Neurosurgical management of Tourette syndrome: A literature review and analysis of a case series treated with deep brain stimulation

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Abstract

Tourette syndrome (TS) is a heterogeneous disorder, which clinical presentation includes both multiple motor and vocal tics and commonly associated psychiatric conditions (obsessive-compulsive disorder, attention deficit hyperactivity disorder, depression, anxiety, etc.). Treatment options primarily consist of non-pharmacological interventions (habit reversal training, relaxation techniques, cognitive behavioral therapy, and social rehabilitation) and pharmacotherapy. In case of the intractable forms, neurosurgical treatment may be considered, primarily deep brain stimulation (DBS). DBS appear to be effective in medically intractable TS patients, although, the preferential brain target is still not defined. The majority of studies describe small number of cases and the issues of appropriate patient selection and ethics remain to be clarified. In this article, we review the main points in management of TS, discuss possible indications and contraindications for neurosurgical treatment, and analyze our experience of DBS in a case series of refractory TS patients with the focus on target selection and individual outcomes.

Keywords

Functional neurosurgery, Psychiatric neurosurgery, Tics, Tourette syndrome, Deep brain stimulation, Outcome, Obsessive-compulsive disorder, Self-injurious behavior

Abbreviations

ADHD	attention deficit hyperactivity disorder
ALIC	anterior limb of the internal capsule
BDI	Beck Depression Inventory
CM-Pf	centromedian-parafascicular complex
DBS	deep brain stimulation
GPe	external globus pallidus
GPi	internal globus pallidus
NAc	nucleus accumbens
OCD	obsessive-compulsive disorder
RVBTRS	Rush Video-Based Tic Rating Scale
SIB	self-injurious behaviour
STN	subthalamic nucleus
TS	Tourette syndrome
YBOCS	Yale-Brown Obsessive Compulsive Scale
YGTSS	Yale Global Tic Severity Scale

1 Tourette syndrome: Definition, etiological and pathophysiological issues

Tics are sudden, brief, repetitive, and nonrhytmic motor or vocal unvoluntary movements, which can be simple or complex (Hartmann, 2014). The term "tic disorder" indicates a condition with pronounced clinical manifestation and may be primary or secondary. The 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013) lists three main types of primary tic disorders: provisional tic disorder, persistent (chronic) motor or vocal tic disorder, and Tourette's disorder (or Tourette syndrome, TS). TS is represented by continuous or intermittent, multiple motor and single or multiple vocal tics, lasting more than 1 year, without tic free intervals more than 3 months, starting at the age <18 years, and not explained by the effect of other medical condition and/or substance use (Hartmann, 2014; Stern, 2018).

TS occurs in 0.3–1% of children (Knight et al., 2012; Scharf et al., 2015; Singer, 2019). The etiology of TS remains elusive and includes strong hereditary component, the risk factors such as perinatal damage, neuroinfections/immunological abnormalities, and neurodevelopmental causes (Kurlan et al., 2015; Dale, 2017). TS is considered to be polygenic with multiple genes associated with the dopaminergic, serotoninergic, and histaminergic pathways, e.g., *DRD2, DRD4, 5-HT2C, SERT, SLITRK1, IMMP2L, CNTNAP2, NLGN4, COL27A1, CELSR3, CNTN6, NRXN1* (Qi et al., 2019; Yu et al., 2019). Yu et al. (2019) conducted a genome-wide association study (GWAS) meta-analysis and concluded that at the genetic level tic disorders represent a continuous spectrum of disease and that fundamental mechanisms of TS include modulation of gene expression through non-coding variants, particularly within the cortico-striatal circuits.

The pathophysiology of TS is supposed to be related to the aberrant focus of striatal neurons, which become inappropriately active causing unwanted inhibition of basal ganglia output neurons (Hartmann, 2014; Yael et al., 2015). The evidence for dysfunction of neural circuits, first of all cortico-basal-thalamo-cortical (CBTC) loops, was provided by the numerous neuropathological and neuroimaging studies (Neuner et al., 2011; Martino et al., 2018; Martino and Cavanna, 2013; Polyanska et al., 2017; Worbe et al., 2015; Maia and Conceição, 2018).

2 Clinical features of Tourette syndrome

Clinical presentation of TS consists of simple or complex motor and vocal tics. Simple motor tics are realized by isolated muscle group(s) of single anatomical location (facial grimacing, eye blinking, nose twitching, shoulder shrugging, etc.). Simple vocal tics include single sounds, vocalizations, usually without articulation (throat clearing, coughing, etc.). Complex motor tics involve multiple muscle groups; they may be slower, seem to be purposeful or can be presented as voluntary movement (facial and hand gestures, jumping, touching objects or self, etc.). Complex vocal tics include syllables, words, and phrases, often in the form of echolalia, palilalia, as well as changes in speech prosody, pauses in speech, exclamations or noises like animal voices. Tics may often have an indecent character, such as making obscene gestures or vocalizing obscene words or profanity (copropraxia, coprolalia), which causes substantial moral suffering to patients. Patients may exhibit a diverse variety of complex repetitive behaviors (echophenomena, paliphenomena, coprophenomena) and non-obscene socially inappropriate behaviors (inappropriate personal comments often in an insulting manner) (Hartmann, 2014; Kurlan et al., 2015). A very particular feature of TS appears to be the premonitory urge, a specific unpleasant sensation that precedes tic and needs to be relieved by movement or vocalization (Cavanna et al., 2017).

TS usually emerges at the age of 4–8 years with transient bouts of simple motor tics (Bloch and Leckman, 2009; Leckman et al., 2014). Tics tend to wax and wane in severity over time. They worsen throughout the childhood with a peak occurring at 10–12 years, usually followed by amelioration of symptoms during the second decade of life in 59–85% of patients. Approximately more than one-third of TS patients become tic free to the early adulthood (Hassan and Cavanna, 2012). The prevalence of tics in adults decreases to 0.05%. Nevertheless, in some TS patients (circa 10.3%), tic severity may increase with age. 5% of patients may develop the "malignant TS" associated with the potentially dangerous or life-threatening conditions, such as severe tics with traumatization, self-injurious behavior (SIB), and suicidal ideation (Cheung et al., 2007). Predictors of increased TS severity in adulthood include a higher childhood tic severity, smaller caudate volumes, poorer fine motor control, comorbid psychopathology, and stressful life events (Bloch et al., 2009).

Besides involuntary movements, up to 90% of patients suffer from a variety of neuropsychiatric problems, such as obsessive-compulsive spectrum disorders (OCD, in 66.1% of patients), attention deficit hyperactivity disorder (ADHD, 54.3%), mood disorders (29.8%), anxiety (36.1%), disruptive and self-injurious behavior (29.7%), which are considered intrinsic to the clinical phenomenology of TS (Freeman et al., 2000; Hirschtritt et al., 2015). The other associated conditions include antisocial activities, oppositional behavior, substance use, personality disorders, suicidality, poor self-concept, reduced self-esteem, eating disorders, etc. In 57.7% of TS patients, the criteria for two or more psychiatric conditions are met. Although TS patients do not usually have major cognitive decline, deficits in inhibitory control, cognitive flexibility, and social cognition may contribute to behavior comorbidities (Morand-Beaulieu et al., 2017). Coexisting psychiatric issues not only influence the execution of tics and reduce the adherence to treatment, but also respond for a significant additional burden in TS patients and may have a greater clinical impact than that caused by tics. They are strongly associated with more severe disease course and functional impairment, such as learning disability, hindering the psychological development, personality formation, and social interaction (Cavanna and Rickards, 2013; Groth et al., 2017; Coffey et al., 2000). Similar to tics, psychiatric symptoms tend to decline with age; however, in some patients, they persist and even worsen in adulthood playing an important role in deterioration of the quality of life and disability. Up to 85% of TS adults have mild to moderate difficulties in social adaptation (Kompoliti, 2016).

3 Treatment options for Tourette syndrome

Individual therapy should be planned in each TS patient and should include non-pharmacological and pharmacological treatment (Billnitzer and Jankovic, 2020). Behavioral and psychosocial interventions are recommended by the European and American guidelines as the primary TS treatment in children and adolescents (Pringsheim et al., 2019b; Verdellen et al., 2011). Behavioral approaches include comprehensive behavioral intervention for tics (CBIT), habit reversal training (HRT), and exposure and response prevention (ERP) (McGuire et al., 2014; Wile and Pringsheim, 2013). The main components of HRT are tic-awareness training, which is designed to help patient in recognizing the oncoming tic, and competing-response training to perform the voluntary movements that are physically incompatible with the targeted tic. CBIT additionally includes different relaxation techniques and function-based intervention procedures that aim to mitigate influences of everyday life on the tic occurrence. In ERP technique, tics are suppressed for a prolonged period providing the possibility to habituate to the premonitory sensations (Zimmerman-Brenner et al., 2022). Cognitive behavioral therapy (CBT) is effective for OCD and mood disorders associated with TS (Conelea et al., 2014).

Pharmacological treatment of tic disorders includes generally two-tiered approach (Pringsheim et al., 2019a; Singer, 2019). Alpha-2 adrenergic agonists

are used for milder tics (clonidine, guanfacine). Dopamine blocking agents are used for more difficult to control symptoms (Badenoch and Cavanna, 2020). Currently, only pimozide, haloperidol, and aripiprazole have US FDA approval for use as tic-suppressing agents. The use of antipsychotics, especially of the first-generation, is limited by the side effects, such as metabolic syndrome, weight gain, sedation, sexual dysfunction, postural hypotension, QT prolongation, drug induced movement disorders, etc. (Pringsheim et al., 2017; Salvador et al., 2017; Cothros et al., 2020).

Dopamine depleting agents, e.g., tetrabenazine, may serve for treating tics. Although, such adverse effects as depression and parkinsonism limit its use. In the last decade, the new VMAT2 inhibitors, deutetrabenazine and valbenazine, have emerged. These drugs may be promising due to their potentially safer side effect profile (Cothros et al., 2020). Antiepileptic drugs (topiramate, levetiracetam) and benzodiazepines are used as adjunctive therapy. Botulinum toxin type A may be applied for reduction of severe localized tics mainly in the cervical region.

Screening and treatment of psychiatric conditions are very important for social adaptation and quality of life maintenance in TS patients. Psychostimulants are used for ADHD; selective serotonin reuptake inhibitors are used for OCD and mood disorders (Billnitzer and Jankovic, 2020).

Despite the wide variety of behavioral and pharmacological treatments that has been studied in treatment of tic disorders, the refractory TS forms occur. Other options for severe and intractable TS patients include repetitive transcranial magnetic stimulation, electroconvulsive therapy, and neurosurgical interventions (Marras et al., 2001; Kious et al., 2016; Rizzo and Gulisano, 2019).

4 Neurosurgical strategies for Tourette syndrome

Neurosurgical approaches are reserved for TS patients who fail the non-pharmacological and pharmacological treatments. In the beginning of the stereotactic era, neurosurgical ablative procedures have been attempted to treat severe intractable TS. Various target structures were used for lesioning, such as the frontal lobe (prefrontal lobotomy and bimedial frontal leucotomy), the limbic system (limbic leucotomy and anterior cingulotomy), the thalamus (bilateral thalamotomy), and the cerebellum (bilateral cerebellar dentatotomy), as well as the combined approaches (anterior cingulotomy with infrathalamic lesions) (Rauch et al., 1995). The outcomes of these procedures were partially successful, although, often associated with neurological complications. More experience has been gained in thalamic surgery. In 1970, Hassler and Dieckmann reported bilateral coagulations of the medial and rostral intralaminar thalamic nuclei and the inner part of the ventral oral thalamic nucleus in three TS patients that led to a significant amelioration of tics (Hassler and Dieckmann, 1970). Altogether, the authors described 15 TS cases with 50–100% tic improvement with the same target (Hassler, 1982).

Starting from the late 1990s', deep brain stimulation (DBS) was increasingly used as a neurosurgical treatment for medically refractory TS. Vandewalle et al. (1999)

described the earliest case of successful thalamic DBS for intractable TS. Target selection was based on the results of the previously reported thalamothomies: the cross point of the centromedian nucleus, CM, substantia periventricularis, Spv, and the nucleus ventrooralis internus, Voi (Cooper, 1969; Hassler and Dieckmann, 1970). In 2003, the same team of authors described the long-term results of DBS of the medial thalamus (CM-Spv-Voi) in three TS patients. DBS was effective with reduction in quantity of tics by 90%, 72%, and 83% after the surgery (Visser-Vandewalle et al., 2003). A positive effect on coexistent behavioral disorders was also noticed. Over time, tic reduction after DBS was reported in the other studies, which included mainly case reports, case series, and retrospective analyses, but also a few prospective randomized studies (Akbarian-Tefaghi et al., 2016; Deeb and Malaty, 2020; Schrock et al., 2015; Xu et al., 2020).

In 2007, Maciunas et al. published a prospective double-blind crossover study of five TS patients, in which the thalamic centromedian-parafascicular complex was used for DBS (CM-Pf). The efficacy of stimulation was a 40% decrease in motor tics and a 21% decrease in vocal tics at the 3-month follow-up (Maciunas et al., 2007). The other loci for electrode placement within the medial thalamus were also reported at that time: CM-Pf and the ventral oral thalamic nuclei (CM-Pf-Voa, Servello et al., 2008), parafascicular nucleus–dorsomedial nucleus–lamella medialis (Vernaleken et al., 2009), the nucleus ventrooralis anterior–ventrooralis posterior–Voi complex of the thalamus (Vop-Voa-Voi, Kuhn et al., 2011), demonstrating beneficial effects on tics. Two further small randomized double-blind studies of bilateral CM-Spv-Voi and CM-Pf DBS followed with variable methodology and outcomes; however, in an open-label on-stimulation period, up to 49% improvement in the Yale Global Tic Severity Scale (YGTSS) was shown after 1 year (Ackermans et al., 2011; Okun et al., 2013). A small prospective open-label study (Huys et al., 2016) explored the region of the ventral anterior and ventrolateral motor parts of the thalamus (VA/VL) in 8 TS patients and demonstrated the beneficial effects regarding tics, anxiety, quality of life, and global functioning, but not OCD symptoms. Presurgical compulsivity, anxiety, emotional dysregulation and inhibition were indicated as the significant predictors of the outcome.

The second brain region often used for DBS in TS is the internal globus pallidus (GPi). van der Linden et al. (2002) and Diederich et al. (2005) reported the early successful experience of DBS of posteroventrolateral part of GPi (pvGPi). Shahed et al. (2007) described a good result of pallidal DBS in a patient with TS and OCD/ADHD, which was an 84% reduction in tics without any significant side effects. Houeto et al. (2005) first reported stimulation of the anteromedial (limbic) part of GPi (amGPi) in a combination with CM-Pf DBS. In this patient with TS and personality disorder, both thalamic and pallidal stimulation had similar beneficial effects on tics, but the thalamic stimulation was more efficacious for mood and impulsivity. Randomized double-blind crossover study by Kefalopoulou et al. (2015) included patients with amGPi and pvGPi DBS. Although, during the 3-month blinded phase the patients showed only a modest decrease in TS severity (15.3% in YGTSS), an open-label evaluation in long-term follow-up revealed an average

improvement in tics by 40% and in quality of life by 39%. Symptoms of depression were also improved. The other randomized double-blind study of amGPi DBS in TS showed no significant improvement in YGTSS score at the end of the blinded period and 39.9% decrease by the end of the open-label period (Welter et al., 2017). Insufficient/lacking improvement in the blinded phases could be attributed to the study design (Jimenez-Shahed, 2015). A possible delay in response to GPi DBS was also suggested, which is longer compared to thalamic DBS.

Among the other targets proposed for DBS in TS were the anterior limb of the internal capsule (ALIC) and the nucleus accumbens (NAc) border (Flaherty et al., 2005; Neuner et al., 2009), the external part of globus pallidus (GPe, Vilela-Filho et al., 2007; Piedimonte et al., 2013), the subthalamic nucleus (STN, Martinez-Torres et al., 2009), and the H1 field of Forel (Neudorfer et al., 2017).

Baldermann et al. (2016) performed a systematic review and meta-analysis of 57 studies, which pooled 156 cases of DBS for TS, and reported an overall tic reduction by 53% from the baseline measured by YGTSS. A symptom reduction of at least 25% was observed in 80.6% of patients and a reduction of at least 50% in 54%. Vocal tics showed a significantly better improvement compared to motor tics. Associated depressive and obsessive-compulsive symptoms also improved. Different brain targets were used for electrode implantation (thalamic loci in 78 cases, amGPi in 44, pvGPi in 20, ALIC-NAc in 9, GPe in 1, and other in 4). Although the individual results varied significantly, the mean improvement rates according to the selected target were comparable. Nevertheless, the sample of patients with ALIC-NAc DBS was the smallest and clinical benefit was less convincing (Baldermann et al., 2016). An interesting finding was a negative correlation of the outcome with the tic severity and a better improvement rates in patients with lower YGTSS or RVBTRS (Rush Video-Based Tic Rating Scale) scores, especially after thalamic stimulation. In amGPi DBS, the association of better results with the higher impairment scores was found. Regarding the associated OCD and depression, the median improvement of 31.3% and 38.9% was found in Yale-Brown Obsessive Compulsive Scale (YBOCS) and Beck Depression Inventory (BDI) scores, respectively, without significant differences between targets.

The study of Martinez-Ramirez et al. (2018) summarized the data from the International Deep Brain Stimulation Database and Registry collected in 31 different institutions across Australia, Europe, Asia, and North America. 185 patients with pharmacoresistant TS who underwent DBS implantation in the period from January 1, 2012, to December 31, 2016, were included into the analysis. YGTSS was used as the main outcome measuring instrument. The following brain targets were implicated for DBS: CM thalamic region (93 patients), anterior GPi (41 patients), posterior GPi (25 patients), and ALIC (4 patients). After 1 year, the mean improvement in YGTSS score was 46.3%, 50.5%, and 27.7% for patients with DBS of the CM thalamic region, anterior GPi, and posterior GPi, respectively. No significant difference in the outcome was found for these structures. The results in ALIC DBS group were similar, however, as opposed to the other targets, the initial benefit decreased over time. Altogether, the patient sample in ALIC group was too small to provide

reliable evidence. According to this study, 35.4% of patients reported some adverse events. Most of them were stimulation-related (dysarthria, paresthesia) and reversible. Several cases of surgery- or device-related complications were also described. Thus, despite the large size of the patient group analyzed, the study was unable to indicate a preferred structure for DBS in TS.

Johnson et al. (2019) collected the data of 123 TS patients operated in 13 international centers and performed image-based analysis of the active contact location (DBS CM in 51 patients, GPi—47, ALIC/NAc—4, and a combination of targets—8). The regions where most of the patients were stimulated were located near the most commonly reported surgical targets in CM and amGPi. The authors demonstrated that there were regions within and surrounding CM and GPi, which stimulation improved tics in some patients and was not effective in the others. DBS of the regions just inferior to GPi was less effective in reduction of OCD symptoms than the regions within, medially or superior to GPi. No significant difference in reduction of YGTSS and YBOCS scores was found across the brain targets. The median time to achieve a 40% improvement in tics was 13 months (Johnson et al., 2019).

Several groups used multiple targets for DBS in TS. Welter et al. (2008) reported the combined stimulation of ventromedial GPi and CM-Pf in three patients, in which both targets appeared to be similarly effective for TS, however, the combination of thalamic and pallidal stimulation showed no further reduction in tic severity. Kakusa et al. (2019) described the case of a young man with severe tic disorder, OCD/AHDH, major depressive disorder, chronic pain syndrome, and opioid use disorder. After multiple diverse medications failed, he was treated with DBS and two brain targets were used simultaneously, CM-Pf and ventral capsule/ventral striatum (VC/VS). After 1 year of bilateral dual-target DBS, patient's YGTSS, YBOCS, and Hamilton Depression Scale (HAMD) scores improved by 84%, 70%, and 95%, respectively. The addition of ALIC stimulation to thalamic DBS was associated with improvement in mood and affect, whereas the ventral NAc stimulation helped to control the cravings (Kakusa et al., 2019).

The other authors proposed the combined use of DBS and stereotactic radiosurgery in cases of TS associated with severe psychiatric disorders. Richieri et al. (2018) described a 47-year-old woman with refractory TS and OCD and poor response to initial pvGPi DBS (YGTSS 39 before surgery and 39 at the 1-year follow-up; YBOCS 20 and 28, respectively). The second neurostimulator was implanted in the ventral anterior and ventrolateral motor regions of the thalamus that resulted in the evident improvement in motor and vocal tics (YGTSS 10/50), but did not ameliorate her OCD symptoms (YBOCS 28/40) at the 1-year evaluation. After 2 more years, the decision was made to perform gamma-knife (GK) radiosurgery targeting the ventral portions of ALIC. The severity of OCD symptoms decreased significantly after 9 months of follow-up and the patient was in clinical remission after 12 months of follow-up (YBOCS 6/40). Moreover, her tics remained abated without DBS. The only adverse effect was the weight gain (Richieri et al., 2018).

Further support to the combination strategy in TS with prominent psychiatric comorbidity was provided in a retrospective study by Zhang et al. (2019a).

The authors summarized the outcomes in 10 patients with TS and OCD/affective disorders treated by the combination of GPi DBS and bilateral radiofrequency anterior capsulotomy. The patients were reported to benefit from the combined surgery with the improvement in tics, psychiatric symptoms, general adaptive functioning, and quality of life. The same approach was successfully applied in a patient with malignant TS and severe SIB (Zhang et al., 2019b).

Coulombe et al. (2018) analyzed the individual data of 58 child and adolescent TS patients (12–21 years old) treated with DBS reported in the literature. DBS appeared to alleviate tic severity irrespectively of the anatomical target and the average improvement comprised 57.5% across 21 studies. Sixty four percent of patients showed the tic reduction more than 50%. In patients with less severe tics, thalamic DBS appeared to have greater effect than pallidal stimulation (69 vs 53% decrease in YGTSS). The outcome correlated negatively with concomitant depression. The improvement in YGTSS after DBS treatment was also associated with a significant reduction in concomitant OCD symptoms and anxiety; the mean YBOCS score decreased by 31% and STAI (State-Trait Anxiety Inventory) by 40%. Overall, adverse event rate not exceeded that in the adult population.

A recent review from Xu et al. (2020) discusses the target and patient selection in DBS for TS, as well as the ethics of DBS in pediatric patients. The authors conclude that DBS is a possible treatment option for adolescent patients suffering from severe intractable TS, however, careful assessment and selection by a multidisciplinary team should be performed. The indications for early DBS interventions in younger TS patients are still considered controversial taking into account the possibility of natural tic reduction in the later life, potential risks, and limited evidence (Coulombe et al., 2018; Pringsheim et al., 2019b; Schrock et al., 2015; Smeets et al., 2018; Xu et al., 2020).

An accurate algorithm of patient selection is very important in neurosurgical management of TS. Schrock et al. (2015) published the updated recommendations of Tourette Syndrome Association on patient selection and assessment for DBS. The following inclusion criteria for surgical candidates were indicated: DSM-5 diagnosis of TS with tics being the major cause of disability, total YGTSS score >35/50, documentation of failed treatment trials with medication of three pharmacological classes, application of CBIT with appropriate adherence of patient to treatment, and exclusion of secondary tic causes. Comorbid conditions should be treated and be stable for at least 6 months. Unlike the 2006 recommendations, which included an age criterion older than 25 years, patient's age was no longer stated as a rigorous eligibility criterion for DBS. In cases younger than 18 years old, the involvement of a local ethical committee was advised. Patient should be able to adhere to the recommended treatments and have adequate social support and a caregiver available to accompany him/her on repetitive follow-up visits. The role of the multidisciplinary team evaluation with standardized pre- and postoperative assessment as well as the management by experienced DBS centers were especially highlighted. Exclusion criteria for DBS included active suicidal or homicidal ideation, active or recent substance abuse, structural lesions on brain MRI, malingering or psychogenic tics (Schrock et al., 2015).

AAN guidelines for TS treatment state the importance of multidisciplinary team in preoperative and postoperative management of TS, including patient evaluation by psychiatrist and neuropsychologist, necessity of exhausted appropriate treatment with implication of multiple medication and behavioral therapy, and exclusion of secondary and psychogenic tics. Severe or progressive cognitive impairment should be absent (Pringsheim et al., 2019b).

In summary, a number of targets located in the CBTC circuit have been used for DBS in TS, which included the thalamic CM-Pf, the cross point of CM-Spv-Voi, Vop-Voa-Voi, ventral anterior and ventrolateral motor parts (VA/VL), the anteromedial and posteroventrolateral parts of GPi, NAc and ALIC, STN, GPe, and H fields of Forel. The details of the procedures, the rationales for target selection, and the outcomes are comprehensively discussed elsewhere (Akbarian-Tefaghi et al., 2016; Casagrande et al., 2019; Deeb and Malaty, 2020; Xu et al., 2020). Most of the reported DBS cases demonstrated an amelioration of tics. However, except of the medial thalamus and internal pallidum the reports are few and do not allow adequate comparison of targets. Up to now, there is no final statement on the best target structure for medically refractory TS. It is unclear if the target choice for TS should be influenced by the co-occurring psychiatric conditions, such as OCD, ADHD, anxiety, and depression. Moreover, there is no clear understanding of the DBS effects of particular brain target on associated psychiatric conditions since existing reports are diverse and controversial. The criteria of patient disability and the definition of treatment resistance require further characterization and development of a specific selection algorithm for DBS. Several ethical issues remain to be solved. The most important of them is the use of DBS in pediatric patients. Since TS is a complex condition that may severely violate social adaptation and even intellectual and psychological development, precise criteria for different treatment options are needed. Not to forget a multidisciplinary approach to comprehensively consider the neurological, psychiatric, and social aspects of the patient condition, as well as to assess the adequacy and efficiency of treatment.

5 A series of Tourette patients treated with DBS in Burdenko Neurosurgical Center

The following algorithm of patient evaluation and selection of surgical candidates is used in the N.N. Burdenko National Medical Research Center of Neurosurgery. At the first visit, the patient is consulted by a neurologist, psychiatrist, neuropsychologist, and neurosurgeon. Clinical features of tic disorder are carefully analyzed for confirming the diagnosis and evaluating the severity of condition. Psychiatric and neuropsychological states are evaluated to assess the spectrum of neuropsychiatric comorbidities and their impact on quality of life. The adequacy of therapy is assessed. The criteria for appropriate surgery candidates are the following: primary tic disorder, severe clinical presentation (YGTSS $>35/50$), absence of acute psychosis and/or significant cognitive decline, failure of adequate treatment trials using different drug groups.

In the period from 2012 till 2020, 49 patients with TS were referred for consultation to the outpatient department of the Center and were evaluated as possible candidates for neurosurgical treatment. The mean age comprised 26.3 ± 8.2 years (range 16–55 years). Thirteen patients (26.5%) received no medication at the time of consultation due to ineffectiveness of previous treatment regimens or drug-induced adverse effects. All these patients were prescribed the rational medication and were left for the follow-up assessment. The rest 36 patients were on medication; however, in most cases, it could be optimized or completed with behavioral therapies. After a comprehensive evaluation, neurosurgical treatment (DBS) was offered to four patients upon the first visit because of the therapy resistance and marked social disadaptation. The other 5 patients were evaluated to undergo DBS implantation after failed trials of treatment optimization upon 2–6 follow-up visits. Two patients abstained from surgery later and in 7 cases (14.3%) the intracerebral electrodes for DBS were implanted. One TS patient (male, 40 years old) with the prominent intractable OCD symptoms, including self-injurious compulsions, and less disabling tics was offered bilateral radiosurgical (GK) anterior capsulotomy.

We used the following scales for evaluation of tics and associated psychiatric conditions: YGTSS, YBOCS, RVBTRS, and BDI. The 36-Item Short Form Health Survey (SF-36) was used to assess the quality of life. Neuropsychological assessment included Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), and clock drawing test (CDT) (Beck et al., 1961; Goodman et al., 1989; Goetz et al., 1999; Storch et al., 2005; Strauss et al., 2006).

With regard to medication, we preferred to keep the original regimen for the first half of the year after surgery, with subsequent adaptation if necessary.

Here, we provide the description of all TS patients who were operated on for DBS in our Center. The demographic data of the patients are shown in Table 1.

Patient 1 (P1)

The first patient is a 32-year-old man, who had a history of TS in childhood from the age of 4 with complex motor tics (waving hands, squats, etc.) and simple vocal tics till adolescence. In early adulthood, tics mostly vanished. From the age of 24, under

Table 1 Demographic data of patients with TS.

Patient	Sex	Age	Symptom duration	DBS target
P1	M	32	28	pvGPi
P2	M	35	23	CM-Spv-Voi
P3	M	26	18	CM-Spv-Voi
P4	M	45	38	pvGPi
P5	F	43	40	pvGPi
P6	M	21	18	CM-Spv-Voi
P7	M	28	23	pvGPi

pvGPi, posteroventrolateral part of the internal globus pallidus; CM-Spv-Voi, medial thalamus at the cross point of the centromedian nucleus, substantia periventricularis, and nucleus ventrooralis internus.

the influence of stress, complex tics exacerbated and severe OCD added. The patient suffered from coprolalia, disabling repetitive behaviors, compulsions, and SIB. He was unable to study or work, was not able to leave the house independently. Multiple treatment regimens were tried without success. The latest medication included risperidone 4 mg/day and tiapride 600 mg/day. At the time of referral to neurosurgery, refractory OCD symptoms were the predominant cause of disability, whereas tics appeared to be reduced.

Because of a history of tic disorder, GPi was chosen for DBS in this patient, despite the evidence that it is not the preferential target structure for OCD. OCD was regarded as associated with TS condition; therefore, we preferred to operate on GPi as one of the common target structures for TS. The patient underwent implantation of DBS electrodes in posteroventrolateral GPi (pvGPi). The improvement, according to YBOCS, was up to 37.5% after the first year of follow-up and 50% after the second year of follow-up. After 3 years of continues DBS, the patient experienced unexpected worsening in OCD and unvoluntary movements. When testing the neurostimulator, it appeared to be switched off, and the patient's condition stabilized after the restoration of DBS. During the following years, the patient showed a slow progressive amelioration of obsessive-compulsive symptoms, improvement in everyday life activities and social adaptation, cessation of SIB. He was able to take care of himself and the pets, maintain the household, travel alone to the follow-up visits, and continue his education. At the last follow-up visit (7.5 years postoperatively), his condition remained relatively stable with sufficient behavioral control while being in society, however, he still experienced some superstitious obsessions and nondamaging compulsions while at home. The only DBS adverse effect was slight disarthria. The medication was reduced to tiapride 400 mg/day.

Six following patients (P2–P7) were randomized to undergo DBS targeting either the medial thalamus or GPi (Table 1). The target in the medial thalamus has been chosen according to that initially used by the group of Vandewalle et al. (1999) at the cross point of CM, Spv, and Voi (Visser-Vandewalle et al., 2003). For GPi, the common target in the posteroventrolateral part (pvGPi) has been adopted, which is used in surgery of dystonia and other hyperkinetic movement disorders (Sakas and Simpson, 2007). Detailed clinical assessment of patients before surgery and during the follow-up is shown in Tables 2–4.

Patient 2 (P2)

The second patient is a 35-year-old male, who suffered from motor tics from the age of 12 (isolated facial tics, arm twitching) and vocal tics from the age of 14. With age, tics became more complex and generalized. The patient experienced a spontaneous remission of tics at the age of 28, which continued for half a year. However, thereafter the tics relapsed, as well as the OCD. The patient suffered from echolalia, coprolalia, touching behavior, pinching the others, bumping his head, and large-amplitude leg throwing, which interfered with the gait. He had been treated with a wide range of medications, including antipsychotics, tryciclic antidepressants,

Table 2 Motor outcome after DBS for each TS patient at 6-, 12-, and 24-month follow-up.

Patient	YGTSS pre-op	YGTSS 6mo post-op	YGTSS 12 m post-op	YGTSS 24 m post-op	RVBTRS pre-op	RVBTRS 6 m post-op	RVBTRS 12 m post-op	RVBTRS 24 m post-op
P2	48	10	26	41	15	9	8	8
P3	46	50	–	–	16	16	–	-
P4	44	34	28	19	15	13	12	6
P5	36	22	20	24	12	11	12	10
P6	46	26	30	–	11	9	8	-

YGTSS, Yale Global Tic Severity Scale; RVBTRS, Rush Video-Based Tic Rating Scale.

Table 3 Non-motor outcome after DBS for each TS patient at 6-, 12-, and 24-month follow-up.

Patient	YBOCS pre-op	YBOCS 6 m post-op	YBOCS 12 m post-op	YBOCS 24 m post-op	BDI pre-op	BDI 6 m post-op	BDI 12 m post-op	BDI 24 m post-op	SF-36 PH pre-op	SF-36 PH 6 m post-op	SF-36-PH 12 m post-op	SF-36 PH 24 m post-op	SF-36 MH pre-op	SF-36 MH 6 m post-op	SF-36 MH 12 m post-op	SF-36 MH 24 m post-op
P1	24	–	15	12	14	–	10	8	25	–	50	50	44	–	60	40
P2	22	10	14	13	3	6	6	3	58.3	90	100	55.8	45.9	60	60	53.6
P3	22	22	–	–	30	32	–	–	60	46.7	–	–	15	25.1	–	–
P4	38	26	13	15	2	12	7	15	43	43.3	31.9	60.9	26	26.4	35.7	39.4
P5	5	12	13	13	10	9	9	7	37	37.3	33.4	36.2	42.5	43.4	41.3	42.3
P6	5	7	0	–	5	2	3	–	43.3	52.2	53.1	–	50	55.7	40.9	–

YBOCS, Yale-Brown Obsessive Compulsive Scale; BDI, Beck Depression Inventory; SF-36, The 36-Item Short Form Health Survey; pH, Physical Health Component; MH, Mental Health Component.

Table 4 Cognitive outcome after DBS for each TS patient at 6-, 12-, and 24-month follow-up.

Patient	MMSE pre-op	MMSE 6 m post-op	MMSE 12 m post-op	MMSE 24 m post-op	FAB pre-op	FAB 6 m post-op	FAB 12 m post-op	FAB 24 m post-op	CDT pre-op	CDT 6 m post-op	CDT 12 m post-op	CDT 24 m post-op
P2	30	30	30	30	14	17	15	15	10	10	10	10
P3	24	23	–	–	16	16	–	–	8	8	–	–
P4	24	24	17	19	16	12	10	12	8	8	7	8
P5	29	28	29	29	17	16	17	17	10	10	10	10
P6	28	29	29	–	11	17	16	–	5	7	7	–

MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; CDT, Clock drawing test.

and anticonvulsants. He was partly responsive to risperidone; however, it caused the side effects (sedation and weight gain). At the time of surgical treatment, he was taking risperidone 4 mg/day.

The patient was assigned for bilateral CM-Spv-Voi DBS. Six months postoperatively, the patient reported a significant reduction in the severity of tics and an amelioration in OCD symptoms. After 1 year of observation, the patient reported a worsening of his condition; however, the tic severity did not reach the initial scores. The improvement in YGTSS score was 79.2%, 45.8%, and 14.6% after 6-, 12-, and 24-months of follow-up, respectively. If evaluating the RVBTRS, the tic reduction comprised 46.7% by the second year of follow-up. YBOCS score decreased by 54.5%, 36.4%, and 40.9% after 6-, 12-, and 24-months of follow-up, respectively. The patient reduced his medication. BDI scores remained low throughout the entire follow-up period. SF-36 scores showed temporary inconsistent amelioration, whereas everyday functioning significantly improved. At the last follow-up visit (2.5 years postoperatively), some non-bothersome tics were still present, and obsessions remained the main complain. In his self-report, the patient noted a reduction in vocal tics and improvement of control over motor tics, as well a decrease in obsessions. In order to optimize the outcome, risperidone has been replaced by aripiprazole with a beneficial effect on tics and behavior. No significant adverse effects were noticed.

Patient 3 (P3)

The male patient, 26 years old, suffered from severe complex motor and vocal tics from the age of 8. Later in adolescence, prominent OCD and self-injurious behavior added. TS symptoms exacerbated at the age of 15–16, when the tics became almost constant with coprolalia, obscene gesturing, punching, kicking, and head banging. Numerous antipsychotics, antidepressants, anticonvulsants, and benzodiazepines were used for pharmacological treatment, however, the patient remained markedly disadaptated and disabled. BDI score revealed severe depression and cognitive tests showed moderate deficit (MMSE 24). Preoperative regimen included olanzapine 15 mg/day, sertraline 300 mg/day, valproate acid 1000 mg/day, oxcarbazepine 300 mg/day, and bromdihydrochlorphenylbenzodiazepine 1.5 mg/day.

Bilateral DBS of the medial thalamus (CM-Spv-Voi) was performed based on randomization. In the early follow-up, this patient noticed some relief in the tic severity; however, the benefit rapidly vanished. Because of the SIB, the patient continued hitting his head that resulted in damage to the device. During the scheduled visit 6 months after surgery, an open circuit at the right lead was identified. The skull X-ray revealed a disconnection of the cranial part of the extension. We performed a revision surgery and restored the integrity of the system. After the procedure, the patient noted some relief of tics control. However, his mental condition soon deteriorated, and he repeatedly hurt the cranial parts of the neurostimulator with the head bangs. In 1 month, the benefit of stimulation was lost; however, the patient did not

come for an urgent visit. At the 1-year follow-up, the stimulation via the right electrode was interrupted again. The second revision surgery revealed substantial damage to the connection point of the lead and extension. Despite the resumption of DBS, the patient broke the neurostimulator charger and then refused to continue stimulation. The patient's caregiver (father) was also disappointed with the unsatisfactory outcome and did not support further follow-up visits. Subsequently, we offered the patient a radiosurgical bilateral anterior capsulotomy in order to influence OCD, but he refused this option either. Since DBS was not properly provided, he had to be excluded from the group analysis.

Patient 4 (P4)

The fourth patient is a 45-year-old man. Motor tics manifested at the age of 7 simultaneously with obsessions and compulsions (opening and closing of desk drawers, shifting items in a school bag, pressing on various objects). At the age of 15, vocal tics started. At the same time motor tics became more frequent and OCD more severe. Particularly noticeable were the abrupt throwing back of the head, pounding on the table with a fist, hitting and breaking objects. His treatment history included a variety of antipsychotics, antidepressants, anticonvulsants, and benzodiazepines. Significant multidomain cognitive impairment with predominant executive dysfunction was found on neuropsychological examination. Despite this, the patient was offered a surgery due to pronounced disability and social disadaptation, even on high-dose and combined medication. In the latest scheme, haloperidol 5 mg/day, olanzapine 10 mg/day, quetiapine 300 mg/day, tiapride 300 mg/day, valproate 1500 mg/day, and clonazepam 3–4 mg/day were prescribed.

The patient underwent bilateral implantation of DBS electrodes in pvGPi. The improvement in YGTSS score was 22.7%, 36.4%, and 56.8% after 6-, 12-, and 24-months of follow-up, respectively. RVBTRS score improved by 60% to the second year of DBS. YBOCS score improved by 31.6%, 65.8%, and 60.5% after 6-, 12-, and 24-months of follow-up, respectively. The neuropsychological outcome was a matter of concern, since his MMSE and FAB scores worsened after the first year of follow-up by 20.8% and 25%, respectively. Head CT scan showed the correct position of the electrodes and no other pathologies were found. There was no clear explanation for cognitive deterioration. It is possible that long-term use of high-dose psychotropic drugs and preoperatively compromised cognition could contribute to such outcome. We tried to reduce and simplify the medication regimen, but the patient was hesitant to make any changes. Regarding stimulation-induced adverse effects, the patient developed some freezing and gait bradykinesia when the ventral GPi contacts were activated. Changing of the active contact and adjustment of the stimulation settings could manage that. At the last follow-up visit (3 years postoperatively), the patient maintained a significant reduction in tics and OCD. He gained partial independence in the everyday life functioning. Besides the marked executive dysfunction, the most bothersome symptoms were remaining obsessions

and compulsions, as well as slight dysarthria. In his self-report, the patient noted a significant improvement in his condition and quality of life.

Patient 5 (P5)

The female patient, 43 years old, who had motor tics started at the age of 3 and vocal tics at the age of 8. Since adolescence, the patient suffered from moderate obsessions and depression. TS was sufficiently controlled by treatment, and then at the age of 15 she abandoned all medications. From the age of 18, she experienced a significant aggravation of tics, which reached a maximum by the age of 24 (jerking, twitching and turning of the head, bending the trunk forward and to the sides, swinging the arms, periodic squats, grimacing, shouting out vowels, syllables or word endings). Medication schemes included multiple antidepressants, benzodiazepines, antipsychotics, and anticonvulsants. Most neuroleptics caused side effects, such as amenorrhea, or aggravated tics. Overall, she could not gain satisfactory control over the tics. Before surgery, the patient took trifluoperazine 2.5 mg/day, clonazepam 1 mg/day, and clomipramine 25 mg/day.

In this patient bilateral pvGPi DBS was performed. The improvement in YGTSS score was 38.9%, 44.4%, and 33.3% after 6-, 12-, and 24-months of follow-up, respectively. Considering the mild OCD symptoms before surgery, the increase in YBOCS score was observed after 6 months of follow-up, but it did not reach clinical significance. After 2 years of DBS, the patient complained of tics worsening due to family stress. At the last follow-up (2.5 years postoperatively), moderate motor tics were present with a consecutive trend to wane (YGTSS 19). There were no significant changes in SF-36 scores compared to the preoperative state. In her self-report, the patient noted some relief in the tic severity. The main disabling postoperative complaint appeared to be hyperhidrosis. We did not consider this symptom being related to surgery or stimulation. Medication adjustment was proposed.

Patient 6 (P6)

The patient is a 21-year-old man, who had a positive family history of tic disorder. His father experienced mild, non-bothersome motor tics. The patient suffered from motor tics since the age of 3 and vocal tics since the age of 4. The patient received aripiprazole and valproate for a long time and achieved clinical remission by the age of 15 years. After the age of 17, vocal and motor tics became more complex and severe. The patient complained of involuntary prolonged screams, shouting obscene words, bouncing and squats with body bending, arm swinging, and twitching of the head and shoulders, which forced him to homeschooling. No significant OCD was found. Pharmacological history included mainly antipsychotics and anticonvulsants. Haloperidol appeared to be the most effective, however, could not be used in the long-term due to the induced facial dyskinesia. Preoperatively, treatment consisted of risperidone 8 mg/day and trihexyphenidyl 4 mg/day.

The patient underwent bilateral CM-Spv-Voi DBS. YGTSS score improved by 43.5% and 34.8% after 6- and 12-months of follow-up, respectively. Six months postoperatively, this patient reported the reduction in vocal tics. One year following DBS, he reported the improvement in gait due to reduction of bouncing and squatting. YBOCS and BDI scores remained low. No significant DBS-related adverse effects were noticed. The dose of risperidone was reduced.

Patient 7 (P7)

The seventh patient is a 29-year-old man without any family history of tics or other movement disorders. Motor tics started at the age of 5, later vocal tics added. In recent years, the patient also suffered from apathy and depression. His treatment included antipsychotics, antidepressants, and benzodiazepines. The patient gained some control over the tics; however, he could not continue with regular medication due to the fatigue and loss of energy induced. The main complains before surgery were short shouts of sounds and words, neck and trunk twitching, facial grimacing, and swinging of the shoulders (YGTSS 38). He also suffered from depression (BDI score 13), while no OCD was observed (YBOCS 2). No significant cognitive deficit was found, except for some decline in verbal memory (MMSE 27). He was relatively socially adapted and was able to work as a loader. Preoperative treatment consisted of aripiprazole 10 mg/day.

He was assigned to bilateral pvGPi DBS. To mention is the particular brain anatomy with pronounced asymmetry of the basal ganglia that required adjustments to target planning. Up to now, a short-term follow-up outcome after 3-month DBS is available. No significant changes in the tic severity or emotional state were observed according to the assessment scales. No side effects were noticed and the patient was advised to maintain the same medication until the next follow-up visit.

6 Discussion

Based on more than the 20-year worldwide experience, DBS could be considered not a experimental, but a valuable option for treatment of refractory TS. The mean improvement in tic severity comprises about 53% across different brain targets according to pooled data from a recent meta-analysis (Baldermann et al., 2016) that reflects the overall reported outcomes. Nevertheless, the particular changes in tic scores following DBS vary greatly among individuals, ranging from excellent to poor results.

There is still no consensus on the preferential brain structure for electrode implantation. Multiple brain structures situated within the CBTC circuit have been tried as possible targets with comparable results overall. Up to now, the thalamus and GPi were used more often (Deeb and Malaty, 2020; Xu et al., 2020). Nevertheless, even within the thalamus, the most studied structure for DBS in TS, several regions may

be targeted, such as CM-Pf, CM-Spv-Voi, Vop-Voa-Voi, or VA/VL. In GPi, DBS both of anteromedial and posteroventrolateral parts have been proven to ameliorate tics. DBS of STN, GPe, and H fields of Forel seems to be promising, but remains under-investigated with only few cases implanted. The region of ALIC-NAc has been abandoned for DBS in TS in the last years due to the impression of less convincing results. While ALIC-NAc DBS continues being used in surgery for OCD, the evidence for its effect in TS remains very limited with only few patients reported (Borders et al., 2018; Burdick et al., 2010; Senova et al., 2019). Several recent pooled comparative studies of DBS in TS did not reveal any significant difference in outcomes between the targets used (Baldermann et al., 2016; Coulombe et al., 2018; Johnson et al., 2019; Martinez-Ramirez et al., 2018). Thus, in most available studies, the patient samples were small, the procedures were heterogeneous, and the outcomes varied depending on the individual features of patients. Among the factors that might influence the outcome were mentioned preoperative impairment, disease duration, and concomitant mood disorders.

While planning our randomized study, we selected the medial thalamus (CM-Spv-Voi) and GPi as the main targets to compare, since they were the most promising targets for TS described in the literature. We preferred to use pvGPi over amGPi based on our early experience of successful DBS in TS patient with OCD (P1). We have decided not to include ALIC-NAc target in the study protocol, despite the fact that the reported higher prevalence of OCD in TS surgical candidates gives the rationales for its use. Our previous experience of ALIC-NAc DBS in a patient with OCD has not shown significant effectiveness (Tomskiy A.A., unpublished data). In contrast, we observed a good effect of pallidal DBS on OCD symptoms in Patient 1. Nowadays, we would consider GPe and STN as attractive targets to explore, taking into account the reports of successful DBS in TS and the possible role of these structures in stereotyped and compulsive behaviors (François et al., 2004; Martinez-Torres et al., 2009; Piedimonte et al., 2013).

Hereby, we were able to include 4 patients in the interim assessment (P2, P4–6). Three patients had the follow-up over 2 years. One patient (P3) was excluded from the analysis because of the continuing interruptions and eventual withdrawal of the stimulation, the other patient (P7) has not yet reached the required follow-up time points. The mean tic reduction according to YGTSS was 46.1%, 40.4%, and 34.9% after 6-, 12-, and 24-months of follow-up, respectively. The mean improvement according to RVBTRS was 20.0%, 23.5%, and 41.1% after 6-, 12-, and 24-months of follow-up, respectively. In patients with CM-Spv-Voi DBS, we observed more pronounced amelioration in vocal tics than motor tics that is consistent with literature data. The mean YBOCS score decreased by 21.4%, 42.9%, and 21.7%, after 6-, 12-, and 24-months of follow-up, respectively. BDI scores, cognitive state, as well as SF-36 physical and mental health components, did not change significantly across the patient sample. On preliminary evaluation, no evident difference in efficacy between DBS of CM-Spv-Voi and pvGPi could be drawn.

Thus, the existence of an optimal stimulation site for TS remains a matter of debate. Comparable outcomes with DBS of different targets support the idea of

the predominant importance of influencing the same pathological network rather than a specific target. The discussion moves from the search of an "ideal" target to a comprehensive characterization of the effects related to DBS of particular region in regard to both movement and psychiatric symptoms of TS. In order to refine the value of distinct brain targets, further investigations are needed, including comparative double-blind randomized controlled studies.

Another relevant question is defining appropriate candidates for DBS in TS. The Dutch-Flemish Tourette Surgery Study Group has established the guidelines for patient selection, which included the severity (YGTSS score $\geq$35/50) and pharmacoresistance of tic disorder as the main necessary criteria. At the same time, a meta-analysis by Baldermann et al. (2016) has shown better outcomes in patients with higher disability and less severe preoperative tic scores. Based on these findings, the authors concluded that the preoperative impairment could be more important in patient selection than the tic severity. This point is not reflected in the current guidelines. In our experience, YGTSS scores have not always reflected true disability. The tics may be not very severe and generalized, however, refractory to treatment and socially disabling. On the contrary, even among the patients with severe TS symptoms not all individuals give consent to surgery. In our center, 2 out of 10 patients (20%) who have been offered surgery eventually declined the intervention. The fluctuating nature of symptoms and the dependency on psychosocial factors contribute to such variability. Overall, the number of patients eventually considered for surgery remains very low across the centers that results in small number of cases in the studies.

The definition of treatment resistance may also be not straightforward. We assume that often patients with TS remain undertreated. For instance, among patients initially who were referred to our Center as possible surgical candidates, in 79% of cases the medication regimen could be adjusted. Thus, a substantial part of patients may still improve their condition by optimizing the treatment. This fact stresses the importance of an experienced team implicated in the primary clinical assessment of a patient, which could provide the appropriate recommendations. Interdisciplinary management with personalized approach is crucial for the optimization of non-pharmacological and pharmacological treatment that may allow avoiding surgery in a decent part of TS patients. A problem that may hinder the adequate treatment is the unavailability of a number of drugs in some countries (e.g., alpha-2 adrenergic agonists, newer dopamine depleting agents). Behavioral therapies may be difficult to access due to the high cost of a treatment course, if is not covered by insurance, or due to the lack of psychotherapists specializing in TS.

The other point of controversy are concomitant psychiatric disorders, whether they are indication or contraindication for DBS in TS. Pooled analysis of available cases revealed the improvement in associated OCD and depression after DBS, however, preoperative scores themselves were relatively low. No significant differences among DBS targets were elucidated (Baldermann et al., 2016). Nevertheless, individual results vary. In our patient sample, clinically significant OCD was present in 4 out of 7 cases (P1–4). In three patients, we observed a reduction in YBOCS score

following DBS (2 patients with pvGPi and one with CM-Spv-Voi DBS). Depression scores were not prominent except for one patient (P3) and remained stable after surgery. In one patient with CM-Spv-Voi (P3), OCD and severe SIB associated with pronounced depression and lower cognition contributed to poor compliance and eventual DBS withdrawal.

Although tic reduction is usually the primary endpoint for DBS, accompanying psychiatric conditions should not be underestimated in treatment of TS, since they affect the quality of life and overall surgery outcome often playing a greater role in patients' disability than tics. The question still remains whether the presence of OCD and/or depression may influence the choice of the target structure for TS, and what would be the optimal target depending on the leading psychiatric symptom. Moreover, patients with prominent psychiatric disorders might benefit from DBS with multiple targets or DBS combined with radiosurgery (Kakusa et al., 2019; Richieri et al., 2018; Zhang et al., 2019a,b). In such cases, the increased surgical risks and risks of adverse effects should be considered.

There are few studies in TS reporting improvements in SIB following NAc and thalamic DBS (Ackermans et al., 2010; Zabek et al., 2008). Based on the encouraging cases of DBS in Lesch-Nyhan syndrome, a genetic disorder associated with severe self-mutilations (Piedimonte et al., 2015; Tambirajoo et al., 2021), GPi may be proposed as a possible target structure for improving SIB in TS. The beneficial effect of DBS GPi on the other forms of obsessive-compulsive behavior might be also discussed, despite that currently it is not considered the preferable brain region for OCD (Hauseux et al., 2017). Our experience with pvGPi DBS in a patient with a history of TS with prominent OCD and SIB (P1), which appeared to be consistently efficacious in the long-term follow-up and improved significantly the psychiatric symptoms, everyday life activity, and social adaptation, supports this assumption. Other evidence comes from the distinct observations of dystonia patients with concomitant OCD and depressive symptoms treated with GPi DBS (Meoni et al., 2015; Tomskiy A.A., unpublished data).

On the other hand, severe SIB and OCD may be a relative contraindication for neurostimulator implantation due to the risk of system damage (as it happened in Patient 3), coexisting low compliance, and treatment-related excessive psychological stress. In such patients, the lesioning procedures might be preferred to avoid the implants. OCD, mood disorders, and possibility of suicidal behavior should be timely identified and properly managed. If mental disorders are found, patients, including those selected for DBS, should be offered psychotherapy along with medications. After surgery, the behavioral therapy might provide additional benefit for TS patients.

Significant cognitive impairment may also be a partial contraindication for DBS in TS because of the patient's limited understanding of the expected effects and potential consequences that are likely to lessen the potential benefit after DBS. In our study, all patients had some deficits in cognitive control preoperatively. Pronounced executive dysfunction was found in two out of 7 patients (P3 and P4). This factor contributed to poor compliance in the one and failure to achieve social independence in the other.

DBS might be considered a relatively safe treatment for patients with severe intractable TS. The procedure does not significantly influence mood and cognitive status. In general, DBS is well tolerated by patients. The following stimulation-related adverse effects after thalamic DBS have been reported in the literature: visual symptoms, gaze disturbances, sexual dysfunction, mood changes, anxiety, apathy, fatigue, weight gain, subjective vertigo, recurrent tension headache, paresthesia, and dysarthria. For pallidal DBS, depressive symptoms, anxiety, weight gain, impaired speech fluency, dizziness, nausea, poor balance, and freezing of gait were described. Most of these side effects are transient and depend on the program settings. A matter of concern remain the hardware-related adverse effects and infectious complications, which seem to be more frequent in TS than in other movement disorders (Akbarian-Tefaghi et al., 2016; Servello et al., 2011; Xu et al., 2020).

An important issue in DBS surgery for TS remains the management of patient expectations. Despite the high response rate to DBS in TS (tic reduction $\geq$25% in more than 80% of patients), tic reduction $\geq$50% can be achieved in about half of patients (Baldermann et al., 2016). Patients should be warned that the outcomes of DBS in TS vary individually, the improvement occurs gradually over time, and the symptoms do not relieve completely (Johnson et al., 2019). Further medication adjustment and behavior therapy should be applied to optimize outcome.

Ethical issues are still unsolved in TS DBS (Smeets et al., 2018). The approach to severe TS in childhood and adolescence is the most controversial because of existing possibility of substantial waning of tic disorder in adulthood. However, tics and associated psychiatric disorders could significantly affect mental development and social adaptation of young patients, not to mention the danger of life-threatening conditions (Cheung et al., 2007; Huasen et al., 2014). The adverse effects of high-dose multimodal medication may also play a role in patient disability. Impaired educational, professional and social formation during adolescence may not compensate later in life, even in case of tic reduction. It is for this reason that the age criterion was excluded from the current recommendations for DBS in TS (Schrock et al., 2015). In support of this, several studies reported a significant improvement in tics and associated psychiatric symptoms in patients younger than 25 years of age (Coulombe et al., 2018; Dowd et al., 2018; Zhang et al., 2014). It remains unclear whether DBS may influence the natural course of TS in young patients. Based on a case of stable tic remission in an adolescent after prolonged DBS discontinuation, Zekaj et al. (2015) discussed the possibility of temporary application of DBS in young severely disabled TS patients. Since we had no experience with surgery for pediatric TS, we cannot provide any particular advice. In any case, careful interdisciplinary evaluation and implication of a local ethical committee is highly recommended if consider surgery in TS patients less than 18 years old. The discussion of surgical treatment should be individualized for each patient with TS, including thorough weighing of the risks and benefits.

7 Conclusion

Tourette syndrome is a complex neurological disorder with commonly associated psychiatric dysfunction. In medically resistant cases, neurosurgical treatment may be considered, predominantly DBS. Careful patient selection, identification of the main disabling factors are necessary to achieve better effectiveness of surgery. In case of referral to a neurosurgical center, preoperative assessment, surgical procedure, and postoperative management of patients should be carried out by an experienced multidisciplinary team, which could consider all the individual features. Initial optimization of conservative treatment in potential surgical candidates, including the adherence to behavior therapy, may facilitate compliance, improve surgical outcome, and, in some cases, avoid surgery.

The main challenges that remain to be addressed are the determination of the optimal DBS target and the selection of appropriate candidates for surgery, as well as ethical issues, especially when treating pediatric patients. Considering the similar effectiveness of DBS targets used today in TS, the limited size of patient groups investigated, and the heterogeneity of procedures, further research in a larger population is needed. It is particularly important to follow patients in the long-term in order to trace all the delayed DBS effects on both tics and psychiatric symptoms. This may allow us to better characterize each stimulated brain region and draw conclusions about the preferential target for TS. Another point to pay attention is the optimization of DBS outcomes in individual patients in the long-term follow-up, regarding not only motor disturbances, but above all the quality of life and social functioning, which may involve both nonsurgical and surgical methods.

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