Bilateral Pallidal Stimulation in Parkinsonism Predominant XDP *

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ABSTRACT

X linked Dystonia Parkinsonism (XDP) is a progressive movement disorder among male inhabitants of the island of Panay in the Philippines[i], it would start as a focal dystonia then become generalised. The disease is believed to be due to a founder mutation of some 50 meiotic generations ago[ii]. Although initially seen in male population, current data shows otherwise. Reports of about 11 female cases are detected and listed in the registry. Male more than female predilection is seen with a ratio of 75:1[iii]. XDP is a very disabling degenerative disease causing involuntary torsion of the body, torticolis, blepharospasm and eventually parkinsonian features[iv]. There is no known treatment, and alleviation of symptoms is difficult to achieve, some patients even die due to infection and self harm. This report will present a case of XDP with predominating parkinsonian feature, who has undergone bilateral Globus Pallidus Interna(GPi) Deep brain Stimulation (DBS). After the operation, return to functionality and improvements in activities in daily living is seen. The UPDRS and FMDRS scores show improvement noted on regular follow up. However adverse effects such as slurring of speech and minimal blepharospasm are still observed.

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INTRODUCTION

X-linked Dystonia Parkinsonism (XDP) is a progressive movement disorder, manifesting predominantly with dystonia in combination with parkinsonism[v]. It is seen predominantly on male population, however recent data shows that female gender can also be affected. Focal dystonia is the most common initial presentation at 93.4% while Parkinsonism are seen in only 5.7%[vi]. The latest XDP Philippine registry demographic data shows a total of 838 individuals with XDP, 827 are males and 11 are females (Philippine XPD Registry 2016) with a ratio of 75.2:1. Challenges in treatment currently faces this disease condition, medications such as Levodopa/Carbidopa, Benzodiazepines, anticholinergic agents and antipsychotics fail to show adequate improvement. One drug that shows benefit is Zolpidem however no clinical trials are yet available. Another strategy for the treatment is the use of Botulinum Toxin type A injection, although this is only limited to focal, multifocal and multisegmental dystonia and the effects would last temporarily and would require frequent injections[vii]. Surgery is the new trend in the management of movement disorders. Deep Brain stimulation (DBS) is being done in Parkinson's Disease and other forms of dystonia, which targets the Subthalamic nuclei and Bilateral Globus Pallidus interna (GPI). The results of these surgeries were impressive. Nonetheless, GPi is the target of choice between the two nuclei due to its proven effectiveness in off dysonias and dyskinesias in Parkinson's disease[viii]. To my knowledge there are five XDP patients who have undergone bilateral GPi DBS from 2009 - 2015 at the Philippine Movement Disorder Surgery Center. All of them have positive outcome and minimal adverse effects like wound dehiscence in IPG site. A continuous success in controlling Dystonia and Parkinsonism noted on 3 cases at 3 years follow up. This is the 2nd case done in 2016 at Philippine Movement Disorder Surgery Center.

Case Presentation:

The patient is a 34 year old Right handed Teacher from Ibajay Aklan an Island in Panay, Philippines. His maternal roots are from that island and has relatives with the same condition. His initial symptoms started as tremors on the right hand which eventually progressed which involved his left hand. He has a tendency to drop hand held objects and is observed both when resting and when in use.

6 months after the onset of his symptoms, the patient developed abdominal muscle spasm and involuntary contractions of the abdominal muscles, lasting for approximately 10 seconds that would spontaneously resolve and would recur infrequently. His posture was now noted to be stoop with difficulty ambulating. Slowness on movement was also noted at this time. Consult was made and Biperiden 2mg/tab three times a day and Clonazepam 2mg/tab three times a day are started. Despite the medications no relief of symptoms were noted. Progression of abdominal muscle contraction and length as well as bowing of posture was observed. Botulinum Toxin A (BOTOX) therapy was injected to the abdominal muscles provided temporary relief lasting for 3 months, he had 7 sessions of Botox.

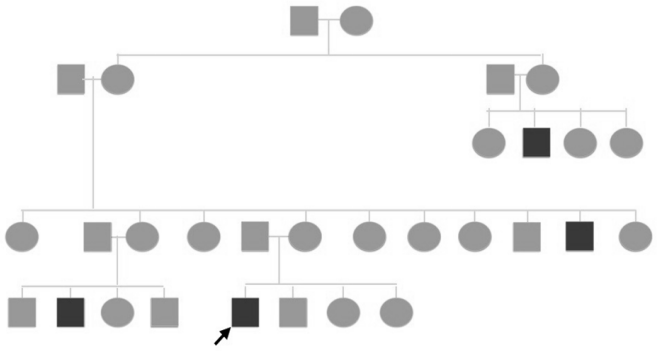


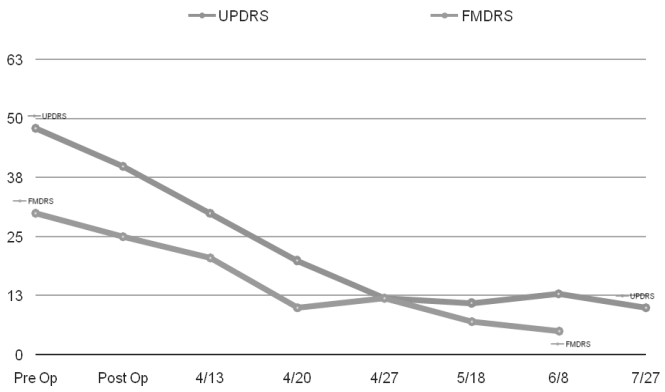
Figure 1: Pedigree of the patient

4 months prior to operation the patient experienced bilateral lower extremity weakness which lead him to require assistance in performing daily activities of living. Slurring of speech was noted thus he resigned as a teacher and became bed bound. He was referred to a neurologist in Cardinal Santos Medical Center for DBS.

The patient would fit to the criteria for a "probable" diagnosis of XDP by the Philippine XDP study group because this patient has a cousin, maternal uncle, and Grandfather with a history of Dystonia. Molecular genetic testing however was not done on this patient.

The pre operative Unified Parkinson's disease rating scale (UPDRS) part III is 48 (out of 108) and the initial Fahn-Mardsen dystonia rating scale (FMDRS) score is 30 (out of 120). The patient underwent Bilateral Pallidal (GPi) DBS last March 2016. Immediately post operatively the UPDRS score and FMDRS score are both recorded and showed great improvement. No immediate post operative complication is observed and he is discharged after 4 days.

Figure 2: UPDRS and FMDRS scores



2 days post operatively, the UPDRS score is 30 and FMDRS score is 20.5, noting marked improvement again. The bowed posture is improved, his gait is now stable and can walk without support, however dysarthria is still noted. Medications are adjusted, Biperiden is decreased to 2mg/tab, 1/2 tab twice a day and Clonazepam 2mg/tab 1/2 tab three times a day. During this time the IPG is activated. Stimulation set up is: amplitude: 2.0 V, pulse width: 60 us, frequency: 160 Hz in both Left and Right GPi. Patient regularly comes back for follow up.

At 1st month follow up, the patient has 70% improvement on his movements, the UPDRS score and FMDRS score further improves, 18 and 10 respectively. The Stimulation setting is adjusted to amplitude: 2.3 V, the pulse width and frequency are both maintained.

On the 6th month, the posture is more straight, no blepharospasm is noted and speech is improved. Biperiden is discontinued. Further adjustment of stimulus setting is done. At the time of writing he is down to Clonazepam 2mg/tab, 1/4 tab three times a day and stimulation setting of amplitude: 3.0 V, pulse width: 60 us, frequency: 130 Hz in both Left and Right GPi.

Discussion

This is a case of X-linked dystonia parkinsonism that started with Parkinsonian features when the patient is on his 28th years of age. Lee et al (2011) have reported that approximately 5.7% cases present initially with parkinsonian traits, whilst majority 93.4% initially presents with focal dystonia. In the XDP registry update of 2016, the mean age of onset is 43.7 years old, with a range of 23-67 years old, this covers the age of productivity. In our case, the disease has progressively worsen and developed into generalised type. So as with other cases of XDP, medications and BOTOX fails to control symptoms of both dystonia and parkinsonism. The patient can be classified as a stage IV in the proposed simplified staging go XDP. However this staging is still undergoing local validation.

Surgical management for movement disorders like dystonia in the Philippines has its roots in 1960 where the first documented bilateral chemopallidotomy is done on two XDP cases. However the results are not impressive, these patients experienced left hemiparesis and speech impairment post operatively, and do not note improvement on the XDP. Multiple class 1 studies of DBS on XDP shows promising results, one study shows 1 year mean improvement of FMDRS movement score of 51%. Another study by Kusch et al., (2006) shows 39% improvement in the severity of dystonia and 38% improvement in disability.

After DBS, our patient improved drastically and in a very short time frame. The initial improvement of UPDRS and FMDRS scores post operatively can be attributed to perilesional effects. We can expect that worsening of movement problems and scores (UPDRS and FMDRS) can be seen prior to the activation of the stimulator. The Stimulation of GPi in this patient improved truncal, appendicular dystonia and focal oral dystonia. It also improves the parkinsonian symptoms like stoop posturing, tremors on the hands and bradykinesia. The possible explanation on the response in this patient is because he is a predominantly parkinsonian type.

Comparing our patient with the 5 XDP patients treated with bilateral pallidal DBS from 2009-2015, all of these 5 patients initially present with focal dystonia and then progressed to generalized before surgery[xii]; but in our patient, the initial feature is parkinsonian then progressed to generalized dystonia. Despite the differences in presentation, there is a note of similarity of results. Seen immediately post operatively the FMDRS scores dramatically fell and would plateau at that point for 6 months. Unfortunately we cannot compare more than 6 months after since our data are still limited. The 1 year follow up of FMDRS scores of the 5 patients has a mean improvement of 66.7% (Range 24.4% to 83.3%)[xiii]. In our case, the improvement of UPDRS score is 79% and the improvement of 83% in FMDRS score is already seen in 6 months time.

DBS is a safe procedure and a very effective treatment option for XDP. As evidenced by this case, the patient is able to tolerate the procedure well and no peri-operative surgical complications are noted. The intellectual capacity, mood of the patient is maintained and the motor function has improved.

There are several target locations in the Basal ganglia where DBS can be applied, one is the subthalamic nuclei and the GPi. In this case the target nuclei is the GPi, based on a class 1 clinical trial and large blinded studies. It has been found that DBS of GPi is effective for primary generalised as well as segmental dystonia [xvi]. In a study by Kupsch et al, a 39% improvement in dystonia severity, 38% improvement in disability, and 30% improvement in quality of life at 3 months are seen[xv]. Thus this case strengthens the evidence in supporting the use of bilateral GPi DBS in patients with XDP. Again comparing our patient with the 5 XDP patients treated with bilateral pallidal DBS from 2009-2015[xvi], the stimulation parameters are amplitude of 1.7-4.7 V, pulse with of 60-90 us and frequency of 130 - 160 Hz. While the stimulation setting in our case ranged between amplitude: 2.0 - 3.0 V, pulse width: 60 us, frequency: 130 - 160s Hz in both Left and Right GPi.

The oral medications are tapered off eventually form 2 drug regimen now down to a low dose Clonazepam. The tapering off of this medications strengthens the claim than GPi stimulation in XDP is an effective procedure and a very good alternative to treatment of XDP.

Aside from the scores, the patients nutritional status improved, he is gaining weight and is able to swallow food without dysphagia. However the patient is noted to have slurring of speech or dysarthria. Dysarthria is the most common adverse event of Bilateral Pallidal DBS[xvii.]

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