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Frequency Distribution of Premotor Symptoms in Gene Positive X-linked Dystonia Parkinsonism

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I. INTRODUCTION

To date, there has been no studies that characterize the prevalence of premotor symptoms of gene positive X-linked dystonia parkinsonism patients. This study may help in characterizing the natural history of the disease and profiling the timing of appearance of symptoms. Research on premotor symptoms of X-linked dystonia parkinsonism may offer an excellent opportunity to further characterize high-risk populations and to develop appropriate and timely treatment or interventions.

II. OBJECTIVES OF THE STUDY

General Objective:

1. To determine the premotor symptoms of Gene positive X-linked dystonia parkinsonism patients

Specific Objectives:

1. To determine the age, sex, educational attainment, co-morbidities, age at diagnosis of gene positive X-linked dystonia parkinsonism, and history of heredofamilial diseases of the subjects.
2. To determine the relationship, age, and age at symptom onset of the relative affected with X-linked dystonia parkinsonism of the subjects.
3. To determine the Montreal Cognitive Assessment score, Unified Parkinson's Disease Rating Scale score (until section III only), Sleep Disorders Inventory scale and Parkinson's Nonmotor symptoms questionnaire and Nonmotor assessment scale of the subjects

III. REVIEW OF RELATED LITERATURE

X-Linked dystonia parkinsonism (XDP) is a progressive neurodegenerative disease affecting mainly male Filipinos. It is an adult onset, sex-linked, predominantly male, progressive movement disorder with high penetrance and a high frequency of generalization (Lee et al., 2011; Rosales, 2010). Their maternal ancestries originate from the island of Panay in the Philippines. XDP usually starts with focal dystonia, eventually generalizes, and develops features of parkinsonism (Rosales, 2010). Previously, motor symptoms were observed to start at the age of 40 years old and the age mean duration of the illness is approximately 16 years (Lee et al., 2011). From the latest account of Lee et al in 2010, there are now 505 cases from 253 families in the registry of XDP with an estimated prevalence rate of 0.31 per 100,000 population with more than 90% of XDP cases initially presenting with focal dystonia. Parkinsonism symptoms usually manifest as periodic resting tremor, bradykinesia, micrographia, hypomimia and shuffling gait.

There have been several studies noting the natural history of XDP. However, these studies all document XDP at the onset of motor symptoms. In several studies, patients usually start with the dystonic phase, and as early as the second year, parkinsonian traits may appear. As the illness reaches the 7th to the 10th year, both dystonia and parkinsonism are now evident; labeled as the combined dystonia-parkinsonian phase (Lee et al., 2002; Rosales, 2010). By the 15th year of illness, the predominant picture is one of parkinsonism - manifesting as tremors, bradykinesia, masked facies, hypomimia and drooling labeled as the parkinsonian phase (Lee et al., 2011). However, in an unpublished study by Matibag et al, it was noted that prior to complaints of dystonia or motor symptoms, these patients have already complained of pain and dizziness. Due to the nature of the disease and its parkinsonian features, it is worth looking into if this disease also has the premotor symptoms of Parkinson's Disease. Several nonmotor symptoms precede the cardinal motor features of Parkinson's disease. These non-motor symptoms may reflect the earliest pathological changes in the nervous system that are associated with Parkinson's disease. Some of these premotor symptoms include sleep dysfunction, impaired olfaction, constipation, and mental and mood changes. In this study, the Montreal Cognitive Assessment score, Unified Parkinson's Disease Rating Scale score until section III only, Sleep Disorders Inventory Scale and Parkinson's Non-motor symptoms questionnaire and Nonmotor assessment scales will be used to screen patients who tested positive for the gene in X-Linked Dystonia Parkinsonism without any motor symptoms. The Montreal Cognitive Assessment (MoCA) is a measure of global cognitive function (Nasreddine et al., 2005).

It was originally developed to detect mild cognitive impairment and is currently frequently used as a screening tool for different neurologic problems such as in dementia, Parkinson's, or evaluation of post stroke patients. The raw score is adjusted according to educational attainment (1 extra point for 10 to 12 years of formal education; 2 points added for 4 to 9 years of formal education). The original study gave the normal range for MoCA as 26 to 30 points. The cut-point is now widely used as the threshold for detecting cognitive impairment. It assesses short-term memory, visuospatial function, executive function, attention, concentration and working memory, language, and orientation (Nasreddine et al., 2005). Due to its parkinsonian features and the similarity of presumed pathology to Parkinson's disease of XDP, the Unified Parkinson's Disease Rating Scale will be used to assess mentation, behavior and mood, ability to do activities of daily living, and motor examination. This questionnaire will be limited to section III only since medication effects will not be monitored at this time. The Unified Parkinson's Disease Rating Scale (UPDRS) has four parts. Each part has multiple points that are individually scored, using zero for normal or no problems, 1 for minimal problems, 2 for mild problems, 3 for moderate problems, and 4 for severe problems. These scores are tallied to indicate the severity of the disease, with 199 points being the worst and total disability and 0 meaning no disability.[7] In this study, we will be limiting the scale to 3 sections: (1) Intellectual function, mood and behavior, (2) activities of daily living, (3) motor examination. The Parkinson's Non-motor symptoms questionnaire and Nonmotor assessment scales will also be utilized since there are over 30 non-motor symptoms associated with Parkinson's including depression, constipation, pain, genitourinary problems, and sleep disorders, some of which may even be present before the diagnosis of Parkinson's (Chaudhuri et al., 2006). The NMS questionnaire can highlight the non-motor issues linked to Parkinson's Disease.[6]

IV. METHODOLOGY

The study employed a prospective descriptive study design. Sampling was done through a non-probability, purposive sampling method due to the rarity of the disease. Recruitment of subjects was extracted from a pool of known gene positive X-linked dystonia parkinsonism patients and their relatives who have also tested positive currently and previously consulted at a private tertiary institution. A total of 15 XDP gene-positive patients without self-reported motor symptoms were included in the study. The subjects were interviewed through videoconferencing application. The following questionnaires: Montreal Cognitive Assessment score, Unified Parkinson's Disease Rating Scale score, Sleep system inventory scale scores and Parkinson's Nonmotor symptoms questionnaire and Nonmotor assessment scale are described using mean and standard deviations were administered by the researcher. The forms include the patient's clinical profile including age, sex, co-morbidities, educational attainment, and history of heredofamilial diseases. Among the questionnaires that were used, only the MOCA has a Filipino version. The other questionnaires have no validated translation in Filipino. Unified Parkinson's Disease Scale parts I and II were only done as these involved the nonmotor symptoms and activities of daily living. The parts involving performance of motor neurological examination was not included due to limitations of seeing the patient through video call only. The parts of the Sleep Disorders Inventory questionnaire administered were questions on daytime functioning, difficulty falling asleep and staying asleep, sleep quality, snoring and difficulty sleeping during sleep, narcolepsy, sleep and sleep-related movements, parasomnias. Basic descriptive statistics were used to treat the data. Mean and standard deviations were applied to the continuous variables, while frequencies were reported in percentages.

V. RESULTS

The total number of participants is 15. Females consist of 87% of the samples, while 13% are males. Majority of the sample population are ages between 31-50 years at 46.67%, and the mean age is 42.8 (SD = 15.56). At the same time, the mean age when the participants were tested for the XDP gene is 40.5 (SD = 15.9). The onset of symptoms in their closest relative with XDP is also most commonly in the ages between 31-50 years, with mean age of 38.3 (SD =4.7). Forty percent of the participants have their brothers as their closest relatives who have XDP. The most common co-morbidity among the participants is dyslipidemia (26.67%). The most common heredofamilial disease aside from XDP that was reported is hypertension (40%), followed by cerebrovascular disease (33.33%). Majority (93.33%) of the study participants achieved equal to or more than 12 years of education. Cognition was assessed using the Montreal Cognitive Assessment Test which yielded that 73% has a normal MOCA score – taking into account that the passing score be increase by a point for participants who have more than or equal to 12 years of education. The mean MOCA score is 27.4 (SD: 1.68). Out of all the domains tested, the participants tested lowest in language with mean score of 62.22% (Table 2).

Table 2. MOCA scores

Domain	**Mean score**	**Mean score in percentage**
Visuospatial	4.8 ± 0.41	96%
Naming	2.67 ± 0.49	88.88%
Attention	5.47 ± 0.74	91.11%
Language	1.87 ± 1.06	62.22%
Abstraction	1.93 ± 0.53	96.67%
Delayed recall	4.53 ± 0.92	90.67%
Orientation	5.93 ± 0.26	98.89%

Table 3 shows the frequency distribution of the nonmotor symptoms present in the participants through the Parkinson's Non-motor Symptoms Questionnaire. Among which, the highest frequency reported was nocturia (53%) and memory loss (53%). Table 4 shows the item level descriptive statistics of the findings of the Non-motor Symptoms Assessment Scale. The items on the Non-motor Symptoms Questionnaire are also found in the Non-motor Symptoms Assessment Scale which quantifies the severity and the frequency of symptoms if present. The total scores for each symptom domain are reported as the sum of the product of the severity and the frequency of symptoms in each domain. Congruently, Attention/Memory and Urinary symptoms domain scored the highest mean in frequency and severity of symptoms at 3.07 ± 3.20 and 3.67 ± 3.37, respectively. Double vision, Fecal incontinence, Change in ability to taste and smell, Delusions, and troubles with falling were absent in this cohort.

Table 3. Frequency distribution of non-motor symptoms based on the Non-motor Symptoms Questionnaire.

Symptom	**Frequency (%)**
Nocturia	53
Memory problems	53
Urinary urgency	40
Unexplained pains	33
Difficulty staying focused	33
Sad or blue	33
Anxious	20
Difficult to have sex	20
Lightheadedness	20
Difficulty falling asleep	20
Less interested in sex	13
Dreaming at sleep onset	13
Sleep-talking or acting out dreams	13
Unpleasant leg sensation	13
Vomiting	13
Dribbling of saliva	6.7
Choking	6.7
Constipation	6.7
Incomplete emptying	6.7
Loss of interest	6.7
Excessive sweating	6.7

Table 4. Non-motor Symptoms Assessment Scale

Symptoms	**Frequency**	**Severity**	**Frequency x Severity**
Cardiovascular			
Lightheaded	0.4 ± 0.63	0.53 ± 0.74	0.6 ± 1.12
Total score			**0.6 ± 1.12**
Sleep/Fatigue			

Fatigue	0.33 ± 0.61	0.47 ± 0.92	0.67 ± 1.59
Difficulty falling asleep	0.73 ± 0.96	0.73 ± 0.96	1.13 ± 1.69
Restless legs	0.2 ± 0.41	0.4 ± 0.88	0.4 ± 0.88
Total score			**2.2 ± 2.51**
Mood/Cognition			
Loss of interest	0.13 ± 0.35	0.2 ± 0.56	0.2 ± 0.56
Nervous, anxious	0.6 ± 1.12	0.33 ± 0.62	0.67 ± 1.18
Depressed	0.53 ± 0.74	0.53 ± 0.74	0.73 ± 1.16
Flat moods	0.2 ± 0.41	0.27 ± 0.59	0.27 ± 0.59
Lack of pleasure	0.13 ± 0.35	0.13 ± 0.35	0.13 ± 0.35
Total score			**2.27 ± 2.96**
Attention/Memory			
Concentration	0.2 ± 0.41	0.4 ± 0.91	0.4 ± 0.91
Forgetting event	0.67 ± 0.90	0.8 ± 1.08	1.33 ± 2.44
Forgetting to do things	0.73 ± 0.70	0.93 ± 1.03	1.22 ± 1.99
Total score			**3.07 ± 3.20**
Gastrointestinal tract			
Dribbling of saliva	0.13 ± 0.35	0.27 ± 0.80	0.27 ± 0.80
Difficulty swallowing	0.13 ± 0.35	0.27 ± 0.80	0.27 ± 0.80
Constipation	0.2 ± 0.41	0.47 ± 1.13	0.47 ± 1.13
Total score			**1 ± 2.65**
Urinary			
Urgency	0.33 ± 0.62	0.53 ± 0.99	0.67 ± 1.29
Frequency	0.27 ± 0.46	0.6 ± 1.24	0.6 ± 1.24
Nocturia	0.73 ± 0.70	1.93 ± 1.80	2.4 ± 2.47
Total score			**3.67 ± 3.37**
Sexual function			
Altered interest in sex	0.47 ± 0.74	0.6 ± 0.99	0.8 ± 1.32
Problems having sex	0.27 ± 0.59	0.27 ± 0.59	0.4 ± 1.06
Total score			**1.2 ± 2.21**
Miscellaneous			
Pain	0.53 ± 0.99	0.67 ± 1.23	1.47 ± 2.95
Total score			**1.47 ± 2.95**
Grand Total			**15.47 ± 20.97**

In the UPDRS (Unified Parkinson's Disease Rating Scale Parts I to III), the most severe symptom under Part I was depression with a mean severity score of 0.87 ± 0.35. Sensory complaints also showed a relatively high mean severity score of 0.67 ± 0.72 for symptoms under Part II. Finally, under Part III, the most severe motor finding was speech with mean score of 0.2 ± 0.56 as seen in Table 5.

Table 5. Unified Parkinson's Disease Rating Scale (Parts I, II and III)

Symptoms	**Severity (mean ± SD)**
Part I. Mentation, behavior and mood	
Intellectual impairment	0.73 ± 0.70
Thought disorder	0.07 ± 0.26
Depression	0.87 ± 0.35
Motivation	0.13 ± 0.35
Part II. Activities of daily living	
Salivation	0.47 ± 0.83
Swallowing	0.33 ± 0.82
Cutting food	0.2 ± 0.41
Dressing	0
Hygiene	0.07 ± 0.26
Turning in bed	0.13 ± 0.35
Falling	0
Freezing	0.07 ± 0.26
Walking	0.2 ± 0.41

Tremor	0.2 ± 0.56
Sensory complaints	0.67 ± 0.72
Part III. Motor	
Speech	0.2 ± 0.56
Facial expression	0.07 ± 0.26
Tremor at rest	0.07± 0.26
Postural tremor of hands	0.13 ± 0.35
Finger taps	0.07 ± 0.26
Hand movements	0.07 ± 0.26
Rapid alternating movements	0.07 ± 0.26
Leg agility	0.07 ± 0.26
Arising from chair	0.07 ± 0.26
Posture	0
Gait	0.07 ± 0.26
Body Bradykinesia and Hypokinesia	0.07 ± 0.26

In terms of Sleep Disorder Inventory, the predominant issues in their sleep environment are: the temperature of their bedroom, comfort of their beddings, and sharing their bed with their children (33.33% for each reported these issues). A glaring issue on sleep hygiene concerning doing other activities in bed such as reading, watching TV, or using mobile phones are reported by all the participants (100%). In terms of symptoms, it was reported that daytime sleepiness mostly manifesting as daytime napping (60%) and falling asleep in a warm room (53%) were the most frequent issues. Nearly half of the cohort (46.6%) felt sluggish, sleepy, or fatigued upon awakening in the morning. About a third of the cohort experienced fatigue throughout the day (13.33%), and had trouble functioning due to sleepiness (26.67%). Remarkably, 1 out of 2 men who participated in the study answered difficulty getting an erection. Forty percent reported waking up too early and finding themselves not being able to go back to sleep. In terms of sleep quality, 40% reported that they feel that they sleep too lightly. Disturbances in sleep noted were frequent use of restroom at night (40%) and having acid peptic disease (40%). Twenty percent reported having sudden sleep attacks. Sleep-related movements noted were painful sensation in the legs, twitching or jerking of the legs, and feet/hands getting cold during sleep (20%). Parasomnias were rarely reported but nightmares was noted by 20% of the participants (Table 6). It was also noted that 33.33% of participants drink caffeinated beverages 6 hours before sleep onset.

Overall, our results indicated that non-motor symptoms, including sleep dysfunction, mental and mood changes, and urinary symptoms, were commonly experienced among gene-positive XDP patients before the onset of motor symptoms. These findings may point towards the existence of premotor symptoms in XDP, similar to those found in Parkinson's disease. Given XDP's parkinsonian features, the use of the UPDRS may be beneficial in future studies exploring non-motor symptoms associated with this disorder. Moreover, our findings provide valuable preliminary data on non-motor symptoms in XDP patients, serving as a foundation for future research and clinical practice. However, the sample's skewed gender ratio warrants further investigation, considering XDP generally tends to affect males predominantly. Clarifying the reasons behind this anomaly might be useful in understanding the disease's presentation and progression amongst carriers, and non-carriers of the pathologic gene.

VI. DISCUSSION

Our study aims to characterize the prevalence of premonitory symptoms in gene-positive X-linked dystonia parkinsonism (XDP) patients before the appearance of frank motor symptoms, drawing crucial attention to the possibility of an existing prodromal phase for this neurodegenerative disorder characterized by nonmotor symptoms. A study done by Steinhardt et al. in 2022 revealed balance and gait abnormalities in asymptomatic gene carriers that precedes the motor symptoms. In terms of cognition, specifically executive dysfunction, non-manifesting gene carriers showed oculomotor deficits which could indicate fronto-striatal affection (Mertin et al., 2023). Majority of the participants in our study are females – this is mostly due to the fact that females have a milder phenotype and an older age of onset compared to men (Evidente et al., 2004). It was initially thought to not manifest in women but since XDP is a homogenic disease in which they found that penetrance is high, the likelihood that the disease will develop is also high (Laabs et al., 2021). A study by Steinhardt et al in 2022 revealed that there are balance and gait abnormalities in non-manifesting gene carriers that precede the onset of XDP. However, they found no clinically overt disease manifestations in these gene carriers (Steinhardt et al., 2022).

This finding corroborates our prodromal hypothesis in XDP, adding a new dimension of motor function to the collection of non-motor symptoms we identified which will be discussed later. The cognitive function as assessed by MoCA, MMSE, and FAB had no significant difference between the non-manifesting carriers and XDP patients. Our study showed a higher mean in MoCA scores compared to the NMCs in the said study (23.7, SD 4.6). The passing score is adjusted based on the number of years of education; taking this into account, 73% of the participants has a normal MoCA score. It was found that they scored lowest in language with a mean score (in percentage) at 62.2%. In XDP patients, a study that looked into the neuropsychological profile using MMSE, Clock Drawing Test (CDT), and Frontal Assessment Battery reported that 24% of them had cognitive impairment – making the most errors in the tests for attention and calculation, orientation, and language (Domingo et al., 2011). It was hypothesized that antidystonic medications (i.e., anticholinergics) may play a part on these cognitive deficits in XDP patients (Kuyper et al., 2011). In patients with dystonia, it was reported that an explanation for the deficits in executive, attentional or visuospatial function is from the dysfunction in the fronto-basal ganglia-thalamus-cortical network (Balas et al., 2006). The striosomes (the area where degeneration is seen early in XDP) have been shown to be relevant for cognitive function and also function as relays of behavioral adaptation (Beste et al., 2017). A concurrent mood disorder which may cause pseudodementia is also presumed to contribute to the cognitive impairment (Kuyper et al., 2011). Several factors might be contributing to this, like age, education level, premorbid cognitive function, the dystonia type, anti-dystonic meds and even a pre-existing mood disorder (Domingo et al., 2011).

Non-motor symptoms, specifically the neuropsychiatric aspect of the disease were reported to be anxiety, depression and suicidality (Morigaki et al., 2013).This was reported during the participants' fifth year of illness on average. Anxiety and depression was reported to be 16.7% and 54.8% in XDP patients (Cenina et al., 2013). Congruently, this study found under Mood/Cognition section in the Non-motor Symptoms Assessment Questionnaire that depression and anxiety also scored the highest mean severity at 0.71 (1.16) and 0.67 (1.18), respectively. This finding could be further explored to trace if these mood issues arise before the onset of motor symptoms and if they could possibly be early signs of XDP. In a recent study on neuroimaging of non-manifesting gene carriers, it was found that basal ganglia atrophy precede the clinical onset of XDP (Hanssen et al., 2023). It is noteworthy that such a genotype-phenotype relationship exists sharing similar neuropathological characteristic to those seen in PD (Kish et al., 1988) and Huntington's disease (Vonsattel et al., 1985). Although striato-frontal circuit dysfunction can explain these mood issues in the neuropathological level, it should be considered that it can be affected by the long-standing disability, pain, deformity and lifestyle changes due to dystonia (Kuyper et al., 2011).

In a longitudinal study of XDP patients and non-manifesting gene carriers which explored the progression of symptoms of XDP (Acuna et al., 2023). They used MDS-UPDRS Parts 1 to 3 to assess the non-motor and motor aspects of daily living. They reported that MDS-UPDRS part 1 – complex behaviors has a mean score at 0.14 (0.38) at baseline and increased to 0.67 (1.21) at 6 months after, and 0.2 (0.45) at 12 months after. MDS-UPDRS part 1 – nonmotor aspects of daily living has a mean score 0.71 (1.11) at baseline, 0.5 (0.55) on the 6^{th} month, and 0.2 (0.45) on the 12^{th} month. The study did not indicate the item level severity scores as well as if there is significant differences in the scores at 6 and 12 months from the baseline. In this, study, the MDS-UPDRS part 1 – complex behavior corresponds most closely with UPDRS part 1 which has a total score of 1.8 (0.94). On the item level, consistent with the findings in the non-motor symptoms assessment score, depression scored the highest with a mean (SD) of 0.87 (0.35). The UPDRS does not include anxious mood, apathy, and features of dopamine dysregulation syndrome as seen in the complex behaviors part in the MDS-UPDRS. As for motor aspects of activities of daily living, the mean of the total score is 2.2 (3.74) in this study, while it is reported to be 0.57 (1.13) at baseline, 0.17 (0.41) at the 6^{th} month, and 0 on the 12^{th} month in the MDS-UPDRS. There are no other studies on the sleep disorders in the non-manifesting gene carriers. Sleep disturbances are mostly only reported in the MDS-UPDRS such as in this study, but specific scores in the items on sleep were not reported. Thus, the reported sleep disturbances in our study such as daytime sleepiness manifesting as daytime napping.

Our study utilized the part III of UPDRS to look into the possible early Parkinonism in the gene carriers who has no self-reported motor symptoms. This information is valuable, especially if the progression is observed because it was found in a study by Evidente et al in 2002 that XDP patients with predominantly Parkinsonian signs and suggested a more benign clinical course. The early identification of Parkinsonism in XDP appears to provide a better prognosis or have less disabling presentations as opposed to those who had early onset of dystonia. The early signs of Parkinsonism that can be easily missed would be mild hypomimia, mild bradykinesia and early or beginning rigidity of one extremity (Ng et al., 2021).

In conclusion, our study suggests a prodromal stage of XDP marked by non-motor and potentially motor symptoms among asymptomatic mutation carriers of XDP. These findings contribute to a broader understanding of XDP's natural history and potential early intervention strategies.

VII. LIMITATIONS OF THE STUDY

Our study has very limited number of participants due to the stringent inclusion criteria and because gene testing in family members of known XDP patients are only recently been tested. The psychological complications that genetic testing bring to the family members can also be a reason for not consenting to the test. The limited number of participants can also be due to the fact that subjects who turned out positive in the gene testing may have already developed motors symptoms at the time the study was done. This study also did not involve the administration of healthy controls due to the limitation of funding – genetic testing for healthy controls to ensure that they indeed do not carry the mutation should be done. Questionnaire materials used are not all available in the local language of the subject participants, and the interpretation of the questions may not be perceived as intended. The mode through which the interviews are done also limits the accuracy of the motor tests done in Part III of UPDRS as this may be easily and unpredictably influenced by the speed of the internet connection and the quality of the video during the call.

VIII. RECOMMENDATIONS

Longitudinal studies exploring the course and onset of these premotor symptoms, coupled with neuroimaging and genetic studies, could unravel the underlying mechanisms of the anticipated motor and non-motor symptom transition in the progression of XDP. Through this, the attributability of symptoms – especially that concerning mood – to XDP can be strongly established.

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