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Case Report

Resolution of tardive tremor after bilateral subthalamic nucleus deep brain stimulation placement

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ABSTRACT

Background: Tardive tremor (TT) is an underrecognized manifestation of tardive syndrome (TS). In our experience, TT is a rather common manifestation of TS, especially in a setting of treatment with aripiprazole, and is a frequent cause of referrals for the evaluation of idiopathic Parkinson disease. There are reports of successful treatment of tardive orofacial dyskinesia and dystonia with deep brain stimulation (DBS) using globus pallidus interna (GPi) as the primary target, but the literature on subthalamic nucleus (STN) DBS for tardive dyskinesia (TD) is lacking. To the best of our knowledge, there are no reports on DBS treatment of TT.

Case Description: A 75-year-old right-handed female with the medical history of generalized anxiety disorder and major depressive disorder had been treated with thioridazine and citalopram from 1980 till 2010. Around 2008, she developed orolingual dyskinesia. She was started on tetrabenazine in June 2011. She continued to have tremors and developed Parkinsonian gait, both of which worsened overtime. She underwent DBS placement in the left STN in January 2017 with near-complete resolution of her tremors. She underwent right STN implantation in September 2017 with similar improvement in symptoms.

Conclusion: While DBS-GPi is the preferred treatment in treating oral TD and dystonia, DBS-STN could be considered a safe and effective target in patients with predominating TT and/or tardive Parkinsonism. This patient saw a marked improvement in her symptoms after implantation of DBS electrodes, without significant relapse or recurrence in the years following implantation.

Keywords: Deep brain stimulation, Subthalamic nucleus, Tardive dyskinesia, Tardive tremor

INTRODUCTION

Tardive dyskinesia (TD) is a complex iatrogenic movement disorder that can manifest as orolingual, truncal, or respiratory dyskinesia as well as dystonia, tremor, chorea, myoclonus, akathisia, or Parkinsonism.[2,24] It is caused by dopamine-blocking agents including typical as well as new-generation antipsychotics and anti-emetics.[12,19] TD can be disabling and socially isolating, its pathophysiology is poorly understood, and treatment is challenging. More than two-thirds of patients will continue to have dyskinetic movements after discontinuation of the offending drug.[29] Conventionally, TD is used to describe orofacial-lingual movements (orolingual TD [oTD]) and is treated with anticholinergic, dopamine depleting, muscle relaxant medications, and botulinum toxin injections. Often, these treatments have significant side effects with unsatisfactory clinical benefits.[11,25]

Tardive tremor (TT) is an underrecognized manifestation of tardive syndrome (TS). It was first described by Stacy and Jankovic and in a few following reports.[20,23] TT is a coarse, 2.5–6 Hz, primarily postural, and is also frequently present with action and at rest. Resting component of this tremor is commonly present in proximal legs and in the whole upper body and it can markedly interfere not only with hand use but also cause distress when simply resting or sitting.[22] TT is typically associated with orofacial dyskinesia or other manifestations of TS. In our experience, TT is a rather common manifestation of TS, especially in a setting of treatment with aripiprazole, and is a frequent cause of referrals for evaluation of idiopathic Parkinson's disease (PD).[26] TT tends not to respond to the essential tremor medications or dopaminergic agents. Reports on the first-line medication for TS, tetrabenazine (TBZ), ranged from marked benefit to no response.[10,20] In addition, TBZ itself can cause resting tremor as part of its Parkinsonism-inducing side effects. Anticholinergics may improve this tremor but the data are lacking and their side effects are often prohibitive in older individuals.[26]

There are reports of successful treatment of tardive orofacial dyskinesia and dystonia with deep brain stimulation (DBS) using globus pallidus interna (GPi) as the primary target, but the literature on subthalamic nucleus (STN) DBS for TD is lacking.[6,8,9,11,16] To the best of our knowledge, there are no reports on DBS treatment of TT. Here, we present a case of a woman with tardive orofacial dyskinesia, TT, and drug-induced Parkinsonism (DIP), treated with bilateral STN DBS.

CLINICAL PRESENTATION

A 75-year-old right-handed female with the medical history of generalized anxiety disorder and major depressive disorder with a history of SI has been treated with thioridazine and citalopram from 1980 till 2010. Around 2008 at the age of 67, she developed orolingual dyskinesia: "*difficulty with her tongue thrusting out of her mouth, causing the tongue to be sore and lips to be chapped, and annoying her.*" Her treatment and symptom timeline are summarized in [Figure 1]. Benztropine and oral lidocaine did not alleviate the movements and thioridazine was discontinued. In January of 2011, quetiapine 50 mg was started. This did not control her oTD, and in addition, she developed an urge to chew (was chewing on carrots or almonds to relieve the urge) and her husband had noticed that she was moving her legs and rocking her body. The patient herself was unaware of these movements. Subsequently in June 2011, she was started on TBZ 12.5 mg bid which successfully relieved her oTD. In December 2011, she was hospitalized for worsening depression, lost her job, and underwent a 13-treatment course of electroconvulsive treatment (ECT). At that time, she was taking 12.5 mg TBZ 3 times daily along with fluoxetine 50 mg, quetiapine 200 mg, and trazodone 100 mg nightly. Her oTD remained under control with TBZ 12.5 mg bid. She had two falls in 2012. By July of 2013, she developed intermittent right foot resting tremor and postural and kinetic hand tremors that were making it difficult for her to eat soup with a spoon, eat with a fork, and write. Propranolol at 10 mg bid was started with possible benefit. When first seen by us in January of 2015, she had mild oral TD, bilateral resting and postural hand tremors, and moderate right leg resting tremor. There was mild to moderate bradykinesia in both lower extremities and she had mildly Parkinsonian gait [Video 1]. With oTD controlled, tremors were the most bothersome symptom. To help with it, the following medications were tried without a success: propranolol up to 20 mg tid, Amantadine, Sinemet, Pramipexole, and Primidone. Propranolol was stopped due to worsened depression. Her tremors had transiently yet significantly worsened with increased TBZ dose to 25 mg tid. It seemed that tremors were aggravated by TBZ and two trials TBZ discontinuation were carried out, one 3 weeks in duration in 2015 and one of 1 week in duration in 2016 (she was unable to stay longer off TBZ due to recurrence of oTD). However, discontinuation of TBZ did not alleviate the tremors. Lowering quetiapine from 200 to 100 mg and tapering off fluoxetine did not improve tremors, either. Unfortunately, overtime both the tremors and Parkinsonism worsened to the point that she was unable to have meals at the table due to violent proximal leg tremor, nor was she able to feed herself. Her balance continued to worsen and in 2015 she had a fall and broke her hip.

A possibility of therapeutic DBS surgery was discussed and the patient was eager to get the treatment. Her dopamine transporter (DAT) scan showed normal DAT in basal ganglia. One possibility for this patient was to target the GPi with the hopes of alleviating her oTD and discontinuing treatment with TBZ. However, due to the two trials of TBZ discontinuation not alleviating the tremors, this was considered too risky. Therefore, a decision was made to target the STN with the goal of alleviating her main complaint which was resting leg and hand tremor, as well as bradykinesia and rigidity.

In January 2017, she underwent left STN implantation with Medtronic DBS system, with initial near-complete resolution of tremors. In September 2017, she underwent right STN implantation with similar improvement, however with the side effect of marked hypophonia and mild cognitive impact [Video 2]. The coordinates used for both implants were 12 mm lateral, 4 mm inferior, and 4 mm posterior to the mid-commissural point. She currently requires stimulation of 3.4 V on the left and 4.2 V on the right for symptomatic relief. Two years after implantation, her leg tremors are not at all bothersome and she is able to feed herself. She feels that she

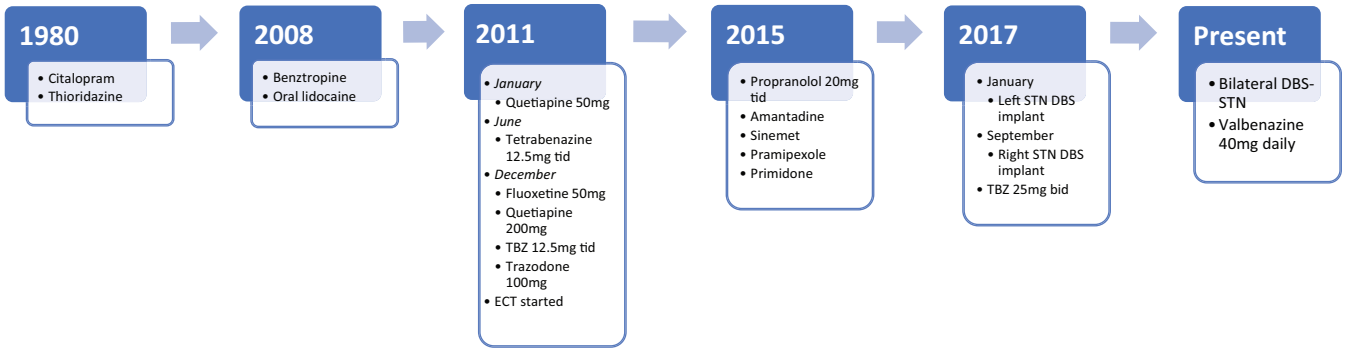

Figure 1: Treatment summary from 1980 to present.

is almost "perfect," but she still has a fear of falling and uses a walker for ambulation. Regardless, she is able to participate in weekly ballet classes and is exercising 2 days/week. She continued to need TBZ 25 mg bid but in the wake of worsening Parkinsonism (small handwriting), she was recently switched to Valbenazine 40 mg daily.

DISCUSSION

The incidence of tardive symptoms has been reported as high as one in three patients on typical antipsychotics.[3] When tardive symptoms are noticed, the strategy is to taper down or stop the offending antipsychotic medication.[2] Unfortunately, only less than a third of patients remit after the anti-dopaminergic medications are stopped.[4] The reasons for that are not understood and the prevailing notion of altered synaptic plasticity does not explain the emergence of TD after very brief, sometimes single-dose exposures to dopamine-blocking agents. Medical and botulinum toxin treatments remain the mainstay of therapy, however, as our case illustrates, this can fail miserably. A special formulation of gingko biloba extract showed a clinically significant benefit in patients with TD in multiple studies and a recent meta-analysis.[27,28] While the benefits of DBS in oral TD and dystonia are clear, medical management remains the mainstay of therapy.

DIP is another condition that is associated with antipsychotic use, affecting up to 4–40% of patients. In addition, TBZ, the most effective medication for oTD, has also been reported to induce Parkinsonism in approximately 30% of patients.[4,13,14,17] Calcium channel blockers, antiepileptic agents, and GI dopamine blockers have also been implicated.[4,17] DIP shares many clinical features with PD and can be misdiagnosed as PD. In fact, the D_2 receptor blockade by antipsychotics results in similar physiological changes that occur in PD due to increased GABAergic inhibition of thalamocortical projections.[17] Time of onset of clinical symptoms in DIP is variable but typically requires months or years of drug exposure. Clinical suspicion of DIP should arise when patients present with a symmetric, bilateral, and often proximal upper and lower extremity tremors that have postural, kinetic, and resting components.[1,17] It can be confirmed by resolution of symptoms after cessation of the offending agent; however, as with TD, in up to 25% of cases, symptoms persist and further workup may be indicated as these drugs may have unmasked a preclinical PD.[18] DAT imaging can be used to distinguish PD (neurodegeneration of dopaminergic neurons) from DIP (dopamine receptor blockade), which was done in our case and was negative for PD.[1,17]

Typically, DBS is considered if medical treatment fails or if medication adverse effects are intolerable to the patient. The common targets for electrode placement, as in PD, are the GPi or the STN; however, the vast majority of research has been conducted in tardive dystonia and has not been well studied in oral manifestations of TD. In a sham stimulation-controlled trial, 25 patients with oral TD and tardive dystonia were randomized into a sham (no stimulation for 3 months) and active treatment group of pallidal DBS. At 6 months, all patients showed 41.5% improvement in symptoms with active treatment.[7] A recent meta-analysis of 117 patients undergoing DBS implantation for TSs found that 109/117 underwent DBS-GPi placement. The remaining underwent DBS-STN placement, but these implants were for tardive dystonia rather than oral manifestations of TD.[11] The most commonly cited explanation for the disparity in target selection is the concern for increased neuropsychiatric disturbances with DBS-STN placement.[21]

Prior studies have shown that STN-DBS is beneficial in treating not only resting but also postural and kinetic tremors.[5,15] Our case is unique in that our patient developed a combination of oral TD and DIP, including bradykinesia and violent resting and kinetic tremors in both upper and lower extremities. Consideration was given to targeting GPi in this case, which might have allowed the patient to stop taking TBZ and subsequently improving her DIP. However, the trials off medication did not yield a significant benefit and

the patient's symptoms would not allow for a prolonged trial off medication. Given the debilitating nature of her tremors, DBS-STN was felt to be the most promising target to address her symptoms. She tolerated the placement in this location with improvement of bradykinesia and near-complete resolution of her tremors. Unfortunately, TD continued. This significantly improved her quality of life and she continues to be content with her decision to undergo the surgery despite the side effects of hypophonia and cognitive impact. While impaired cognition is a concern with DBS-STN, our patient's cognitive issues are likely multifactorial, with age, history of mood disorder, and multiple treatments of ECT contributing. This case provides more evidence that DBS-STN treatment can be beneficial for tardive Parkinsonism and tardive resting and kinetic tremors.

CONCLUSION

Tardive movement disorders are complex conditions that require highly personalized management. In addition to well-known manifestations with tardive oral dyskinesia and tardive dystonia, they may include the less acknowledged TTs and tardive Parkinsonism. While DBS-GPi is the preferred treatment in treating oral TD and dystonia, DBS-STN could be considered a safe and effective target in patients with predominating TT and/or tardive Parkinsonism.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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