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Frequency of non-motor symptoms in parkinson disease: experience from Pakistan

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FREQUENCY OF NON-MOTOR SYMPTOMS IN PARKINSON DISEASE: EXPERIENCE FROM PAKISTAN

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ABSTRACT

Objectives:

The objective of this study was to determine the frequency of non-motor symptoms (NMS) in patients with Parkinson's disease (PD) and to compare frequency in mild and severe disease. **Materials and methods:** This descriptive observational study was done from January 2015 to June 2015 at Department of Neurology, Pakistan Institute of Medical Sciences, Islamabad. We used Non-Motor Symptom Questionnaire (NMS-Q); a validated scale using 30 questions related to 9 different domains of symptoms. **Results:** 62 patients were enrolled in the final data set of study (male 46, Female 16) with average age of 62.4 years (range=33-80). Non-motor symptoms were reported very commonly in all stages of PD including urinary urgency (74%), dizziness (71%), memory problems (71%), sexual difficulty (69%), constipation (67%) and depression (62%). Only non-motor symptom that was statistically significantly higher in the severe stages was "reported falls" (Mild 39%, severe 61%, p < 0.01). Some were more common (lightheadedness, falls, sexual difficulty) while others were less (hyposmia). **Conclusion:** Non-motor symptoms are very common in Pakistani population of PD and are seen equally in mild and severe PD with exception of "reported falls". The high prevalence of non-motor symptoms (especially in mild stages) should be kept in mind while managing PD. Furthermore, there may be the likely need for a culturally appropriate screening scale for our population.

Keywords:

Parkinson Disease, Non-motor symptoms, Pakistani population, NMS-Q, falls.

INTRODUCTION

Parkinson's (PD) is the second most common neurodegenerative disorder. Its risk increases with advancing age. Parkinson's Disease has been known since ancient times with the earliest mention in Indian medical manuscripts Ayeur Veda around 1000BC as "Kampavata." [1, 2] It was named after James Parkinson who wrote a detailed monograph titled "an easy on shaking palsy" in 1817. [2, 3] European PD association estimates prevalence of PD as 6.3 million worldwide, affecting all races and cultures. Prevalence in Pakistan has been estimated to be 0.4 million by Pakistan Parkinson Disease Society. [4]

Since its first description to until recently, it's been largely dealt as a motor disease involving dopaminergic deficit. However various non-motor symptoms have

been recognized over the years in PD including symptoms of gastrointestinal system, urinary system, sleep disturbance, psychiatric, sensory and cognitive impairment. [5] The exact etiology has not been fully elucidated but there is evidence of involvement of non-dopaminergic pathways (such as cholinergic and serotonergic). Non-motor symptoms often precede motor symptoms by up to several decades, most commonly olfactory dysfunction (hyposmia), Rapid Eye Movement (REM) sleep behavior disorder (RBD), constipation, depression, and pain. [6] Non-motor symptoms may be classified based on neurotransmitter pathways involved however most of them involve wide spread connections within the brain and thus hard to be classified separately. The non- motor symptoms are an integral part of the disease but are generally under recognized by the treating physician and under reported by the patients. Assessment of non-motor symptoms

should be a part of management of PD and there are many validated tools available such as Non-Motor Symptom Questionnaire (NMSQ), Non-motor Symptoms Survey (NMSS),EQ -5D, Parkinson Disease Questionnaire(PDQ)39.[7]

The frequency of non-motor symptoms in Pakistani PD population is not known (though assumed to be similar to western population). The non-motor symptoms are also considered to be a problem of severe disease and thus routinely ignored in early disease by practicing physicians. In this study we intended to find the frequency of non-motor symptoms in Parkinson's Disease and compare frequency between mild and severe disease.[8,9]

MATERIALS AND METHODS

This study was a cross-sectional, observational, descriptive study; carried out on population of PD patients presenting to Outpatient clinics at Department of Neurology, Pakistan Institute of Medical Sciences (PIMS), Islamabad (a Tertiary Care Center). This study was internally funded and approved by the local ethics committee in accordance with Declaration of Helsinki.

All the patients who full-filled the clinical criteria of Parkinson's Disease were included in the study according to UK Brain Bank Criteria (Annexure I).[10] Other inclusion parameters were age ≥ 18 years, able to give consent and able to answer questions independently or with help. Exclusion criteria were concern for atypical Parkinson's, history of psychiatric disease or co-morbid conditions that could contribute to NMS like diabetes mellitus. Mild Parkinson's Disease was defined as stage I&II of Hoehn and Yahr scale while severe disease was defined as stage III, IV & V of Hoehn and Yahr scale.[11] Informed consent was obtained from the patients. The data was recorded with following variables: demographic details; age and gender, staging of Parkinson's Disease according to Hoehn and Yahr Scale (Figure 1). We used Non-Motor Symptom Questionnaire (NMS-Q); a validated scale using 30 questions related to 9 different domains of symptoms (Annexure II).

The NMS-Q was filled by the patient either independently or assisted by family member(s). Where there was language problem, the author helped in translating the questionnaire to the patient.[10]

Figure 1: Hoehn &Yahr Scale of PD

STAGING OF PD – HOEHN & YAHR SCALE	
Stage 1	Unilateral disease (affects one side of body)
Stage 2	Bilateral disease without balance impairment
Stage 3	Mild to moderate bilateral disease. Some postural instability, physically independent
Stage 4	Severe disability: unable to live alone independently
Stage 5	Unable to walk/ stand without assistance

Statistical Analysis

Data was analysed through SPSS version 17. The numerical data was expressed as mean and standard deviation (SD). The categorical data was expressed as frequency and percentages. Pearson's Chi square test was used to compare the frequency of NMS in mild and severe disease. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Over the course of the study, 81 patients were screened. Those fulfilling the criteria for the study were included in the final data set. A total of 62 patients with Parkinson's Disease were recruited over 6 months period. The average age was 62.4 ± 11.57 years with youngest being 33 years and oldest 80 years of age. Males were more common (n=46, 74.1%) then females (n=16, 25.8%) with a ration of 3:1.
13 Patients were aged less than 60 (young onset PD) including 3 patients in stages II and IV each and 7 in stage III. No patient was seen in stage I (likely cultural bias, as very early PD does not seek treatment potentially from lack of awareness and other differences). Majority of patients were above age 60 (n=49) and had relatively milder disease (59% in stage

I & II) compared to younger population. None were seen in Stage 5. Similarly, looking at Stage distribution between males and females, males were proportionately more in mild disease (Stage I & II) in comparison with females (males 60%, females 25%) (Figure 2 & 3).
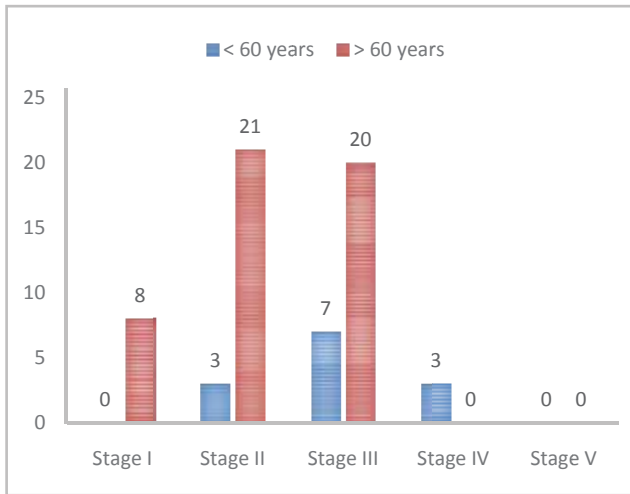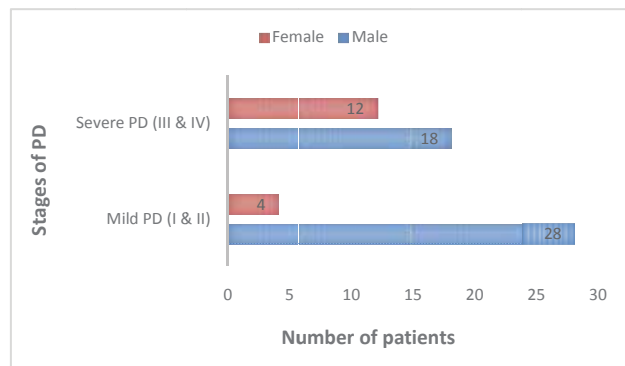
Figure 2: Stages of PD with age distribution

Figure 3: Gender Distribution of severity of PD

The urinary symptoms (urgency and nocturia) were most frequent (74.1% and 51.6% respectively) (see Table1). The gastro-intestinal symptoms were next in frequency with constipation being most common at 67.7%. Neuropsychiatric symptoms were considerably high, including memory problems, low mood, anxiety and abnormal libido (71%, 62.9%, 51.6%, 67.7% in respective order). Autonomic symptoms like feeling light-headed and falling as a result were common (71% and 66.1%) while swelling of legs was uncommon at 29%. Difficulty in performing sex was reported by 67.7%. The sleep related problems also showed

significantly high frequency with difficulty staying asleep being 58.1% and Restless Leg Syndrome being 59.7%, while unexplained pains and unexplained weight change were reported to be 61.3% and 38.7% respectively. Symptoms like dribbling saliva, double vision, dysphagia and hyposmia were in frequency of 32.3%, 29%, 35.5% and 37.1% respectively. The p value was only significant for falling (p<0.01) when comparison was done between frequency of non-motor symptoms for mild and severe Parkinson's Disease. The complete list of questions asked and frequency of symptoms is listed in Table 1.

Table 1. Frequency of Non-Motor Symptoms

Non-motor Symptoms	All patients	Mild PD (I/ II)	Severe PD (III/ IV)	p value
Urinary Urgency	46 (74.1)	25 (54.3)	21 (45.7)	0.46
Nocturia	32 (51.6)	14 (43.7)	18 (56.2)	0.54
Hyposmia	23 (37.1)	13 (56.5)	10 (43.5)	0.55
Dysphagia	22 (35.5)	13 (59.1)	09 (40.9)	0.38
Nausea/ vomiting	06 (9.7)	04 (66.7)	02 (33.3)	0.43
Constipation	42 (67.7)	24 (57.1)	18 (42.9)	0.20
Incontinence	18 (29.0)	08 (44.4)	10 (55.6)	0.47
Tenesmus	27 (43.5)	13 (48.1)	14 (51.9)	0.63
Memory impairment	44 (71.0)	24 (54.5)	20 (45.5)	0.47
Loss of interest	25 (40.3)	14 (56.0)	11 (44.0)	0.57
Hallucinations	23 (37.1)	15 (65.2)	8 (34.8)	0.10
Loss of concentration	25 (40.3)	15 (60.0)	10 (40.0)	0.27
Low mood	39 (62.9)	21 (53.8)	18 (46.2)	0.64
Anxiety	32 (51.6)	15 (46.9)	17 (53.1)	0.44
Libido	42 (67.7)	21 (50.0)	21 (50.0)	0.71
Sexual dysfunction	43 (69.4)	20 (46.5)	23 (53.5)	0.22
Delusions	20 (32.3)	09 (45.0)	11 (55.0)	0.47
Somnolence	23 (37.1)	12 (52.2)	11 (47.8)	0.94
Insomnia	36 (58.1)	17 (47.2)	19 (52.8)	0.41
Nightmares	26 (41.9)	14 (53.8)	12 (46.2)	0.76
Parasomnia	22 (35.5)	12 (54.5)	10 (45.5)	0.73
Restless legs	37 (59.7)	16 (43.2)	21 (56.8)	0.10
Orthostatic hypotension	44 (71.0)	21 (47.7)	23 (52.3)	0.33
Falls	41 (66.1)	16 (39.0)	25 (61.0)	<0.01*
Pedal edema	18 (29.0)	10 (55.6)	08 (44.4)	0.69
Excessive sweating	23 (37.1)	14 (60.9)	09 (39.1)	0.26
Double vision	18 (29.0)	08 (44.4)	10 (55.6)	0.47
Unexplained pains	38 (61.3)	19 (50.0)	19 (50.0)	0.74
Weight change	24 (38.7)	09 (37.5)	15 (62.5)	0.07
Drooling	20 (32.3)	10 (50.0)	10 (50.0)	0.86

DISCUSSION

In this study we highlight the overall high frequency of NMS in PD in Pakistani population, and their comparison between mild and severe disease. Some of the components differ in frequency compared to other studies carried out around the world which will be discussed below.

In our study the highest overall NMS was found to be urinary urgency at 74%, comparatively higher than

other studies. Bonnet et al. in 2012 described the urinary urgency in more than 50% of patients and Khoo et al. described urinary urgency in spectrum of NMS in Early PD at 46 %.[6, 10] Constipation was the next frequent NMS found in this study at 67.7%. This was higher than study of Bonnet et al (45 to 60%), but similar to studies by Khoo et al (67%) and Azmin et al (67%) who looked at Malaysian population.[6, 10, 11]
There was no significant difference between mild versus severe disease in our study; however study carried out in Italy (PRIAMO), constipation was found to be lower in Stage 1 (37%) and much higher in Stage 5 (73%). The constipation is treated in PD in usual manner like avoiding dehydration, use of laxatives and judicious use of fiber. [11]

Neuropsychiatric symptoms (low mood and memory impairment) involve cholinergic pathways and may predate onset of clinical PD with motor symptoms.[8, 9, 10, 11, 12] We found neuropsychiatric symptoms like forgetting things and low mood was common (71% and 62% respectively), with no significant difference between mild and severe disease (p 0.47 and 0.6 respectively) (Table 1). Other studies have reported slightly lower incidences of 53-67%.[9, 10, 11, 12] The dopamine effect is variable on psychiatric domain, with some patients responding positively while in others the effect remains unpredictable. Depression is linked with mortality and morbidity.[12, 13, 14] It needs to be addressed properly at every stage of Parkinson's disease and should be treated aggressively.

Sexual problems were also reported very high in our cohort in the form of decreased libido (67.7%) and difficulty in performance (69.4%) with no difference in frequency between mild and severe (p 0.7 and 0.2 respectively) (Table 1). According to Bronner et al., the sex problems correlated more with severity of motor disease and male gender compared with age, depression and use of L-dopa.[15] Khoo et al. reported significantly lower incidence of impaired libido and sexual dysfunction (17% and 28% respectively).[10] Similarly Azmin et al. reported it to be only 8%.[11] One explanation of such marked difference could be different culture and social norms and biases against reporting. It is pertinent that this topic should be approached with due respect with the patient and managed appropriately.[16]

Among all the NMS, incidence of falling was the only reported symptom that was statistically significant (p< 0.01) between mild and severe disease in our study. Fear of falling has been shown to be directly related to actual falling.[16] Orthostatic hypotension (feeling light headed and dizziness) were present in 71%, and falling was also common at 66.1%. The incidence of these symptoms was extremely low in PRIAMO study (14.2% and 1% respectively).[12] Khoo et al. reported somewhat higher number but still lower than our population (33% and 23% respectively).[10] Sleep related problems (insomnia and Restless Leg Syndrome (RLS) were present in frequency of 58.1% and 59.7% (Table 1) with no difference in mild and severe disease (p 0.1 and 0.4 respectively). This is similar to some studies such as study in Norwegian population reported incidence of sleep problems to be 60%.[17,18] Another study by Prudon et al. looking at primary sleep disorder prevalence in patients with newly diagnosed Parkinson's disease reported similar results.[19]

The prevalence of self-reported hyposmia was only 23%. This is in contrast to other studies which report this finding to be almost universal such as Xiao et al. described its prevalence of almost 90% while another study by Haehner reported it to be 95%.[20, 21] This gross difference in the prevalence can be explained by the fact that simple question may not reveal the underlying problem unless tested by specific kits.[21] Since hyposmia in recent trials has been shown to be a predictor of PD as well as dementia, it suggests a need for a better designed screening question for hyposmia as it pertains to our population to carry out further research in our population. [22, 23, 24]

Our study had some limitations including gender bias with males being more common than females (ratio 3:1), slightly more than western population (2:1) and likely represent culture bias (men more likely to seek treatment). Similarly, we noticed men to be in relatively milder disease compared with females. This may represent a treatment bias (where females are less likely to take medications or seek early treatment) and may also represent less access to healthcare by females (considered at-risk population). We also used a questionnaire not designed or validated in our population due to lack of such. The study population was small number and having a single site may have resulted in selection bias (studying only patients presenting to our hospital).

CONCLUSION

We have shown that non-motor symptoms are extremely common in Parkinson's disease in Pakistani population and the frequency of symptoms is similar in mild and severe disease except for frequent falls (more common in severe Disease)."This is in contrast to findings in other population groups with many

symptoms being much more common in our population (such as orthostatic hypotension and falls). Others are either lower or more difficult to screen (such as hyposmia)." This highlights the strong need for larger scale studies to understand the incidence and the likely need for a culturally appropriate screening scale for our population.

DISCLAIMER

The authors declare no conflict of interest.

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ANNEXURE I

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome
- Bradykinesia
- At least one of the following
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease
- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease
Three or more required for diagnosis of definite Parkinson's disease in combination with step one
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

PD NMS QUESTIONNAIRE

Name: ....   Date: ....   Age: ....

Centre ID: Male ☐   Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it **during the past month.** The doctor or nurse may ask you some questions to help decide. If you have **not** experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐
6. Bowel (fecal) incontinence	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐
9. Getting up regularly at night to pass urine	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐
13. Loss of interest in what is happening around you or doing things	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐
15. Difficulty concentrating or staying focussed	☐	☐

	Yes	No
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐