International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

An Observational Study on the Effect of Levodopa/Carbidopa on Parkinsonian Features of X- Linked Dystonia Parkinsonism after Pallidal Stimulation

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INTRODUCTION

XDP or X-Iinked dystonia parkinsonism is progressive neurodegenerative movement disorder endemic in the Island of Panay, Philippines affecting male population with a phenotypical symptom of focal dystonia, eventually generalizes and later on presents with Parkinsonism like tremors, bradykinesia, hypomimia and shuffling gait. The estimated record of XDP patients in the Philippines is 1 in 322,000 with highest prevalence in Capiz of 1 in 4,000 among male population.[1] Because of its rarity and highly variable clinical course, limited treatment is being offered. The emergence of Deep Brain stimulation, a neurosurgical treatment offers a promising and significant outcome with this neurodegenerative disease. However, the high cost of this intervention becomes a limitation to XDP patients. Up to this date, there is still no proven cure for XDP. The medical treatment is projected towards symptomatic relief for dystonia. Published data using various oral medications are scarce with some using benzodiazepines, anticholinergic, nonbenzodiazepine hypnotic and antiparkisonisms but the efficacy and safety of these drugs remains a controversy. Levodopa/Carbidopa is used widely to XDP that provides pharmacologic treatment used in dystonia both as diagnostic and therapeutic. It's availability and cost readily make this available for patients with XDP. In one published study, Levodopa was studied for its efficacy and safety among XDP patients however did not show any effect in alleviating the parkinsonism in patients with XDP.[2]

There has been no reported study of XDP patients who underwent deep brain stimulation and was treated with Levodopa/Carbidopa hence the investigators of this research will look into the effect of levodopa/carbidopa in parkinsonism in XDP post DBS. This study will aim to determine if there is an effect of Levodopa/Carbidopa in parkinsonism among XDP patients post deep brain stimulation.

REVIEW OF RELATED LITERATURE

X-linked Dystonia Parkinsonism is a condition that is unique because of the combined dystonic and parkinsonian features. Both features are present even in the initial part of the disease. Some patients can be more dystonic while others have more parkinsonism. As the disease progresses the features are more parkinsonian. The more disturbing to most patients especially in the initial part of the disease is the dystonia.

The treatment options that have been tried range from medications to chemodenervation, pallidal ablation and neuromodulation. Amongst the treatment options pallidal stimulation has caused improvement mostly in dystonic features. The parkinsonism has no notable improvement with the Levodopa/Carbidopa. A double-blind, randomized clinical trial by Jamora et. al was the first drug trial that involved levodopa in patients with XDP. In this trial, there was a reduction in the UPDRS part III score (9.25 vs 5.62) in the levodopa group which was not statistically significant.[2]

According to this study, levodopa did not alleviate the dystonic or parkinsonian symptoms of XDP because the pathology in XDP is not amenable to dopamine replacement. Moreover, it is stated in the same study that during the phase of dystonia, there is depletion of striosomes leading to increased striatal dopamine action, therefore treatment with levodopa could even have worsened the dystonia while in the parkinsonian phase where there is depletion of the matrix leading to decreased matrix-based projections, levodopa replacement could conceivably have no effect.

Some studies showed that the response to some treatment options that were initially noted to have negative effect showed notable good effect after modulation. In a retrospective study by Soh and Fasano they included 36 patients who met their inclusion criteria of recruits who have had undergone DBS and at least one treatment with Incobotulinumtoxin A at any given point in time.[3] Due to the limitation with small sample size, non-parametric Wilcoxon and Mann-Whitney tests were used for paired and unpaired comparison and statistical treatment was considered significant when p- value was <0.05. The study results showed no significant difference when comparing the use of Incobotulinumtoxin A before and after DBS in terms of the number of sessions and average duration of sessions. On the other hand, through this study, it showed a highly significant difference between groups with the number of units used analyzed together, post DBS $p<0.001$.[3] In one published case series and a pilot study by Gupta et. Al, six patients with Parkinson's disease with deep brain stimulation who were experiencing disabling foot dystonia were injected with 250-400 units of onabotulinum toxin (Botox).[4] These six patients were assessed pre and post Botox injection using Burke Fahn Marsden Dystonia score, visual analogue score of pain, UPDRS ,Timed up and go test (TUG), 6-Minute Walk Test (6MWT), gait velocity, cadence in an instrumented walkway, and Goal Attainment Scale (GAS). The Botox injection for the patient's with Parkinson disease after DBSS showed significant reduction in foot dystonia was well as improvement in pain and number of lower limb functional outcomes.

There is limited effect of Levodopa on parkinsonism in a study by Jamora et. Al (9.25 vs 5.62) in the levodopa group and this was not statistically significant.[2] This study showed no effect on both Dystonia and Parkinsonism of Levodopa on XDP. But there is no available literature on the effect of Levodopa on Parkinsonian features of XDP after DBS. The long-term outcome of DBS in XDP showed improvement in dystonia and parkinsonism in about three out of eleven patients from October 2009-September 2018.[5]

Neurosurgical intervention for XDP like deep brain stimulation currently offers a positive result to alleviate the symptoms but is only offered in very limited institution. However, the cost of this treatment remains to be a hindrance to these patients. Post DBS, there have been limitation in the available literature as to the effect of medical treatment after undergoing DBS.

METHODS

Study Design and Patient Eligibility

This study was a retrospective, descriptive-analytical study. The authors used purposive sampling in choosing participants in the study considering that there is limitation of the desired population; rarity of XDP and the few XDP patients who underwent deep brain stimulation. The participants of this study included the patients in a single- center movement disorder clinic who were eligible upon the basis of the inclusion criteria set by the investigators which included at least 18-80 years old male, gene confirmed with X-Linked Dystonia Parkinsonism, XDP diagnosed patient who underwent deep brain stimulation and XDP patients post DBS who develop parkinsonism and treated with levodopa/carbidopa. The investigators compared the scores of eligible patients before and after using levodopa/carbidopa post DBS using the MDS-UPDRS scale (part III-motor) of these patients available in the movement disorder clinic. The Authors excluded the XDP patients who were females; XDP patients post DBS who did not receive levodopa/carbidopa; XDP patients who were already taking levodopa/carbidopa prior to DBS and XDP patients who did not undergo deep brain stimulation.

The sample size for this study was computed using G* Power version 3.1.9.7. The effect size of 0.504 was based on the study of Jamora,R.D.G., et. al.,(2018)[1] which showed that the mean change in total UPDRS part III score from baseline was 9.25 with standard deviation of 18.35. The power used was 80%. At 95% confidence level, result showed that the minimum sample size is 33.

The investigators, including a movement disorder specialist, reviewed the video recordings of the participants and assessed if these patients developed parkinsonism symptoms after undergoing deep brain stimulation and they were scored according to UPDRS part III- motor section. Next, the investigators reviewed these XDP patients post DBS who develop parkinsonism and treated with levodopa/carbidopa for a minimum of 1 month and was scored again according to the UPDRS part III-motor section. The investigators compared if the scores was lessened after the treatment with levodopa/carbidopa. After getting all the comparison, the UPDRS part III-motor section scores were tabulated and analyzed if there is any significant difference among XDP patients post DBS with and without levodopa/carbidopa treatment.

Statistical Analysis

Descriptive statistics such as mean and standard deviation was used to present data on demographic and clinical profile of the recruited subjects. Frequency and percentage was used to present categorical data. Shapiro-Wilk test was used to test for normality of the distribution of motor scores in the sampled patients. A dependent t-test was then used to compare the means between the MDS-UPDRS part III (motor part) scores of patients who were post-DBS before and after treatment with levodopa-carbidopa.

RESULTS

All XDP patients from a single center movement clinic were screened. There were a total of 26 (N=26) patients included in this study, screened and reviewed based on the eligibility criteria set by the

authors. All the other patients were excluded since these patients was already taking levodopa/carbidopa prior to the DBS.

Descriptive Analysis

Among these 26 patients, the mean age was 41 years old with a standard deviation 7. Among them, the most common initial presentation of the XDP was cervical dystonia (50%) N = 13/26, followed by focal dystonia of the upper extremity (11%) N= 3/26 and focal dystonia of the lower extremity (11%) N= 3/26. Other symptoms that were found to be as the initial symptom among these patients were abdominal spasm 8% (N =2/33) , blepharospasm 8% (N =2/26) as well as parkinsonism such as tremors 4% (N=1/26) and bradykinesia 4% (N=1/26). Some patients presented with other symptoms such involuntary mouth movement.

Figure 1. Among the XDP patients post DBS included in this study, cervical dystonia was the most common initial presentation of the disease with 50% total percentage (N =13/26).

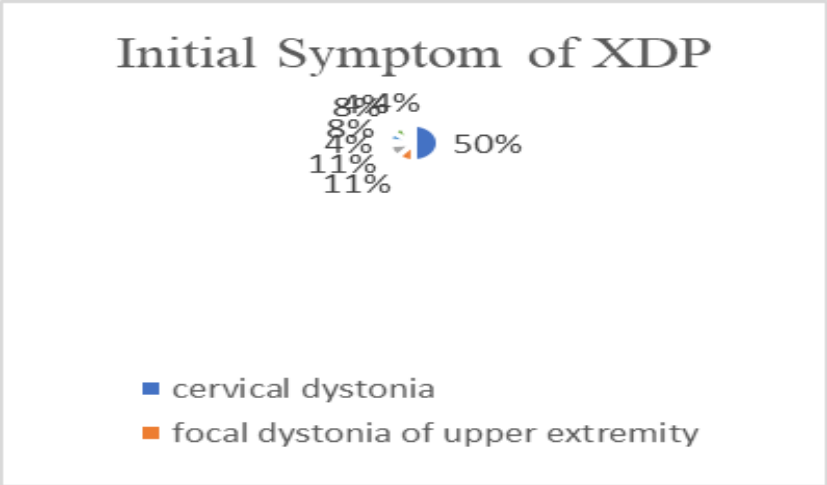
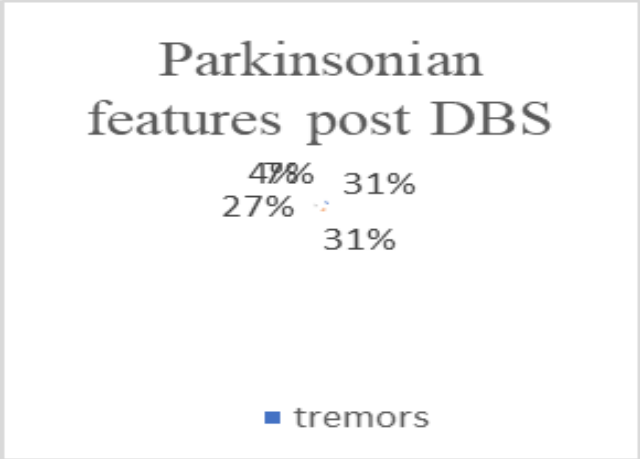


Figure 2. Among the parkinsonian symptoms, the top three symptoms which developed or progressed from XDP patients after DBS were tremors (31%), rigidity (31%) and bradykinesia (27%).

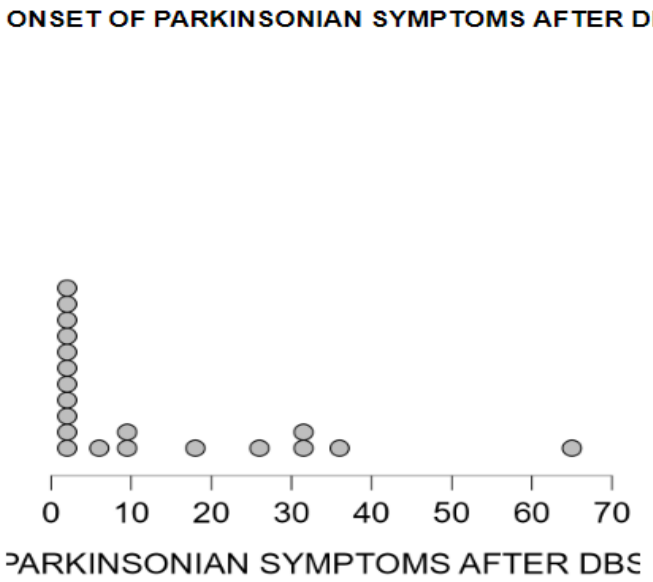


Post deep brain stimulation, patients develop various Parkinsonian symptoms including bradykinesia, rigidity, tremors, and shuffling gait. Among these, tremor and rigidity were the most common parkinsonian feature patients develop with 31% (N=8/26) percentage respectively. The next most common parkinsonian feature was bradykinesia, 27% (N= 7/26) Other parkinsonian symptoms include mixed parkinsonian symptom, shuffling gait and mixed symptoms of parkinsonian features.

Statistical Analysis

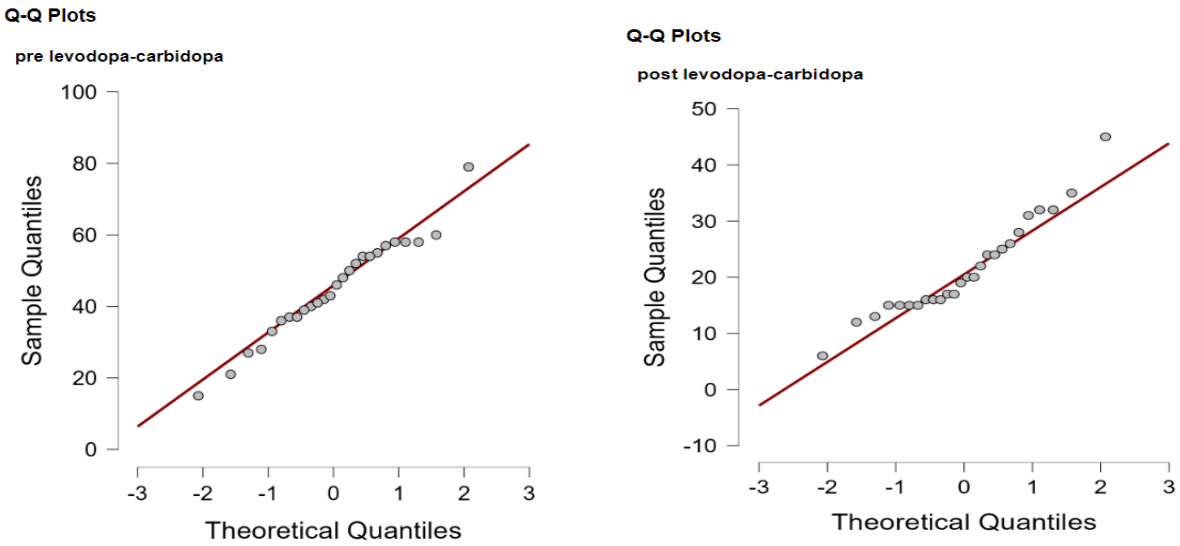
The central tendency onset of parkinsonian symptoms post-DBS (in months) is shown in Figure 3 below. Since the data was not normally distributed, which is visualized by Figure 3 below, we report here the median onset of parkinsonian symptoms post-DBS which is 3 months. Median (3.000) Mean (12.550) with a standard deviation of (SD 17.185)

Figure 3. Frequency distribution of the duration (in number of months) to onset of parkinsonian symptoms post-DBS shows a left-skew.



Shapiro-Wilk test was used to test for normality of the distribution of MDS- UPDRS motor scores in the sampled patients. There was no significant deviation from normality ($p<.05$) hence normality was assumed. Inspection of Q-Q plots also did not identify any significant outliers.

Figure 4. Normality of the distribution of MDS-UPDRS part 3(motor section) scores in the sampled patients pre and post levodopa/carbidopa



There was a significant difference in the MDS- UPDRS part III (motor scores) pre-levodopa-carbidopa treatment (M=44.92, SD=14.01) and post-levodopa-carbidopa treatment (M=21.39, 8.59); t(25) = 9.651, p<.001.

Figure 5. A dependent t-test was then used to compare the means between the motor scores of patients who were post-DBS before and after treatment with levodopa-carbidopa

Paired Samples T-Test

Paired Samples T-Test

Measure 1		Measure 2	t	df	p	Cohen's d	SE Cohen's d
pre levodopa-carbidopa	-	post levodopa-carbidopa	9.651	25	< .001	1.893	0.334

Note. Student's t-test.

DISCUSSION

This study is the first retrospective descriptive-analytical study to assess the effect of levodopa/carbidopa in parkinsonian features among XDP patients post DBS in the country. Firstly, this study shows that among these chosen population, the mean age is 41 years old from age ranges of 25-60 years old. In a study by Acuna et. al (April 2023) the consensus of available reports is that XDP symptoms begin at an average age of 39.7 year old although there are several reports of its wide age range. [6] The challenge remains as to how this rare neurodegenerative disease present in terms of its phenomenology and course overtime. Among the included patients in this study, dystonia is the most common presenting symptom at the time of their diagnosis. This may be because included patients in this study, majority were diagnosed within their 1st or 2nd year of illness. These are the years where dystonic phase predominates. Other initial presenting symptoms include blepharospasm, abdominal spasm even parkinsonian symptoms like tremors and bradykinesia that were also reported. This just

shows that clinical course of XDP is still highly variable. In a study by Evidente (2018), it is stated that the presenting symptom of this debilitating disease was initially thought to be dystonic symptoms commonly seen in the jaw, neck, trunk, and eyes but on longitudinal follow up, it was found out that parkinsonism was appreciated early even to asymptomatic genetically confirmed individuals.[7] Patients may present as pure parkinsonism or no dystonia alone. Presented in this study that among XDP patients post DBS, the median onset of parkinsonian symptoms is 3 months, (5 out of 26 had parkinsonian symptoms even before DBS). Tremor and rigidity presented to be the most common parkinsonian symptom. Although some also presented with bradykinesia, shuffling gait and mixed symptoms. Deep brain stimulation surgery alleviates dystonic features more than parkinsonian features. Abejero et. Al (2018) studied the long term effect of DBS among XDP patients which found out that there was minimal improvement in the parkinsonian symptoms (mean post-DBS UPDRS-III score was 20 + 10.39 from a mean baseline of 24.04 + 8.74)[4]. Improvements seen in these cases were on speech, facial expression, hand movements, posture, gait and rigidity but less compared to dystonia. On the other note when levodopa/carbidopa was started among XDP patient post DBS included in this study , there was an improvement in the parkinsonian symptoms. This study revealed a statistically significant result ($p<.001$) after levodopa/carbidopa treatment. Post DBS there was worsening of parkinsonian features ($M=44.92$, $SD=14.01$) which could be explained by the supposed natural history of the disease in which parkinsonism supersedes the dystonia over time. The setting of IPG may have also contributed to its worsening motor symptoms. Although not yet proven, DBS surgery plus levodopa/carbidopa may have an ablative effect on motor symptoms of XDP. In a study by Herzfeld et al. interference by DSC3 is a likely pathological mechanism in XDP and is found to have effect in the disturbance of dopamine function. [8] Connection to this disease specific changes is yet to be studied. Moreover, DBS is based on targeting the globus pallidus interna (GPi) which has been reported to be a safe therapeutic option on the other hand there are no available study to understand its affect in the depletion of the matrix leading to decreased matrix-based projections during the parkinsonian phase of the disease. The mechanism of dopamine involvement in XDP still remains to be uncertain. Levodopa/carbidopa functions by addressing the disruption of the nigrostriatal pathway and thus increases the striatal dopamine levels. In XDP, presynaptic nigrostriatal and postsynaptic striatal may be either both be affected. This study could be promising in terms of treatment and approach to patients with XDP post DBS who still develop worsened parkinsonian symptoms. Levodopa/carbidopa remains safe and effective among patients involved in this study. In the Philippines, DBS remains to be minimal in number because the high cost remains to be a limiting factor.

LIMITATIONS AND RECOMMENDATIONS

The primary limitation of this study is that the grading using the MDS-UPDRS part 3 although was done by a movement disorder specialist was made by reviewing the videos of these patients taken during their follow up. Hence the authors recommend for future follow up to grade parkinsonian symptoms during actual visits in order to eliminate biases from the quality of the video recordings. Although a minimum of 1 month use was considered in this study, the dosage and timing of the levodopa/carbidopa was not uniform to all patients. Future study is needed to set a safe dosage for parkinsonian symptoms of XDP patients post DBS. In addition, some patients in this study has concomitant medications such as benzodiazepines and anticholinergics which can mask the motor symptoms. Another limitation of this study is that patients were graded in different time frame. Since

there are some patients in this study who actually developed parkinsonian features even before deep brain stimulation, future studies are needed to prove if these are part of the disease process, effects of deep brain stimulation in the basal ganglia circuitry hence a recommended study is a randomized control trial for XDP patients to compare population of those who receive levodopa/carbidopa post DBS versus XDP group with levodopa/carbidopa alone. The authors also recommend to include baseline MDS-UPDRS scores at baseline for future studies.

CONCLUSION

In summary, Levodopa/Carbidopa offers a promising effect on the parkinsonian symptom among XDP patients after pallidal stimulation. Future studies are needed to prove the benefits of this new approach to offer ease in the burden of XDP patients with dystonic and parkinsonian features even after surgery.

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