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Non-motor symptoms in Thai Parkinson's disease patients and the correlation with motor symptoms

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Abstract

*Background and objective:*to identify the prevalence of non-motor symptoms (NMS) and to determine the association between NMS and motor symptoms in Thai Parkinson's disease (PD) patients. *Methods:* A cross sectional study was performed in PD patients at Maharat Nakhon Ratchasima Hospital between January-June 2014. The NMS were assessed by using Non-Motor Symptoms Questionnaire-Thai version. All data were analyzedfor identifying the prevalence of NMS and determining the correlation between NMS and motor symptoms. *Results:*One hundred thirty six PD patients were enrolled. The severity of disease according to Modified Hoehn and Yahr (MHY) was 1-1.5=33.1% of the patients, 2-2.5=52.2% and 3-5=14.7%. All patients (100%) had NMS with mean number of 13.2±6.7 symptoms (ranging from 1-29). Nocturia was the commonest symptom (82.4%), followed by constipation (74.3%) and forgetfulness (69.9%). Bowel incontinence was the least frequent symptom (19.9%). Sleep disorder was the mostprevalent domain (92.6%), followed by digestive domain (91.9%) and urinary domain (89.0%). The number of NMS significantly increased with the degree of severity of disease and was higher in patients with motor complications.
*Conclusion:*NMS were reported by every Thai PD patients, and at all stage of the disease. Nocturia symptom and sleep disorder domain were the most frequent NMS. The number of NMS strongly correlated with motor complications and the severity of motor symptoms. However the presence of motor complications appears to have stronger association with some NMS domains than the motor severity.

INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative disease with high clinical heterogeneity. The clinical features of PD are combination of motor symptoms (tremor, rigidity, bradykinesia and postural instability) and non-motor symptoms (NMS) such as neuropsychiatric problems, sensory symptoms, sleep disorders and autonomic dysfunctions.[1,2] There is now increasing evidences that NMS in PD are common, occur in any stages of disease, associate with poor quality of life and mayhave equally or more significant disability than motor symptoms in some PD patients.[3-5] Although NMS are common, they are not well recognized in clinical practice. One study in US showed some NMS were not identified by neurologistsin over 50% of cases.[6] From this reason, the American Academy of Neurology in 2007 has developed the questionnaires for physicians detecting NMS in PD.[7] In Thailand, the prevalence of PD patients is 0.24% of population (about 170,000 Thai citizens)[8] whereas the prevalence of NMS is about 97-100% of PD patients.[5,9] The aim of this study was to identify the prevalence of NMS and the relationship of this condition with motor symptoms in Thai PD patients at Maharat Nakhon Ratchasima Hospital (MNRH), the tertiary care hospital in northeastern region of Thailand.

METHODS

This was a cross sectional study. The data were collected from consecutive PD patients that attended the neurological clinic, MNRH between January and June 2014. Every subject was diagnosed as PD by neurologists according to the United Kingdom Parkinson's Disease Society Brain Bank criteria.[10]

After informed consent was obtained, the baseline characters such as age, sex, duration of disease, duration of treatment, medications and dosage, presence of motor complications (MC) and disease severity were collected. The severity of disease was determined according to Modified Hoehn and Yahr (MHY) stage[11], and was categorized into 3 levels as followed: mild

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(MHY stage 1-1.5), moderate (MHY 2-2.5) and severe (MHY more than 3). The MC were ascertained from patient and caregiver interview based onhistory of dyskinesia, fluctuation of motor symptoms such as wearing-off, delayed-on, and off-dystonia, which occurred in past 3 months.

Non-Motor Symptoms Questionnaire-Thai version (NMSQ-Thai) was used to assess the NMS in the study. This test was translated from Non-Motor Symptoms Questionnaire (NMSQ), the standard test for detecting NMS in PD.[12]The test consisting of self completed 30 items questionnaires (yes or no question) used as the screening tool containing nine NMS domains designed for rapidly alerting the physicians to detect NMS that patients complained in outpatient setting. All patients (with the aid of caregiver where necessary) completed the questionnaires with explanation on the ambiguous item by the study nurse or physician. The data were analyzed for identifying the prevalence of NMS (each symptom and by domain classification). The statistical analyses were performed to determine the correlation between NMS and disease severity according to MHY stage and MC.

The study protocol was approved by MNRH Institutional Review Board in accordance with ethical standards on human experimentation and with the Helsinki Declaration.

Statistical analysis

The data were presented as mean and standard deviation for continuous variables with normal distribution (according to Kolmogorov-*Smirnov* test) and as median and interquartile ranges for non-parametric distribution. Categorical data were expressed as frequency and percentage. The data analyses were performed by using student t-test or one-way ANOVA and Mann-Whitney U test or Kruskal–Wallis test as appropriate. The significance level was set at *p*-value less than 0.05 (2-tailed test).

RESULTS

One hundred and thirty-six PD patients with 73 males (53.7%) with mean age ± standard deviation of 63.2±10.2 years were enrolled into the study. The median time of disease duration (interquartile range) and treatment duration were 52.9 (56) and 40.1 (57) months respectively. The mean dosage of levodopa was 510.1±325.3 mg/d. The mean MHY stage was 1.9±0.7 which was classified into mild (33.1% of the patients), moderate (52.2%) and severe (14.7%). MC was seen in 38 patients (27.9%).The baseline features for the other variables were summarized in Table 1.

From the total of 136 PD subjects, all patients (100%) had NMS based on the NMSQ-Thai

Table 1: Baseline features of 136 Parkinson's disease patients

Factors	N (%) or Mean±standard deviation	Median (range)
Male	73 (53.7)	
Age-year	63.2±10.2	64 (33-83)
Levodopa dose-mg/d	510.1±325.3	450 (0-1,500)
Dopamine agonist therapy	57 (41.9)	
Duration of disease-months	59.9±51.9	52.9 (1-350)
Duration of treatment-months	49.3±51.6	40.1 (1-350)
Modified Hoehn and Yahr stage		2.0 (1-4)
1-1.5	45 (33.1)	
2-2.5	71 (52.2)	
3-5	20 (14.7)	
Motor complications	38 (27.9)	
NMSQ-T Scores	13.2±6.7	11.0 (1-29)

NMSQ-T, Non-Motor Symptoms Questionnaire-Thai version

with mean number of NMS of 13.2±6.7, range 1-29. Nocturia was the commonest symptom in our study and was reported in 112 patients (82.4%). The second common reported NMS was constipation (101 patients, 74.3%) followed by forgetfulness (69.9%). Excessive daytime sleepiness, restless leg syndrome, insomnia and positional dizziness were found about 60% of the patients. Bowel incontinence was the least frequent symptom (19.9%). According to the domain of NMS, sleep disorder domain was the most prevalent found in 126 patients (92.6%), followed by digestive domain (91.9%), urinary domain (89.0%) and autonomic nervous system dysfunction domain (80.9%). The least frequent effected domain in the study was perceptual domain (41.2%). The prevalence of NMS classified by domain waslistedin Table 2.

The number of NMS significantly increased with the severity of disease according to MHY stage, 11.5±5.8 points in mild stage, 13.6±6.1 points in moderate stage and 15.9±5.9 points in severe stage (p=0.02). Moreover, the number of NMS was significantly higher in patients with MC (16.5±6.1) when compared with the patients without MC (11.9±5.6, p<0.01). The detailed results are shown in Table 3.

Table 4 documented the relationship between each NMS domain and motor symptoms. The domains that significantly associated with MC were digestive, sleep disorder, autonomic dysfunction, perceptual, mood disorder, memory problem and miscellaneous. However, only two domains (digestive and urinary) were associated with progression in MHY stage.

DISCUSSION

We found that all our PD patients had NMS symptoms. Previous studies[5,12] have shown that NMS is seen in all stages of PD, though more frequent in the later stage. This is consistent with Lewy body deposition, the hallmark neuropathological finding in PD, begin to occur years or even decades before the onset of motor symptoms. This pathology occurs in peripheral nervous system and slowly extends into the central nervous system and leads to neuronal

Table 2: The prevalence of non-motor symptoms (NMS) in 136 Parkinson's disease patients according to Non-Motor Symptoms Questionnaire-Thai version (NMSQ-T)

NMS	N (%)	NMS	N (%)
Digestive		**Sleep Disorder**	
Constipation	101 (74.3)	Daytime sleepiness	84 (61.8)
Bowel emptying	62 (45.6)	Insomnia	81 (59.6)
Dribbling	59 (43.4)	Restless leg	81 (59.6)
Swallowing	56 (41.2)	Vivid dream	62 (45.6)
Taste/smelling	49 (36.0)	Acting dream	54 (39.7)
Vomiting	28 (20.6)	**Perceptual**	
Bowel incontinence	27 (19.9)	Delusion	36 (26.5)
Urinary		Hallucination	35 (25.7)
Nocturia	112 (82.4)	**Mood**	
Urgency	72 (52.9)	Depression	66 (48.5)
Memory		Anxiety	50 (36.8)
Forgetfulness	95 (69.9)	**Sexual Function**	
Loss concentration	55 (40.4)	Loss of libido	75 (55.1)
Loss of interest	41 (30.1)	Sex difficulty	68 (50.0)
Autonomic		**Others**	
Dizzy	82 (60.3)	Pains	60 (44.1)
Sweating	61 (44.9)	Weight change	33 (24.3)
Falling	55 (40.4)	Diplopia	32 (23.5)
		Swelling	30 (22.4)

Table 3: The relationship between NMSQ-T score and motor symptoms (displayed as mean±standard deviation)

Factors	NMSQ-T score	*p*-value
Motor complications		
No (98 patients)	11.9±5.6	<0.01
Yes (38 patients)	16.5±6.2	
Modified Hoehn and Yahr stage		
1 - 1.5 (45 patients)	11.5±5.8	0.02
2 - 2.5 (71 patients)	13.6±6.1	
3 - 5 (20 patients)	15.9±5.9	

Analyses by using student t-test or one-way ANOVA test.
NMSQ-T, Non-Motor Symptoms Questionnaire-Thai version

dysfunction and degeneration in many parts of the nervous system other than substantia nigra pars compacta. As such, NMS can occur before the onset of motor symptoms (premotor symptoms), be common in every stage of disease and likely to worsen as the disease progress. This suggests that physicians should not only attend to motor symptomsin PD patients, but also give attentions to NMS in every PD subjects.

Nocturia was the most common NMS in our study, whereas bowel incontinence was the least frequent, similar to the reports from previous studies.[3-5] In our study, 47.9% of males and 58.7% of females had urinary urgency, while 83.6% of males and 81.0% of females had nocturia. These results were not different between sexes in both symptoms. Consistent with the questionnaires, urodynamic study revealed that the most common

Table 4: The frequency of non-motor symptoms domain classified by Non-Motor Symptoms Questionnaire-Thai version and the relationship with motor symptoms (n=136)

Domain	Number of items	N(%) present	N(%) with maximum no. of symptom	Median (range)	*p*-value	
					MHY	Motor complications
Digestive	7	125 (91.9)	5 (3.7)	3 (0-7)	0.02	<0.01
Urinary	2	121 (89.0)	63 (46.3)	1 (0-2)	<0.01	0.58
Sleep disorder	5	126 (92.6)	19 (14.0)	3 (0-5)	0.14	<0.01
Autonomic	3	110 (80.9)	18 (13.2)	2 (0-3)	0.8	<0.01
Sexual function	2	79 (58.1)	64 (47.1)	1 (0-2)	0.46	0.22
Perceptual	2	56 (41.2)	15 (11.1)	0 (0-2)	0.19	<0.01
Mood	2	81 (59.6)	35 (25.7)	1 (0-2)	0.13	0.03
Memory	3	107 (78.7)	25 (18.4)	1 (0-3)	0.28	0.02
Others	4	92 (67.6)	3 (2.2)	1 (0-4)	0.51	0.01

Analyses by using Man-Whitney U test or Kruskal–Wallis test.
MHY, Modified Hoehn and Yahr stage

urinary symptom in PD was nocturia (60-77%) and did not differ between male and female subjects. As the prevalence of these symptoms are higher than that seen in the healthy population of similar age, we can conclude that the urinary symptoms in PD patients was caused by abnormality of detrusor muscle from PD pathology, and not by local problem such as prostate gland hypertrophy or pelvic floor relaxation. The involvement of dopamine-basal ganglia circuit in PD subjects suppressed the micturition reflex, which led to dysfunction of detrusor muscle.[13] This was confirmed by cystometric study in PD patients, where detrusor muscle overactivity was found to be common (67%) followed by detrusor underactivity (12.2%).[14,15]

Sleep disorder was the most prevalent domain in the study. This result was consistent with the previous study from Thailand that found 96.6% among PD patients having nocturnal symptoms.[16] The causes of these symptoms include those due to the motor symptoms and medication side effect such as dyskinesia.[17] It was thus not surprising that this domain was significantly associated with MC in our patients.

In general, the identification of different NMS which fluctuate with motor symptoms is important. The adjustment of dopaminergic treatment may benefit those with fluctuation associated with MC, while specific symptomatic therapy might be initiated in non-fluctuating symptoms. In the present study, the frequency of all NMS (except sexual function and urinary symptom) was associated with the presence of MC while only urinary and digestive symptoms were associated with disease severity. This finding was explained by the strong association between the fluctuation of motor and non-motor symptoms. The NMS were more frequent and severe in "off" compared to "on" state.[18-20] Storch*et al*.[18] had reported similar result as our study that all NMS except dysphagia, excessive sweating and bladder urgency were linked with motor fluctuations. Some studies[21-22] have investigated the possible neurobiological basis for link between motor complications and dopamine–response NMS. However, the relationship were complex, with the NMS being due to neurodegenerative process in both dopaminergic and non-dopaminergic neuronsfrom peripheral to central nervous system of PD patients.

If we focus on each of the urinary symptoms, the prevalence of nocturia and bladder incontinence was associated with PD severity (p=0.01 and p=0.02 in that order) and were not associated with MC. Moreover, PD patients with urinary incontinence were older than the patients without this symptom (67.3±9.9 and 62.2±10.0 years, respectively, $p< 0.01$) but there was no difference in age between subjects with and without nocturia. Hence, there may be many factors resulting in urinary symptoms other than the PD process. Further study of the urinary abnormality on specific subgroup of symptomsis required to clarifythe relationship.

Hypothalamic dysfunction is probably responsible for the sexual dysfunction (decrease in libido and erection) in PD, via altered dopamine-oxytocin pathways which normally promote libido and erection.[23]A total of 60% of men with PD had reported erectile dysfunction, as compared with 37.5% in age-matched controls. This symptom is also common in young patients with PD (mean age 49.6 years).[24] Previous study had reported the association between sexual dysfunction in PD with male sex, earlier disease onset and adverse effect of levodopa or dopamine agonist therapy. In the present study, male patients had significantly higher frequent sexual problems than female patients, 64.4% of male subjects complained of loss of libido as compared with 44.4% of females (p=0.02, OR=2.26; 95% confidence interval=1.13-4.50), and 61.6% of males had problem with sex difficulty as compared with 36.5% of females (p<0.01, OR=2.79; 1.39-5.62). However, sexual functions were not correlated with MC. The reason is probably because this domain is influenced by many factors including culture, gender, age, underlying disease and health status, and spouse factor. Further study on sexual problems focusing onsexually active male subjects of younger age may be interesting.

There were some limitations in our study. Firstly, the NMSQ-T is a screening test for detection and awareness of NMS. The results depend on subjective complain and does not reflect the specificity and severity of NMS. Some NMS such as dementia require special test for diagnosis. The prevalence of dementia was lower in the study that was assessed by using specific test (30.5% from Thai Mini-mental State Examination and 60.9% from patients who complained about forgetfulness in our study).[25] More specific test further examination is required to determine the real prevalence and severity in each NMS. Secondly, this study did not explore the correlation between NMS and quality of life.Thus, future study should include quality of life of both the patients and their caregivers. Thirdly, MHY in the study was scored when the patients were seen in

the clinic. Thus, the exact time after last dose of levodopa administration and MHY measurement could not be controlled. For this reason, the varying degree of PD symptoms between "on" and "off" states lead to the non-motor fluctuation, this fluctuation had been reported in about 70%.[20] Future study is required to assess the role of on-off states to determine its contribution.

In conclusion, NMS were reported by every Thai PD patients, and at all stage of the disease. Nocturia symptom and sleep disorder domains were the most frequent NMS. The number of NMS strongly correlated with MC and the severity of motor symptoms. However the presence of MC appears to have stronger association with some NMS domains than the motor severity. The assessment of NMS is an important issue and should be part of the holistic care in PD patients.

DISCLOSURE

Conflicts of interest: None

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