Non-Motor Symptoms in Thai Patients with Parkinson's Disease Studied at Phramongkutklao Hospital

Kiratikorn Vongvaivanich MD*,
Samart Nidhinandana MD*, Chesda Udommongkol MD, PhD*,
Parnsiri Chairungsaris MD*, Yotin Chinvarun MD, PhD*,
Wanna Wongmek MD*, Seema Suphakasem MD*,
Jithanorm Suwantamee MD*, Pasiri Sithinamsuwan MD*

** Division of Neurology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand*

Background: *Non-motor symptoms (NMS) of Parkinson's disease (PD) have been recently recognized to be as disabling as motor symptoms in PD. However, these symptoms are still under recognized causing delay in treatment and inadequate management. This study aimed to identify NMS in Thai PD patients using the NMS screening questionnaire (NMSQuest).*
Material and Method: *Patients with idiopathic Parkinson's disease visiting the neurology clinic in 2008 were enrolled. NMSQuest-Thai version (NMSQ-T) was applied to patients to identify NMS.*
Results: *Collected data from questionnaires completed by 165 probable idiopathic PD was analyzed. The demographic profiles showed mean age of 68.6 years with mean disease duration 5.4 years, and male 56.4%. Patients had Hoehn & Yahr staging, stage-2: 43%, stage-3: 24.8%, stage-1: 24.2% and stage-4: 7.9%. The average dosage of levodopa was 456.4 mg/d.*

Mean total NMSQ-T score was 9.5. Most prevalent of non-motor symptom was nocturia (64.2%). The domains which gained most positive answers were urinary domain (54.55%). Inter-domain correlations were significantly found in all, except the sexual domain. Multivariate analysis revealed the duration of PD and stages were significantly correlated with the total score of NMS. Only three percent denied having any non-motor symptoms.
Conclusion: *Almost all Thai PD had NMS. Urinary domain is the most prevalent in our series. Screening using NMSQ-T to recognize NMS would be a helpful tool to improve the quality of life in Thai Parkinson's disease.*

Keywords: *Non-motor symptoms, NMS, Idiopathic Parkinson's disease, Thai*

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Parkinson's disease (PD) is a common degenerative brain disease first described in 1817 by James Parkinson[1,2]. The cardinal symptoms include resting tremors, bradykinesia, rigidity and postural instability[3]. Disease symptoms can be classified into motor symptoms and non-motor symptoms. The motor symptoms have been well recognized and developed many rating scales, disease staging as well as treatment strategies[4,5]. The non-motor symptoms (NMS) complex tends to underrecognized and undertreatment leading to a major cause of disability for PD patients[6,8].

The non-motor symptoms involve a multitude of functions including neuropsychiatric symptoms, sleep-wake cycle regulation, autonomic nervous system function, gastrointestinal sexual function and sensory function[9]. NMS can occur in any stages of Parkinson's disease. Some symptoms could identify even before the development of motor signs; for example, olfactory dysfunction[10], REM sleep behavior disorder[11,12] depression[13], constipation[14]. From many studies, non-motor symptoms have been recently recognized to be the most disabling features of PD[15,16].

Although the non-motor features of PD are common, these symptoms are often not well recognized in clinical practice. It has been reported that around half of NMS of PD are not identified even by neurologists causing delay in treatment and inadequate management[17-19]. To improve the recognition of NMS in PD patients and to evaluate new and existing strategies, the NMS screening questionnaire

Correspondence to:
Sithinamsuwan P, Division of Neurology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok 10400, Thailand.
Phone: 0-2354-7600 ext. 93027, Fax: 0-2354-7637
E-mail: pasiripmk@gmail.com

(NMSQuest) was developed in 2006 by a multi-disciplinary group of experts and patient representatives[20-22]. This screening tool is a 30-item self-completed questionnaire in which each item contains nine NMS domains designed for rapidly alerting the health care professionals to a range of NMS. A pilot study using NMSQuest showed that NMS were significantly more prevalent in PD patients than in controls and the number of NMS significantly increased with advanced disease[20]. Urinary symptoms, for example, either nocturia or urgency have been reported approximately 60% in PD patients[21]. This practical questionnaire can be rated in out-patient clinic and used as an assessment tool in day to day clinical practice related to a comprehensive care for people with PD[21].

The study aimed to identify NMS in Thai Parkinson's disease patients using the NMS screening questionnaire (NMSQuest) and to find the correlation of the total score of the test to PD characteristics, including age, gender, the duration of illness, Hoehn & Yahr staging[23] and the levodopa dosage.

Material and Method

Patients

From January to December 2008, 182 consecutive patients visiting our out-patient Neurology Clinic and diagnosed as probable idiopathic Parkinson's disease by the UK. Parkinson's Disease Brain Bank criteria[24] were enrolled to the study. Exclusion criteria were secondary Parkinsonism, Parkinson's plus syndrome, severe cognitive impairment and failure to complete the questionnaire. Demographic data, age, gender, duration of disease and Hoehn & Yahr (H&Y) staging, levodopa dosage, number and detail of antiparkinsonian medications, were recorded by researching physicians.

NMS questionnaire

The original questionnaire composes of 30 items. They were grouped into nine relevant domains including gastrointestinal tract (question [q] 1-7), urinary tract (q 8,9), apathy/attention/memory (q 1,2,13,15), hallucinations/delusions (q 14,30), depression/anxiety (q 16,17), sexual function (q 18,19), cardiovascular (q 20,21), sleep/fatigue (q 22-26) and miscellaneous (q 10,11,27-29).

This self rating test was translated into Thai (NMSQ-T) as shown in Appendix 1. Thirty questions of NMSQ-T were then used to identify NMS in Thai Parkinson's patients. NMSQ-T was completed by patients with or without assistance from caregivers. Average time to complete the questionnaire was approximately 5-7 minutes.

Statistical analysis

SPSS version 15.0 was used to analyze the result. Prevalence of each NMS was calculated on the total sample by computing the number of positive responses and transformation to percentage. To obtain a standardized ranking of prevalence for each domain, the sum of item positive responses was transformed to percentage on the maximum possible number of positive responses in the domain. These included the descriptive statistics of the sample and computation of responses. For each item, there was a comparison between the proportion of "yes" and "no" responses. Although there was not designed as a quantitative scale, a total score for the questionnaire was calculated by summing all the positive ("yes") responses for every subject included in the present study. Person's correlation was analyzed. The significance was determined by Mann-Whitney U test, being *p*-values <0.05 considered significant.

Ethical approval

Protocol and consent form were approved by the Research Ethics Committee of Phramongkutklao medical college, Bangkok, Thailand.

Results

Of 182 patients with idiopathic Parkinson Disease, 165 PD patients were eligible to participate the study and completed questionnaire. Seventeen patients were excluded according to: 5 Parkinson plus syndrome, 1 patient with drug-induced Parkinsonism, 4 cases of severe cognitive and language impairment, and 7 cases with incomplete questionnaires. The demographic profiles were mean (SD) age 68.6 (9.4) years (range 41-98), male 93 patients (56.4%) and female 72 patients (43.6%). Mean duration of PD was 5.4 years (range 1-20). For disease severity by Hoehn&Yahr stageing, the higest proportion of patients was in stage 2-71 cases (43%), while stage 3- 41 patients (24.8%), stage 1-40 patients (24.2%), and stage 4: 13 patients (7.9%). The average dosage of levodopa was 456.4 mg/d (range 0-1,600 mg/day). Demographic data and patients' characteristic were shown in Table 1.

Anti-Parkinson medications were reviewed. Seventy-four patients (45.1%) were taking mono-therapy (levodopa 33.5%, controlled release levodopa 1.8%, dopamine agonist 3.7%, combined-levodopa/

carbidopa/entacapone 4.9%, and selegiline 1.2%. Ninety patients were on polytherapy: 62 cases on 2 medications (37.8%), 26 cases on 3 medications (15.9%) and only 2 cases on more than 3 medications. Levodopa was prescribed in 132 patients (80.5%), of those, 28 patients (17.1%) were on controlled-release levodopa. The detail of disease specific medications used was illustrated in Table 1.

Mean total score Non-Motor Symptoms screening questionnaire-Thai (NMSQ-T) was 9.5 (range 0-24). The most prevalence of non-motor symptoms was nocturia (64.2%), followed by dizziness (60.6%) and forgetfulness (56.4%), whereas the least frequency was bowel incontinence (13.9%). The domains which accounted of most positive answers were urinary domains (54.55%), then cardiovascular (43.6%), and sexual function (42.7%). There were significant correlations between domains in all, except the sexual domain. Multivariate analysis revealed that the duration of PD and Hoehn & Yahr stages were significantly correlated with the total score of NMS. Only 5 patients (3%) denied having any non-motor symptoms. The frequencies of individual NMS were shown in Table 2 and 3 respectively. The ranking of NMS by domains was highlighted in Fig. 1.

Total NMSQ-T was highly correlated with age and age at PD onset (r = -0.281, p<0.009), duration of disease (r = -0.226, p = 0.004), Hoehn and Yahr stages (r = -0.784, p<0.0001) and levodopa dosage (r = -0.272, p<0.0001). In contrast, there was no association with gender (r = -0.006, p = 0.337) and the numbers of drugs (r = -0.184, p = 0.058). Multivariate analysis revealed that the duration of PD (r = -0.625, 95% CI -0.316-0.039, p = 0.012) and Hoehn & Yahr stages (r = -0.613, 95% CI 4.587-5.887, p<0.0001) were significantly correlated with the total score of NMS. The NMS correlated with

Table 1. Demographic characteristic

Variables	Total n = 165 n (%)
Male	93 (56.4%)
Age (years), mean ± SD	68.6±9.4
Disease duration (years), mean ± SD	5.39±4.2
Hoehn & Yahr stages; median (range)	2 (1-4)
Monotherapy	74 (45.1)
Polytherapy	90 (54.9)
Levodopa used	132 (80.5)
Levodopadosage (mg/d); mean ± SD	456.4±306.0
Dopamine agonist	43 (26.2)
Combined levodopa/carbidopa/entacapone	25 (15.2)
COMT-inhibitor (entacapone)	30 (18.3)
Anticholinergic	21 (12.8)
MAO-B inhibitor (selegiline)	21 (12.8)
NMSQ-T; mean ± SD	9.5±5.5

COMT = Catechol-O-methyl transferase; MAO-B = monoamine oxidase; NMSQ-T = non-motor symptoms Questionnaire in Thai language

Table 2. The individual non-motor symptoms

Q	Symptoms	Yes (%)	No (%)	Q	Symptoms	Yes (%)	No (%)
q1	Dribbling	37 (22.4)	128 (77.6)	q16	Sad/blues	58 (35.2)	107 (64.9)
q2	Taste/smelling	40 (24.2)	125 (75.8)	q17	Anxiety	50 (30.3)	115 (69.7)
q3	Swallowing	44 (26.7)	121 (73.3)	q18	Sex drive	68 (41.2)	97 (58.8)
q4	Vomiting	34 (20.6)	131 (79.4)	q19	Sex difficulty	73 (44.2)	92 (55.8)
q5	Constipation	93 (56.4)	72 (43.6)	q20	Dizzy	100 (60.6)	65 (39.4)
q6	Bowel incontinence	23 (13.9)	142 (86.1)	q21	Falling	44 (26.7)	121 (73.3)
q7	Bowel emptying incomplete	37 (22.4)	128 (77.6)	q22	Day time sleepiness	71 (43.0)	94 (57.0)
q8	Urgency	74 (44.9)	91 (55.2)	q23	Insomnia	82 (49.7)	83 (50.3)
q9	Nocturia	106 (64.2)	59 (35.8)	q24	Intense vivid dream	27 (16.4)	138 (83.6)
q10	Pains	46 (27.9)	119 (72.1)	q25	Acting out during dreams	42 (25.5)	123 (74.6)
q11	Weight	25 (15.2)	140 (84.9)	q26	Restless legs	74 (44.9)	91 (55.2)
q12	Memory impairment	93 (56.4)	72 (43.6)	q27	Swelling	30 (18.2)	135 (81.8)
q13	Loss of interest	29 (17.6)	136 (82.4)	q28	Sweating	36 (21.8)	129 (78.2)
q14	Hallucinations	30 (18.2)	135 (81.8)	q29	Diplopia	37 (22.4)	128 (77.6)
q15	Concentrating	44 (26.7)	121 (73.3)	q30	Delusions	27 (16.4)	138 (83.6)

duration and stages of PD were demonstrated in Table 4.

Discussion

The assessment of NMS of PD is essential for holistic appraoch. A strong correlation with heath-related quality of life with NMS has been evidenced as in the PDLIFE study. Many patients left NMS untreated at diagnosis may have worsening quality of life, despite stable motor symptoms[25]. The NMSQuest is a simple instrument which can be used by physicians or nurses to search for NMS of PD in a practical manner in clinical practice[26]. Non-motor symptoms, if detected early, are easier to treat as well as a better result, which absolutely bring about a better functioning. Certain symptoms including constipation, postural dizziness, sleep problems, nocturia, daytime sleepiness, restless legs, depression, nausea and wearing off are related to NMS[27-29]. It is important to put forward other symptoms such as sexual problems, diplopia, fatigue, weight change, ankle swelling which may not be detected unless NMSQuest is specifically employed. After being detected, NMS may require focused management, which could aid the diagnosis[30].

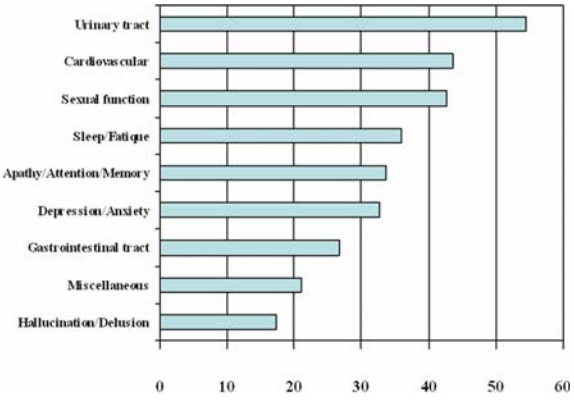

Fig. 1 The ranking of non-motor symptoms by domains. The bar chart showing the ranking of non-motor symptoms by domains. The most common symptoms were urinary, cardiovascular and sexual domains. By contrast, the least common domain was psychotic symptoms.

This was the first study conducting on NMSamong PD patients in Thailand. Using the validated self-completed instrument in our referring medical centre appeared to be practical and can comprehensively indicate the presence or absence of NMS across all stages in real life clinical setting. Translation into Thai had been reliably undergone for patients and personal' convenience in response to

Table 3. The frequency of NMS-T by domains

Domain	Number of item	Positive answer (%)	Mean ± SD	Range
Gastrointestinal tract	7	26.7	1.9±1.5	0-6
Urinary tract	2	54.6	1.1±0.8	0-2
Apathy/attention/memory	3	33.5	1.0±0.9	0-3
Hallucination/delusion	2	17.3	0.4±0.6	0-2
Depression/anxiety	2	32.7	0.7±0.8	0-2
Sexual function	2	42.7	0.9±0.7	0-2
Cardiovascular	2	43.6	0.9±0.7	0-2
Sleep/fatigue	5	35.9	1.8±1.5	0-5
Miscellaneous	5	21.1	1.1±1.1	0-4

Table 4. NMSQ-T correlated with Parkinson disease duration and Hoehn and Yahr stages

Variables	Detail	n (%)	NMSQ-T mean ± SD
Duration (year)	<5	86 (52.1)	8.1±5.7
	5-9	46 (27.9)	10.9±4.9
	10-14	26 (15.8)	11.7±4.6
	≥15	7 (4.2%)	10.7±6.45
Hoehn and Yahr Stage	1	40	3.3±2.4
	2	71	9.1±3.5
	3	41	13.8±4.5

better communication and to certainly lessen the language barrier. The researchers expereinced that this translated version was uncomplicated and not time-consuming. In addition, the usefulness of NMSQ-T as a practical tool in clinic and empowering patients to discuss NMS with their physicians or nurses, was confirmed.

The main finding of the present study was similar to the result of the NMSQuest validation study[20] that NMS were common across all stages of PD. It was apparently shown that PD individuals had 9-14 different NMS. Moreover, the present study highlighted the percentage of patients with different NMS. The major non-motor disabilities were urinary symptoms of nocturia (64.2%), dizziness (60.6%), and memory problem (56.4%). Other symptoms such as perception, sexuality, and sleep were also found of more than 30%. From NMS Quest study, the correlation between score and disease's activities were found. Another clinical observation study also reported that nondopaminergic NMS dominated clinical features of the PD at 15 years[15]. Similar to other studies in the western countries, the more advanced of Parkinson's disease rated by H&Y stageing, the longer duration of the disease clearly showed an increase in NMS score in our Thai patients.

Conclusion

Non-motor symptoms questionnaire in Thai language (NMSQ-T) is a practical and useful battery in screening of non-motor problems in Thai Parkinson's disease. Most of Thai patients with Parkinson's disease have NMS. Urinary domain is the most prevalent on NMSQ-T screening in this study. NMS is significantly correlated with the duration of disease and Hoehn and Yahr stages. Screening using NMSQ-T to recognize NMS in Thai Parkinson's patients would be helpful in prompt treatments which may improve the quality of life in PD.

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Authors' role

Research project (conception & organization): KV, SN, PS, YC, PC, CU, WW, SS, JS

Research project (Execution): KV, SN, PC

Statistic analysis: KV, SN, PS

Manuscript (writing the first draft): KV

Manuscript (review and critique): SN, PS, YC, PC, CU, WW, SS, JS

Potential conflicts of interest

None.

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Appendix 1. *Non-motor Symptoms Questionnaire for Parkinson's disease in Thai language (NMSQ-T)*

แบบสอบถามอาการของในโรคพาร์กินสันที่ไม่เกี่ยวกับการเคลื่อนไหว (non-motor symptoms)

ชื่อ-สกุล_____เพศ_____

อายุ_____ วันที่ทำแบบสอบถาม_____

ท่านเป็นโรคพาร์กินสันมาเป็นระยะเวลาเท่าใด_____ปี_____เดือน

โรคประจำตัวอื่นๆ_____

ยาที่ใช้_____

การที่ไม่เกี่ยวกับการเคลื่อนไหวในโรคพาร์กินสันอาการสั่นอาการแข็งเกร็ง หรือการเคลื่อนไหวช้าเป็นอาการของโรคพาร์กินสันที่รู้จักกันดีแต่สามารถพบอาการอื่นที่เกิดขึ้นจากโรคพาร์กินสันเองหรือเกิดจากการรักษา ซึ่งเป็นอาการสำคัญที่ควรแจ้งให้แพทย์ทราบเพื่อการรักษาที่เหมาะสมต่อไป จากอาการต่างๆ ตามหัวข้อด้านล่าง ถ้าท่านมีอาการดังกล่าวภายในช่วง 1 เดือนที่ผ่านมากรุณากรอกเครื่องหมายที่ช่อง "ใช่" ถ้าท่านไม่มีอาการดังกล่าวในช่วง 1 เดือนที่ผ่านมากรุณากรอกเครื่องหมายที่ช่อง "ไม่ใช่"

ในช่วง 1 เดือนที่ผ่านมาท่านมีอาการดังต่อไปนี้หรือไม่?

ข้อ	*คำถาม*	*ใช่*	*ไม่ใช่*
1	*มีน้ำลายหยดหรือไหลจากปากในช่วงเวลากลางวัน*		
2	*มีการเปลี่ยนแปลงหรือเสียการรับรู้กลิ่นหรือรส*		
3	*กลืนน้ำหรืออาหารลำบากหรือมีปัญหาการสำลัก*		
4	*อาเจียนหรือรู้สึกคลื่นไส้*		
5	*ท้องผูก (ถ่ายหนักน้อยกว่า 3 ครั้งต่อสัปดาห์) หรือต้องเบ่งอุจจาระ*		
6	*กลั้นอุจจาระไม่อยู่*		
7	*มีความรู้สึกถ่ายไม่สุดหลังจากอุจจาระเสร็จแล้ว*		
8	*มีความรู้สึกกลั้นปัสสาวะไม่อยู่ต้องรีบไปเข้าห้องน้ำเวลาปวดปัสสาวะ*		
9	*ตื่นขึ้นมาปัสสาวะกลางคืนเป็นประจำ*		
10	*มีอาการปวดที่ไม่สามารถอธิบายได้ (ไม่ใช่อาการปวดจากโรคที่ทราบเช่นปวดจากข้อเสื่อม)*		
11	*น้ำหนักเปลี่ยนแปลงโดยไม่สามารถอธิบายได้ (ไม่ได้มีการเปลี่ยนแปลงการรับประทาน)*		
12	*ปัญหาเกี่ยวกับความจำเรื่องที่พึ่งเกิดขึ้นหรือลืมว่าจะไปทำอะไร*		
13	*ไม่มีความสนใจสิ่งที่เกิดขึ้นรอบตัวหรือสิ่งที่ทำอยู่*		
14	*เห็นหรือได้ยินในสิ่งที่รู้ว่าไม่มีอยู่จริง*		
15	*ไม่มีสมาธิหรือไม่สามารถจดจ่อในสิ่งที่ทำ*		
16	*รู้สึกเศร้าหรือหดหู่*		
17	*รู้สึกกระวนกระวายหวาดกลัวหรือตกใจ*		

ข้อ	คำถาม	ใช่	ไม่ใช่
18	มีความรู้สึกทางเพศลดลงหรือมากขึ้นกว่าปกติ		
19	มีเพศสัมพันธ์ลำบาก		
20	รู้สึกหน้ามืดหรือเวียนศีรษะเวลาเปลี่ยนจากท่านอนหรือนั่งมาเป็นท่ายืน		
21	หกล้ม		
22	มีความลำบากในการตื่นตัวขณะทำงานขับรถหรือทานอาหาร		
23	มีความลำบากในการหลับหรือตื่นง่ายกว่าปกติตอนกลางคืน		
24	มีการพูดหรือเคลื่อนไหวขณะที่นอนอยู่ ,ออกท่าทางเหมือนในฝัน		
25	มีความฝันที่รุนแรงน่ากลัวเหมือนจริง		
26	มีความรู้สึกไม่สบายที่ขาตอนกลางคืนหรือขณะพักและมีความรู้สึกต้องขยับ		
27	ขาบวม		
28	เหงื่อออกมากผิดปกติ		
29	มองเห็นภาพซ้อน		
30	คิดว่าสิ่งที่คนอื่นบอกว่าเกิดกับท่านไม่เกิดขึ้นจริง		

ภาวะ Non-motor symptoms ในผู้ป่วยไทยที่เป็นโรคพาร์กินสัน

กิรติกร ว่องไววาณิชย์, สามารถ นิธินันทน์, เจษฎา อุดมมงคล, ปานศิริ ไชยรังสฤษดิ์, โยธิน ชินวลัญช์, วรรณา วงศ์เมฆ, สีมา ศุภเกษม, จิตถนอม สุวรรณเตมีย์, พาสิริ สิทธินามสุวรรณ

ภูมิหลัง: ภาวะ Non-motor symptoms (NMS) ในผู้ป่วยโรคพาร์กินสัน [Parkinson's disease (PD)] พบว่าเป็นภาวะที่ก่อให้เกิดปัญหาได้พอ ๆ กับความผิดปกติทางการเคลื่อนไหว (motor symptoms) แต่ภาวะนี้มักถูกเพิกเฉยทำดูแลรักษาไม่เหมาะสม การศึกษานี้ต้องการค้นหาภาวะ NMS โดยการใช้แบบสอบ NMSQuest

วัสดุและวิธีการ: สอบถามผู้ป่วยโรคพาร์กินสันที่มารับการรักษาแบบผู้ป่วยนอก โดยใช้แบบสอบถามเพื่อค้นหาภาวะ Non-motor symptoms (NMS)

ผลการศึกษา: จากผู้ป่วยโรคพาร์กินสัน 165 คน อายุเฉลี่ย 68.6 ปี ป่วยเป็นโรคเฉลี่ย 5.4 ปี เป็นเพศชายร้อยละ 56.4 ใช้ยา levodopa เฉลี่ย 456.4 มก./วัน คะแนน NMSQ-T เฉลี่ย 9.5 โดยอาการ non-motor ที่พบบ่อยที่สุด คือ ปัสสาวะกลางคืนร้อยละ 64.2 และภาวะปัสสาวะผิดปกติเป็นคำตอบที่พบบ่อยที่สุดคือร้อยละ 54.55 จากการวิเคราะห์แบบ Multivariate analysis พบว่าระยะเวลาของการเป็นผู้ป่วยโรคพาร์กินสันเป็นปัจจัยที่มีความสัมพันธ์กับคะแนนมากที่สุด พบผู้ป่วยโรคพาร์กินสันเพียงแค่ร้อยละ 3 ที่ไม่พบว่ามีภาวะ non-motor

สรุป: ผู้ป่วยโรคพาร์กินสันเกือบทุกรายมีอาการทาง non-motor และพบความผิดปกติทางระบบปัสสาวะมากที่สุดการใช้แบบสอบถาม NMSQ-T น่าจะช่วยคัดกรองภาวะนี้เพื่อรักษาและนำมาซึ่งคุณภาพชีวิตของผู้ป่วยโรคพาร์กินสัน