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Non-motor symptoms in Thai Parkinson's disease patients: Prevalence, manifestation and health related quality of life

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Abstract

Background & Objective: Non-Motor Symptoms (NMS) are common in Parkinson's disease (PD). While prevalence of each NMS in Thai PD patients is unknown, these NMS might have an impact on patients' wellbeing. The aim of this study is to identify the prevalence, pattern and impact of NMS on the quality of life in Thai PD patients. *Methods:* A cross-sectional study in 115 PD patients was conducted at Thammasat University hospital. Subtype of PD, Schwab & England activity of daily living (ADL scale), Unified Parkinson's Disease Rating Scale (UPDRS) motor score and the modified Hoehn & Yahr (H&Y scale) were recorded. NMS and quality of life were assessed using Thammasat University Non-Motor Symptoms Questionnaire (TU-NMSQuest) and Parkinson's Disease Questionnaire-8 (PDQ-8). *Results:* All patients reported at least one NMS. A mean number of 15.94 ± 6.48 NMS was reported by each patient. Nocturia (79.1%), urinary urgency (73%), and fatigue (71.3%) were the most prevalent NMS. Significant correlations were observed between TU-NMSQuest and UPDRS motor score, H&Y scale, ADL scale, subtype of PD, and PDQ-8.
Conclusion: NMS are common and have a significant impact on the quality of life in PD patients. Advanced disease stage, poorer motor or ADL function, and non-tremor dominant subtype are associated with a higher number of NMS and lower quality of life in Thai PD patients.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects about 1-2% of elderly population with the age over 60 years old.[1] The prevalence of PD is expected to increase significantly with ageing of the population. Recent study in Thailand showed the prevalence of 0.24%[2], which means approximately 170 thousand Thai citizens now live with PD.

PD has a highly clinical heterogeneity and various clinical symptoms. The most recognized symptoms, known as "motor symptoms" are; resting tremor, bradykinesia, rigidity and postural instability. There are more symptoms of PD that both physicians and patients are often under-recognized in clinical practice. These symptoms are called as "non-motor symptoms", including various types of autonomic symptoms, cognitive impairment, neuropsychiatric symptoms, pain and sleep disorders.[3,4] Non-Motor Symptoms (NMS) are usually left untreated and most PD patients continue to suffer from these symptoms. As the average age and life expectancy of the population increases, the NMS of PD patients become increasingly important. The aim of this study is to identify the prevalence of Non-Motor Symptoms and the impact on the quality of life in Thai PD patients.

METHODS

A cross-sectional study was conducted between June to December 2013 at the outpatient neurology department of Thammasat University Hospital. The study was approved by the Institutional Review Broad and the Ethics Committee. Patients included in the study were diagnosed with PD by neurologists with expertise in movement disorders according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria (UKPDSBB).[5] General demographic data of each patient including sex, age, age of onset, family history, educational level, medication history, levodopa-related motor complications, and Schwab & England activity of daily living scale (ADL) were recorded. Subtype of PD were classified tremor dominant (TD) and non-tremor dominant (NTD), according to the method

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used by Jankovic *et al.*[6] Motor symptoms were assessed using Unified Parkinson's Disease Rating Scale (UPDRS) motor score and modified Hoehn & Yahr (H&Y) stage. To assess NMS, Thammasat University Non-Motor Symptoms Questionnaire (TU-NMSQuest) was applied. Cognitive functions were assessed using Thai-Mental State Examination (TMSE) and Montreal Cognitive Assessment (MoCA). Thai-Geriatric Depression Scale-15 (TGDS-15) with the cut-off point of 4/5 (87% accuracy, 88% sensitivity, 85% specificity) was used to screen and identify degree of depression in PD patients.[7] Health related quality of life was assessed by Parkinson's Disease Questionnaires-8 (PDQ-8).

Thammasat University Non-Motor Symptoms Questionnaire (TU-NMSQuest)

The TU-NMSQuest consists of 40 questions completed by the patient (unless a patient required assistance marking responses) featuring response as "yes" and "no" to each item in Thai language. The 40 questions were derived, translated and modified from the 30-item Non-Motor Symptoms Questionnaire (NMSQuest), the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP) and other reported NMS from published literatures. An additional 10 questions to the standard 30-item NMSQuest were included in this study. These questions included; 4 questions aimed to identify other NMS such as fatigue[8], multitasking deficits[9], seborrheic dermatitis[10] and sense of presence.[11] Another 6 questions were used for screening of common impulse control disorders (ICD) in PD patients. The questionnaires and their related NMS are demonstrated in Figure 1. The TU-NMSQuest was designed for rapid screening of NMS during the past month and the questions were grouped to 10 relevant domains. All positive responses on the TU-NMSQuest were summarized for each patient in the TU-NMSQuest score.

Statistical methods

Statistical analyses were conducted using the SPSS version 13. The percentages of positive answers for each question were calculated as well as the reported prevalence of each symptom. The Crohnbach's alpha model was used to test internal consistency reliability of the TU-NMSQuest. Statistical analysis methods used included; unpaired t-test, analysis of variance, correlation coefficient and linear regression analysis where appropriate. Predictors of health related quality of life were sought through multiple linear regression analysis. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

The TU-NMSQuest in this study was completed by 115 PD patients with a mean age ± standard deviation of 68.77 ± 11.59, (range: 39-90) and disease duration of 4.64 ± 3.85 years. Among 115 patients, 60 (52.2%) patients were males and 55(47.8%) were females, 12 (10.4%) patients had early-onset PD (onset age <50 years) and 42 patients (36.5%) were considered as having tremor dominant subtype (TD). The mean Modified H&Y stage was 2.36 ± 0.88 and the mean Levodopa Equivalent Dose (LED) was 503.38 ± 421.99 milligrams. Of the 115 patients studied 87% were treated with levodopa, 27% were treated with dopamine agonists (DA) and only 4.3% were treated with anticholinergic medications. Motor complications were assessed by clinical interviewing during the examination and were found in 40% of the patients with predominant motor fluctuation, 36.5% and dyskinesia, 18.3%. Further demographic and clinical characteristics of the study participants are shown in Table 1. Crohnbach's alpha model was used to test the internal consistency reliability of the TU-NMSQuest. The result showed an alpha score of 0.835, which is considered to be good internal consistency.

Parkinson's Disease Dementia (PDD), assessed by TMSE < 24 was presented in 27.7% of the patients while PD-mild cognitive impairment (PD-MCI); assessed by TMSE ⩾ 24 and MoCA < 25, was present in 56.4% of the total patients. There were statistical significant correlations between MoCA score and TMSE (r=0.799, p <0.001) as well as years of education (r=0.605, p <0.001). The study also found 61 patients (53%) screened positive for depression (GDS-15⩾ 5). Among these patients, 9.6% were considered as having major depressive disorder (GDS-15 ⩾10).

All patients reported at least one item of NMS on TU-NMSQuest. A mean number of 15.94 ± 6.48 NMS were reported per patient. The most prevalent NMS's in the total study population were nocturia (79.1%), followed by urinary urgency (73%), fatigue (71.3%), insomnia (70.4%) and pain (69.6%). (Figure 1) The prevalence of ICD and related behavior symptoms were found in 27.8% and the frequency of each symptom was as follows; compulsive gambling (7%), compulsive buying (7.8%), compulsive sexual behavior

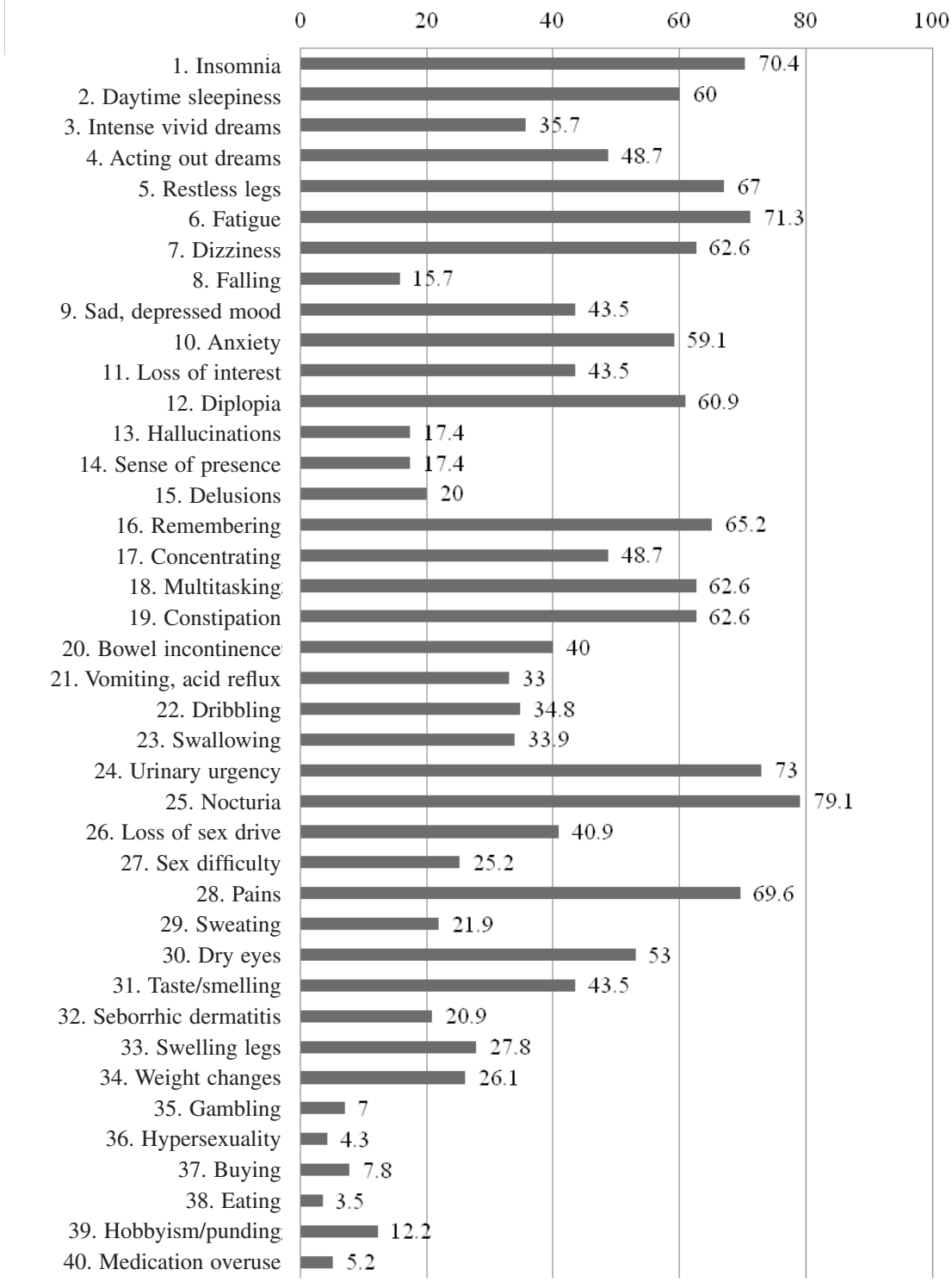

Figure 1. Aspects of non-motor symptoms in PD and percentage for each item of Thammasat university non-motor symptoms questionnaire (TU-NMSQuest)

Table1: Demographic and clinical characteristics of the study participants (n = 115)

	Mean ± SD	Range	Percent
Age (years)	68.77 ± 11.59	39-90	
Sex, % men			52.2%
Disease duration (years)	4.64 ± 3.85	0-20	
Newly diagnosed cases, %			8.7%
Age at onset (years)	64.14 ± 11.22	36-89	
Early onset PD, %			10.4%
Family history of PD, %			9.60%
Schwab and England ADL score	76.09 ± 16.58	30-100	
Modified Hoehn &Yahr stage	2.36 ± 0.88	1-4	
UPDRS motor score	22.71 ± 12.20	3-61	
Tremor dominant subtype, %			36.5%
Levodopa therapy, %			87.0%
Total LED (mg/day)	503.38 ± 421.99	0-2323.75	
Levodopa dose (mg/day)	424.56 ± 337.33	0-1750	
Dopamine agonist therapy, %			27.0%
Dopamine agonist-LED (mg/day)	33.22 ± 64.95	0-300	
Motor complication, %			40.0%
- Motor fluctuation, %			36.5%
- Dyskinesia, %			18.3%
- Freezing of gait, %			24.3%
Thai GDS-15 score	5.20 ± 3.38	0-15	
- 5-9 points			43.4%
- ≥ 10 points			9.6%
- Treated for depression, %			10.4%
TU-NMSQuest score	15.94 ± 6.48	3-30	
PDQ-8 score	9.95 ± 6.65	0-28	
TMSE (n = 101)	24.95 ± 4.94	6-30	
- TMSE <24, %			27.7%
MoCA (n = 101)	18.50 ± 5.20	6-27	
- MoCA <25, %			84.1%
Treated for impaired cognition, %			5.2%
Education (n = 101, years)	8.82 ± 5.57	0-20	

PD = Parkinson's disease, ADL = activities of daily living, UPDRS = unified Parkinson's disease rating scale, LED = levodopa equivalent dose, GDS = geriatric depression scale, TU-NMSQuest = Thammasat university non-motor symptoms questionnaire, PDQ = Parkinson's disease questionnaire, TMSE = Thai mental state examination, MoCA = Montreal cognitive assessment

(4.5%), compulsive eating (3.5%), punding and hobbyism (12.2%) and dopamine dysregulation syndrome (5.2%). (Figure 1) The TU-NMSQuest can be grouped into ten domains. The domains with the highest mean percentage of positive answers in the total population were urinary symptoms (76.05%), sleep and fatigue (58.85%), cognition and concentration (58.83%), mood and apathy (48.7%) and gastrointestinal symptoms (40.86%). (Figure 2)

There were significant correlations between the TU-NMSQuest score and UPDRS motor score (r=0.436, p <0.001), modified H&Y scale (r=0.487, p <0.001), Schwab & England ADL scale (r=-0.469, p <0.001), and TGDS-15(r=0.594, p <0.001). No significant correlation was observed between the TU-NMSQuest score and sex, age of onset, duration of disease, LED, MoCA score or TMSE score. Total TU-NMSQuest score significantly increased with increasing severity and progression of disease as indicated by modified H&Y scale.(Table 2) Interestingly, patients with non-tremor dominant subtype (NTD) and patients who had motor complications had significantly higher TU-NMSQuest score than patients with TD (17.25±6.53 vs. 13.67±5.79, p =0.003) and patients without motor complications (18.07±6.23 vs. 14.52±6.29, p =0.004). Multiple

Table 2: Relationship between the TU-NMSQuest score and severity of disease

PD severity	Mean TU-NMSQuest	SD	n
Mild (H&Y: 1-2)	12.67	4.986	45
Moderate (H&Y: 2.5-3)	17.49	6.215	61
Severe (H&Y: 4-5)	21.78	7.362	9

One-way ANOVA, p <0.001
H&Y = modified Hoehn &Yahr stage
TU-NMSQuest = Thammasat university non-motor symptoms questionnaire

linear regression analysis showed only TGD-15 was a statistically significant factor for the TU-NMSQuest.

In terms of health related quality of life, we found statistically significant correlations between PDQ-8 and TU-NMSQuest score (r=0.642, p <0.001), TGDS-15(r=0.569, p <0.001), Schwab & England ADL scale (r=-0.571, p <0.001), UPDRS motor score (r=0.468, p <0.001), modified H&Y scale (r=0.520, p <0.001), TMSE score (r=- 0.247, p <0.013), and MoCA score (r=-0.241, p <0.015), but not with sex, age of onset, duration of disease or LED. As expected, patients with motor complications and patients with NTD significantly had higher mean PDQ-8 score than patients without motor complications (12.17±6.59 vs. 8.46±6.32, p =0.003) and patients with TD (11.93±6.49 vs. 6.50±5.47, p <0.001). Patients who reported any of ICD also had statistically significant higher mean PDQ-8 score than the other (12.44±6.22 vs. 8.99±6.59, p =0.011). Multiple linear regression analysis showed TU-NMSQuest score, TGD-15, Schwab and England ADL score, and tremor related subtype of PD were the most significant factors for the PDQ-8. (Table 3)

DISCUSSION

This study is a comprehensive assessment of NMS in Thai PD patients using a TU-NMSQuest questionnaire to identify the prevalence and pattern of NMS and its impact on quality of life in Thai PD patients. The results suggest that NMS are common in all stages of PD and more common as the motor symptoms progression regardless of age of onset, levodopa dosage or disease duration. The most prevalent NMS in this study were highly similar to other previous international studies using the 30-item NMSQuest.[12-14] Urinary tract symptoms, insomnia and fatigue were the most prevalent NMS in Thai PD patients. Numerous other NMS such as pain, dizziness, diplopia, restless legs, constipation and difficulties with multitasking were observed more than 60% of PD patients. We observed a significant increase in

Table 3. Multiple linear regression model of the PDQ-8 scale

	Adjusted Rs	Standardized beta	t	*p*-value
PDQ-8 model	0.541	-	-	-
(Constant)	-	(10.501)	3.469	0.001
TU-NMSQuest	-	0.349	4.189	0.000
GDS-15	-	0.226	2.819	0.006
Schwab & England ADL score	-	0.177	2.201	0.030
Tremor dominant subtype	-	-0.146	-2.093	0.039

PDQ = Parkinson's disease questionnaire, TU-NMSQuest = Thammasat university non-motor symptoms questionnaire, GDS = geriatric depression scale, ADL = activities of daily living

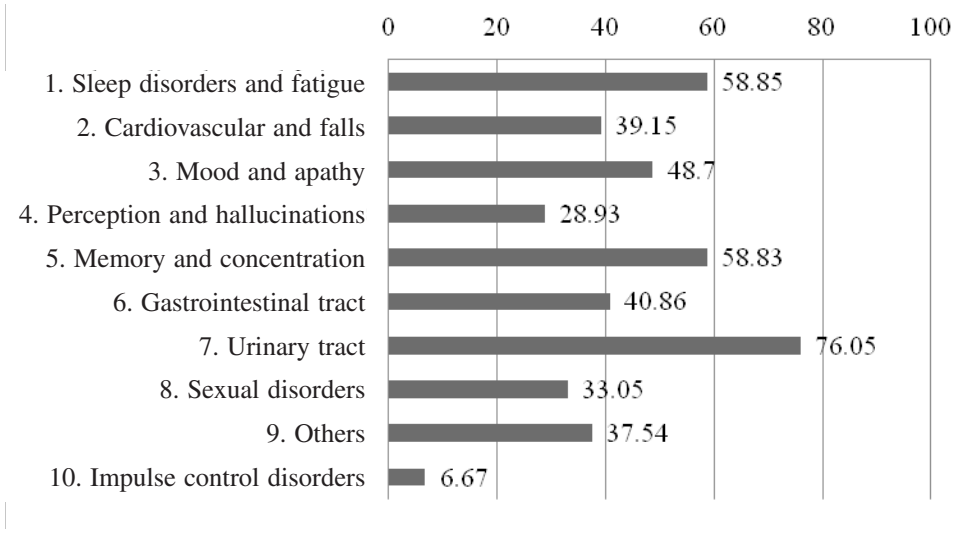

Figure 2. Percentage of patients experiencing each non-motor domain

the number of NMS with advance disease stage, poor motor function, decreased ADL function, and non-tremor dominant subtype. Furthermore, the number of NMS highly correlated with degree of depression in PD patients. This finding suggested that not only motor symptoms have impact on NMS, but psychological symptoms also have an influence on NMS.

Urinary dysfunction is the most prevalent NMS among individuals with PD in most studies.[12-14] It is a manifestation of autonomic involvement and frequently caused by detrusor over activity. The common presenting symptoms are nocturia and urinary urgency. Since many patients with PD have a disturbed sleep pattern and comorbidities, the actual prevalence of nocturia may be overestimated.[15] The mechanism of urinary dysfunction in PD is highly complex and could be influenced by abnormalities of dopaminergic neurons in both central and peripheral nervous systems. Also, urinary dysfunction may be influenced by antiparkinsonian medications.[16]

Fatigue is a very common symptom in PD patients but hard to describe and even harder to measure. The etiology of fatigue is unclear and can be caused by both mental and physical symptoms. Fatigue can worsen by motor impairment, muscle stiffness, depression, sleep disturbance and even medications. It can also be experienced throughout the day or only when medications are wearing off.[8]

Sleep disturbances are seen in more than 70% of our patients. The causes of sleep disturbance are multifactorial, but degeneration of central sleep regulation centers in the brainstem and thalamocortical pathways may play an important role. Sleep disturbances may manifest as insomnia, sleep fragmentation, excessive daytime sleepiness, REM sleep behavior disorder.[8] These sleep problems may be influenced by motor symptoms at night and antiparkinsonian medications. Furthermore, some NMS have a secondary effect on the sleep quality, such as nocturia, depression and hallucinations.

Parkinson's disease dementia (PDD) was observed in about 30% of the patients, which was consistent with the previous reports.[17] However, we observed higher prevalence of mild cognitive impairment (MCI) as indicated by MoCA score in our patients. This could possibly be explained by the lower education level of our population and the high prevalence of depression in our patients. Cognitive dysfunction in PD is characterized by impairment of executive and visuospatial functions. Subcortical Lewy bodies, imbalance of striato-cortico-frontal partway and cholinergic impairment are likely to be causative of this problem. Impairment of concentration, planning and multitasking ability are common and associated with older age at the onset and longer duration of the disease.[17] Moreover, there is a strong relationship between cognitive impairment and neuropsychiatric issues.

Depression can occur in any stage of PD, even many years before the onset of the disease. It may involve serotoninergic, noradrenergic and dopaminergic pathways. Our study indicated that depression is one of the strongest factors on quality of life in PD patients. Interestingly, depression as indicated by TGDS-15 score was

found more than 50% of the patients, but only 10% of the patients had received treatment. This finding indicated that many of NMS were often under-recognized or not declared to physicians, and usually left untreated.

Psychotic symptoms, defined as hallucinations, delusions and sense of presence occurred in about 20% of our patients which was comparable to other studies.[8,11,13,14] Risk factors for hallucinations are older age, long duration of the disease, cognitive impairment, visual disorders and higher dose of dopaminergic drugs. Visual hallucinations are often complex but benign and not distressing. Passage hallucinations (seeing someone passing by) and sense of presence (sensation of the presence of somebody) are also frequent and often short-lasting, occur at the peripheral visual field, beside or behind the patient.[11]

In this study, ICD was identified in about 28% of the patients. We did not find a statistically significant correlation between ICD and the use of DA, age, sex or duration of the disease as in previous studies.[18,19] This could be a result of a low prevalence and dosage of DA in our patients as well as a less specific of ICD screening questionnaires. However, we found that patients with ICD tended to be younger and take higher dose of DA as well as total LED. As the high prevalence of ICD in our study, we advocated for an increased awareness of ICD among Thai PD patients.

The TU-NMSQuest is a screening questionnaire that aims to identify the NMS and also ICD in Thai PD patients. Some of these symptoms such as nocturia, insomnia, and pains are not specific symptoms for PD and could be found in general elderly population. While some other symptoms such as depression, constipation, REM sleep behavior disorder and smell/taste difficulties are more common in PD than controls and often found predate to motor symptoms.[12] This is important as they may suggest the non-dopaminergic involvement in PD pathology.[20,21] This study also emphasizes the association between number of NMS and worse quality of life. In addition, NMS have greater impact on quality of life than motor symptoms, which is consistent with previous studies.[14,22]

Several study limitations should be noted. First, TU-NMSQuest is a screening questionnaire, and there is no symptoms severity weight score. Patients who reported these symptoms may not meet diagnostic criteria for an actual disorder. It is important that all patients with screening positive of each NMS undergo a detailed clinical interview to determine the actual symptoms. Second, most of the patients in the study were on dopaminergic therapy, which could affect the prevalence of NMS as the fact that dopaminergic therapy is possibly effective against some NMS. Lastly, there was no control of medication stage while patients were completing the questionnaire, which could effect on Non-Motor Fluctuations (NMFs). Patients who completed the questionnaire while being off state might reported more NMS than patients with on state. The most frequent NMFs are anxiety, excessive sweating, slowness of thinking, pain, fatigue and hallucinations[23].

In conclusion, NMS are common comorbidity in PD patients and have a significant impact on quality of life. We would recommend routine use of the TU-NMSQuest in clinics as a comprehensive screening tool for NMS in PD. Recognition and proper management of each NMS could improve not only non-motor symptoms but also quality of life of PD patients. More research is needed into NMS and the affects on the quality of life of patients with PD.

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DISCLOSURE

Conflict of interest: None

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