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Long-term outcomes of pallidal deep brain stimulation in X-linked dystonia parkinsonism (XDP): Up to 84 months follow-up and review of literature

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ABSTRACT

Introduction: X-linked dystonia-parkinsonism (XDP/DYT3/Lubag) patients had improved dystonia and parkinsonism with bilateral pallidal deep brain stimulation (DBS) in the literature.
Method: We reviewed eleven XDP patients who underwent bilateral pallidal DBS from October 2009 to September 2018. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Unified Parkinson's Disease Rating Scale (UPDRS)-III scores were reviewed from baseline up to the longest follow-up together with the demographic and clinical data. The published case reports on DBS in XDP were also reviewed.
Results: The mean age was 39 ± 9.2 years with a mean disease duration of 3 years (range 1–9 years). An immediate response for dystonia post-DBS (1 month) was seen in all cases, with a mean BFMDRS score of 23.3 ± 12.12 [from a mean baseline of 36.3 ± 12.1] and a small change in the mean UPDRS-III score of 20 ± 10.39 [from a mean baseline of 24.04 ± 8.74]. At 12 months (n = 10), the mean BFMDRS score was 13.7 ± 10.63 and the mean UPDRS-III score was 19 ± 13.19. There was improvement in the clinical and functional stage of the patients, with majority in Stage 1 (n = 3) and Stage 2 (n = 5) at their last follow-up.
Conclusion: Bilateral pallidal DBS should be considered as a treatment option for XDP. It is effective in the first 12 months in controlling dystonia with variable response in controlling parkinsonism. It may be effective in up to 72–84 months, as seen in three patients.

1. Introduction

X-linked dystonia-parkinsonism (XDP/DYT3/Lubag) is a hereditary and progressive neurodegenerative disease. It affects primarily Filipino adultmen with their maternal ancestry originating from the Panay Island, Philippines. As of 2010, the prevalence of XDP is 5.74/100,000 in Panay Island and 0.31/100,000 in the entire country [1]. The clinical presentation is focal or segmental dystonia during the early stage of the illness, later becoming generalized causing severe disability. At the latter stage, they develop parkinsonism in the form of bradykinesia, tremors and rigidity [1]. The XDP gene locus has been narrowed down to TATA-binding protein associated factor (*TAF1*), with an XDP-specific SINE-VNTR-Alu (SVA) insertion causing intron retention and reduced expression of *TAF1* [2,3].

The medical management for XDP consists of various forms of oral medications such as anti-cholinergics, anti-convulsants, anti-histamines, hypnotic-sedatives and anti-parkinsonian agents such as levodopa-carbidopa. These drugs have shown inconsistent benefit in improving their symptoms [4,5]. Another treatment option is chemodenervation using botulinum toxin A. It has shown to be effective

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in controlling focal or segmental dystonia. However, it is mainly limited by its duration of effectivity and its cost [6].

Neuroablative surgery were done among XDP patients in the 1960s by targeting the bilateral pallidus or thalamus. The cases reported showed no improvement of dystonia with significant morbidities such as hemiparesis and speech impairment [7]. The outcomes were poor that it discouraged the subsequent patients to undergo this type of surgery. Deepbrain stimulation surgery (DBS) targeting the globus pallidus interna (GPi) has been reported to be a safe therapeutic option in segmental and generalized dystonias [8]. The use of DBS has been tried in different types of dystonia and this includes its application among heredodegenerative conditions such as XDP. To date, there are eleven reported cases in the literature including the first case done in the Philippines. These cases have shown immediate improvement of their dystonia based on their Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). It had less persistent adverse outcomes and longer duration of effectiveness based on their follow-up (range 9–24 months) [7,9–18].

Due to its success of improving dystonia and with less adverse effects, DBS has been introduced as one of the treatment options for XDP in the Philippine Movement Disorder Surgery Center (PhilMove) in 2009. We present the treatment outcomes of all XDP patients who underwent pallidal DBS in the Philippines and compared it to previous cases reported in the literature.

2. Materials & methods

This was a retrospective review of eleven XDP patients who underwent bilateral pallidal DBS from October 2009 to September 2018 at the PhilMove. The charts were retrieved and reviewed. The data reviewed were the age and sex of the patients, genetic test results, duration of the disease before DBS, initial symptoms and their symptoms prior to surgery, pre-operative up to last follow-up scores of BFMDRS and Unified Parkinson's Disease Rating Scale (UPDRS)-III, length of follow-up, peri- and post-operative adverse events and symptoms improved after DBS surgery. The mean and individual scores of their BFMDRS and UPDRS-III scores for the patients were plotted from their pre-operative scores up to their last follow-up. Aside from those scores, the clinical and functional staging of the patient were determined using the staging of XDP prior to DBS and at their last follow-up [1].

A search of online databases was done to identify all articles on DBS and XDP. The data from our patients and the cases reported in the literature were then tabulated and summarized.

This protocol was submitted and approved by the Cardinal Santos Medical Center Ethics Review Committee (CSMC 2017-009).

3. Results

3.1. Patient characteristics & clinical presentation

There were 11 XDP patients who underwent bilateral pallidal DBS from October 2009 until September 2018. All patients were genetically confirmed to have the TAF1 gene mutation. The mean age was 39.27 ± 9.24 years. The mean duration of the disease prior to surgery was 3.64 ± 2.46 years (range 1–9 years) (see Table 1). Prior to surgery, the symptoms that were causing significant disability despite medications were neck dystonia (n = 7), truncal dystonia (n = 6), dysphagia (n = 4) and generalized dystonia (n = 3), with one patient needing percutaneous endoscopic gastrostomy (PEG) (Case B). The clinical features of the 11 XDP patients who had bilateral pallidal DBS in PhilMove is summarized in Supplemental Table 1.

A total of 11 case reports were found, including the first case done in PhilMove in 2009 [7,9–18] (see Supplemental Table 2). An additional 12 cases have been operated in Luebeck, Germany, but the final paper has not been reported yet [19]. In the published literature (excluding Case A) with 12 months follow up (n = 6/10), the median BFMDRS score was 16 (range 4.5–39.5) from a median baseline score of 57 (range 14–87). The median UPDRS-III score at 12 months was 20.3 (range 8–43) from a median baseline score of 38.5 (range 24–95) [9,11–15,17].

The most common medications used (as of their last follow up) were clonazepam (n = 7), biperiden (n = 7), zolpidem (n = 7) and carbidopa/levodopa (n = 3) (see also Supplemental Table 1).

Table 1
Baseline demographic characteristics of the patients.

Age	39.27 ± 9.24 years
Duration of disease prior to surgery	3.64 ± 2.46 years
Presenting symptoms[a]	
Focal extremity dystonia	6
Neck dystonia	5
Blepharospasm	4
Oral dystonia	2
Truncal dystonia	1
Cranial MRI	
Abnormal	9
Normal	2
Length of follow up	38.73 ± 28.06 months
Years of education	14.36 ± 1.21 years
Baseline BFMDRS score	36.3 ± 12.1
Baseline UPDRS score	24.04 ± 8.74
Medications prior to surgery[a]	
Clonazepam	9
Biperiden	7
Zolpidem	4
Baclofen	2
Amantadine	1
Carbamazepine	1

[a] N is more than 11 due to multiple presenting symptoms and medications.

3.2. Operation

All surgeries were performed in PhilMove at Cardinal Santos Medical Center by the same surgeons (JAA and TSV) with the same anesthesiologist (MSV). Post-operative cranial MRI (1.5 T) T2-weighted axial, inversion recovery (IR) axial images and T1-weighted volumetric 3D Magnetization-Prepared Rapid Gradient Echo (MPRAGE) sequences was obtained showing placement of leads along the inferior border of the postero-ventral GPi.

The adverse events observed peri-operatively were transient left-sided weakness and slurred speech, arrhythmia (premature ventricular contractions) with transient hypoxemia and tachypnea and transient medial rectus palsy on the right eye. Of the 11 patients, 2 patients had facial twitching at 5–7 V. All of these cases had no significant post-operative morbidity. However, it led to the delay of the implantation of the contralateral electrode and pulse generator (IPG) for the two cases (Cases B & C).

3.3. Follow-up

The mean length of follow-up was 38.73 ± 28.06 months. Case A had the longest follow-up at 84 months (see Video A), followed by Case B (see Video B) & Case C at 72 months. During follow up, the BFMDRS and UPDRS-III scores were recorded for all cases. The first programming of the IPG was done at least one month from the time the patient had the operation. All patients were under the care of a single neurologist/movement disorder specialist (RDJ). The medications were then adjusted by reducing the dosage and the number of drugs used to control dystonia. However, once the parkinsonism became more prominent, carbidopa/levodopa was tried. The DBS settings were adjusted based on the subjective reports and objective findings of dystonia and parkinsonism.

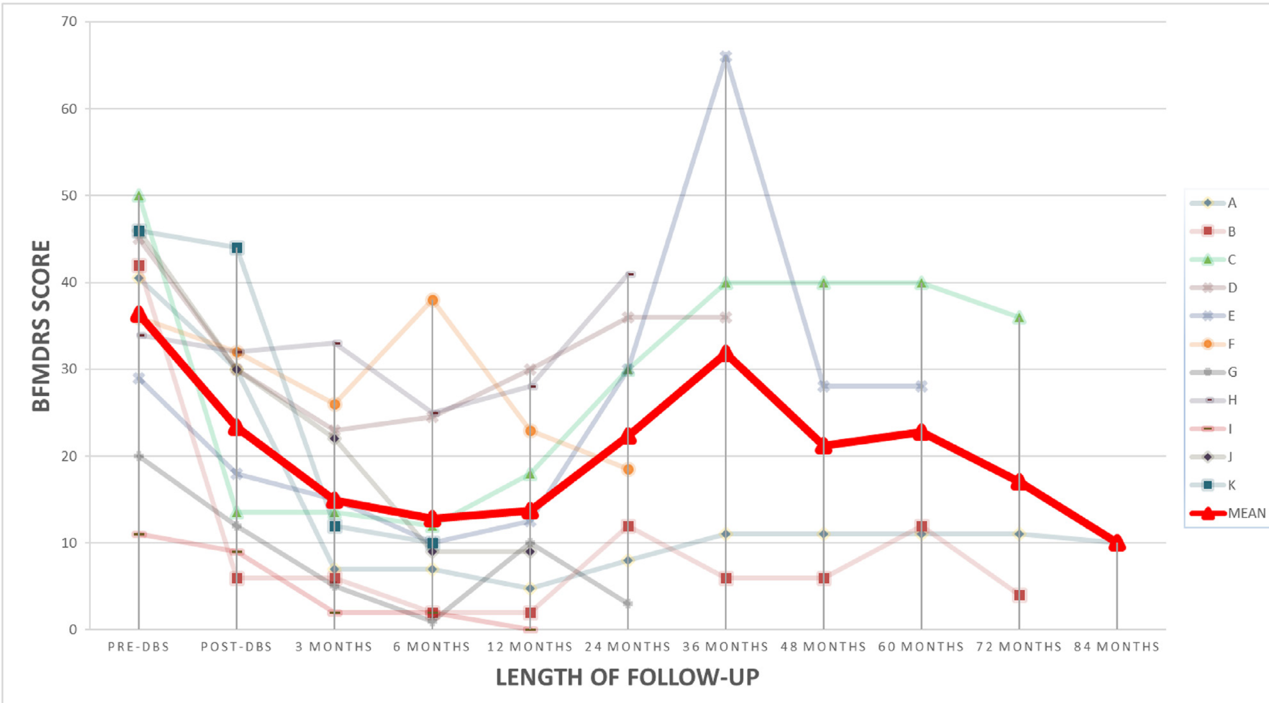

Fig. 1. Mean and individual scores of the BFMDRS from 11 patients: from pre-operative baseline scores up to the longest follow up of 84 months.

Supplementary video related -to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.022.

There was an immediate response to treatment of the dystonic symptoms post-DBS (one month after surgery) with a mean BFMDRS score of 23.3 ± 12.12 from a mean baseline of 36.3 ± 12.11. The highest improvement was seen in Case B with a score difference of 40 (95% improvement). The most improved symptoms post-DBS were truncal dystonia (n = 5), orofacial dystonia (n = 5), neck dystonia (n = 5), focal extremity dystonia (n = 4) and ambulation (n = 6). Case B had significant improvement in his swallowing and weight allowing removal of the PEG.

Upon plotting the BFMDRS mean and individual scores over time (see Fig. 1), there was a trend towards improvement over time up to 12 months of follow-up with a mean score of 13.7 ± 10.63 compared to the mean baseline score. Of the 8 cases that had a follow-up of 24 months and beyond, 4 cases (Cases C, D, E & H) showed worsening of the BFMDRS scores. These cases had an increase in the number and dosage requirement of medications for symptomatic control of dystonia (baclofen, biperiden, clonazepam and zolpidem) on succeeding follow-ups. They eventually underwent intermittent chemodenervation using botulinum toxin A to control their dystonic symptoms. In contrast, Cases A and B had relatively stable improvement of dystonia until 84 and 72 months of follow-up respectively.

In contrast to the dystonia symptoms, there was minimal improvement in the parkinsonian symptoms. The mean post-DBS UPDRS-III score was 20 ± 10.39 from a mean baseline of 24.04 ± 8.74. Four cases had a significant improvement (Cases B, E, G & I), with the highest improvement seen in Case G (67% improvement). The improvements seen in these cases were on speech, facial expression, hand movements, posture, gait and rigidity. There was note of a variable response of the UPDRS-III scores up to 12 months follow up. The mean UPDRS-III scores at 12 months was 19 ± 13.19. Thereafter, there was a trend towards worsening in the scores (see Fig. 2). Anti-parkinsonian drugs (carbidopa/levodopa) were tried in three cases (Cases B, C & G) with minimal improvement.

The worsening of symptoms was exacerbated by the short battery life of the IPG (Kinetra) in two cases (12 months for Case D and 36 months for Case A). Their dystonia and parkinsonism improved after the battery replacement. A case of skin erosion with secondary infection in the IPG pocket occurred at 36 months for Case E. It resolved after placing the IPG in the abdomen. In contrast to the variable responses as reflected by both the BFMDRS and UPDRS-III scores over time, there were subjective improvements of symptoms perceived by the patients ranging from 30 to 80%.

Using the clinical and functional staging of XDP [1], majority of patients prior to DBS were in Stage 4 (n = 5) and Stage 5 (n = 4). This indicated that these patients had generalized dystonia and/or moderate to severe parkinsonism associated with severe impaired function requiring assistance in activities of daily living. In contrast, after the DBS, there was an ordinal shift towards improvement of their clinical and functional staging based on their last follow-up. The majority of patients were in Stage 1 (n = 3) and Stage 2 (n = 5), indicating a focal or segmental dystonia or one to two parkinsonian traits, with independent to minimal impairment of function and independent in their activities of daily living (see Fig. 3).

4. Discussion

This was the first and only study that looked at the outcome of bilateral pallidal stimulation in XDP over a period of time (range of follow up: 6 mos–84 mos). Our results showed an improvement in the BFMDRS score ranging from 18 to 95% at 12 months. In contrast, the published cases reported an improvement in the BFMDRS score between 47 and 81% [9,11,14,15,17]. None of our patients had initial worsening of their dystonia, unlike that of a published case where there was a worsening of about 7% [13]. The initial and immediate improvement noted in these patients may be due to the lesion-like effect brought about by the DBS. The progressive and delayed response to stimulation has been observed in primary generalized dystonia, probably mediated by cortical reorganization [20].

In comparison to primary dystonia, at post-surgery there was a 51.8% mean percent improvement in the BFMDRS scores but the exact timeline was not mentioned in the meta-analysis [21]. A 6^{th}-month improvement of the BFMDRS scores was determined from the same

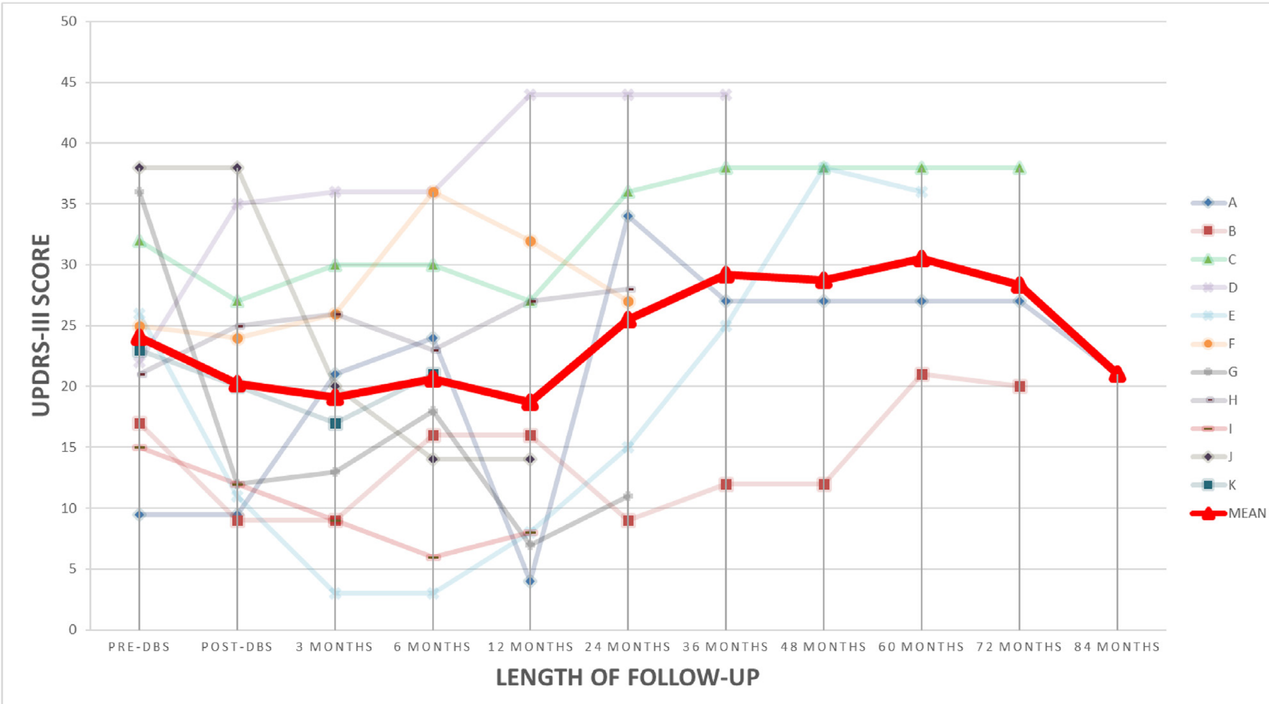

Fig. 2. Mean and individual scores of UPDRS-III from 11 patients: from pre-operative baseline scores up to the longest follow up of 84 months.

study showing that deep brain stimulation resulted to a mean percent improvement of 44.2%. This was comparable to our study with a mean percent improvement of 64.7%. A sustained improvement of around 37.3–79.1% of the BFMDRS scores for up to 72 months was also reported for primary dystonia [21] which is similar to our study showing a percent improvement of 28–90% at 72 months.

The heredodegenerative nature of XDP and its response to DBS for dystonia was better compared to similar heredodegenerative diseases such as Huntington's and rapid-onset dystonia parkinsonism (DYT12). In this subset of patients, the application of DBS showed poor response and progressive worsening of their dystonia and other symptoms [22,23].

In contrast to its effectiveness on dystonia, our results showed a variable response in the UPDRS-III scores, where some had worsening {range –(28–100%); Cases D, F & H} and improvement in the others (6–81%, Cases A, B, C, E, G & J) at 12 months. This was different from the published cases, where all had improvement between 5 and 78% [9–11,13–15,17] at 12 months. While the parkinsonism was not very pronounced in our patients (baseline UPDRS-III score range 9.5–38), the worsening of the parkinsonism in some of our patients may be due to an unmasking of the underlying parkinsonian symptoms after surgery or as a side effect of the bilateral pallidal DBS [24,25]. Moreover, the worsening over time could also be explained by the supposed natural history of XDP, where parkinsonism co-exist with dystonia by the 7th – 10th year or replaces the dystonia beyond the 10th year of illness [1]. In addition, the short battery life of the IPG (hence, subsequent IPGs were of the Activa RC type) and the infection also contributed to the worsening of the scores.

There were peri-operative adverse events reported in this case series with no significant post-operative morbidity. There was a case of skin erosion and infection at the IPG pocket in this case series, which was not reported in previous cases. Although rare due to the limited number

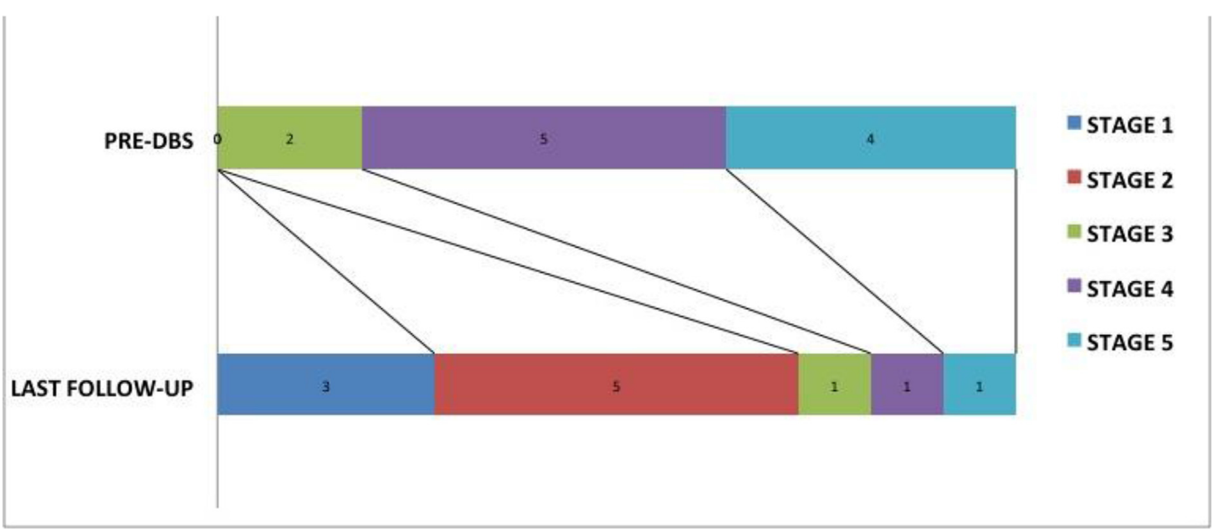

Fig. 3. Clinical and functional staging of XDP patients from pre-deep brain stimulation up to their last follow-up based on the proposed simplified staging of XDP [1].

of cases, this should be regularly evaluated. This is because the most common hardware-related complication of DBS was infection (5.12% of patients) [26]. No impulse control disorder was reported in this case series. However, this should be routinely screened as it had been reported as a complication of bilateral GPi DBS for an XDP patient [13].

The total number of DBS being done for XDP remains minimal. The biggest limiting factor is the cost of DBS in the Philippines, costing between US$35,000-40,000 and with only 2 Manila-based centers doing it. It is also not reimbursed by the national health insurance system [27]. The average annual Filipino family income is US$3808.72, while the average annual family expenditure is US$3131.62 [27]. A sample computation of the cost for an XDP patient taking at least one medication would be US$51.12–2398.56/year (USD:PHP 54:1, as of September 2018). Chemodenervation with botulinum toxin A would cost US$1111.11 per year at 4 month injection interval. Given these costs, it is unlikely patients can maintain a regular chemodenervation interval and take their medications as well or even afford a DBS.

Despite a variable response and decline in their scores, there was improvement in the patient's overall functional and clinical staging of the disease. A majority of our patients (n = 8, 73%) improved to Stages 1 and 2 from Stages 4 and 5 (n = 9, 81%). It is important to emphasize that DBS improves not only the symptoms but also the functional outcomes of the patients.

While this study only involved 11 patients, in various stages of follow up, this provided additional evidence that DBS is indeed beneficial for XDP. Additionally, we present the longest follow-up of the youngest patient at 84 months and two patients at 72 months.

5. Conclusion

In summary, bilateral pallidal DBS is an excellent option for XDP. It was shown to be effective in the first 12 months in controlling dystonia, with variable response in controlling parkinsonism with good functional outcome. It was generally safe with no significant post-operative morbidity. The long-term benefit beyond 12 months suggested benefit for controlling dystonia as seen in cases with longest follow-ups but parkinsonism seemed to progress despite this treatment.

Author roles

Dr. Abejero: study concept and design, acquisition of data, analysis and interpretation, writing of the initial draft and critical revision of the manuscript.

Dr. Jamora: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for intellectual content, study supervision.

Dr. Vesagas: study concept and design, analysis and interpretation, critical revision of the manuscript for intellectual content.

Dr. Teleg: study concept and design, analysis and interpretation, critical revision of the manuscript for intellectual content.

Dr. Rosales: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for intellectual content, study supervision.

Dr. Anlacan: study concept and design, analysis and interpretation, critical revision of the manuscript for intellectual content.

Dr. Velasquez: study concept and design, analysis and interpretation, critical revision of the manuscript for intellectual content.

Dr. Aguilar: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for intellectual content, study supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.09.022.

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