Unilateral Transcranial Magnetic Resonance-guided Focused Ultrasound Pallidothalamic Tractotomy in X-linked Dystonia-Parkinsonism: A Case Report

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ABSTRACT

X-linked dystonia-parkinsonism (XDP) is an adult-onset debilitating neurodegenerative disorder presenting with motor and nonmotor symptoms. The treatment options for XDP are limited. We described a patient with XDP who underwent a unilateral transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) pallidothalamic tractotomy with a one-year follow-up. The patient reported an immediate improvement in his pain after the procedure. Compared to baseline, there was an improvement in his scores in the dystonia (31%), parkinsonism (35.1%), and activities of daily living (71%) subscales at 1-year follow up. The overall improvement at one year was 46%. There were no adverse events noted. Additional studies with larger sample size and follow-up would be needed to document its long-term safety and efficacy.

Keywords: Focused ultrasound, pallidothalamic tractotomy, pallidothalamic tract, XDP, X-linked dystonia parkinsonism

INTRODUCTION

X-linked dystonia-parkinsonism (XDP) is an adult-onset neurodegenerative disorder with motor and nonmotor symptoms.[1,2] Oral medications and botulinum toxin (BoNT-A) injections are utilized in the management with mixed results.[3,4] Lesioning procedures such as bilateral chemopallidotomies, bilateral cryothalamotomy bilateral thalamotomy (ventrocaudal nucleus), unilateral cryothalamotomy, and bilateral thalamotomy followed by a cerebellar stimulation device implantation have been tried on eight patients with XDP with poor outcomes.[5]

Recent long-term outcome studies showed that pallidal deep brain stimulation (DBS) surgery is effective in improving the symptoms of the disease.[6,7] However, not everyone can undergo DBS, partly due to cost.[8] There have been reports on the utility of transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) for dystonia, including XDP.[9,10] Given the limited options for patients with XDP, we considered pallidothalamic tractotomy for our patients. Here, we report a patient with XDP who underwent a unilateral tcMRgFUS pallidothalamic tractotomy with 1-year follow-up.

**Dr. Jamora, Dr. Lin, Dr. Chang and Dr. Taira share primary authorship for this manuscript.*

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CASE REPORT

A 52-year-old man with a family history of generalized dystonia presented with 5-year leg pain on walking and progressive involuntary movements of the extremities. On examination, there was a right arm dystonia and flexion contractures at the level of the interphalangeal joints with severe pain (Visual analogue scale, VAS, 8/10), flexion of the left toes, right hallux hyperextension, right leg flexion, left leg extension when seated, and difficulty ambulating. He has moderate dysarthria, mild masked facies, rigidity (neck and upper extremities, worse on the right), moderate bradykinesia (right worse), and gait difficulty. A movement disorder neurologist (RDJ) utilized the XDP-Movement Disorder Society of the Philippines (MDSP) scale[11] in examining the patient. Another movement disorder neurologist blindly scored the videos for the dystonia and parkinsonism subscales (except for the rigidity) only. His mean baseline XDP-MDSP scale score was 80.5/200: part I (dystonia) 21/44, part II (parkinsonism) 27/76, part III (nonmotor) 8/40, and part IV (activities of daily living) 17/40 (Table 1).

His cranial MR imaging (MRI) showed moderate caudate head atrophy and bilateral symmetric hyperintensities in the moderately atrophic lateral putaminal regions. His genetic testing showed the presence of an SVA insertion within the *TAF1* gene using polymerase chain reaction

Table 1. Summary of XDP-MDSP scale scores before and after treatment with tcMRgFUS left pallidothalamic tractotomy

XDP-MDSP Scale	Baseline score (pre-tcMRgFUS)	After 1 week	After 1 month	After 9 months	After 12 months
I – Dystonia*					
I.1 Eyes and upper face	0.5	0	0	0	0
I.2 Jaw, tongue, and lower face	2	2.5	2	2.5	2
I.3 Larynx	1	3	2	1	1
I.4 Neck and shoulder	3	3	3	1	1
I.5 Upper and lower trunk	3	3	2	0	0
I.6a Right upper extremity	4	4	4	4	4
I.6b Left upper extremity	0	1	1	1	1
I.7a Right lower extremity	1	2	1	0	0
I.7b Left lower extremity	2	3	2	2	2
I.8 Posture	2.5	4	2	2	2
I.9 Gait and ambulation	2	3	2	1.5	1.5
I – Dystonia subtotal (maximum score of 44)	21	28.5	21	15	14.5
***II – Parkinsonism**†*					
II.1 Speech	2	4	4	2.5	2.5
II.2a Rest tremors: face, lips, chin	0	0	0	0	0
II.2bi Rest tremors: right upper extremity	0	0	0	0	0
II.2bii Rest tremors: left upper extremity	0	0	0	0	0
II.2ci Rest tremors: right lower extremity	0	0	0	0	0
II.2cii Rest tremors: left lower extremity	0	0	0	0	0
II.3ai: Rigidity: right upper extremity	3	3	3	1	1
II.3aii: Rigidity: left upper extremity	1	1	1	0	1
II.3bi: Rigidity: right lower extremity	2	2	2	0	0
II.3bii: Rigidity: left lower extremity	2	2	2	1	1
II.3c: Rigidity: neck	2	3	2	1	1
II.4a: Finger taps: Right	3.5	3	3	2.5	2.5
II.4b: Finger taps: Left	2	3	3	2	2
II.5a: Alternating hand movements: Right	3	2	3	2	2
II.5b: Alternating hand movements: Left	1.5	2	1	1	1
II.6a: Leg agility: Right	1.5	2	2	1.5	1.5
II.6b: Leg agility: Left	1.5	3	2	1.5	1.5
II.7: Arising from a chair	0	1	0	0	0
II.8: Gait freezing and shuffling	2	2	2	1.5	1.5
II – Parkinsonism – subtotal (maximum score of 76)	27	33	30	17.5	17.5

Table 1. Summary of XDP-MDSP scale scores before and after treatment with tcMRgFUS left pallidothalamic tractotomy *(continued)*

XDP-MDSP Scale	Baseline score (pre-tcMRgFUS)	After 1 week	After 1 month	After 9 months	After 12 months
IIIA – Behavioral					
IIIA.1 Cognition	0	0	0	0	0
IIIA.2 Apathy	1	1	1	0	0
IIIA.3 Anxiety	2	1	2	0	1
IIIA.4 Depression	0	0	0	0	1
IIIA.5 Irritability and aggression	1	2	1	1	1
IIIA – Behavioral – subtotal (maximum score of 20)	4	4	2	1	3
IIIB – Non-behavioral					
IIIB.1 Sleep disturbance	0	1	0	1	0
IIIB.2 Pain and other sensations	2	1	2	1	1
IIIB.3 Bladder incontinence	0	0	0	0	0
IIIB.4 Fatigue	1	1	1	1	1
IIIB.5 Saliva and drooling	1	1	1	1	1
IIIB – Non-behavioral – subtotal (maximum score of 20)	4	4	4	4	3
IV – Activities of Daily Living					
IV.1 Speech	3	3	3	1	2
IV.2 Chewing and swallowing	0	1	0	0	0
IV.3 Eating/ feeding	1	2	1	0	0
IV.4 Dressing	1	1	1	0	0
IV.5 Hygiene	1	1	1	0	0
IV.6 Handwriting	2	3	2	2	2
IV.7 Doing hobbies and other activities	4	4	4	0	0
IV.8 Turning in bed	1	1	1	0	0
IV.9 Transferring/getting out of bed or deep chair	1	0	1	0	0
IV.10 Walking and balance	3	1	2	1	1
IV – Activities of Daily Living – subtotal (maximum score of 40)	17	17	16	4	5
Total (I-IV)	80.5	86.5	73	41.5	43

**Average scores are done by 2 movement disorders neurologists*
†Average scores done by 2 movement disorders neurologists, except for the 5 items on rigidity
XDP, X-linked dystonia parkinsonism; MDSP, Movement Disorder Society of the Philippines; tcMRgFUS, transcranial magnetic resonance-guided focused ultrasound

confirming XDP. His medications were zolpidem 15 mg/day and biperiden 6 mg/day, with a reported relief of about 40%. His last BoNT-A injection was 6 months before the pallidothalamic tractotomy.

The patient was awake during the procedure. The procedure for MRgFUS thermoablation has been described in several published papers.[12,13] His head was fixed with a stereotactic frame in the approximate orientation of the anterior commissure –posterior commissure (AC-PC) under local anesthesia. The patient did not receive any sedation or other analgesics. He reported some discomfort during the stereotactic frame fixation. Degassed and chilled (15–20°C) water was circulated in the area between the head and the transducer. The procedure was performed in a 3 Tesla MRI (GE) and the ExAblate Neuro (InSightec, Israel) tcMRgFUS system. A reference scan was performed to position the transducer to the target. Anatomical MRI scans were fused to the preoperative computed tomography scan for the skull-correction algorithm.

Three targets aimed at the left pallidothalamic tract (PTT) were selected (Table 2). A series of low-power sonications (150 to 250 W) confirmed accurate focusing in three orthogonal planes using MR thermography.

Table 2. Target parameters in the identification of the left pallidothalamic tract

Target location	Left pallidothalamic tract		
AC-PC length (24.33 mm)	Target 1	Target 2	Target 3
From PC	12.2	10.7	10.2
From midline	9	10.5	10.5
From AC-PC level (mm)	1.5	0	0
From wall (mm)	7.7	9.2	9.2

AC, Anterior commissure; PC, Posterior commissure

Table 3. Sonications details during the left pallidothalamic tractotomy

Sonication	Power (Watt)	Duration (seconds)	Temperature (°C)	Energy (Joule)
1	231	12	43	2519
2	373	12	43	4025
3	523	13	47	6217
4	704	12	48	8014
5	801	15	51	11109
6	894	20	58	15527
7	950	26	54	23747
8	952	35	57	31413
9	907	29	56	25223
10	902	27	58	23764
11	944	38	56	34492
12	948	39	56	34477
13	956	38	57	34432
Mean ± SD	775.8 ± 236.6	24.3 ± 10.5	52.6 ± 5.4	19612.2 ± 11783.8

Therapeutic sonications were implemented by gradually escalating the power and monitoring the temperature. In total, 13 sonications were delivered (Table 3). The MRI T2-weighted images showed an anisotropic 10.7 x 10.7 x 11.6 mm lesion including the central necrosis and peripheral edema right after the treatment (Figure 1). Using the Morel atlas,[14] the target was shown to be in the PTT. Patient communication was maintained throughout the treatment and clinical neurological assessment for improvement of motor symptoms and presence of any side effects were performed after each sonication. The procedure lasted three hours.

Pain relief (VAS 1/10) was immediate and persistent. However, there was a transient worsening of the symptoms at 1 week follow-up: dystonia (35.7%) and parkinsonism (22%) (Table 1). Although formal testing at 9- and 12-month follow up showed improvement for both the dystonia (28.6%, 31% respectively) and parkinsonism (35.1%), there was a noticeable appearance of tongue protrusion, oromandibular dystonia, and anterocollis (Table 1), causing moderate to severe dysarthria and minimal dysphagia. There was no marked difference in parts IIIA and IIIB. A marked improvement was seen in part IV, 76.5% and 71%, respectively. The total XDP-MDSP scale score showed improvement at 9- and 12-month follow up (48.4% and 46.5%, respectively). His medications remained the same. No further BoNT-A injections were done.

DISCUSSION

The utility of tcMRgFUS for essential tremors, dystonia, and tremor-predominant Parkinson's disease (PD) has been reported.[15-17] However, the evidence for other movement disorders is lacking. Only three patients with XDP have undergone unilateral tcMRgFUS.[10]

Our patient underwent left pallidothalamic tractotomy. The PTT connects the globus pallidus internus with the ventroanterior/ventrolateral thalamus.[9] Targeting the PTT improves the dystonia by interrupting the cortico-basal ganglia-thalamo-cortical circuit through the modulation of the pallidal efferents to the thalamus.[9] In XDP, there is loss of the striosome compartment of the striatum.[18] Thereafter, there are reduced striatopallidal and striatonigral projections, correlating with the degree of striatal neuronal loss.[19,20] The said pallidothalamic tractotomy resulted in an overall improvement of 46.5% at one year for our patient. This was better than the reported outcome (30.1%) in a recent publication.[10] There was a significant improvement in our patient's pain sensation involving the right arm dystonia. In PD, the pain has been reported to be the only one that improved after pallidothalamic tractotomy.[17] A unilateral procedure was decided on by the team as there is no published literature on the safety of a bilateral pallidothalamic tractotomy in XDP. However, a staged procedure has been done in patients with essential tremor and PD.[21-23]

At 1-year follow up, bilateral pallidal DBS on XDP has shown improvement in the dystonia (n=16, 18–100%) with one patient worsening (-7%) and improvement in the parkinsonism (n=14, 6–81%) and three patients worsening (-[29–100%]).[6,7,24] Longer follow-up (29–84 months) still showed improvement compared to baseline, albeit at a lower degree (n=13, 3–98%) and 1 patient worsening (-20%). For the parkinsonism phase, there was an improvement of 24–41.7% (n=5) and in 6 patients, worsening (-[17–100%]).[6,7,24] In another study (n=16), they concluded that there was a marked improvement in dystonia and a variable response in the parkinsonism.[7] In all these patients, they used the BFMDRS and the UPDRS; hence, it will be difficult to directly compare with our results. Nevertheless, in both procedures, improvement was noted. The advantage of using the XDP-MDSP scale lies in the fact that it was specifically developed and validated for use in XDP patients.[11] Moreover, aside from the dystonia and parkinsonism subscale, it

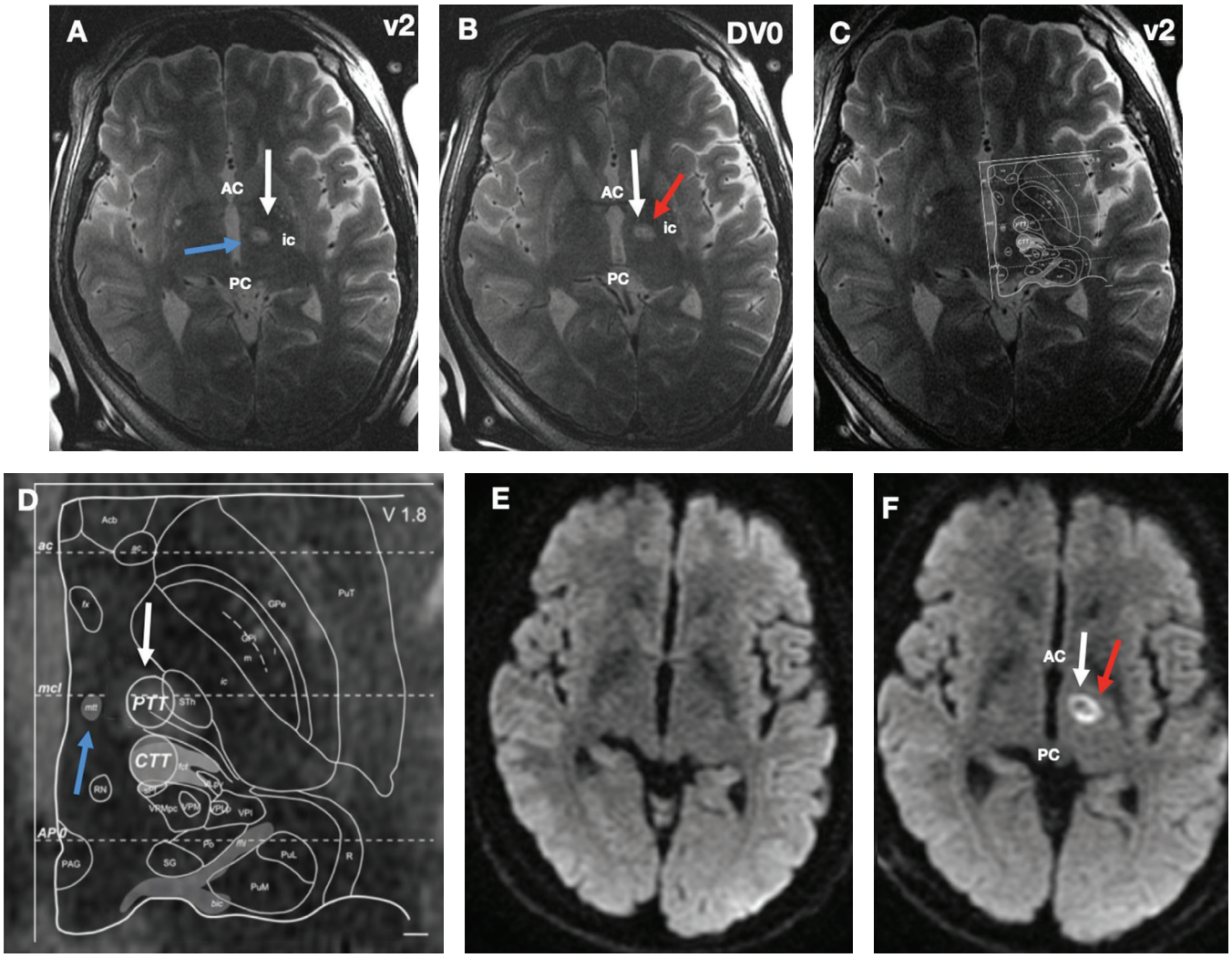

Figure 1. **(A)** Intra-operative MRI axial T2 scan done after sonications, at 2mm ventral (V2) to AC-PC (anterior commissure; posterior commissure) plane (*blue arrow:* mammillothalamic tract (MTT); *white arrow:* target 1). **(B)** At the level of AC-PC plane (DV0: dorsal-ventral), first and second targets *(white and red arrows)* are well visualized with central necrosis. **(C)** At the level of 2mm ventral (V2) to AC-PC plane, with the Morel atlas, showing that the target is on the pallidothalamic tract (PTT). **(D)** Closer view of overlay with Morel atlas showing target 1 *(white arrow)* and MTT *(blue arrow)*. **(E)** Pre-operative diffusion weighted imaging (DWI). **(F)** Postoperative DWI, with targets 1 and 2 *(white and red arrows)* visualized.

includes subscales on the nonmotor symptoms and activities of daily living.

The use of tcMRgFUS is a promising transcranial technique and its incisionless approach is a factor in its favor. Lesional procedures have some distinct advantages over DBS. Lesioning would not entail frequent visits as there is no programming required. Overall, it costs less than DBS and there is no need for battery replacement.[25]

There are no available long-term studies on tcMRgFUS for dystonia. For MRgFUS thalamotomy for essential tremors, the common side effects include balance disturbance, mild weakness of the contralateral lower limb, mild sensory loss in the contralateral hand and mouth area.[26] These side effects are mild and usually resolve within three months. Some complications of tcMRgFUS were skull heating and necrosis, transient headaches, and scalp burns.[12]

We were unable to get a tractography at baseline as well as after 12 months as this would entail longer imaging time and the need for sedation. There was also limited mobility of the people in the city due to the COVID-19 quarantine imposed by the government. Another limitation would be that we do not have any data on who would be the best candidate for tcMRgFUS or how soon it should be done. In DBS for XDP, they are suggesting that the DBS should be done early in the disease, before caudate atrophy sets in.[7] It would be interesting to see the effects of a staged procedure to control the generalized dystonic symptoms. However, its effects on the parkinsonian phase of the disease

are unknown at this time and will need to be observed. Despite these limitations, this was a case of a successful tcMRgFUS pallidothalamic tractotomy in an XDP patient, with a one-year outcome.

A unilateral tcMRgFUS pallidothalamic tractotomy may be considered for patients with XDP. Patients with asymmetric dystonia may be the best candidates for the procedure. However, more patients with longer follow-ups are needed.

Ethical Compliance Statement

This study was approved by the Show Chwan Memorial Hospital Institutional Review Board (SCMH IRB No. 1080201). The procedure was likewise approved by the Taiwan Food and Drugs Authority (Case No: 1080006867). The video of the patient was taken after written informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Acknowledgments

The authors gratefully acknowledge the patient and his family for allowing us to report this. We would like to thank President Min-Ho Huang of the Show Chwan Health Care System for his support of this project. We also thank Prof. Arlene Ng and Ms. Estrela Silverio of the Movement Disorders Service of St. Luke's Medical Center – Quezon City for their assistance and Prof. Christine Klein and her team at the Institute for Neurogenetics, University of Luebeck, Germany for the genetic testing of our patient.

Statement of Authorship

RDGJ: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. WL: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. KWKT: Data curation, formal analysis, interpretation of data, writing-review, and editing. HCL: Data curation, formal analysis, interpretation of data, writing-review, and editing. PYC: Data curation, formal analysis, interpretation of data, writing-review, and editing. ATP: Data curation, formal analysis, interpretation of data, writing-review, and editing. WCC: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. TT: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing.

All authors approved the final version submitted.

Author Disclosure

Drs. Lin and Chang have received lecture fees from InSightec. Dr. Tsai is now with InSightec. The rest of the authors have no financial relationships relevant to this article to disclose. We declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

All authors declared no conflicts of interest.

Funding Source

No specific funding was received for this study.

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