GPi Deep Brain Stimulation for Tourette Syndrome Improves Tics and Psychiatric Co-morbidities

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ABSTRACT

OBJECTIVE: To describe the response of a medication-refractory, 16-year old male with severe Tourette syndrome (TS) and typical co-morbidities to bilateral deep brain stimulation (DBS) of the globus pallidus interna (GPi). **BACKGROUND:** Case reports suggest efficacy of DBS in treating severe TS. A medication-refractory, 16-year old male with severe Tourette syndrome (TS) and typical co-morbidities underwent DBS of the globus pallidus interna (GPi). **METHODS:** Pre-surgical neuropsychological, psychiatric, and neurological evaluations were compared to 6 month follow-up evaluations. Measures included Yale Global Tic Severity Scale (YGTSS), Tic Symptom Self Report (TSSR), Modified Rush Video-Based Tic Rating Scale (VTRS) scored by an independent, "blinded" rater, behavior rating scales (BASC-2, BRIEF), Child Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), a quality of life measure (SF-36v2), and neurocognitive tests. **RESULTS:** YGTSS improved by 84% (from 90 to 14), TSSR improved by 88% (from 94 to 11), and VTRS improved by 21% (from 14 to 11). BASC-2 showed marked reduction in co-morbid symptoms including depression (120 to 41, Z-score 7.83), anxiety (94 to 42, Z-score 5.12), and hyperactivity (93 to 50, Z-score 4.21). Mild social introversion and withdrawal remained at 6 months. The Behavioral Regulation Index improved from 87 to 49 (Z-score 3.47), the Metacognition Index improved from 80 to 61 (Z-score 1.64), and the Global Executive Composite improved from 86 to 57 (Z-score 2.60). CY-BOCS improved by 69% (from 16 to 5). Neurocognitive testing showed improved verbal reasoning, psychomotor speed, mental flexibility, and visual-perception, with somewhat poorer performance on a test of memory. The SF-36v2 improved by 65% (from 86 to 142). He returned to school part-time. **CONCLUSIONS:** Both tics and co-morbid conditions including OCD, depression, anxiety, and AD/HD improved following bilateral GPi DBS, resulting in markedly improved quality of life. The residual mild social avoidance may have been a result of learned/reinforced pre-surgical behavior patterns. Careful selection of patients, experience with DBS, and comprehensive assessments at baseline and at follow-up visits are essential for successful outcome of DBS in TS.

INTRODUCTION

Tourette syndrome (TS) is characterized by vocal and motor tics, along with varying degrees of psychiatric co-morbidities including attention-deficit (+/- hyperactivity) disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, depression, and oppositional defiant disorder (Jankovic, 2001). The majority of patients experience significant improvement in or remission by the late teenage years (Leckman et al, 1998), although many will have milder, persistent tics and OCD even into adulthood (Pappert et al, 2003; Bloch et al, 2006). A subset experience a dramatic, debilitating worsening of symptoms that may persist into adulthood. Recent years have seen growing interest in the management of neuropsychiatric conditions with deep brain stimulation (DBS) (Kopell et al, 2004). Several cases of marked improvement of severe TS symptoms have been reported with DBS (**Table 1**).

Here, we describe our rationale for and experience with DBS of the bilateral globus pallidus interna (GPi) in a 16-year-old boy with severe, medication-refractory TS.

The GPi (motor) was chosen as the target for the following reasons:

- Increased parvalbumin-staining neurons in the GPi of TS patients is associated with an increase in GPi volume (Kalanithi et al, 2005).
- Irregular firing patterns in the GPi of TS patients have been observed.
- The GPi has connections to the prefrontal cortex (PFC), an area that influences cognition and mood (Yoshida et al, 1993; Middleton and Strick, 2002).
- Previous successful treatment of severe TS with GPi DBS (**Table 1**).

Table 1. Previous reports of deep brain stimulation in medication refractory TS*

Ref.	N [age, yrs]	Target	F/U	Outcomes	Adverse Events
(1)	1 [27] (tics only)	Medial thalamus (MT) and/or GPi (4 electrodes)	6 mos	80% tic reduction with high intensity MT; 95% reduction with low intensity GPi → chronic bilat GPi stimulation	None reported
(2)	3 [28-45] (tics & OCB)	Bilateral Thalamus	8 mos - 5 yrs	Reduced tics (72%-90%); No comment on change in OCB	Sexual dysfunction, "reduced energy" at higher stimulation settings
(3)	1 [30]	Bilateral thalamus	3 mos	100% tic reduction	None reported (*?psychogenic)
(4)	1 [37] (tics only)	Anterior limb of internal capsule	18 mos	17% reduction in total tic score (YGTSS); increased tic suppressibility	Dysarthria, rhythmic teeth clenching at certain stim. settings; apathy, depression at settings near NAc; hypomania when in body of capsule
(5)	1 [27] (tics, dep/ anx & CBs)	Bilateral GPi	14 mos	55% reduced total YGTSS, improved depression, anxiety; no change in "mild" OCB	Left hemiparkinsonism (hemorrhage around right electrode)
(6)	1 [36] (tics, dep/ anx & pers d/o)	Centro-median nucleus of the thalamus and/or GPi (4 electrodes)	11 mos	65% reduced total YGTSS, improved coprolalia and self-injurious behaviors with either site; thalamic stim w/ less depression and emotional instability	None reported
(7)	2 [27, 45] (tics & OCB)	Medial thalamus (Pt 1), and GPi (Pt 2)	1 yr	Improved tics (20 to 3 tics/min for MT and 28 to 2 tics/min for GPi) and OCBs	Sexual dysfunction, "reduced energy"

Ref. = Reference, N = number of patients, F/U = follow-up, GPi = globus pallidus interna, OCB = obsessive-compulsive behaviors, dep = depression, anx = anxiety, pers = personality, NAc = nucleus accumbens, stim = stimulation, Pt = patient, YGTSS = Yale Global Tic Severity Scale.
*** Shahed et al, 2006**

METHODS

Neuropsychological evaluation assessed suitability for the procedure and established baseline cognitive and psychiatric functioning.

Staged, bilateral GPi DBS electrodes were placed using techniques employed for dystonia. The internal pulse generators (IPGs) were placed after 2 weeks, and programming took place after 4 weeks.

Each evaluation included tic rating scales, video recordings, DBS interrogation and adjustment, and neurocognitive and neuropsychological testing.

Pre-surgical results were compared to those at 6 months and 1 year:

- Yale Global Tic Severity Scale (YGTSS, administered by JP)
- Tic Symptom Self-Report
- Behavior Assessment System for Children – 2nd Edition (BASC-2)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)
- Quality of life (SF-36v2)
- Neurocognitive tests (**Table 2**)

A movement disorders neurologist (CK) "blinded" to the patient's history, stimulator parameters, and timing of the videos scored the VTRS.

Baseline dosages of tetrabenazine, venlafaxine, and amitriptyline were not changed during follow-up.

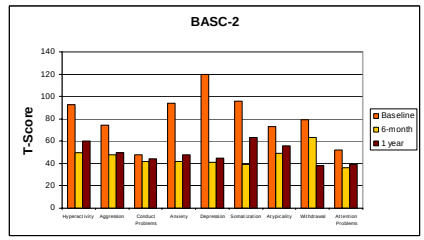
PATIENT HISTORY

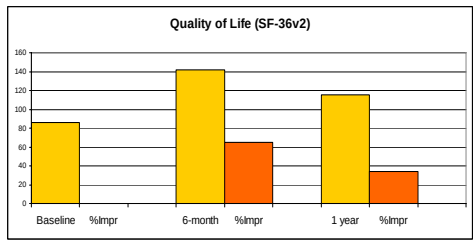
- 16-year old, left-handed male delivered at full-term via C-section for breech presentation.
- Normal birth and development except for speech delay until age 3.
- Onset of simple motor and vocal tics at age 3.
- OCBs and ADHD by age 5.
- Coprolalia and copropraxia were present by the age of 7.
- Overall progression in severity and frequency until presentation to our clinic at age 15.
- Haloperidol, pimozide, fluphenazine, benzodiazepines, guanfacine, SSRIs, tetrabenazine, and botulinum toxin injections (vocal cords) had failed to relieve symptoms.
- Tics, OCBs and self-injurious behaviors (SIBs) included inappropriately touching or grabbing others; self-gagging until emesis (resulting in significant weight loss), eye-poking, facial self-excoriations, self-hitting, and screaming until hoarse (**see Video**).
- Anxiety, depression, hyperactivity, and impulsivity were notable, while inattention and opposition were less problematic
- He and his family were no longer able to socialize or attend church. He failed classes, could not attend school, and would not go out in public.
- His marked academic and social impairment prompted consideration of DBS surgery.

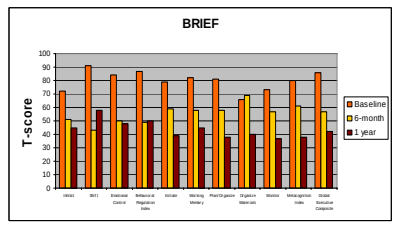
RESULTS

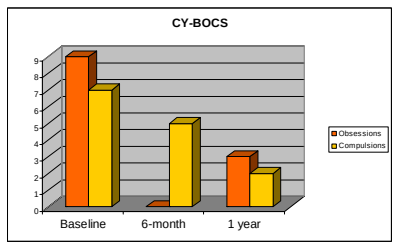
Cognitive Measure	Baseline	6-month	1 year
Weschler Abbreviated Scale of Intelligence			
Verbal IQ	99	127	N/A
Performance IQ	89	92	N/A
Full Scale IQ	94	109	N/A
Symbol Digit Modalities Test	64	107	95
Buschke Selective Reminding Test			
Long Term Storage	93	96	95
Consistent Long Term Recall	85	74	80
Delis-Kaplan Executive Function System			
Trail Making Number Sequencing	105	115	95
Trail Making Letter Sequencing	100	100	110
Trail Making Number/Letter Switching	75	100	110
Verbal Fluency (FAS)	90	90	105
Category Fluency	100	105	100
Category Switching	95	120	105
Design Fluency Total Score	105	100	105
Judgment of Line Orientation *(4 year-old norms)*	66	115	109

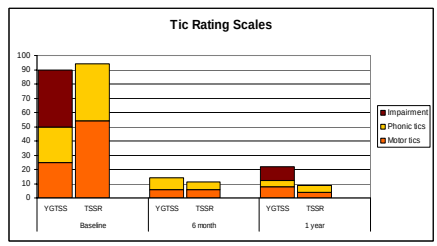
- No changes were seen in tic severity in the one month between electrode implantation and the 1st programming session.
- Significant tics, anxiety, and OCD behaviors were noted, including pushing on the IPG site, which initially required the use of a body shield to protect the apparatus from damage and the patient from SIBs.











	R	L
Amp	5	5
PW	90	90
Freq	160	145
leads	C+2-	C+2-

The final DBS parameters were achieved at 6 weeks.

Target coordinates: 22mm to the left and right of, 3mm in front of, and 4mm beneath the AC/PC midpoint.

CONCLUSIONS

- Based on a single case, GPi DBS may be considered safe and effective in treating both tics and co-morbidities in severe TS.
- Improvements were sustained at 1 year follow-up.
- Verbal reasoning, psychomotor speed, mental flexibility, and visual perception all improved.
  - May reflect primary beneficial DBS effects, although test-retest practice effects and improved mental clarity secondary to reduced co-morbidities cannot be excluded.
- The persistent social avoidance at 6 months may have resulted from learned/reinforced pre-surgical behavior patterns, but improved to the normal range at one year.
- Neuropsychological and psychiatric co-morbidities in TS should not necessarily preclude treatment with DBS.
- As surgical management of TS remains investigational, a rigorous selection process, extensive experience with DBS, and comprehensive baseline and follow-up are essential for successful outcomes (Mink et al, 2006).
- Larger studies comparing GPi to other targets are needed to determine the optimal target and stimulation parameters for management of disabling tics and co-morbidities associated with TS.

VIDEO LEGENDS

Segment 1. The patient is shown at baseline exhibiting a severe screaming and clenching tic, along with copropraxia. The patient and his mother describe the impact of his tics on their quality of life.

Segment 2. At 6 months follow-up, the patient and his mother describe a dramatic reduction in his severe motor and vocal tics, and a significant improvement in their quality of life. He has only minor motor tics on exam.

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