Validation of TU-NMS Questionaire, Prevalence, and Benefit of Botulinum Toxin Injection on Non-Motor Symptoms in Primary Craniocervical Dystonia

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ABSTRACT

Introduction: CCD is a group of disorders characterized by involuntary muscle contractions affecting the periocular, perioral, lingual, laryngeal, and cervical muscles. Each condition may appear in isolation or combined with other forms of CCD. Validated screening tool of NMS in Thai patients with dystonia is limited. Awareness of common features of NMS in CCD could improve patients' QOL.

Objectives: To validate the Thammasat University Non-Motor Symptoms Questionnaire (TU-NMS-Quest) for screening non-motor symptoms (NMS) along with the prevalence and benefit of botulinum toxin injection on NMS in patients with craniocervical dystonia (CCD).

Materials and Methods: A prospective cohort study in 27 patients with CCD and 29 controls was conducted at Thammasat University Hospital. Demographic data, severity, NMS, and QOL were assessed pre and post botulinum toxin injection treatment. NMS and QOL were assessed using TU-NMS and Thai EQ-5D-5L questionnaire.

Results: TU-NMS showed high construct validity with DNMSQuest (rs 0.805) and moderate concurrent validity with EQ5D5L (rs 0.594). Patients with CCD reported an average of 11 NMS (range: 0-24). Insomnia was the most prevalent NMS. Severity of cervical dystonia by TWSTRS is also associated with number of NMS (P = 0.0488). There was no difference in NMS between dystonia subtypes. NMS and QOL were significantly improved after Botulinum toxin therapy.

Conclusion: Non-motor symptoms are common and affect QOL in CCD patients. The TU-NMSQuest could be used as a screening tool for evaluating

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NMS in Thai CCD patients. Treatment of dystonia with botulinum toxin could improve NMS, QOL, and overall well-being in patients with CCD.

Keywords: Non-motor symptoms, Craniocervical dystonia, Blepharospasm, Cervical dystonia, Segmental dystonia

Introduction

Dystonia is a common movement disorder characterized by sustained muscle contraction resulting in abnormal posture.[1] Craniocervical dystonia (CCD), is a sustained facial or neck muscles contraction causing abnormal posture or repetitive patterned movements of the areas, is the most common idiopathic dystonia. CCD consists of benign essential blepharospasm (BEB), oromandibular dystonia (OMD), lingual dystonia, laryngeal dystonia, and cervical dystonia (CD), which could be presented isolated or together as segmental dystonia (SD). The global prevalence of CCD is 30.85 cases per 100,000.[2] CCD not only presents with motor symptoms, but also with non-motor symptoms such as pain, paresthesia, sleep disturbance, fatigue, depression, anxiety, or autonomic dysfunction.[3-8] The non-motor symptoms (NMS) also affect the quality of life (QOL) of patients with CCD.

There are a few questionnaires made for screening NMS for dystonia patients. Muller J, et al. developed and validated the Craniocervical Dystonia Questionnaire (CDQ-24) which is a 24-item for measuring the QOL in patients with CCD, focusing on 5 subscales: stigma, emotional well-being, pain, the activity of daily living (ADL), and social/family life.[9] Also, Klingelhoefer L, et al. developed and validated the Dystonia Non-Motor Symptoms Questionnaire (DNMSQuest) a 14-item questionnaire enquiring about the presence of a range of NMS in patients with CCD, focusing on 7 subscales: sleep, autonomic symptoms, fatigue, emotional wellbeing, stigma, activities of daily living, and sensory symptoms.[10] At present, there are no NMS questionnaires developed for Thai patients with dystonia.

Recently, the Thammasat University Non-Motor Symptoms Questionnaire (TU-NMSQuest) has been developed and validated for screening of NMS in Thai Parkinson's disease (PD) patients.[11] The TU-NMSQuest consists of 40 questions in 10 domains of NMS, completed by the patient featuring response as “yes” and “no” to each item in the Thai language. Since the pathophysiology of PD and dystonia were associated with the basal ganglia and cortico-striatal-thalamo circuits dysfunction. The NMS in dystonic patients would expected to be similar to PD.

This study aimed to validate TU-NMSQuest for screening of NMS in patients with CCD together with the prevalence of NMS and benefit of botulinum neurotoxin (BoTN) injection on NMS and QOL in patients with CCD.

Materials and Methods

A prospective cohort study was conducted between January and December of 2023 at BoTN Clinic of Thammasat University Hospital. Patients enrolled in this study must be age over 18 years and were diagnosed with CCD by neurologists according to the diagnostic criteria.[12] Patients with significant cognitive impairment, secondary dystonia, generalized dystonia, focal limb dystonia, deep brain stimulation, and illiteracy were excluded from the study. The patient should not been treated with BoTN injection within the last 3 months prior to

the first assessment. This study was approved by the Institutional Review Broad and the Ethics Committee. All participants provided written informed consent before the trial.

General demographic data of each patient including sex, age, occupation, family history, history of head/neck injury, and history of psychiatric medication were obtained. Motor symptoms were assessed in all participants using Global dystonia severity rating scale (GDS)[13] and Unified dystonia rating scale (UDRS)[14] with additional using Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[15] in participants with cervical dystonia. NMS were assessed with TU-NMSQuest and DNM-SQuest. Cognitive functions were assessed using Thai- Mental State Examination (TMSE). Quality of life was assessed using Thai EQ-5D-5L.[16] Visual analog scores (VAS) were used to assess participants' perception of general wellbeing and severity of their dystonia. A telephone follow-up of TU-NMSQuest, EQ-5D-5L, perception of general wellbeing, severity of their dystonia, and improvement of dystonia were done a month after BoNT injection.

Statistics

The prevalence of each NMS was determined by calculating the percentage of positive responses comparing between CCD patients and the healthy control group (HC). Additionally, the total and TU-NMSQuest domain scores were computed by summing the answers in each domain. Nonparametric statistical methods were employed for the data that did not exhibit a normal distribution, as confirmed by the K.-S.-Lilliefors test.

The applied statistical analysis methods comprise the unpaired T-test, Fisher's exact test, Mann-Whitney U-test, McNemar test, and Spearman's rank correlation coefficient test. Spearman's rank correlation coefficient test was considered: 'very weak' if if the r_s-value was 0.0-0.2', 'weak' if 0.2-0.4, 'moderate' if 0.4-0.6, 'high' if 0.6-0.8, and 'very high' if > 0.8.[17] A *p-value* below 0.05 was considered statistically significant.

Result

The data were obtained from 27 patients diagnosed with CCD and 29 subjects with age-sex-matched controls. Demographic data, medical history, disease duration, dystonic subtype, therapeutic details, total and domain TU-NMSQuest scores, and EQ5D5L score of pre and post treatments are summarized in Table 1. There were 3 cases (11.10%) that had never been treated with BoNT injection. Among the cases, 6 patients (22.20%) were BEB, 14 patients (51.90%) were CD, and 7 patients (25.90%) were SD (combination of BEB, OMD and CD). Patients with BEB significantly had older age than others (75.00 ± 9.12 vs 57.36 ± 12.62 vs 57.14 ± 10.37, p = 0.01) and lowest dystonic severity by GDSRS and UDRS as in Table 2. Patients with SD significantly had higher GDSRS and UDRS scores than patients with BEB and CD. There was no statistically significant difference in disease duration, sex, and TMSE between groups.

Table 1. Demographic and clinical characteristics of the study participants (n = 27) and HC (n = 29)

Characteristic	Patients		*p-value*
	Case (27)	Control (29)	
Age; mean (SD)	61.22 (13.29)	61.14 (8.80)	0.98
Male; number (%)	10(37.00%)	13(44.80%)	0.56
Underlying disease			
Neck disease; number (%)	2 (7.40%)	0	
HT; number (%)	7 (25.90%)	3 (10.30%)	0.17
DM; number (%)	3 (11.10%)	4 (13.80%)	1.00
DLP; number (%)	3 (11.10%)	5 (17.20%)	0.71
Parkinson; number (%)	1 (3.70%)	0	
Stroke; number (%)	1 (3.70%)	0	
Heart disease; number (%)	0	1 (3.40%)	1.00
Joint disease; number (%)	1 (3.70%)	4 (13.80%)	0.35
Cancer; number (%)	1 (3.70%)	0	
History			
Neck injury history; number (%)	6 (22.20%)		
Family history of dystonia; number (%)	0		
History of psychiatric medication use; number (%)	4 (14.80%)		
Disease detail			
Disease duration; mean (SD)	5.33 (3.42)		
Dystonia subtype			
Blepharospasm; number (%)	6 (22.20%)		
Cervical dystonia; number (%)	14 (51.90%)		
Segmental dystonia; number (%)	7 (25.90%)		
Treatment detail			
Botox; number (%)	24 (88.90%)		
Oral medication; number (%)	11 (40.70%)		
Anti-cholinergic medication; number (%)	7 (7.40%)		
No previous treatment; number (%)	3 (11.10%)		
Previous times of BoTN; mean (SD)	14.44 (11.33)		
months after the last (BoNT) injection; mean (SD)	3.70 (0.56)		
TU-NMS			
Total TU-NMS; mean (SD)	11.00 (6.13)	8.00 (4.15)	0.05
Domain 1 Sleep disorders and fatigue; mean (SD)	2.44 (1.74)	1.76 (1.38)	0.09
Domain 2 Cardiovascular disorders and falls; mean (SD)	0.67 (0.56)	0.24 (0.44)	< 0.01
Domain 3 Mood and apathy; mean (SD)	0.70 (1.10)	0.24 (0.64)	0.11
Domain 4 Perception and hallucinations; mean (SD)	0.41 (0.89)	0.03 (0.19)	0.02
Domain 5 Cognition and concentration problems; mean (SD)	1.26 (0.90)	1.24 (0.99)	0.97

Characteristic	Patients		*p-value*
	Case (27)	Control (29)	
Domain 6 Gastrointestinal tract problems; mean (SD)	1.44 (1.28)	0.66 (1.01)	< 0.01
Domain 7 Urinary tract problems; mean (SD)	1.15 (0.82)	0.86 (0.79)	0.19
Domain 8 Sexual disorders; mean (SD)	0.41 (0.75)	0.86 (0.86)	0.03
Domain 9 other	1.78 (1.22)	1.34 (1.23)	0.14
Domain 10 Impulse control disorder and dopamine dysregulation syndrome; mean (SD)	0.74 (0.94)	0.76 (0.79)	0.74
TMSE; mean (SD)	27.07 (1.71)		
EQ5D5L; mean (SD)	9.37 (3.15)	5.79 (1.05)	< 0.01
VAS of perception of general wellbeing; mean (SD)	67.59 (14.03)	79.03 (17.41)	< 0.01
Severity Assessment			
GDS; mean (SD)	12.57 (11.25)		
UDRS; mean (SD)	7.57 (4.96)		
TWSTRS; mean (SD)	28.15 (15.35)		

Table 2. Demographic and clinical characteristics of each dystonia subtypes

Characteristic	Diagnosis			*p-value*
	Blepharospasm (6)	Cervical dystonia (14)	Segmental dystonia (7)	
Age; mean (SD)	75 (9.12)	57.36 (12.62)	57.14 (10.37)	0.01
Sex				
Male; number (%)	1 (16.00%)	6 (42.8.00%)	3 (42.80%)	0.50
Medical history				
Neck disease; number (%)	0	2 (14.20%)	0	0.37
HT; number (%)	2 (33.00%)	4 (28.50%)	1 (14.20%)	0.70
DM; number (%)	1 (16.00%)	1 (7.10%)	1 (14.20%)	0.79
DLP; number (%)	1 (16.00%)	1 (7.10%)	1 (14.20%)	0.79
Parkinson; number (%)	0	1 (7.10%)	0	0.62
Stroke; number (%)	1 (16.00%)	0	0	0.16
Heart disease; number (%)	6 (100.00%)	14 (100)	7 (100%)	
Joint disease; number (%)	1 (16.00%)	0	0	0.16
Cancer; number (%)	1 (16.00%)	0	0	0.16
History				
Neck injury history; number (%)	1 (16.00%)	2 (14.2%)	3	0.31
Family history of dystonia; number (%)	6 (100.00%)	14 (100%)	7 (100%)	
History of psychiatric medication use; number (%)	1 (16.00%)	3 (21.4%)	0	0.42
Disease detail				
Disease duration; mean (SD)	6.17 (4.58)	5.36 (2.90)	4.57 (3.69)	0.72

Characteristic	Diagnosis			*p-value*
	Blepharospasm (6)	Cervical dystonia (14)	Segmental dystonia (7)	
Treatment detail				
Botox; number (%)	5 (83.00%)	12 (85.70%)	7 (100.00%)	0.55
Oral medication; number (%)	1 (16.00%)	6 (42.80%)	4 (57.00%)	0.32
Anti-cholinergic medication; number (%)	6 (100%)	10 (71.40%)	4 (57.00%)	0.20
No previous treatment; number (%)	1 (16.00%)	2 (14.20%)	0	0.55
Previous times of BoTN; mean (SD)	17.17 (13.56)	13.36 (9.26)	14.29 (14.38)	0.80
months after the last (BoNT) injection; mean (SD)	3.33 (1.75)	3.14 (1.41)	3.00 (1.41)	0.92
TU-NMS				
Total TU-NMS; mean (SD)	12.5 (5.99)	11.00 (5.72)	9.71 (7.61)	0.73
Domain 1 Sleep disorders and fatigue; mean (SD)	3.00 (1.41)	2.57 (1.70)	1.71 (2.06)	0.40
Domain 2 Cardiovascular disorders and falls; mean (SD)	0.67 (0.52)	0.79 (0.58)	0.43 (0.54)	0.40
Domain 3 Mood and apathy; mean (SD)	0.83 (1.33)	0.64 (1.15)	0.71 (0.951)	0.94
Domain 4 Perception and hallucinations; mean (SD)	0.67 (1.63)	0.36 (0.63)	0.29 (00.49)	0.73
Domain 5 Cognition and concentration problems; mean (SD)	1.50 (0.84)	1.21 (0.89)	1.14 (1.07)	0.76
Domain 6 Gastrointestinal tract problems; mean (SD)	1.67 (1.03)	1.43 (1.34)	1.29 (1.50)	0.87
Domain 7 Urinary tract problems; mean (SD)	1.67 (0.52)	1.07 (0.829)	0.86 (0.90)	0.18
Domain 8 Sexual disorders; mean (SD)	0.00	0.57 (0.85)	0.43 (0.79)	0.30
Domain 9 other	1.83 (0.98)	1.71 (1.38)	1.86 (1.22)	0.96
Domain 10 Impulse control disorder and dopamine dysregulation syndrome; mean (SD)	0.67 (0.82)	0.64 (0.93)	1.00 (1.16)	0.72
TMSE; mean (SD)				
EQ5D5L; mean (SD)	9.83 (2.48)	9.29 (3.27)	9.14 (3.81)	0.92
VAS of perception of general wellbeing; mean (SD)	61.67 (16.02)	69.64 (14.34)	68.57 (12.150)	0.51
VAS of dystonia severity; mean (SD)	51.67 (19.41)	66.79 (20.06)	56.43 (21.74)	0.27
Severity Assessment				
GDS; mean (SD)	4.25 (2.23)	9.36 (8.26)	26.14 (9.41)	**0.00**
UDRS; mean (SD)	4.33 (1.17)	5.96 (3.12)	13.57 (5.10)	**0.00**
TWSTRS; mean (SD)	-	26.85 (16.20)	30.57 (14.51)	0.62

The total TU-NMSQuest score demonstrated very high construct validity with the DNMSQuest (r_s 0.81, $p < 0.01$) and moderate concurrent validity with EQ-5D-5L questionnaire (r_s 0.59, $p < 0.01$). This result suggested that TU-NMSQuest could be use as a screening questionnaire for NMS in CCD. There was no significant association of NMS with age, disease duration, wellbeing, dystonia severity, TMSE, GDS and UDRS scores. The total TU-NMSQuest score is moderately correlated with TWSTRS (r_s 0.45, $p = 0.05$) and EQ5D5L (r_s 0.59, $p < 0.01$). The prevalence of each NMS in all patients with CCD is demonstrated in Figure 1. Detailed aspects of NMS in the BEB, CD, and SD subgroups are presented in Figure 2-4, respectively. The most common NMS in overall CCD patients was insomnia, although it did not show a statistically significant difference when compared with the HC group. The mean NMSQuest score in the CCD group tended to be higher than HC, however, it does not reach statistical significance (11 ± 6.13 vs. 8 ± 4.15, $p = 0.05$). However, statistically significant differences were shown in certain domains of the NMS; cardiovascular disorders and falls ($p < 0.01$), perception and hallucinations ($p = 0.02$), gastrointestinal tract ($p < 0.01$), and sexual disorders ($p = 0.03$). In terms of specific questions, patients with CCD demonstrated significantly higher prevalence in items number 6, 7, 9, 22, 23, 24, 26, 29, and 34 which were questions about fatigue, dizziness, depressed mood, drooling, swallowing difficulty, urinary urgency, sexual drive, sweating, and weight change respectively. There was no significant difference in the prevalence of NMS between dystonic subtypes. Patients with CCD significantly had higher mean total EQ-5D-5L scores ($p < 0.01$) and VAS-general wellbeing ($p < 0.01$) than in HC.

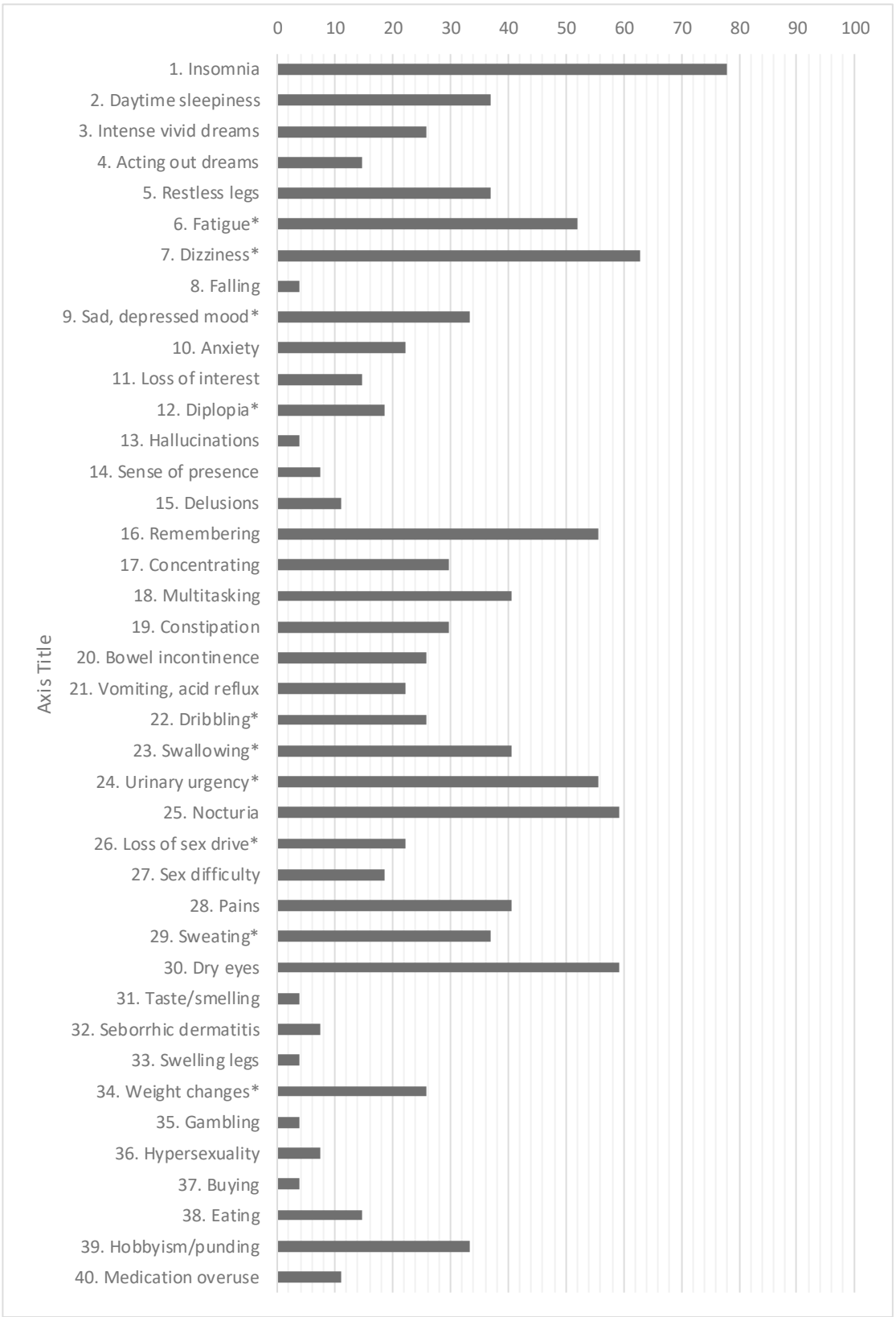

Figure 1. Aspects of NMS in CCD and percentage for each item of TU-NMSQuest (* = Significant difference from in HC)

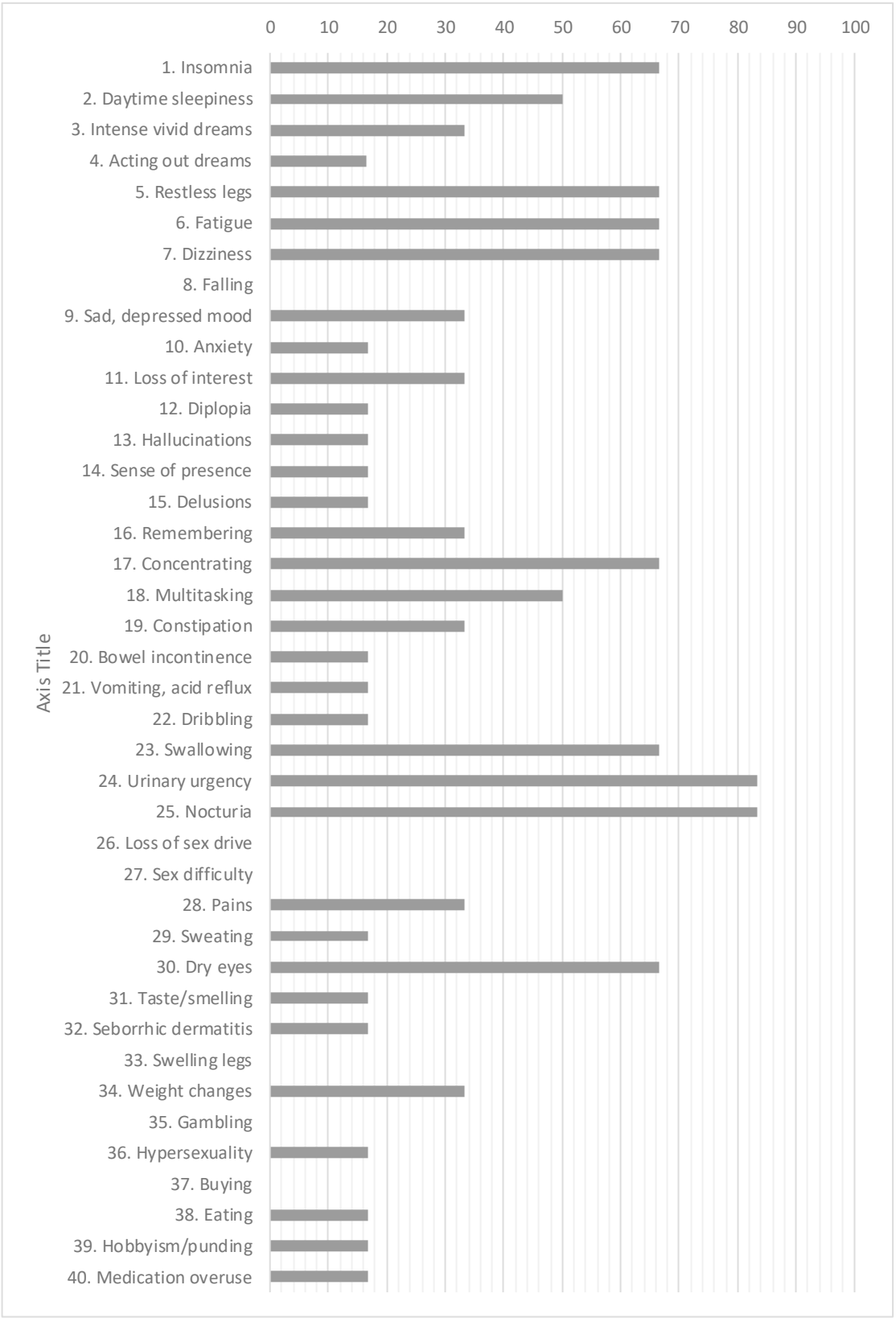

Figure 2. Aspects of NMS in BEP and percentage for each item of TU-NMSQuest

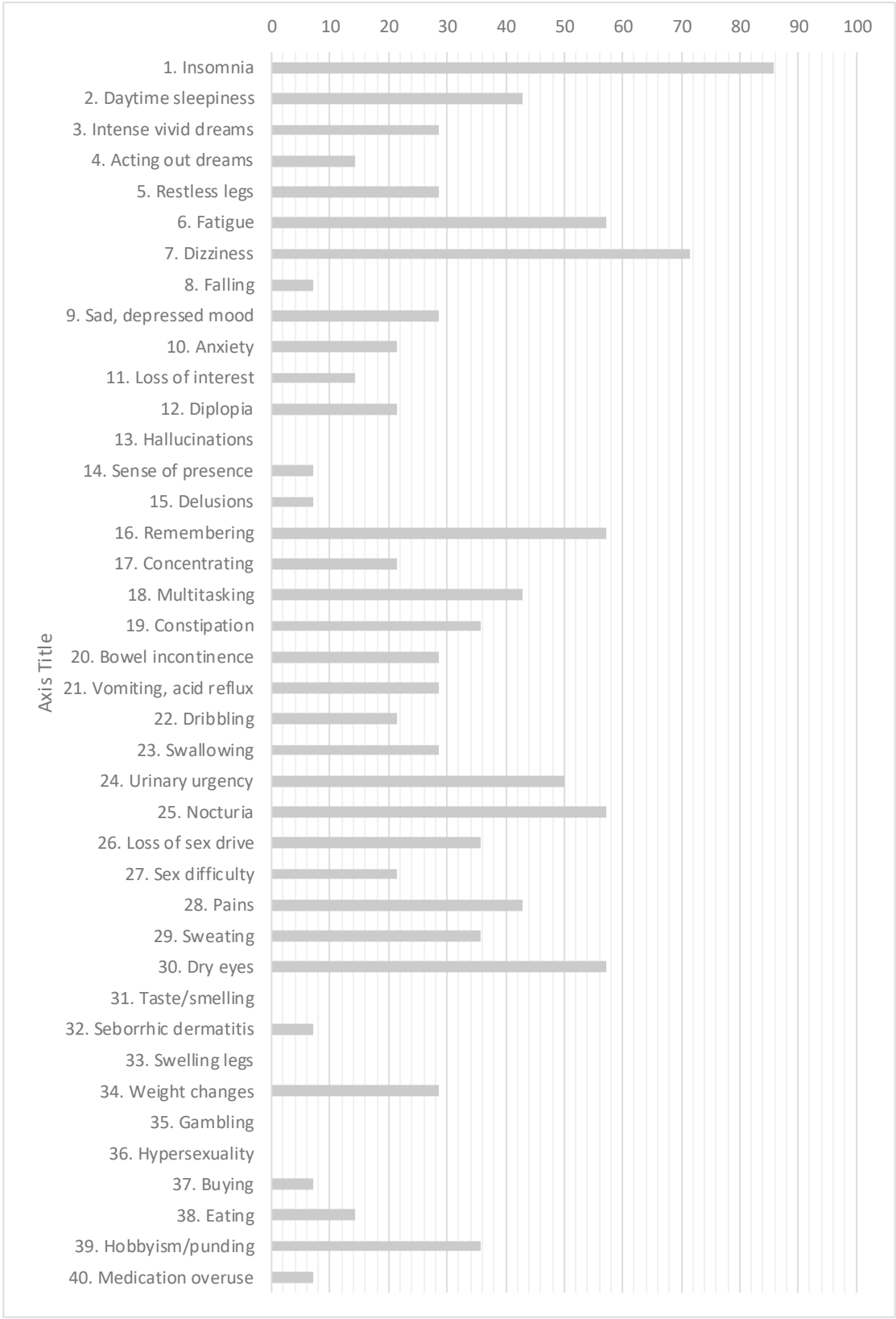

Figure 3. Aspects of NMS in CD and percentage for each item of TU-NMSQuest

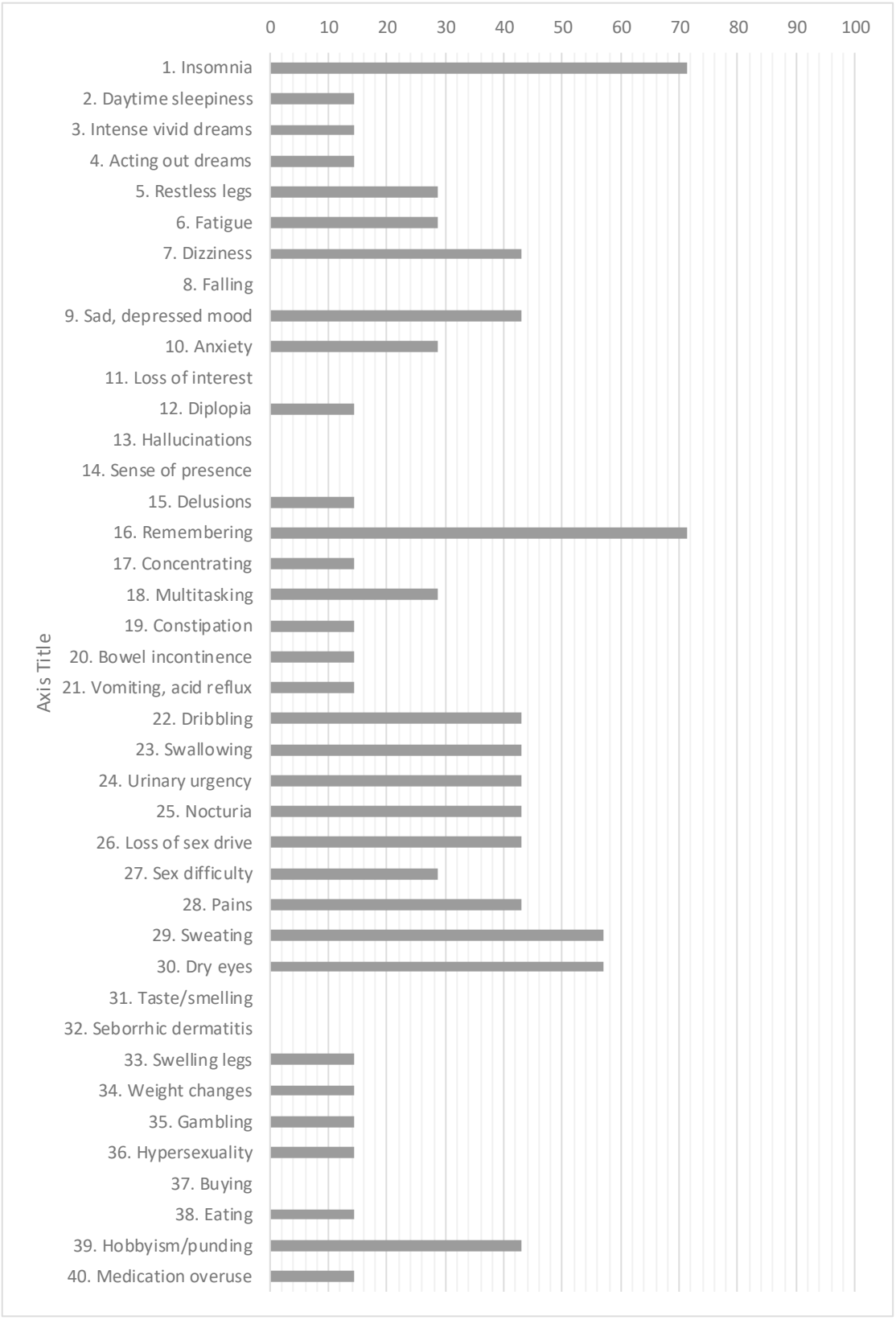

Figure 4. Aspects of NMS in SD and percentage for each item of TU-NMSQuest

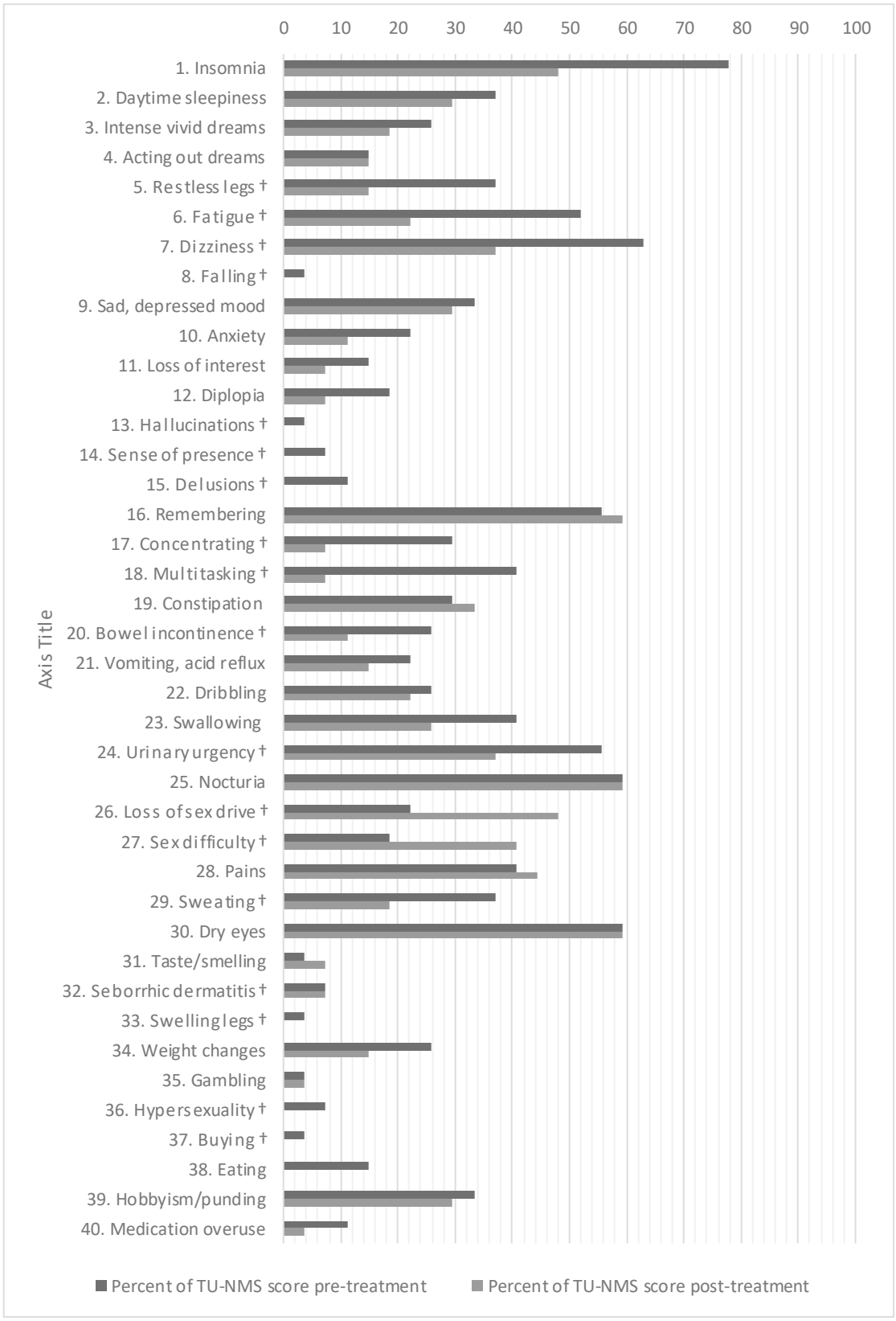

Figure 5. Aspects of NMS in CCD and percentage for each item of TU-NMSQuest, comparing pre- to post-treatment (†= Significant difference)

The data of pre and post-BoTN injection treatments are shown in Table 4. The total TU-NMSQuest score exhibited a significant improvement after BoNT injection (11.00 vs 7.96, $p < 0.01$). This improvement was particularly notable in specific domains: sleep disorders and fatigue ($p < 0.01$), cardiovascular disorders and falls ($p = 0.0191$), perception and hallucinations ($p = 0.03$), cognition and concentration ($p = 0.01$), and sexual disorders ($p = 0.01$). There was also a notable and statistically significant improvement in specific NMS questions which is demonstrated in Figure 5. The EQ-5D-5L, VAS-wellbeing, and VAS-dystonia were all significantly improved after BoTN injection with *p-values* of 0.01, 0.01, and < 0.01 respectively.

Table 3. Frequency table of each TU-NMSQuest item

Characteristic	Patients		*p-value*
	Case (27)	Control (29)	
Domain 1 Sleep disorders and fatigue			
1. Insomnia; number (%)	21 (77.8%)	18 (62.10%)	0.16
2. Daytime sleepiness; number (%)	10 (37.00%)	6 (20.70%)	0.14
3. Intense vivid dreams; number (%)	7 (25.90%)	4 (13.80%)	0.21
4. Acting out dreams; number (%)	4 (14.80%)	8 (27.60%)	0.20
5. Restless legs; number (%)	10 (37.00%)	10 (34.50%)	0.53
6. Fatigue; number (%)	14 (51.90%)	5 (17.20%)	**< 0.01**
Domain 2 Cardiovascular disorders and falls			
7. Dizziness; number (%)	17 (63.00%)	7 (24.10%)	**< 0.01**
8. Falling; number (%)	1 (3.70%)	0	0.48
Domain 3 Mood and apathy			
9. Sad, depressed mood; number (%)	9 (33.30%)	2 (6.90%)	**0.02**
10. Anxiety; number (%)	6 (22.20%)	4 (13.80%)	0.32
11. Loss of interest; number (%)	4 (14.80%)	1 (3.40%)	0.15
Domain 4 Perception and hallucinations			
12. Diplopia; number (%)	5 (18.50%)	0	**0.02**
13. Hallucinations; number (%)	1 (3.70%)	0	0.48
14. Sense of presence; number (%)	2 (7.40%)	0	0.23
15. Delusions; number (%)	3 (11.10%)	1 (3.40%)	0.28
Domain 5 Cognition and concentration problems			
16. Remembering; number (%)	15 (55.60%)	17 (58.60%)	0.52
17. Concentrating; number (%)	8 (29.60%)	7 (24.10%)	0.44
18. Multitasking; number (%)	11 (40.70%)	12 (41.40%)	0.59

Characteristic	Patients		*p-value*
	Case (27)	Control (29)	
Domain 6 Gastrointestinal tract problems			
19. Constipation; number (%)	8 (29.60%)	6 (20.70%)	0.32
20. Bowel incontinence; number (%)	7 (25.90%)	2 (6.90%)	0.06
21. Vomiting, acid reflux; number (%)	6 (22.20%)	6 (20.70%)	0.57
22. Dribbling; number (%)	7 (25.90%)	1 (3.40%)	**0.02**
23. Swallowing; number (%)	11 (40.70%)	4 (13.80%)	**0.02**
Domain 7 Urinary tract problems; mean (SD)			
24. Urinary urgency; number (%)	15 (55.60%)	8 (27.60%)	**0.03**
25. Nocturia; number (%)	16 (59.30%)	17 (58.60%)	0.59
Domain 8 Sexual disorders			
26. Loss of sex drive; number (%)	6 (22.20%)	16 (55.20%)	**0.01**
27. Sex difficulty; number (%)	5 (18.50%)	9 (31.00%)	0.22
Domain 9 others			
28. Pains; number (%)	11 (40.70%)	9 (31.00%)	0.31
29. Sweating	10 (37.00%)	3 (10.30%)	**0.01**
30. Dry eyes; number (%)	16 (59.30%)	15 (51.70%)	0.38
31. Taste/smelling; number (%)	1 (3.70%)	5 (17.20%)	0.11
32. Seborrhic dermatitis; number (%)	2 (7.40%)	6 (20.70%)	0.15
33. Swelling legs; number (%)	1 (3.70%)	0	0.26
34. Weight changes; number (%)	7 (25.90%)	1 (3.40%)	**0.02**
Domain 10 Impulse control disorder and dopamine dysregulation syndrome			
35. Gambling; number (%)	1 (3.70%)	0	0.48
36. Hypersexuality; number (%)	2 (7.40%)	2 (6.90%)	0.67
37. Buying; number (%)	1 (3.70%)	2 (6.90%)	0.53
38. Eating; number (%)	4 (14.80%)	1 (3.40%)	0.46
39. Hobbyism/punding; number (%)	9 (33.30%)	15 (51.70%)	0.13
40. Medication overuse; number (%)	3 (11.10%)	0	0.16

Table 4. shows data of pre and post- treatment with BoTN therapy.

	Before treatment	After treatment	*p-value*
Total TU-NMS; mean (SD)	11.00 (6.13)	7.96 (4.45)	**< 0.01**
Domain 1 Sleep disorders and fatigue; mean (SD)	2.44 (1.74)	1.48 (1.58)	**< 0.01**
Domain 2 Cardiovascular disorders and falls; mean (SD)	0.67 (0.56)	0.37 (0.49)	**0.02**
Domain 3 Mood and apathy; mean (SD)	0.70 (1.10)	0.48 (0.85)	0.12

	Before treatment	After treatment	*p-value*
Domain 4 Perception and hallucinations; mean (SD)	0.41 (0.89)	0.07 (0.27)	**0.03**
Domain 5 Cognition and concentration problems; mean (SD)	1.26 (0.90)	0.74 (0.76)	**< 0.01**
Domain 6 Gastrointestinal tract problems; mean (SD)	1.44 (1.28)	1.07 (1.14)	0.08
Domain 7 Urinary tract problems; mean (SD)	1.15 (0.89)	0.96 (0.81)	0.19
Domain 8 Sexual disorders; mean (SD)	0.41 (0.75)	0.89 (0.97)	**0.01**
Domain 9 others; mean (SD)	1.78 (1.22)	1.52 (1.09)	0.29
Domain 10 Impulse control disorder and dopamine dysregulation syndrome; mean (SD)	0.74 (0.94)	0.37 (0.49)	0.10
EQ5D5L; mean (SD)	9.37 (3.15)	6.96 (1.89)	**< 0.01**
VAS of perception of general wellbeing; mean (SD)	67.59 (14.03)	76.48 (11.34)	**0.01**
VAS of dystonia severity; mean (SD)	60.74 (20.65)	41.11 (23.91)	**< 0.01**
VAS of improvement of dystonia after BoTN therapy; mean (SD)		76.67 (14.41)	

Discussion

The results of this study underscored the high construct and concurrent validity of the TU-NMS-Quest for screening NMS in CCD patients. This questionnaire offers a valuable tool for pre-visit screening, enabling healthcare providers to focus precisely on patient NMS, leading to more targeted treatment interventions.

In comparison to a previous study in Thailand by Ornarnong et al.,[18] our results demonstrate a comparable prevalence of anxiety (22.20% vs. 31.00%), depression (33.30% vs. 23.80%), and sleep problems (77.80% vs. 78.80%) evaluated by the Thai Hospital Anxiety and Depression Scale (HADS) and the Thai Pittsburgh Sleep Quality Index (PSQI). The prevalence of pain is lower than the previous study (40.70% vs. 71.40%) due to the screeening technique that we use only a yes/no question instread of VAS. Notably, our study excluded patients with cognitive impairment and isolate limb dystonia.

Our findings revealed that CCD patients experience a spectrum of NMS, including cardiovascular disorders and falls, perception and hallucinations, gastrointestinal tract problems, sexual disorders, fatigue, sadness or depressed mood, incontinence or frequent voiding, excessive sweating, and unintentional weight loss. Numbers of NMS were associated with a diminished QOL. Although insomnia was the most common NMS in CCD, it did not show a statistically significant difference from the HC. Nocturia, memory problems, and dry eyes were also common in both groups. Quantitative measurement or specific objective evaluation of these problems should be investigated. Dizziness, fatigue, and urinary urgency were common NMS specifically found in CCD patients and these were improved after the BoTN injection. This finding suggested that these NMS were predominantly affected by dystonic symptoms. Remarkably, our study demonstrated numerous autonomic nervous system (ANS) symptoms in patients with CCD. The hypothesized

causes of ANS dysfunction include abnormal parasympathetic-sympathetic interaction, abnormal neck posture, and alterations in neurotransmitters.[19] Further studies on the objective measurement of ANS dysfunction in these areas such as tilt table tests, urodynamic and thermoregulatory sweat tests are suggested to determine the correlation. The other possible cause of this finding is the use of anticholinergics in CCD patients. Furthermore, the severity of cervical dystonic affected the presence of NMS also intensifies. This may be attributed to the pain assessment component in TWSTRS, aligning with the pain-related aspects evaluated in the TU-NMSQuest, or it may signify the broader impact of cervical dystonia on patients. The BoTN injection is a treatment of choice for patients with focal and segmental dystonia which not only improves motor symptoms but also numbers of NMS and QOL. The positive outcomes emphasize the comprehensive benefits of BoNT therapy in managing CCD.

Unexpectedly, the prevalence of sexual dysfunctions presents a distinctive pattern deviating from other domains. Patients with CCD significantly had a lower rate of loss of sexual drive than the HC, and the prevalence got higher after BoNT treatment, which is comparable to HC. This finding could imply the dysregulation of neurochemicals related to dopamine (DA), serotonin (5HT), and noradrenaline in modulating sexual behavior.

We acknowledge that our present study has some limitations. First, our study was based on one center and the number of participants was limited. It is recommended that larger-scale studies be conducted to ascertain whether NMS are significantly elevated in the patient population. Second, the TU-NMSQuest is a screening questionnaire, and there is no symptom severity weight score. Patients who reported these symptoms may not meet the diagnostic criteria for an actual disorder. All patients with screening positive for each NMS undergo a detailed clinical interview to determine the actual symptoms. Lastly, our study was an open-label study. Patients would expect improved outcomes not only motor symptoms but also NMS after treatment.

Conclusion

In conclusion, our study not only validates the TU-NMSQuest for NMS screening in CCD patients but also provides insights into the multifaceted nature of NMS in this population. The findings underscore the importance of addressing NMS in CCD management and highlight the significant positive impact of BoNT therapy on both motor and non-motor aspects, ultimately improving the quality of life for patients with CCD.

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