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The first and foremost unilateral pallidothalamic tractotomy done in India for Parkinson's Disease. An interesting case report

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ABSTRACT

Background. Pallidothalamic tractotomy" can be effective in Parkinson's disease by exhibiting anti-parkinsonian effects.

Case presentation. The patient was a 53 years old gentleman, having Parkinson's disease for the last 14 years. The disease onset was on the left side and slowly moved to the right side. He had tremors, slowness of body movements and stiffness of the movements. The first right Pallidotomy was done in January 2019. There was a noticeable improvement in a few weeks. He continued to have symptoms on the right side. The preoperative Unified Parkinson Disease Rating Scale (UPDRS) part 3 score in 2019 was 53 while the postoperative score was only 26 showing drastic improvement after right Pallidotomy. After 2 years of the first surgery, a new technique called Pallido Thalamic Tractotomy (PTT), an MRI-guided stereotactic surgery was done on the left side. Tremors reduced gradually by 99% in 3 weeks after surgery. This is the first case of PTT performed on a patient with Parkinson's disease in India.

Conclusion. PTT is an effective procedure in PD that acts by disconnecting the pallidothalamic tract. Unilateral pallidothalamic tractotomy done on the left side improved contralateral side rigidity, tremors and bradykinesia.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily affecting the body's movements [1]. It is characterized by global slowing of body movements, known as bradykinesia, and other symptoms such as resting tremors and rigidity. James Parkinson first described Parkinson's disease in 1817 [2,3]. Initially, the term shaking palsy was used by medical writers like Parkinson for Parkinson's disease [2]. It was further refined, characterized, and expanded by Jean-Martin Charcot in the mid-1800s [3]. It affects, on average, one to two people per 1000 population at any time.

PD is a multifactorial disease [4]. The etiology is unknown in the majority of the cases, with genetic and environmental risk factors also playing a role [4,5]. The prevalence increases with age affecting about

Keywords
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1% of the population aged more than 60 years [6]. The prevalence of PD generally increases with an increase in age [7,8]. The incidence is higher in males in all age groups, with a significant difference in incidence between 60-69 and 70-79 years [8]. According to "The Parkinson's Foundation Prevalence Project," it was estimated that around 930,000 people in the United States would have PD by the year 2020, and it is expected to rise to 1.2 million by 2030 [9]. Symptoms start gradually, sometimes starting with a barely noticeable tremor in just one hand. Tremors are typical, but the disorder mainly causes stiffness or slowing of movement [1,4,10]. Postural instability occurs with the progression of the disease. But, the detailed clinical course has not yet been elucidated [10].

The primary pathophysiology appears to be due to the accumulation of alpha-synuclein in various parts of the brain, primarily the substantia nigra, leading to degeneration and subsequent loss of dopamine in the basal ganglia that control muscle tone and movement [4,11].

Parkinson's disease is typically treated with medication. The medication usually works very well in the first few years of treatment, but it becomes less effective after some time. The best management then usually involves placing a pacemaker inside the brain by inserting electrodes and modulating the pacemaker's frequency. It produces a result for the patient for the symptoms of the disease. It is known as Deep brain stimulation surgery (DBS) [12]. But it is costly, especially considering the cost of the pacemaker. As known, there is no cure for Parkinson's Disease at all. Parkinson's is a progressive degenerative disease that can only be treated by medicines to curb rapid growth or sustain tremors. It progresses faster in some and slow in some patients. All Parkinson's patients do not benefit from surgery.

The Pallidothalamic tract is a part of the basal ganglia. It connects the internal globus pallidus and thalamus (a ventrolateral portion of the thalamus). It is comprised of ANSA lenticularis and fasciculus lenticularis [13]. Both of them take their origin from the internal part of the pallidum. These tracts merge into the fasciculus thalamicus before entering the thalamus [13]. Pallidothalamic fibres of the Ansa reticularis and fasciculus lenticularis are funneled into the thalamic fasciculus (H1 forel field) before reaching the thalamus. They join two to three

millimeters below the intercommissural plane (H2 forel field). Hence interruption of the Pallidothalamic tract at the H1 level amounts to Pallidotomy functionally because the major pallidal outputs go through it and can be achieved with smaller lesion size. PTT can be compared to a pallidotomy that is optimized, as it is capable of extensive liberation of the dynamics of the thalamocortical system by leaving intact thalamus using a very restricted ablation of the tissue. Neurosurgical ablation of the pallidothalamic tract is called Pallidothalamic Tractotomy (PTT). It has been reported as an effective treatment for PD in a few studies by exhibiting anti-parkinsonian effects [14,15]. But there is a lack of literature in India regarding PTT.

CASE PRESENTATION

Case description

The patient was a 53 yrs old gentleman, having Parkinson's disease for the last 14 yrs. It started with mild tremors in his left hand and progressed to some stiffness and difficulty moving the hand. He had tremors, slowness of body movements, and stiffness. Over the next few years, it involved his entire body, with the left side more affected than the right side to the extent of losing his confidence in even walking or performing his daily activities. With this situation, he was unable to do his tailoring, which was his sole source of revenue for him and his family. He approached doctors, took treatment, and was put on regular medications. They were given since the disease started. An increase in the dosage of drugs did not alter the symptoms. It was started with two doses of Levodopa and carbidopa and increased gradually. The medication included tablet levodopa and carbidopa 100/25 mg used four times a day, T.Ropinorole 6mg per day, and T.Trihexyphendyl 4mg per day. The patient was intolerant to drugs for further enhancement. His tremors would subside when he took medicines and aggravate once their effect was over, the medicines' so-called on and off period. He was suggested to undergo Deep brain stimulation surgery (DBS). But it was not affordable for him. Medical treatment was started at various places for nearly 12 years without full benefit. The patient had developed a side effect called Drug-induced dyskinesia (Levodopa). He presented in 2018 - 2019 to a tertiary care institute with symptoms despite medications. Levodopa (400 mg/day) was required to maintain daily activities. The

timeline of the clinical presentation and management is shown in Figure 1.

Fig. 1. Timeline of the clinical presentation and management of the patient.

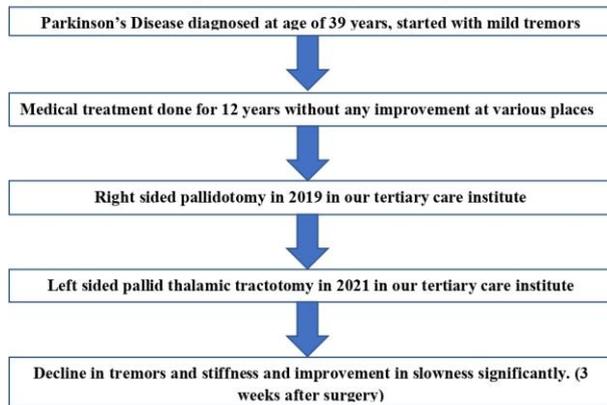


Figure 1. T1 axial MRI of the brain showing the first operation pallidotomy scar on the right side.

First surgery (2019)

The first right pallidotomy was done in January 2019. It was an MRI-guided macro stem controlled, stereotactic right pallidotomy [16,17]. It was done on 2 Postero Ventral Pallidum (PVP) tracks with 3 lesions each, using a 1x4 electrode at 70 degrees centigrade for 40 seconds. There was a noticeable improvement in a few weeks. Tremors, stiffness, and slowness improved significantly on the left side. He continued to have symptoms on the right side. The preoperative Unified Parkinson Disease Rating Scale (UPRDS) part 3 score in 2019 was 53, while the postoperative score was only 26 showing drastic improvement after right Pallidotomy. The old pallidotomy scar on the right side can be seen in Figure 2.

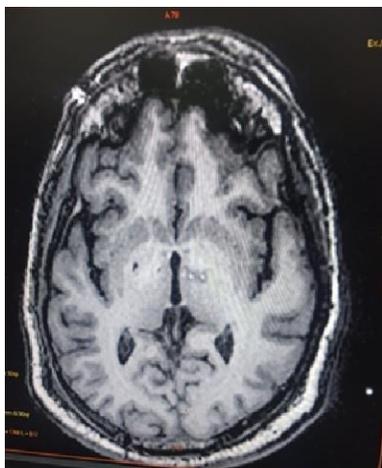


Figure 2. Surgiplan software post-op MRI, showing the precision of targeting with pre-op planned targets in Green and the post-op lesion. Green indicates Pallidothalamotomy lesion in PTT lesion area.

Second surgery (2021)

After 2 years of the first surgery, a new technique called Pallido Thalamic Tractotomy (PTT), an MRI-guided stereotactic surgery was done on the left side [14,15,18,19]. On 7th July 2021, he underwent PTT surgery. There is a risk of dysphagia and dysarthria with bilateral Pallidotomy, even if it is a staged pallidotomy. Hence, we decided to use a white matter target - the PTT or the Pallido Thalamic Tract. This tract is just lateral to the mamillothalamic tract. It covers the cZI/ PSA area (including the fields of Forel H1 & H2) [13]. These 2 references were based on the Schaltenbrand-Wahren atlas [20], and studies reported by Aufenberg C et al. (2005) [19], and Magara A et al. (2014) [21]. This is located just above the superior border of the STN, seen as low-intensity areas on T2 MRI and the location where we usually get the best results in STN DBS. MRI-guided, stereotactic, macro stem-controlled lesioning in PTT-1 and PTT-2. One lesion each using 1x4 electrode, at 70 degrees centigrade for 40 secs. The pre-op targets fixed for PTT can be seen in Figure 3.

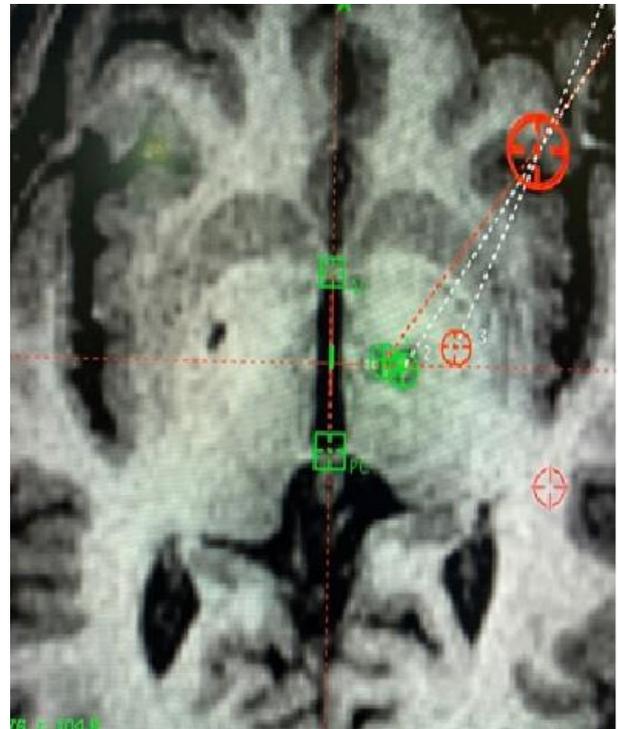


Figure 3. Surgiplan software post-op MRI, showing the precision of targeting with pre-op planned targets in Green and the post-op lesion.

Stereotactic MRI is taken to mark the exact location with the help of special software to locate the target

circuit to be burnt. Stereotaxic surgery or stereotactic surgery is a three-dimensional surgery technique [13,18,22]. It enables the detection of deep lesions in the tissues to be located and then treated using heat or cold, or chemicals. The procedure itself is so complicated. It is a procedure that involves fixing a particular frame called a stereotactic frame on the skull by drilling 4 screws [23].

A 14 mm hole is made in the skull. An electrode is inserted inside the brain. The correct location is tested by giving a mild current and burning the circuit at 70 degrees for 40 seconds with a Radio Frequency Lesion generator. This procedure is called an MRI-guided stereotactic Pallidotomy, which goes 9 to 11 cm deep inside the brain [16]. As soon as the lesioning was done, Tremors came down gradually, and the hand became loose. Rigidity, stiffness of their body - both in his hand and leg improved gradually.

Within a few weeks, there was a decline in tremors, stiffness, and improvement in slowness significantly. Tremors reduced gradually and significantly within 3 weeks after surgery as measured by the UPDRS scale. He had no memory or other intellectual brain issues. He can carry out day-to-day activities without any difficulties. PTT surgery on the left side resulted in a significant fall in the Right side UPDRS off phase score from 25 in the preoperative period to 4 in the postoperative period. Unilateral Pallidothalamic Tractotomy on the left side improved contralateral side rigidity, tremors, and bradykinesia.

Table 1. Comparative table for total score of part 3 UPDRS (Unified Parkinson Disease Rating Scale)

Year	Surgery done	Pre-operative (or) Post-operative	UPDRS Score
2019	Right Pallidotomy	Pre op	53
		Post op	26
2021	Left Pallidothalamic tractotomy	Pre op - off phase	30
		Post op - off phase	10

Table 1 describes the UPDRS (Unified Parkinson Disease Rating Scale) scores preoperatively and postoperatively after right Pallidotomy in 2019 and left Pallidothalamic tractotomy in 2021, respectively.

The preoperative UPDRS part 3 score in 2019 was 53, while the postoperative score was only 26 showing drastic improvement after right Pallidotomy. The preoperative UPDRS part 3 score in 2021 was 30, while the postoperative score was 10, thereby demonstrating significant clinical improvement after left pallidotomy tractotomy. There was no alteration in cognitive function before and after surgery.

Table 2 describes the comparison of right and left UPDRS scores preoperatively and postoperatively after left Pallidothalamic tractotomy in 2021, respectively, in the off phase. The preoperative UPDRS score was 25 in the off phase in the right, while the postoperative score was only 4 showing drastic improvement after right pallidothalamic tractotomy in 2021.

Table 2. Comparative table for right and left UPDRS scores before and after left Pallidothalamic tractotomy done in 2021

Pre-operative (or) Post-operative	Right	Left
Pre op - 2021 off phase	Off- 25 (On- 11)	Off-5 (On-4)
Post op - 2021 off phase	Off- 4	Off-6

DISCUSSION

The present case report describes a staged lesioning surgery with Pallidotomy and PTT for treating Parkinson's Diseases symptoms. It is the first time in India Pallidothalamic tractotomy has been done to cure Parkinson's or any other Movement Related Disorder. In other countries like the U.S. and Japan, PTT has been used to manage Parkinson's Disease and other Movement Disorders. Stereotactic surgery has become popular in treating Parkinson's disease (PD) due to the long-term complications of levodopa therapy, causing significant disability.[24] Surgery for Parkinson's disease has evolved from ablation with careful lesion placement in various brain structures to stimulating particular brain targets in the basal ganglia.[25] There has been a better understanding of the physiology and the circuit of basal ganglia in recent decades with the improvement of neuroimaging and surgical techniques.

The first surgery we did in 2019 is called the Pallidotomy, and the surgery done in the area of the brain is called GPi – Globus Pallidus interna. The second surgery is called the Pallidothalamic tractotomy (PTT), where the surgery was an MRI-guided stereotactic surgery.

PTT is a part of the brain circuit that connects two nucleus - Globus pallidus and the thalamus deep inside the brain, which plays a vital role in the symptoms of Parkinson's disease. Lesioning or burning a circuit inside the brain has been a standard of care treatment and has been there for around several decades [13,26,27]. Burning this circuit can alleviate Parkinson's symptoms. The brain circuit connects two prominent nucleus in the brain. Alteration of the activity due to the disease process causes Parkinson's symptoms on the opposite side. By burning this circuit - pallido-thalamic tract (PTT), the symptoms of Parkinson's disease. This is the first case of PTT performed in a patient with Parkinson's disease in India. It has been reported as an effective treatment for PD in a few descriptive studies worldwide by exhibiting anti-parkinsonian effects [14,15]. Our current approach, i.e., targeting the pallidal efferent fibers in the subthalamus as shown in Figure 3, was proposed by Meyers R [28]. Then, Pallidothalamic tractotomy was explicitly done for PD by Aufenberg C et al.[19], Godinho F and Magnin M et al.[29]

There was a drastic improvement in postoperative score after right Pallidotomy in the present case. After 2 years of the first surgery, PTT surgery was done. The UPRDS off-phase preoperative score (in 2021) was 30, while the postoperative score was only 10 after PTT surgery. There was no alteration in cognitive function before and after surgery. PTT surgery is done on the left side, resulting in a significant fall in the right side UPDRS off phase score from 25 in the preoperative period to 4 in the postoperative period. Horisawa S et al.[14] in 2019 presented the first single case report of PTT performed in a patient with Parkinson's disease, with a follow-up of one year. Their patient was a 68-year-old woman who had a similar presentation of PD in comparison with the present case. She started to experience the "wearing-off" phenomenon after 14 years of medical management. She also required Levodopa (300 mg/day) to maintain daily activities similar to the present case. During the preoperative, She underwent PTT on the left side without any perioperative complications.

On follow-up after 1 year, she had daily maintenance levodopa (200 mg) without an "off" condition all day. The 1-year UPDRS scores showed significant improvement, similar to the present case.

They concluded that PTT might be useful in PD subjects who don't desire device implantation. Horisawa Set al.[15] in 2021 studied Unilateral pallidothalamic tractotomy for akinetic-rigid Parkinson's disease in 14 patients. They observed that the total MDS-UPDRS Part III score significantly improved from 45 ± 4.6 at baseline to 32.9 ± 4.8 at 12 months postoperatively ($p = 0.005$) in the 10 patients available for follow-up. They also observed, similar to our case, that contralateral side rigidity and bradykinesia significantly improved. They also observed no severe permanent neurological deficits similar to our study.

Horisawa S et al. [14] in 2019 presented the first single case report of PTT performed on a 68-year-old female patient with Parkinson's disease, with a follow-up of one year on Levodopa (300 mg/day) for maintaining daily activities. Her preoperative Unified Dyskinesia Rating Scale (UDysRS) and Parkinson's Disease Questionnaire-39 (PDQ-39) scores were 102 and 46, respectively. She underwent left-sided PTT, and no perioperative complications were observed. Her UDysRS and PDQ-39 scores after one year of surgery were 20 and 20, respectively. PTT might be useful in patients who do not desire device implantation. Gallay MN et al.[18] in 2021 did Bilateral MR-Guided Focused Ultrasound PTT for 10 patients suffering from chronic and therapy-resistant PD. They were followed up for 1 year after the operation of the second side. They observed a reduction in total UPDRS score off-medication similar to the present case at 1 year after the second PTT by 52% compared to baseline on-medication ($p < 0.007$). They concluded that bilateral PTT effectively controls PD symptoms compared to medical management at its best.

CONCLUSIONS

Preliminary case reports across the globe have shown reasonably good outcomes. The present case report, the first of its kind in India, reports this procedure's effectiveness and safety. It was the first time in India, Pallidothalamic tractotomy had been done to treat motor symptoms of Parkinson's or any other Movement Related Disorder. It is also the first time in India, Bi-Lateral Lesioning surgery for treating Parkinson's Diseases symptoms has been done. This surgery will be a boon for patients with PD as it will improve their quality of life. The cost associated with this surgery is much less than the cost of pacemaker

implantation in the brain. This case report gives substantial evidence to support the need for future studies. Larger scale interventional studies with randomization are required to make evidence-based recommendations.

LIMITATIONS

Being a single case report, the reliability of the present study findings is poor. There was also no control to compare the results. The data available from this study is not enough to advocate the use of PTT and its relatively low risk profile.

LESSONS

PTT is an effective procedure in PD that acts by disconnecting the pallidothalamic tract. Unilateral pallidothalamic tractotomy on the left side improved contralateral side rigidity, tremors, and bradykinesia. It is the first time in India that PTT has been done for treating symptoms of Parkinson's Disease. It will enable them to carry out their day-to-day activities without support. The cost associated with this surgery is much less than the cost of pacemaker implantation in the brain.

ABBREVIATIONS

PTT - PallidoThalamic Tractotomy,
 PD - Parkinson's disease,
 UPDRS - Unified Parkinson Disease Rating Scale,
 DBS - Deep Brain Stimulation Surgery

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