Deep brain stimulation for Gilles de la Tourette syndrome in children and youth: a meta-analysis with individual participant data

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OBJECTIVE Gilles de la Tourette syndrome (GTS) is a disorder characterized by motor and vocal tics. Although by definition the onset of GTS is before age 18 years, clinical trials of deep brain stimulation (DBS) have been conducted only in adults. Using individual participant data (IPD) meta-analysis methodology, the current study investigated the safety and efficacy of DBS as a treatment for GTS in children and youth.

METHODS A systematic review with no date or language restrictions was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Three electronic databases were searched: PubMed, EMBASE, and Web of Science. From 843 articles screened, the IPD of 58 children and youth (ages 12–21 years) extracted from 21 articles were collected and analyzed. A mixed-effects univariable analysis followed by multivariable hierarchical regression was performed using change in the Yale Global Tic Severity Scale (YGTSS) score as the primary outcome and reported measures of comorbidities as secondary outcomes.

RESULTS The authors' results showed an average improvement of $57.5\% \pm 24.6\%$ across studies on the YGTSS. They also found that comorbid depression and stimulation pulse width each correlated negatively with outcome ($p < 0.05$). In patients with less severe GTS, greater improvements were evident following thalamic stimulation. More than one-quarter ($n = 16$, 27.6%) of participants experienced side effects, the majority of which were minor.

CONCLUSIONS DBS in the pediatric population may be an effective option with a moderate safety profile for treatment of GTS in carefully selected children and youth. Large, prospective studies with long-term follow-up are necessary to understand how DBS influences tic symptoms and may alter the natural course of GTS in children.

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KEYWORDS Gilles de la Tourette syndrome; deep brain stimulation; neuropsychiatric disorder; functional neurosurgery

GILLES de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterized by motor and vocal tics. A tic is a sudden, rapid, recurrent, non-rhythmic movement or vocalization. By definition, onset of the disorder occurs before age 18 years. Typically, tic symptoms have their onset in early childhood, peak dur-

ing the prepubertal period, and then gradually decrease during adolescence.³ In fact, approximately 75% of children with GTS will experience remission of their disease or demonstrate considerable improvements in tic severity once brain maturation is complete.^{19,24,32} Although the majority of affected patients are able to function normally

ABBREVIATIONS ADHD = attention-deficit/hyperactivity disorder; DBS = deep brain stimulation; GPi = globus pallidus pars interna; GTS = Gilles de la Tourette syndrome; GTS-QOL = GTS Quality of Life; HDRS = Hamilton Depression Rating Scale; IPD = individual participant data; NA = nucleus accumbens; OCD = obsessive-compulsive disorder; SIB = self-injurious behavior; STAI = State-Trait Anxiety Inventory; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale. **SUBMITTED** May 18, 2018. **ACCEPTED** July 25, 2018.

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and require no treatments beyond psychoeducation and psychosocial support,⁴ some manifest severe and debilitating symptoms that can lead to physical injury, emotional distress, and psychosocial impairment.^{4,6} Furthermore, GTS is frequently associated with comorbidities such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, depression, and self-injurious behavior (SIB).^{16,23,47} These comorbidities may further contribute to decreased quality of life.¹⁷

The pathophysiology of GTS is incompletely understood. Involvement of the cortico-striato-thalamo-cortical network is generally described.^{12,25,36} Various investigations have implicated dopamine receptors in the disease pathophysiology, providing a biological rationale for the use of antipsychotic agents.³¹ Alterations in GABA and glutamate neurotransmission have also been reported. The main treatment approaches are evidence-based behavior therapy and pharmacotherapy, including antipsychotic agents, alpha-2 agonists, and other medications. Although these treatments are effective for many patients, some still experience intractable symptoms or cannot tolerate medication side effects.^{4,6}

For patients with treatment-resistant tics that are severe and impairing, initial positive experience with ablation of the median and rostral intralaminar thalamus²⁵ generated enthusiasm for neuromodulation through deep brain stimulation (DBS). Although DBS has clear advantages over other surgical treatments,³⁴ numerous questions remain unanswered, such as the ideal target in GTS. Several putative targets have been described, including the globus pallidus pars interna (GPi), the thalamus, and the nucleus accumbens (NA).⁴⁵

The role of DBS as a treatment for GTS in pediatric populations is a subject of ongoing controversy. Although published guidelines recommend its use primarily in patients 25 years and older,³⁸ DBS has been used successfully in children with GTS as young as 12 years of age.²⁶ Authors of the 2011 European guidelines proposed that because tic symptoms often improve or resolve with brain maturation, surgical interventions should be delayed. The authors did not, however, identify inferior outcomes in 11 children younger than 25 years treated with DBS, compared with older cohorts. Given the poor quality of evidence supporting its use, most recent Canadian and American guidelines recommend against the use of DBS in children.^{39,55}

In order to address knowledge gaps in our understanding of the safety and efficacy of DBS in young people with GTS, we performed a systematic review and meta-analysis of the published literature involving children and youth (≤ 21 years). Individual participant data (IPD) were extracted from each case report and series, and a multilevel statistical model was applied to identify putative predictors of treatment response.

Methods

Search Strategy and Eligibility Criteria

We applied IPD meta-analysis methodology, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, to evaluate the safety and efficacy of DBS for GTS in children. This

methodology increases statistical power and is particularly helpful to investigate questions that were not originally addressed in the individual publications.²⁹ Our study protocol was developed, but not registered, by authors with content and methodological expertise (G.M.I., N.L., and N.M.A.) prior to conduct of the review.

A systematic review was performed by searching 3 electronic databases: PubMed, EMBASE, and Web of Science. All articles reporting on DBS for pediatric GTS that were published before October 2017, including case reports and cohort studies, were identified. To be included, studies were required to 1) involve pediatric patients (age ≤ 21 years) living with GTS and treated with DBS; and 2) report outcome by administering the Yale Global Tic Severity Scale (YGTSS) pre- and postoperatively.³³ Studies were excluded if 1) IPD were not available; or 2) the same patients were presented in different studies (duplicates). Electronic databases were searched using the following search terms: “pediatric deep brain stimulation,” “Tourette deep brain stimulation,” “Tourette’s deep brain stimulation,” and “children deep brain stimulation.” No language restriction was used.

Data Extraction

Data were collected independently by 2 reviewers (L.M.E. and M.A.C.), and a third reviewer verified accuracy (G.M.I.) and adjudicated disagreements. Studies were screened for predefined variables, including YGTSS pre- and postsurgery, age at surgery, age at GTS onset, sex, descriptive tic severity (phonetic, motor, coprolalia), number and types of medications tried, family history (tic disorder or other psychiatric disorder), nuclei targeted in DBS, bilateral versus unilateral stimulation, stimulation parameters, reported complications, and follow-up duration. When available, standardized scores describing the severity and changes in comorbid conditions were extracted. These included scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),⁴⁸ GTS Quality of Life Scale (GTS-QOL),⁸ and State-Trait Anxiety Inventory (STAI).⁵⁴ Measurements of depression were also extracted using a variety of outcome measures, as reported by individual studies (Beck Depression Index, Hamilton Depression Rating Scale [HDRS],²² Hospital Anxiety and Depression Scale).

The reference lists of all articles identified were reviewed for any additional articles that met our inclusion and exclusion criteria. We also performed a search of highly published authors on DBS treatment for GTS, based on authorship of adult clinical trials. A list of all articles screened was compiled. All excluded articles underwent adjudication, and specific justifications were noted. All data, particularly studies from the same institution, were reviewed for duplicates. All duplicate publications or participants were removed. In cases of identical cohorts described in more than 1 article, only the article with the longest follow-up time was included. In cases of uncertainty regarding duplicate patients, the authors of the articles were contacted.

Endpoints

The primary outcome measure in this meta-analysis

FIG. 1. Search results and included articles as per the PRISMA guidelines.

was the percentage change in the YGTSS total score (pre-operatively vs last follow-up). The scores were adjusted such that a change with a positive value reflected postoperative improvement. Secondary outcomes were changes in comorbidities of GTS, measured using the Y-BOCS, the STAI, and the HDRS, as reported by individual studies and pooled in the IPD database.

Risk of Bias Assessment and Quality of Evidence

Since all patients were observational, unmatched case series and reports, risk of bias and quality of evidence were considered “high risk of bias” and “low to very low quality of evidence” as per the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool.²¹

Statistical Analysis

Univariable mixed-effects generalized linear models were performed for each covariate of interest. Covariates

with $p < 0.05$ on mixed-effects univariable analysis were included in a hierarchical multivariable mixed-effects model. All analyses were performed using R statistical software (RStudio version 0.99.484).

Results

Search Results

The search strategy identified 829 articles. Fourteen additional articles were added following review of reference lists, resulting in a total of 843 articles. Thirty-nine duplicates were removed, leaving 804 articles to be screened. Of these, 532 articles were excluded through title and abstract screening. The 272 remaining articles underwent full-length review. From these, 251 articles did not meet inclusion criteria or met exclusion criteria. A total of 21 articles reporting IPD for 58 patients were included (Fig. 1). There were 10 case reports and 11 case series. There were no controlled or open trials identified. A complete description of each study is included in Table 1.

Individual Participant Data

Demographic information for all IPD of treated children and youth is presented in Table 2. The patients were on average 17.9 ± 2.7 years old (range 12–21 years) and had onset of their tics at a mean age of 7.4 ± 3.4 years. Almost three-quarters (72.4%) had at least 1 psychiatric comorbidity (ADHD, OCD, anxiety, or depression disorders). A substantial minority (27%) also manifested patterns of SIB. Overall, the cohort had a mean preoperative YGTSS score of 78.3 ± 17.5 (ranging from 25 to 100). Six patients had a score lower than 50.

Electrodes were placed in the GPi in 33 patients (anteromedial GPi in 6 patients, posteroventral region GPi in 1 patient, and exact localization not specified for 26 patients). The thalamus was targeted in 24 youths: the centromedian-parafascicular and ventralis oralis complex of the thalamus (CM-Pfc) in 20, fields of Forel in 1, and exact localization not specified for 3. Finally, 1 patient underwent DBS implantation in the centromedian-parafascicular thalamic complex, which improved tic severity, but also had electrodes implanted in GPi and later NA, to target OCD specifically. The specific stimulation parameters used are presented in Table 3. Stimulation parameters differed between patients and were selected at the discretion of the treating neurosurgeon.

Primary and Secondary Outcomes Following DBS

Following DBS, the mean percentage change on our

primary outcome measure, the YGTSS, was $57.5\% \pm 24.6\%$ ($p < 0.001$) over a mean follow-up period of 34.2 ± 23.4 months (range 3–95 months). Nearly all children (96.6%) demonstrated some improvement in tic symptoms, with 91.4% and 64.0% showing greater than 20% and 50% improvement, respectively.

The pre- and postoperative scores on the YGTSS, Y-BOCS, STAI, and GTS-QOL are presented in Table 4. Significant improvements were also identified on 2 secondary outcome measures, the Y-BOCS and STAI. Moreover, changes in Y-BOCS, STAI, and GTS-QOL scores were significantly associated with percentage change in the YGTSS.

Moderator Analyses

On univariable hierarchical mixed-effects analysis, comorbid anxiety, comorbid depression, and low pulse width of stimulation were each significantly associated with less improvement in YGTSS scores (Tables 2 and 3). On hierarchical multivariable analysis, the associations with comorbid depression and pulse width remained significant, whereas the association with comorbid anxiety did not (Table 5).

Patients with less severe GTS (defined by excluding the most severe quartile on the basis of the preoperative YGTSS score) were evaluated as a separate cohort in order to account for a potential ceiling effect of treatment. Within this cohort, thalamic stimulation (as opposed to GPi stimulation) was associated with greater improvements in

TABLE 1. Articles included in meta-analysis

Authors & Year	Journal	Total No. of Patients	No. of Patients Included*	DBS Target (GPi/thalamus)	Age Range of Included Patients, yrs
Dwarakanath et al., 2017	<i>Neurol India</i>	1	1	1/0	18
Hauseux et al., 2017	<i>Eur J Paediatr Neurol</i>	3	3	3/0	12–18
Dowd et al., 2018	<i>J Neurosurg</i>	13	10	10/0	16–21
Testini et al., 2016	<i>Mayo Clin Proc</i>	12	3	1/2	17–18
Servello et al., 2016	<i>Neurosurgery</i>	48	4	3/1	12–20
Huys et al., 2016	<i>Biol Psychiatry</i>	8	1	0/1	19
Zekaj et al., 2015	<i>Surg Neurol Int</i>	1	1	0/1	17
Patel & Jimenez-Shahed, 2014	<i>Parkinsonism Relat Disord</i>	1	1	1/0	21
Sachdev et al., 2014	<i>PLoS One</i>	17	5	4/1	17–19
Nair et al., 2014	<i>J Clin Neurosci</i>	4	2	2/0	15–21
Huasen et al., 2014	<i>Mov Disord</i>	1	1	1/0	19
Zhang et al., 2014	<i>Mayo Clin Proc</i>	13	9	9/0	16–21
Wårdell et al., 2015	<i>Neuromodulation</i>	5	2	2/0	19–21
Massano et al., 2013	<i>J Neurol</i>	1	1	1/0	14
Motlagh et al., 2013	<i>Tremor Other Hyperkinet Mov (N Y)</i>	8	3	1/2	16–19
Savica et al., 2012	<i>Mayo Clin Proc</i>	3	1	0/1	17
Porta et al., 2012	<i>Acta Neurochir (Wien)</i>	18	4	2/2	17–20
Kaido et al., 2011	<i>Neuromodulation</i>	3	3	1/2	19–21
Dueck et al., 2009	<i>Neuropediatrics</i>	1	1	1/0	16
Shahed et al., 2007	<i>Neurology</i>	1	1	1/0	16
Neudorfer et al., 2017	<i>Front Hum Neurosci</i>	2	1	0/1	19

* Number of patients meeting inclusion criteria.

TABLE 2. Individual participant characteristics and univariable analysis for studies reporting change in YGTSS (n = 58)

Variable	Value*	No. of Patients†	No. of Studies‡	Estimate (SE)	t-Value
Age at onset (yrs)	7.4 (3.4)	44	15	0.3 (1.2)	0.3
Age at surgery (yrs)	17.9 (2.7)	58	21	-1.4 (1.1)	-1.2
Male sex	35 (78%)	45	18	11.1 (8.0)	1.4
Duration (yrs)	10.5 (3.1)	44	15	-1.0 (1.2)	-0.8
Family history (vs none)					
Tic disorder	6 (60%)	10	7	1.5 (25.5)	0.1
Other psychiatric disorder	1 (10%)			12.5 (41.7)	0.3
Comorbidities					
ADHD	22 (46%)	48	17	-0.5 (7.4)	-0.1
Anxiety	13 (25%)	52	18	-17.3 (8.3)	-2.1§
Depression	22 (42%)	52	18	-17.4 (7.0)	-2.5§
SIB	13 (27%)	48	17	-11.5 (9.0)	-1.3
OCD	33 (63%)	52	18	-5.6 (7.1)	-0.8
Preop status					
YGTSS	78.3 (17.5)	58	21	-0.1 (0.2)	-0.3
GTS-QOL	47.1 (14.4)	15	3	-0.3 (0.5)	-0.7
Y-BOCS	17.1 (9.0)	29	10	-0.3 (0.5)	-0.7
Severity of disease					
No. of drugs attempted	6.8 (3.2)	26	14	-2.5 (1.9)	-1.3
Motor tics (complex vs simple)	28 (93%)	30	15	5.7 (16.3)	0.4
Vocal tics (complex vs simple)	5 (33%)	15	7	18.6 (18.4)	1.0
Coprolalia	11 (44%)	25	13	3.8 (10.6)	0.4
Follow-up duration (mos)	34.2 (23.4)	38	15	0.1 (0.2)	0.8
% change in YGTSS total score	57.5 (24.6)	58	21		

* Values are presented as the mean (SD) or number of patients meeting the variable (%).

† Number of patients for whom the information was provided.

‡ Number of studies providing the information.

§ Significant association with outcome on univariable analysis.

YGTSS score on univariate analysis (GPi [mean $\pm$ SEM]: 53.0% $\pm$ 4.7%, thalamus [mean $\pm$ SEM]: 68.6% $\pm$ 5.8%; $p = 0.0387$, Mann-Whitney test [Fig. 2]).

Adverse Events and Safety

Over one-quarter (n = 16, 27.6%) of participants experi-

enced side effects (Table 6). These included neck stiffness, headaches, blurred vision, decreased visual acuity, light-headedness, nausea, decreased memory, and dizziness. Dysarthria, anxiety, and suicidal thoughts were noted in 2 patients. Other complications included tremor, disinhibition, agitation, and mild paresthesia. However, most side

TABLE 3. DBS parameters and univariable analysis for studies reporting change in YGTSS

Variable	No. of Patients Meeting Variable (%)	No. of Patients*	No. of Studies†	Estimate (SE)	t-Value
DBS target					
GPi vs non-GPi	33 (57%)	58	21	7.4 (8.1)	0.9
Thalamus vs nonthalamus	25 (43%)	58	21	12.7 (7.2)	1.8
GPi vs thalamus	33 (59%)	58	21	14.0 (7.6)	1.8
Stimulation parameters‡					
Frequency (<130 vs $\geq$ 130 Hz)	39 (75%)	52	19	-3.3 (10.0)	-0.3
Amplitude (<3.25 vs $\geq$ 3.25 V)	25 (52%)	48	18	-8.7 (6.5)	-1.3
Pulse width (<120 vs $\geq$ 120 μ sec)	25 (52%)	48	18	-18.3 (7.6)	-2.4§

* Number of patients for whom the information was provided.

† Number of studies providing the information.

‡ Parameters dichotomized by median values; in cases of discrepancy between right and left side, the mean was calculated.

§ Significant association with outcome on univariable analysis.

TABLE 4. Changes in comorbidities of GTS following DBS

Tourette's Patients (n = 58)	No. of Patients	Mean ± SD	Range	t-Score	p Value
YGTSS					
Severity preop	31	40.1 ± 8.5	20 to 50	15.93	<0.001
Severity postop	31	18.2 ± 11.2	0 to 42		
Severity % change	31	55.7 ± 24.7	6.67 to 100		
Impairment preop	39	41.9 ± 9.0	10 to 50	11.93	<0.001
Impairment postop	39	16.4 ± 11.7	0 to 40		
Impairment % change	29	60.1 ± 27.2	20 to 100		
Total score preop	58	78.3 ± 17.5	25 to 100	11.96	<0.001
Total score postop	58	33.4 ± 21.8	0 to 86		
Total score % change	58	57.5 ± 24.6	0 to 100		
Y-BOCS					
Total score preop	31	15.9 ± 9.8	0 to 30	3.657	<0.001
Total score postop	31	10.7 ± 10.0	0 to 39		
Total score % change	31	30.6 ± 44.7	-75 to 100		
GTS-QOL					
Total score preop	14	47.1 ± 14.4	20 to 70	1.184	0.256
Total score postop	14	39.2 ± 22.3	13 to 80		
Total score % change	14	6.1 ± 61.3	-100 to 77		
STAI					
Total score preop	8	47.1 ± 8.4	38 to 60	5.212	<0.001
Total score postop	8	27.5 ± 7.4	20 to 39		
Total score % change	8	40.2 ± 20.1	-2.6 to 58		
HDRS					
Total score preop	8	10.4 ± 9.0	0 to 27	1.441	0.193
Total score postop	8	6.3 ± 8.0	0 to 18		
Total score % change	8	39.9 ± 63.3	-80 to 100		

Paired t-test; p value was set to $p < 0.007$ to account for multiple comparisons (α /number of comparisons).

effects are reversible and present only at high voltages of stimulation. A substantial minority ($n = 8$, 13.8%) experienced surgical complications following device installation (Table 6). These included infections in 3 patients, abdominal wall hematoma, wound revision, and hardware malfunction. Finally, 6 devices were removed for various reasons, as outlined in Table 6. Of note, not all removals were related to complications; in 3 of 6 cases the patient improved sufficiently such that DBS was no longer felt necessary.

One patient, originally described in a case report by Duits et al. but not included in our analysis due to missing primary endpoint data, died 3 years after surgery.¹⁴ In

this extreme example, the 20-year-old patient developed abrupt hypertonia and difficulty swallowing and refrained from hospital admission for intravenous infusion; she subsequently died at a palliation facility.

Discussion

The current IPD meta-analysis is the first to investigate the efficacy and safety of DBS as a treatment for GTS in children and youth and provides a comprehensive synthesis of the published literature on DBS in this population.⁵⁶ DBS has been previously reported in adult populations as an effective treatment, reducing tic severity and improving comorbid symptoms, such as OCD, anxiety, and depression.⁴⁶ Although DBS is an established treatment for other pediatric conditions, such as dystonia,³⁴ its application to GTS remains controversial given the limited evidence to date, the potential risks, and the consideration that even without treatment, the majority of affected children experience improvement in their tics during adolescence.

Overall, we found that DBS appeared to improve tic severity, irrespective of the anatomical target for stimulation. Our IPD analysis revealed that 91.4% of children demonstrated YGTSS score improvements greater than 20%, with 64% showing improvement greater than 50%. These

TABLE 5. Multivariable hierarchical mixed-effects analysis of covariates associated with changes in YGTSS using independent participant data

Variable	Estimate (SE)	t-Value	Model Coefficient (95% CI)
Comorbid anxiety	-9.5 (8.9)	-1.1	-9.5 (-26.6 to 7.5)
Comorbid depression	-19.0 (7.8)	-2.4*	-19.0 (-34.0 to -4.1)
Pulse width	-17.3 (6.1)	-2.8*	-17.3 (-28.9 to -5.6)

* Significant association with outcome.

FIG. 2. Greater improvements in YGTSS score after thalamic DBS compared with GPi DBS in children and youth with less severe (excluding the most severe quartile, based on preoperative YGTSS score) GTS on univariate analysis. Bars indicate the mean and error bars the SEM.

uncontrolled data, drawn from case reports and case series, provide preliminary support for the efficacy of DBS treatment in youth. Whether DBS alters the natural history of GTS in young patients remains unclear. Clinical evidence for the role of DBS in GTS should be complemented by research efforts to distinguish the minority of children who will have persistent, debilitating tics and may benefit from DBS earlier in the disease course from the majority who will improve over time.

In the literature, a variety of targets have been utilized, and it remains unclear which is the most effective for GTS.⁴⁵ In this study, the anatomical target of DBS was not significantly associated with tic symptom improvement, as both pallidal and thalamic stimulation appeared effective (Table 3). These findings are consistent with previous observations in adults from Baldermann and colleagues.^{2,9} When we exclude the most severely impaired quartile of children (YGTSS score lower than 92/100), the thalamus was a significantly better target than the GPi, at least on univariable analysis. This may reflect the widespread cortical circuitry involved in the pathogenesis of GTS.⁵⁷

Our findings also suggested that stimulation parameters might influence clinical outcomes. We observed that pulse width correlated with tic improvement measured on the YGTSS. This correlation potentially has important clinical implications, as currently there are no precise guidelines in the published literature regarding the frequency and pulse length of stimulation. The correlation was not observed in previous studies, and stimulation parameters are generally set individually.² These findings further highlight the importance of involvement of an expert in DBS programming when considering DBS for GTS.⁵⁵

DBS for GTS in children carries a moderate risk profile. The complications noted include hardware malfunction, battery changes, and infections. From the pooled data set, 8 children had some form of surgical complications. Only 2 of them resulted in the removal of the electrodes. In a previous study, Servello and colleagues reviewed 531

TABLE 6. Adverse events in GTS children treated with DBS (n = 58)

	No. of Pts (%)	Notes
Surgical complications		
Total	8 (13.8)	
Infection	3 (5.2)	2 of 3 had their lead removed
Hematoma	1 (1.7)	
Subcutaneous hydrops	1 (1.7)	
Hardware malfunction	1 (1.7)	Retitration needed
Lead tip cyst	1 (1.7)	Lead removed
Lead fracture	1 (1.7)	Lead replacement
Needed wound revision	2 (3.4)	After 6 yrs & after 1 mo
Side effects		
Total	16 (27.6)	
Tension headache	1 (1.7)	
Worsening of preexisting tremor	2 (3.4)	
Transient blurring of vision	5 (8.6)	At the initiation of stimulation or at certain voltage amplitude
Dizziness	2 (3.4)	Resulting from voltage increase
Decreased memory	1 (1.7)	
Seizure-like episode	1 (1.7)	One occurrence
Suicidal thoughts	1 (1.7)	
Decline of attention & mental flexibility	1 (1.7)	
Neck tightness	1 (1.7)	
Paresthesia (mild)	1 (1.7)	Stimulation related
Light headedness	1 (1.7)	Stimulation related
Parkinsonism	1 (1.7)	
Increased OCD	1 (1.7)	
Anxiety	3 (5.2)	
Agitation	2 (3.4)	
Disturbance of eye mobility	1 (1.7)	
Dysarthria	4 (6.9)	
Nausea	1 (1.7)	At high intensity
Lead removal		
Total	6 (10.3)	
After 5 yrs & 7 mos		For personal reasons; stimulation increased anxiety & OCD
After 3 yrs & 2 mos		Infection, rejection of pouch, possibly resulting from excessive self-grooming
After 5 yrs		Symptoms almost completely resolved

CONTINUED ON PAGE 243 »

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TABLE 6. Adverse events in GTS children treated with DBS (n = 58)

	No. of Pts (%)	Notes
Lead removal (<i>continued</i>)		
Total (<i>continued</i>)	6 (10.3)	
After 4 yrs		Pt had sustained benefit & reported having “a normal life”
After 3 yrs		No aggravation of symptoms & stable
After 2 yrs		Lead fracture w/ replacement; infection of the new electrode followed by its removal; reimplantation 4 mos later, then an aseptic cyst appeared on the tip of the electrode, which lead to its removal (unilat removal)
Part-time activation		To spare the battery & decrease side effect

Pt = patient.

DBS implantation procedures done in 272 patients. They observed a greater prevalence of infections and complications in patients with GTS (18% in GTS vs 3.7% overall) compared to other movement disorders,⁵¹ perhaps as a result of a compromised immune system or compulsive touching of the wound. Various articles alluded to the latter, highlighting the occurrence of behaviors such as “too much self-grooming,” and patients “compulsively push[ing] on IPG for four weeks,” or “picking at their incision.” In the current study, the rate of infection was 5.2%, which, albeit lower than Servello and colleagues’ proportions, remains higher than that of reports in other pediatric populations. For example, in a meta-analysis of 307 children with dystonia, 11 infections were noted (3.6% infection rate).¹⁹ The risks of complication related to the intervention, however, continue to decrease with advances in surgical techniques.^{5,29} Worsening of symptoms or unexplained new symptoms have been described. In one case described by Duits et al.,¹⁴ a 20-year-old female patient had hypertonia and dysphagia following DBS, which ultimately led to her death. Overall, 27.6% of the participants described some side effects, generally described as mild and related to the activation or the voltage amplitude of the stimulation.

Role of Comorbidities and SIB

Psychiatric comorbidities are common in GTS. In our IPD database, 72.4% of children manifested at least 1 comorbidity, most frequently OCD, followed by ADHD and depression. Compared with the statistics of the International Tourette Deep Brain Stimulation Database and Registry (<https://tourettedeepbrainstimulationregistry.ese.ufhealth.org>), we observed a slightly higher percentage of patients with OCD and ADHD, a lower percentage of patients with anxiety and depression, and a similar percent-

age of patients with SIB. From a descriptive perspective, many studies reported significant improvement of comorbid symptoms. However, in some cases DBS increased OCD, anxiety, and depression symptoms (Table 6).

In secondary analyses we found that the presence of comorbid anxiety and depression was each inversely associated with change in YGTSS score when we did not control for covariates. However, only depression remained inversely associated with change in YGTSS score when controlling for covariates. These results differ from previous findings in adults.³⁶ Interestingly, significant associations were identified between change in YGTSS score and change in Y-BOCS, STAI, and GTS-QOL scores. This result provides additional support to previous findings that patients with severe GTS are prone to increased stress and decreased quality of life.^{7,20} It was also suggested that DBS could influence OCD symptoms, anxiety, and depression, which could greatly influence the patient’s quality of life, independent of its effects on tics.⁴¹

Our results showed that 27% of patients had a history of SIB, but we did not have sufficient data to measure improvements. In the adult literature, there are reports of improvement of SIB following thalamic and NA DBS.^{1,59} In addition, many studies on Lesch-Nyhan disease showed good efficacy of pallidal stimulation for improvement of SIB.⁴⁴

Limitations

Our study has several limitations. First, the absence of a control cohort prevents inferences about whether DBS alters the natural history of GTS in youth. Indeed, the absence of controls raises the question of whether the initial improvement in tic symptoms is due to DBS or instead reflects the natural waxing and waning of tics, the placebo effect, or other factors. As such, the efficacy of DBS in youth with GTS remains uncertain. Second, most articles were case reports or case series, in which validity and specificity of information were sometimes questionable. However, several articles included in this meta-analysis recruited sizable cohorts and included years of follow-up using validated instruments. These study designs are still prone to selection bias and lack internal validity due to the absence of a control group, as previously mentioned. The differences in the quality of the data between these large cohorts and smaller case reports/series were often details surrounding adverse events. Similarly, heterogeneous reporting of primary and secondary outcomes led to the exclusion of some articles describing the use of DBS in children and youth. Third, as with many meta-analyses, publication bias limits the interpretability of our findings. It is possible that negative studies of DBS in children were not published. Fourth, sparse data are available to guide the administration of DBS in youth with GTS, including optimal timing of the intervention, ideal anatomical targets, and stimulation parameters. Importantly, prospective, longitudinal multicenter databases with long-term follow-up are required to further elucidate the role of DBS for children with GTS.

Ethical Perspective in Pediatric DBS for GTS

Decisions regarding treatment of children and youth

with DBS are complex and value-laden.^{10,50} Despite the increasing popularity of DBS in adult populations, its use in younger patients is limited for multiple reasons. Evidence for efficacy is limited, observed improvements are variable, and long-term effects are unknown.⁵² There are multiple risks, including those related to hardware malfunction, battery changes, and infection. The risk-to-benefit profile must be weighed for each patient individually. At minimum, requirements for DBS in children and youth should include demonstration of treatment resistance, exclusion of secondary causes, and the potential for physical injury. Particular caution should be exercised with children and younger adolescents, where there is still a good likelihood that the tics will improve as a function of their natural course. Involvement of a multidisciplinary team and a comprehensive informed consent discussion are essential. Authors also have often suggested the involvement of institutional ethics committees, particularly in pediatric cases.^{38,50}

Conclusions

In the current IPD meta-analysis based on uncontrolled case reports and case series, the use of DBS for the treatment of GTS in youth was associated with clinically significant improvements in tic severity. Pallidal and thalamic stimulation both led to good outcomes, but thalamic stimulation had greater effect in less severely affected youth. Higher depression scores and low pulse width of stimulation were each associated with less improvement in tics. A sizable minority of patients had adverse events related to the surgery, or to the stimulation intensity. These adverse events led, in few cases, to the removal of the electrodes. Further research involving multicenter databases and long-term, prospective follow-up is required to clarify the benefits and risks of DBS in youth with GTS, establish potential indications and timing for the intervention, and elucidate precise anatomical targets and stimulation parameters in order to personalize the procedure for specific symptoms in patients.

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Conception and design: Ibrahim, Elkaim. Acquisition of data: Coulombe, Elkaim. Analysis and interpretation of data: Ibrahim, Coulombe. Drafting the article: Coulombe. Critically revising the article: Elkaim, Alotaibi, Gorman, Weil, Fallah, Kalia, Lipsman, Lozano. Approved the final version of the manuscript on behalf of all authors: Ibrahim. Statistical analysis: Ibrahim, Coulombe. Study supervision: Ibrahim.

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