. These may include: bilateral loss of facial expression, decreased blinking, speech abnormalities, soft voice, monotony, fading volume after starting to speak loudly, slurring, stiffness (rigidity) of truncal muscles making the patient appear stiff or resulting in neck and back pain postural abnormalities causing generalized slowness, usually the diagnosis is easy at this Stage if it has been preceded by a clear cut tremor or other symptom on one side.

Stage III:

First signs of impaired righting reflexes. This is evident as the patient turns or is demonstrated when he or she is pushed from standing equilibrium with the feet together and eyes closed.

Loss of balance, with the inability to make the rapid, automatic and involuntary movements necessary to protect against falling, is one of the most troubling and dangerous aspects of PD and one of the least easily treated. Even when manifested by only slight unsteadiness, it is the criterion separating Stage II and Stage III. All other aspects of PD are evident and usually diagnosis is not in doubt. However, the most important factor identifying Stage III (as opposed to stage IV) is that the patient is still fully independent in all activities of daily living (dressing, hygiene, eating).

Stage IV:

Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

The patient is unable to lead an independent life because of the need for help with some activities of daily living. It is this inability to live alone which marks the transition from Stage III to Stage IV.

Stage V:

Confinement to bed or wheelchair unless aided. The patient may exhibit: inability to arise from a chair or get out of bed without help, a tendency to fall when standing or turning, freezing, stumbling or pulsion when walking. Without someone immediately present to provide assistance, the patient is in danger of falling.

Clinical features

I- Motor symptoms

Four cardinal motor manifestations are the central features of PD:

Resting tremor, bradykinesia (slowness of movement), rigidity often with a cogwheel quality, and postural instability with impairment of postural reflexes ***(Simuni & Rezak, 2007).***

Symptoms when the dominant hand is involved include micrographia (abnormally small, cramped hand writing) and impairment in other fine tasks, such as fastening buttons.

Motor symptoms usually begin asymmetrically but gradually spread to the contralateral side ***(Simuni & Pallone, 2007).*** although the side of initial involvement tends to remain the most severely affected throughout the course of the disease ***(Frank et al., 2006).***

Common initial symptom is asymmetric rest tremor in (70%-90%) of patients. This usually involves the thumb or wrist more commonly distal. A "pill-rolling" motion of the fore finger and thumb at a frequency of 3 to 6cycles/second is the classical presentation. Slow vertical jaw or tongue tremors may be evident or leg tremors at rest. Tremors is more likely to be the presenting symptom in younger patients, whereas older patients may have more prominent bradykinesia. Tremors may be the most visible sign of PD, but it isn't the major cause of disability ***(Poewe, 2006).***

Bradykinesia is the most disabling feature of the disease; in 80%-90% of patients. It contributes to the inability to arise from a chair or difficulties getting in and out of a car ***(Pallon, 2007).***

The "cogwheel pattern" of rigidity (fluctuating intensity of resistance while limb is passively moved) is often best detected in the distal part of the limbs, mainly the wrist joint. More than 90% of patients show resistance to the passive movement occurring in both flexor and extensor muscles throughout entire range of motion may be "cogwheel" or "lead-pipe" ***(Hofmann & Shakil, 2006).*** Postural instability is a sign of more advanced PD, and one of the most disabling motor features ***(Simuni & Pallone, 2007).***

II- Non-motor Features

The clinical course of PD is not limited to motor symptoms. A variety of non-motor symptoms and disorders are common and significantly affect health-related quality of life (HRQOL) of both patient and caregiver.

Surveys in PD patients have revealed that close to 90% have at least one of non-motor-symptom, with about 10% exhibiting all non-motor symptoms ***(Weintraub et al., 2004)***

Non-motor symptoms dominate the clinical picture as PD progresses and may also contribute to shortened life expectancy ***(Poewe, 2006).*** Most do not respond to and may be exacerbated by dopamine replacement therapy ***(Chaudhuri et al., 2006).***

Depression is frequent in PD and the most common neuropsychiatric disorder, affecting up to 50%of patients. Depression is often comorbid with anxiety and can occur at any stage of the illness, including prior to onset of motor symptoms ***(Simuni, 2007, Chaudhuri et al., 2006, Weintraub & Stern, 2005).***

Other non-motor features that may occur early in PD are autonomic dysfunction, cognitive impairment, and olfactory dysfunction (hyposmia, a reduced ability to smell odors, or anosmia, which is loss of smell). Anosmia and hyposmia are so common in PD that smell-testing is undergoing evaluation as an

early biomarker to identify patients at risk of developing PD; loss of smell is also a sign that has usefulness in differential diagnosis, helping to distinguish PD from other conditions, anosmia does not respond to dopaminergic therapy ***(Simuni, 2007).***

Cognitive impairment in PD is characterized by deficits in executive abilities, memory retrieval deficits, and impairments in attention and visuo-spatial abilities ***(Weintraub & Stern, 2005).*** Dementia is rare in early IPD, and its early occurrence should call into question the diagnosis of PD and may suggest a diagnosis of dementia with Lewy bodies (DLB) ***(Simuni, 2007 & Frank et al., 2006).***

Psychosis, specifically hallucinations and delusional thinking, is also common in PD, seen in 15%to 40% of treated patients and tending to occur later in the disease course. Although there is a clear association between dopaminergic therapy and psychosis ***(Weintraub & Stern, 2005)***.