Levodopa Induced Motor Complications in Thai Parkinson's Disease Patients

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Background: *Long-term levodopa usage in Parkinson's disease (PD) patients is known to cause several motor complications. It may be related to several factors such as levodopa dosage, duration of treatment and severity of disease.*
Objective: *To study the prevalence of levodopa motor complications and associated factors in Thai Parkinson's disease patients.*
Material and Method: *The authors prospectively collected baseline characteristics of PD patients, details of treatment and complications from 3 hospitals in various parts of Thailand. These patients were diagnosed by UK PD Brain Bank criteria.*
Results: *A total of 154 patients aged 68.1 9.5 years were recruited. Age of onset was 61.2 9.8 years. Most patients were in Hoehn-Yahr stage 1-3. The common clinical features were bradykinesia, rigidity and resting tremor. Treatments were levodopa (98.1 per cent), anticholinergic (29.9 per cent), dopamine agonists (26 per cent) and COMT inhibitor (9.1 per cent). Eighty-five per cent of the patients had excellent response to levodopa. However, 25 per cent of patients developed motor complications, which were wearing off (79 per cent), on-off fluctuation (45 per cent), freezing (42 per cent), morning dyskinesia (10.5 per cent) and permanent dyskinesia (23.7 per cent). Twelve patients developed severe levodopa induced chorea. Factors associated with levodopa side effects were earlier age of onset, long duration of disease, advanced stage, higher levodopa dosage and long duration of levodopa treatment. In the present study, age of onset was inversely correlated with H-Y stage, while dosage of levodopa was positively correlated with H-Y stage but inversely correlated with lower ADL score, which may be due to advanced disease state.*
Conclusion: *Levodopa motor complications are common in Thai PD patients. Wearing off, on-off fluctuation and freezing are common forms of motor complications.*

Keywords: *Levodopa, Parkinson's disease, Thailand, Motor complications*

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases worldwide. Dopaminergic neuronal death in substantia nigra is subsequently found to be the main pathologic process leading to motor disability[1]. Levodopa was the first and is still a highly effective drug for symptomatic treatment of PD. The treatment is associated with improvement in the ability to perform activities of daily living, to maintain employability and in quality of life. Furthermore, administration of levodopa is associated with a decrease in mortality compared to the pre-levodopa era[2]. However, chronic use of levodopa is associated with certain limitations including development of motor and neuropsychiatric complications in the majority of patients. The most common motor complications are drug-induced dyskinesias and response fluctuations. These problems can seriously compromise function and limit the patient's ability to benefit

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fully from the drug. The incidence of motor complication is quite varied, ranging from 30-50 per cent of patients after approximately 2 years of therapy[3,4]. Nevertheless, most data was reported from Western populations. Therefore, the present study was designed to evaluate the characteristics and clinical progression of Thai PD patients and to determine the prevalence of levodopa-induced motor complications and associated factors.

Material and Method

Setting and subjects

The present study was a two-year multicenter study, including 3 hospitals in Thailand (Ramathibodi Hospital, Bangkok, Srinagarind Hospital, Khon Kaen and Thammasat University Hospital, Pathumtani). It was part of the study funded by the Thailand Research Fund on susceptibility of idiopathic Parkinson's disease in association with mitochondrial complex I nuclear genotypes. The protocol was approved by the ethical committee from all participating hospitals. All patients were informed and consented.

PD patients of both sexes from each hospital, were diagnosed as idiopathic Parkinson's disease according to UK Parkinson's disease Brain Bank Criteria[5]. Patients with secondary Parkinsonism, young-onset PD patients and levodopa non-responders were excluded.

Statistical analysis

Statistical analyses were using SPSS version 9.0 (SPSS, Inc, Chicago). Results were expressed as the mean and standard deviation (SD). The prevalence of medication use, motor complications was expressed as percent. The correlations between age, age of onset, duration of disease, Hoehn-Yahr (H-Y) stage and Schwab and England activity of daily living (ADL) were determined using Pearson's correlation coefficient. Comparisons of risk factors between patients with and without levodopa side effects were performed using the unpaired *t*-test. Statistical significance was defined as a p value < 0.05.

Results

A total of 154 PD patients were recruited in the present study. Their demographic information is shown in Table 1. The majority was male (56.5 per cent) with an average age of onset at 61.2 years old and duration of disease of 9.6 years. The ethnic origins were Thai and Chinese or mixed race. Few of them were smokers or had a family history of PD. The key features of PD which were bradykinesia, rigidity and resting tremor were present in almost all patients. Postural instability was present in only one fifth of the patients. Some unique features such as unilateral onset, persistent asymmetry of tremor or rigidity and excellent response to levodopa were also present in most patients. Most patients were still ambulatory and physically independent with H-Y stage between 0-3 and high Schwab England activities of daily livings score.

Treatments were levodopa (98.1 per cent), anticholinergic (29.9 per cent), dopamine agonists (26 per cent) and catechol-o-methyl transferase (COMT) inhibitor (9.1 per cent) (Table 2). Eighty-five per cent of the patients had excellent response to levodopa. However, 38 patients (25 per cent) developed motor complications, which were wearing off (79 per cent), on-off fluctuation (45 per cent), freezing (42 per cent), morning dyskinesia (10.5 per cent) and permanent dyskinesia (23.7 per cent). Factors associated with levodopa-induced motor complications are earlier age of onset, long duration of disease, advanced disease state, higher levodopa dosage and long duration of levodopa treatment (Table 3). Twelve patients developed severe levodopa induced chorea, which correlated with later H-Y stage, low ADL score, long duration and high dose of levodopa usage, $p < 0.05$. The correlation between age of onset is inversely correlated with H-Y stage, $p < 0.05$. The dosage of levodopa are positively correlated with H-Y stage and inversely correlated with lower ADL score, which may be due to advanced disease state (Table 4).

Discussion

PD clinical features in the present study are quite similar to those in a previous report in a Thai population by Nidhinandana S, et al[6] and in Western reports. Male patients were slightly predominating in the PD population. The average age of patients was 68.1 years and age of onset was 61.2 years old. Most Thai patients were in H-Y stage 1-3 and had gradual progression to next stage after several years of illness. The average Schwab and England ADL score was 80.4 which indicates relatively preserved activity of daily living. In comparison, a report from China showed a much higher age of onset (68 years old) and higher H-Y staging (average stage: 2.81)[7]. The key clinical features, which are bradykinesia, rigidity and resting tremor were present in almost all the patients. From the presented data, the other common supportive features for diagnosis of PD are unilateral onset, persistent asymmetry affecting side of onset most, progressive

Table 1. Patient demographic data (n = 154)

Demographic data	Numbers	%
Male n (%)	87	56.5
Female n (%)	67	43.5
Age (years)	68.1±9.5 (range 48.4-91 years)	
Age of onset (years)	61.2±9.8 (range 40-82 years)	
Duration of disease (years)	6.9±5 (range 1-25.5 years)	
Ethnics		
- Thai	93	60.4
- Chinese	33	21.4
- Mixed Thai and Chinese	28	18.2
Family history of PD	10	6.5
Smoking	34	22.1
Clinical features		
- Bradykinesia	152	98.7
- Rigidity	149	96.8
- Rest tremor	142	92.2
- Postural instability	32	20.8
- Unilateral	148	96.1
- Progressive disorder	100	64.7
- Rest tremor present	135	87.7
- Persistent asymmetry affecting side of onset most	86	55.8
Levodopa responses		
- Excellent response to levodopa	131	85.1
- Severe levodopa-induced chorea	12	7.8
- Levodopa response ≥ 5 years	33/154	21.4
- Levodopa response ≥ 5 years (esp duration of disease > 5 years)	33/80	41.3
- Clinical course of 10 years or more	21	13.6
Hoehn-Yahr Stage	2.0±0.9 (range 0-5)	
0	4	2.6
1	29	18.8
1.5	28	18.2
2	47	30.5
2.5	10	6.5
3	28	18.2
4	7	4.5
5	1	0.6
ADL (Schwab and England score)	80.4±17.2 (range 20-100)	

course and excellent response to levodopa. Postural instability and severe levodopa induced chorea are uncommon in the presented population. This could be due to a relatively short duration of illness with less severity.

Virtually all patients were on levodopa and half of them received adjunctive medications. The common adjunctive medications are dopamine agonists and anticholinergic drug. Levodopa induced motor complications were present in 25 per cent of the patients after an average disease duration of 6.9 years. From Sinemet CR First study, 20 per cent of patients developed motor complications after 5-years follow up[8], whereas in the DATATOP study more than 50 per cent had motor complications after less than 2 years of levodopa treatment[9]. The present incidence is somewhat lower than

Table 2. Medication use and dosage

Medication	Number (%)	Dose (mg)
1. Levodopa + benserazide (Madopar)	117 (76.0)	365.0±239.5 (100-1500) (Levodopa dose only)
2. Levodopa + Carbidopa (Sinemet)	34 (22.1)	453.0±254.0 (100-1250) (Levodopa dose only)
3. Entacapone (Comtan)	14 (9.1)	557.1±198.9 (300-1000)
4. Trihexyphenidyl (Artane)	46 (29.9)	4.4±5.7 (1-40)
5. Bromocryptine (Parlodel)	28 (18.2)	6.7±7.1 (1-40)
6. Pergolide (Celance)	8 (5.2)	0.44±0.33 (0.1-1.0)
7. Selegiline (Jumex)	7 (4.5)	5.7±1.9 (5-10)
8. Piribedil (Trivastal)	4 (2.6)	125.0±50.0 (50-150)

Table 3. Factors associated with levodopa side effect

Factors	Yes	No	p value
1. Age (yr)	66.8±9.8	68.5±9.4	0.354
2. Age of onset (yr)	55.8±10.5	63.1±8.9	0.000
3. Duration of disease (yr)	11.0±4.9	5.5±4.2	0.000
4. Hoehn-Yahr stage	2.9±0.7	1.7±0.7	0.000
5. ADL score	65.3±20.4	85.5±12.6	0.000
6. Levodopa dosage (mg)	658.5±283.9	307.8±283.9	0.000
7. Duration of levodopa (month)	95.5±52.4	29.4±24.7	0.000

There were 38 patients who had levodopa motor complications

Table 4. Levodopa dosage and Schwab and England ADL score, according to H-Y stage

Hoehn-Yahr stage	Levodopa dose (mg)	ADL-Score (%)
0	287.5±154.8	93.3±5.8
1	256.7±140.9	95.5±5.1
1.5	303.7±181.8	87.1±6.6
2	342.1±161.7	84.3±8.3
2.5	462.5±358.5	72.0±10.3
3	641.9±295.1	68.2±11.2
4	635.7±295.4	28.6±6.9
5	550*	30*

* only 1 patient in stage 5

previously reported numbers which might be explained by lower levodopa dosage in the Thai population. The important risk factors for levodopa-induced motor complications are higher age of onset, long duration of disease, advanced H-Y stage, lower ADL score, high levodopa dose and long duration of levodopa treatment.

Obeso JA, et al also opined that there are 3 important factors which could predict future development of levodopa-related adverse events. They are daily levodopa dosage higher than 600 mg, more disease severity and age of onset below 50 years old[10]. Recently, the data from dose-ranging, double blinded, placebo controlled study confirmed direct dose-response relationship of levodopa, i.e. higher levodopa dosage will provide more symptomatic relief, but it is compromised by a higher risk to develop motor complications[11]. The dosage of levodopa in the present study is positively correlated with H-Y stage and inversely correlated with lower ADL score, which may be due to advanced disease state. If the patient's disease state

advances beyond stage 2, it has remarkable impact on ADL. Therefore, postural instability plays a significant role in the quality of life in these patients.

The most common type of motor complications is wearing off, followed by on-off fluctuation, freezing, and dyskinesia. This is well recognized and correlated with disease duration and levodopa usage. However, the management of these complications in the presented patients is quite different from the international treatment guidelines[12]. For example, anticholinergic drug, which has many serious side effects in elderly and limited anti-Parkinsonian efficacy, are still used in 30 per cent of patients. Dopamine agonist dosages are quite low compared to recommended dosages and compared to previous studies in Thai patients[13,14]. Although it is specifically approved for wearing off management[15], entacapone usage is still limited despite a high proportion of wearing off patients. These differences may be due to several factors, such as reimbursement policy of each drug, availability in each hospital and local physician practice.

Regarding patients who developed severe levodopa induced chorea, they were in the more advanced stage of disease, had received longer duration and more levodopa dosage. This had compromised their activities of daily living and poor quality of life. The management of this problem is very complicated and not very successful. Interestingly, the correlation between age of onset is inversely correlated with H-Y stage. It indicates better prognosis in older onset patients who might have a slower progression of disease and are less likely to develop motor complications. However, older onset patients may have a higher risk of developing dementia, depression and psychosis[16].

It is well known that the natural history of PD in each individual is quite heterogeneous and there are attempts to classify subtypes of idiopathic PD[17]. Generally, tremor-dominant type of PD has better outcome than akinetic-rigid type of PD. If dementia is present, it is also significantly correlated with coexistent neuritic Alzheimer's pathology[18]. In the present study the authors did not separate the subtype of PD or look into other non-motor complications. The autonomic nervous system manifestations and dementia are also common in Thai PD patients as shown in previous reports by Nidhinandanas S, et al[6] and Poungvarin N, et al[19].

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References

1. Ebadi M, Pfeiffer RF. Parkinson's disease. Boca Raton, Florida: CRC Press; 2004.
2. Koller WC, Tse W. Unmet medical needs in Parkinson's disease. Neurology 2004; 62(Suppl 1): S1-8.
3. Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson's disease. JAMA 2000; 284: 1931-8.
4. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 1997; 42: 747-55.
5. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181-4.
6. Nidhinandana S, Suwantamee J, Chinvarun Y, Udommongkol C, Sirichana S. Natural history of Parkinson's disease in Thai patients. Neurology J Thai 2003; 3: 28-32.
7. Huang JB, Zhang ZX, Wu JX. Clinical characteristics of Parkinson's disease in natural population. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2001; 23: 19-22.
8. Block G, Liss C, Reines S, Irr J, Nibbelink D. Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. A multicenter 5-year study. The CR First Study Group. Eur Neurol 1997; 37: 23-7.
9. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. Ann Neurol 1996; 39: 37-45.
10. Obeso JA, Rodriguez-Oroz MC, Chana P, Lera G, Rodriguez M, Olanow CW. The evolution and origin of motor complications in Parkinson's disease. Neurology 2000; 55(Suppl 4): S13-20.
11. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351: 2498-508.
12. Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Mov Disord 2005; 20: 523-39.
13. Poungvarin N, Prayoonwiwat N, Devahastin V, Viriyavejakul A. An open label trial of Pergolide in Thai patients with Parkinson's disease. J Med Assoc Thai 1996; 79: 205-9.

14. Suwantamee J, Nidhinandana S, Srisuwananukorn S, Laptikultham S, Pisarnpong A, Chankrachang S, et al. Efficacy and safety of Piribedil in early combination with L-dopa in the treatment of Parkinson's disease: a 6-month open study. J Med Assoc Thai 2004; 87: 1293-300.
15. Schrag A. Entacapone in the treatment of Parkinson's disease. Lancet Neurol 2005; 4: 366-70.
16. Giladi N, Treves TA, Paleacu D, Shabtai H, Orlov Y, Kandinov B, et al. Risk factors for dementia, depression and psychosis in long-standing Parkinson's disease. J Neural Transm 2000; 107: 59-71.
17. Foltynie T, Brayne C, Barker RA. The heterogeneity of idiopathic Parkinson's disease. J Neurol 2002; 249: 138-45.
18. Jellinger KA, Seppi K, Wenning GK, Poewe W. Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. J Neural Transm 2002; 109: 329-39.
19. Poungvarin N, Prayoonwiwat N, Devahastin V, Viriyavejakul A. Dementia in Thai patients with Parkinson's disease: analysis of 132 patients. J Med Assoc Thai 1996; 79: 278-84.

ภาวะแทรกซ้อนทางการเคลื่อนไหวที่เกิดจากยาลีโวโดปา ในผู้ป่วยไทยที่เป็นโรคพาร์กินสัน

ก้องเกียรติ กูณฑ์กันทรากร, สมศักดิ์ เทียมเก่า, ฉัตรเลิศ พงษ์ไชยกุล, ธีรธร พูลเกษ

***ความรู้พื้นฐาน**: การใช้ยาลีโวโดปาระยะยาวในผู้ป่วยพาร์กินสันก่อให้เกิดภาวะแทรกซ้อนทางการเคลื่อนไหวหลายชนิด ซึ่งเกี่ยวข้องกับปัจจัยต่าง ๆ เช่น ขนาดของยาลีโวโดปา ระยะเวลาและความรุนแรงของโรค*

***วัตถุประสงค์**: เพื่อศึกษาอุบัติการณ์ของภาวะแทรกซ้อนทางการเคลื่อนไหวที่เกิดจากยาลีโวโดปาและปัจจัยที่เกี่ยวข้อง*

***วัสดุและวิธีการ**: ผู้วิจัยได้เก็บข้อมูลพื้นฐานและลักษณะของโรคในผู้ป่วยไทย รายละเอียดของการรักษาตลอดจนภาวะแทรกซ้อน โดยศึกษาใน 3 โรงพยาบาลในประเทศไทย ผู้ป่วยเหล่านี้ได้รับการวินิจฉัยโรคพาร์กินสันโดยใช้เกณฑ์มาตรฐาน*

***ผลการศึกษา**: มีผู้ป่วยจำนวน 154 รายในการศึกษานี้ โดยมีอายุเฉลี่ย 68.1 $\pm$ 9.5 ปี และเริ่มเป็นโรคอายุ 61.2 $\pm$ 9.8 ปี ผู้ป่วย ส่วนใหญ่มีความรุนแรงของโรคในระยะที่ 1 ถึง 3 ลักษณะทางคลินิกที่พบบ่อยได้แก่ การเคลื่อนไหวช้า แข็งเกร็ง และอาการสั่นขณะอยู่นิ่ง การรักษาที่ใช้ได้แก่ ยาลีโวโดปา ยาต้านโฆลีน ยาเสริมโดปามีน และยายับยั้งเอนไซม์ซีโอเอ็มที ผู้ป่วยร้อยละ 85 ตอบสนองดีมากต่อลีโวโดปา อย่างไรก็ตามผู้ป่วยร้อยละ 25 เกิดภาวะแทรกซ้อนทางการเคลื่อนไหว เช่น ยาหมดฤทธิ์ก่อนกำหนด มีการเคลื่อนไหวที่ไม่สม่ำเสมอ แข็งเกร็ง และการเคลื่อนไหวที่ควบคุมไม่ได้ ผู้ป่วย 12 ราย มีอาการเคลื่อนไหวอย่างรวดเร็วที่เกิดจากยาลีโวโดปา ปัจจัยเสี่ยงต่อผลข้างเคียงจากยาลีโวโดปาได้แก่ เริ่มเป็นโรคตั้งแต่อายุน้อย เป็นโรคมานาน มีความรุนแรงของโรคสูง ใช้ยาลีโวโดปาในขนาดที่สูงและเป็นเวลานาน อายุ ที่เริ่มเป็นโรคแปรผกผันกับความรุนแรงของโรค ขนาดของยาลีโวโดปาที่ใช้จะแปรผันตามระยะความรุนแรงของโรค และแปรผกผันกับคะแนนของกิจกรรมในการดำรงชีวิต ซึ่งเกี่ยวข้องกับโรคที่เป็นมากขึ้น*

***สรุป**: ภาวะแทรกซ้อนทางการเคลื่อนไหวจากยาลีโวโดปาพบได้บ่อยในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและชนิดที่พบบ่อยได้แก่ ยาหมดฤทธิ์ก่อนกำหนด มีการเคลื่อนไหวที่ไม่สม่ำเสมอ แข็งเกร็ง และการเคลื่อนไหวที่ควบคุมไม่ได้ตามลำดับ*