THE UNIFIED PARKINSON'S DISEASE RATING SCALE SCORE IN PARKINSON'S DISEASE PATIENTS WITH AND WITHOUT COGNITIVE IMPAIRMENT

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ABBREVIATIONS

ADL	activities of daily living
CAMCOG	Cambridge cognitive examination
COMT	cathecol-O-methyl transferase
CT	computed tomography
DBS	deep brain stimulation
EEG	electroencephalogram
HUSM	Hospital Universiti Sains Malaysia
MAOB	monoamine oxidase-type B inhibitor
MMSE	mini-mental state examination
MPTP	1-methyl-4-phenyl-1,1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MSA	multisystem atrophy
NS	not significant
NUDS	Northwestern University Disability Scale
PD	Parkinson's disease
QOL	quality of life
SD	standard deviation
UKPDSBB	United Kingdom Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's disease Rating Scale

ABSTRAK

Latarbelakang: Penyakit Parkinson sering dikenali sebagai penyakit 'motor', tetapi ia juga mempunyai manifestasi bukan-motor seperti masalah kognitif. Masalah kognitif boleh memberikan kesan yang besar ke atas beberapa aspek penyakit ini. Masih belum terdapat kajian yang dilakukan berkenaan masalah kognitif dan penyakit Parkinson yang melibatkan populasi tempatan.

Objektif: Untuk membuat perbandingan skor 'Unified Parkinson's Disease Rating Scale' (UPDRS) di antara pesakit yang mengalami masalah kognitif dan yang tidak mengalami masalah kognitif. Kedua, untuk menentukan prevalens masalah kognitif di kalangan pesakit-pesakit Parkinson yang menjalani rawatan susulan di Hospital Universiti Sains Malaysia (HUSM).

Kaedah: Ini adalah kajian 'cross-sectional' yang dijalankan di Klinik Neurologi HUSM bermula dari Jun hingga November 2006. Lapan puluh pesakit yang memenuhi kriteria kajian telah terlibat dalam kajian ini. Fungsi kognitif mereka telah di nilai menggunakan ujian 'Mini-Mental State' yang telah di sahkan ke dalam Bahasa Melayu. Skor $\leq$ 24/30 menandakan wujudnya masalah kognitif manakala skor > 24/30 adalah normal. Kemudian, semua pesakit telah menjalani ujian menggunakan UPDRS. UPDRS mengandungi 4 item iaitu keadaan mental, kelakuan, dan perasaan; aktiviti harian, pemeriksaan fungsi motor, dan komplikasi rawatan. Skor diambil dari setiap item, dan

kemudian di campur untuk mendapatkan jumlah skor. Protokol untuk kajian ini telah disemak dan diluluskan oleh Jawatankuasa Etika dan Penyelidikan USM.

Keputusan: Tiga puluh dua (40%) pesakit telah dikesan mempunyai masalah kognitif, dari peringkat sedikit hingga teruk, berdasarkan ujian MMSE. Pesakit-pesakit yang mempunyai masalah kognitif mempunyai skor yang lebih teruk untuk setiap item UPDRS berbanding pesakit-pesakit yang tidak mengalami masalah kognitif ($p < 0.05$). Mereka juga mempunyai skor yang lebih teruk untuk tahap kekerasan anggota badan dan kelambatan pergerakan aggota badan ($p < 0.05$). Setelah mempertimbangkan faktor-faktor seperti umur pesakit dan tempoh mengalami penyakit Parkinson, didapati skor UPDRS masih lebih teruk bagi pesakit yang mengalami masalah kognitif ($p < 0.05$).

Kesimpulan: Kajian ini telah menunjukkan bahawa masalah kognitif menyebabkan skor UPDRS menjadi lebih teruk. Ramai pesakit Parkinson yang menjalani rawatan susulan di HUSM mengalami masalah kognitif. Oleh sebab itu, pesakit-pesakit Parkinson perlu menjalani ujian seringan yang kerap untuk mengesan masalah kognitif.

ABSTRACT

Background: Parkinson's disease (PD) is widely known as a 'motor' disease, but it also has several non-motor features including cognitive impairment. Cognitive impairment has significant impacts on several aspects of PD. There is as yet a study on cognitive impairment and PD done involving our population.

Objectives: To compare the Unified Parkinson's Disease Rating Scale (UPDRS) score between PD patients with and without cognitive impairment. Secondly, to determine the prevalence of cognitive impairment in patients with PD under Hospital Universiti Sains Malaysia (HUSM) follow-up.

Methods: This was a cross-sectional study done at the HUSM Neurology Clinic, beginning from June till November 2006. Eighty PD patients who satisfied the study criteria were recruited into the study. Their cognitive status was assessed using the validated Malay version of the Mini-Mental State Examination (MMSE). A score of $\leq$ 24/30 signified presence of cognitive impairment while > 24/30 was normal. Regardless of their MMSE scores, all the patients then underwent assessment using the UPDRS. The UPDRS contains four items i.e. mentation, behaviour, and mood; activities of daily living; motor examination; and complications of therapy. Scores were taken from each item, and they were then totaled to obtain a total score. The study protocol was reviewed and approved by the USM Ethics and Research Committee.

Results: Thirty two patients (40%) had cognitive impairment, ranging from mild to severe, based on the MMSE. Patients with cognitive impairment had significantly worse

scores for each UPDRS item compared to the non-cognitive impairment group ($p < 0.05$). They also had worse rigidity and bradykinesia compared to the other group ($p < 0.05$). After adjusting for potential confounders e.g. age and disease duration, the cognitive impairment group still performed worse in the UPDRS assessment ($p < 0.05$).

Conclusions: The study showed that the presence of cognitive impairment resulted in worse UPDRS scores. There was a high prevalence of cognitive impairment in PD patients under HUSM follow-up. Therefore, PD patients should be routinely screened for cognitive impairment.

CHAPTER 1

INTRODUCTION

1.1 General Consideration

Parkinson's disease (PD) is now increasingly recognized as a chronic progressive neuropsychiatric disorder. It is predominantly a disease of the elderly, affecting those over 50 years of age. It is a multisystem neurological disorder which affects cognitive process, emotion and autonomic function. It is the second most common cause of chronic neurological disability in the UK.

Management of PD, therefore, should address all the aspects involved as a result of its multisystemic nature. PD patients' quality of life (QOL) depends not only on the stage of the disease but also on the level of depression, optimism, and satisfaction (Global Parkinson's Disease Survey). At the Sixth International Congress of Parkinson's Disease and Movement Disorders in June 2000, many presenters confirmed that the effects of

treatment on QOL are dependent upon factors other than the quality of movement. Factors such as cognitive impairment, depression, disability and postural instability seem to have the greatest influence on QOL in PD (Schrag *et al.* 2000). PD has a marked effect on QOL at all stages of the disease, and at all ages. Impaired QOL and carer strain increase with advancing disease and age (Findley *et al.* 2000). The total costs of the condition increase with advancing age and advancing disease stage. In younger patients the greatest costs are for the drugs and loss of earnings, while in older patients the largest the largest costs are social and long-term institutional care. These cost burdens fall on patients, carers, health and social agencies (MacMahon *et al.* 2000)

At present there is no local data or literatures that look at different aspects of PD in the community. This study was designed in the hope that it could examine a few aspects of PD in this community, and that it would trigger more research involving our own PD patients in the future.

1.2 Definitions

1.2.1 Parkinsonism

Making a proper diagnosis of PD is quite challenging because PD has many imitators. A patient who presents with bradykinesia, rigidity and tremor does not necessarily have PD. In fact, these symptoms only suggest a clinical syndrome called parkinsonism. The causes of parkinsonism can be classified into three major groups: (i) PD; (ii) atypical

parkinsonian syndromes (parkinsonism plus) and other neurodegenerative disorders; and (iii) secondary or symptomatic causes e.g. drug-induced or cerebrovascular related. PD remains the most common cause of parkinsonism at all ages. However, the prevalence of the atypical parkinsonism, drug-induced parkinsonism, cerebrovascular-related parkinsonism also increases with advancing age.

Despite the similarities in the main clinical presentation, there are useful atypical features which can differentiate PD from other diagnoses. Presence of early dementia in the course of the disease, early falls and postural instability, severe autonomic dysfunction, poor or transient benefit from drug treatment, striking asymmetry of motor signs, absence of rest tremor may suggest diagnoses other than PD (Rotnitzky 2000).

A correct diagnosis is vital because management and outlook differ between PD and parkinsonian-like syndromes. Misdiagnosis may result in fruitless treatment with dopaminergic drugs, which may produce neuropsychiatric side effects especially in susceptible older subjects.

1.2.2 Parkinson's Disease

PD has characteristic clinical features and natural history. It is recognized as levodopa-responsive parkinsonism. Pathologically, it shows degeneration of cells in substantia nigra, resulting in striatal dopamine deficiency and the presence of surviving cells of inclusions called Lewy bodies.

There is no precise clinical definition of PD yet, but most experts consider the presence of two or more cardinal motor signs (one of which must include bradykinesia) and a consistent response to levodopa as indicative of PD. Asymmetric onset is a strong indicator of PD (Hughes 1992).

1.3 Epidemiology

Epidemiological studies describe PD in terms of prevalence, incidence, mortality, and the natural history of the disease. Epidemiological reports vary between centers, and the variation could be due to different methods used in studies e.g. different diagnostic criteria used.

1.3.1 Prevalence

PD affects all races and has a fairly uniform worldwide distribution, though the prevalence in Africa, China and Japan has reduced (Zhang 1993). Differences in prevalence between racial groups may reflect differing environmental rather than genetic factors (Jendroska 1994). Studies around the world based on all ages suggest a prevalence of 120 per 100 000 population.

1.3.2 Incidence

The crude incidence of PD world-wide is estimated between 2 and 24 cases per 100 000 per year (Morens 1996). Obviously, the incidence rises with age, and is greatest in the eighth decade of life (Zhang 1993). Limited data suggest that the annual incidence is significantly higher in men than women (Zhang 1993).

1.3.3 Mortality

It used to be that PD patients were three times more likely to die compared to their peers (Hoehn 1967). This occurred prior to the introduction of levodopa therapy. However, several studies from around the world indicate that mortality is still at least doubled in PD despite drug treatment (Bennet 1996). People aged over 70 years who have PD are significantly more likely to die than their peers (Bennet 1996). Those whose disease has been present for more than 10 years (Morens 1996), and those with gait disturbance (Bennet 1996), may be more likely to die than their peers. However, these latter findings were not confirmed in other studies.

1.3.4 Malaysian data

There is no published data on PD from Malaysia. Generally, however, the prevalence is estimated at 160 per 100 000 population (Jusoh MR, 2000). The number of new cases attending the neurology clinic in Hospital Kuala Lumpur was 91 in 1998, and increased to 107 in 1999. It is estimated that 3% of all new cases is made up of PD patients. These figures are likely to increase in the future as people understand more about this disease.

1.4 Aetiology

The cause of PD is unclear in the majority of cases. However, various studies have suggested possible causes such as:

1.4.1 Genetics

Researchers have found that a mutation in alpha-synuclein gene in a few Greek and Italian families that appear to cause a dominantly transmitted form of PD (Golbe *et.al* 1990; Polymeropoulis *et al.* 1997). Another gene, Parkin, may be the causal factor in some young onset (< 40 years) and juvenile onset (< 20 years) parkinsonian patients, and may also play a role causing susceptibility in individuals of typical age (50's) or later age of onset of symptoms (Kitada *et al.* 1998; Jarman 1999). It is likely that the onset of symptoms of PD in individuals younger than the age of 50 years is related to a combination of genetic and toxic factors.

1.4.2 Environmental toxins

In the 1980's, a number of drug addicts developed symptoms similar to those of PD after injecting a synthetic narcotic known as 1-methyl-4phenyl 1,2,3,6 tetrahydropyridine (MPTP). MPTP is a toxin than can destroy dopamine neurons in the substantia nigra.

1.4.3 Welder's exposure

Some preliminary data exist that suggest that individuals who experience exposure to manganese in the fumes from welding rods may be at higher risk than the general

population to develop PD. It appears that this exposure leads to a younger age of onset of symptoms (approximately 46 years old) than the general population (Racette *et al.* 2005).

1.5 Diagnosis

1.5.1 Diagnostic criteria

A number of diagnostic criteria for PD have been formulated which usually require the presence of cardinal signs (rigidity, bradykinesia, tremor) in association with exclusionary and supportive features (Gelb *et al.* 1999). There is no ideal criteria yet established because of the clinical variability in pathologically confirmed PD (Hughes *et al.* 1993). Levodopa responsiveness and dyskinesia are supportive features for PD in most criteria, yet 2% of autopsy-proven cases show a poor or absent response to levodopa (Hughes *et al. 1993*). Conversely, a positive response is not specific to PD. Patients with progressive supranuclear palsy and multiple system atrophy (MSA) may show an initial response to levodopa.

At present, neuropathological brain examination in conjunction with clinical history is the 'gold standard' for diagnosis of PD. The United Kingdom (UK) Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria are now the most widely accepted criteria for the diagnosis of PD (Litvan *et al.* 2003). Bradykinesia is required, plus the presence of rigidity, rest tremor or postural instability. Three or more supportive criteria and absence of a list of 16 exclusion criteria are required (Appendix A).

1.5.2 Neuroimaging and neurophysiologic studies

The differentiation of PD from other causes of parkinsonism is largely based on careful clinical observation and examination. In some instances, however, neuroimaging or neurophysiologic studies may enhance the certainty of the clinical diagnosis. Neuroimaging studies are almost never of significant benefit in confirming a diagnosis of PD. Neither the magnetic resonance imaging (MRI) of the head nor computed tomography (CT) of the head, reveal any consistent findings. Subtle abnormalities are sometimes found in the region of the substantia nigra in MRI of the brain in late stage of PD (Stern *et al.* 1989) but they are not sufficiently common or definitive to be of great practical benefit in everyday practice. Similarly, neurophysiologic tests such as electroencephalogram (EEG), evoked potentials, and blink reflex studies, while revealing subtle abnormalities, are seldom useful in establishing a diagnosis of PD. Neuroimaging is occasionally useful in evaluation of patients with other forms of degenerative parkinsonism. The primary rationale behind obtaining a neuroimaging study in a patient with parkinsonism is not to confirm the diagnosis of PD, but to determine if a multisystem degenerative or vascular form of parkinsonism is present (Anouti and Koller 1996).

1.6 Clinical Features

As described earlier, the diagnosis of PD remains entirely clinical. There are no discrete biological markers available to confirm diagnosis. Some investigations are useful in recognizing other causes of parkinsonism. To establish a diagnosis of PD (or other parkinsonian syndromes), a two-step process is required. Firstly, one needs to confirm the presence of true parkinsonism by clinical examination. Secondly, whether it is PD or other parkinsonian syndromes, will depend on the presence of other clinical features, progression of the disease and response to treatment. This requires regular clinical review of the patient.

The four cardinal features of PD are described below.

1.6.1 Bradykinesia

A generalized slowness of movement is arguably the defining feature of PD and other parkinsonian disorders. This is a major cause of disability in PD. Patients usually notice a delay in the initiation of voluntary movement, with difficulty multitasking or executing sequential actions. Family members will first notice a decrease of spontaneous associated movements, such as loss of gestures during conversation, decreased eye blinking or facial masking. The voice may become softer (hypophonia), with the patient frequently needing to repeat sentences. Bradykinesia of the pharyngeal musculature leads to pooling of saliva in the mouth and drooling, even though normal amount of saliva produced.

Assessment of bradykinesia in elderly can be a challenge. Slowing of motor performance is common with advancing age (van Hilten *et al.* 1995). However, age-related slowing is usually symmetrical and does not show the marked fatigability that defines true bradykinesia. Other diseases of peripheral and central nervous systems as well as focal pathology such as arthritis may also simulate bradykinesia. Therefore, meticulous clinical assessment remains the principal tool in distinguishing imitators from PD.

1.6.2 Rigidity

Rigidity is a hypertonic state and is defined as an increase in resistance to passive movements around a joint. The 'cogwheel' rigidity particularly occurs in PD, and is thought to be tremor superimposed on rigidity. 'Lead pipe' rigidity, which can also occur in PD, is smooth throughout the entire range of motion.

Rigidity or cog wheeling may not be detectable on routine testing, but Froment's manoeuvre may be helpful in unmasking the abnormality. Rigidity may be elicited when the contralateral limb is activated e.g. drawing a circle in the air, making a fist. Asymmetrical augmentation of tone with cogwheeling is suggestive of PD. PD can also affect axial musculature and contributes to the postural deformities seen in PD.

A mild increase in tone may occur in healthy elderly persons, so caution in interpretation is necessary in some cases.