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Review article

Deep brain stimulation for intractable tardive dystonia: Literature overview

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ABSTRACT

Background: Tardive dystonia (TD) represents a side effect of prolonged intake of dopamine receptor blocking compounds. TD can be a disabling movement disorder persisting despite available medical treatment. Deep brain stimulation (DBS) has been reported successful in this condition although the number of treated patients with TD is still limited to small clinical studies or case reports. The aim of this study was to present the systematical overview of the existing literature regarding DBS for intractable TD.

Methods and results: A literature search was carried out in PudMed. Clinical case series or case reports describing the patients with TD after DBS treatment were included in the present overview. Literature search revealed 19 articles reporting 59 individuals operated for TD. GPi was the target in 55 patients, while subthalamic nucleus (STN) was the target in the remaining 4. In most studies the motor part of Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) was improved by more than 80% when compared to preoperative BFMDRS scores.

Conclusions: The performed literature analysis indicates that bilateral GPi DBS is an effective treatment for disabling TD. The response of TD to bilateral GPi DBS may be very rapid and occurs within days/weeks after the procedure. The efficacy of bilateral GPi DBS in TD patients is comparable to results achieved in patients with primary generalized dystonia.

1. Introduction

Chronic intake of dopamine receptor blocking compounds may have as a consequence the development of tardive movement disorders including tardive dyskinesia and tardive dystonia (TD) [1]. Both tardive movement disorders cause emotional and social distress but TD develops faster, is more painful, distressing and disabling than tardive dyskinesia [1]. TD usually does not differ from focal, segmental or generalized primary dystonia. In two-thirds of all cases TD affects cervical muscles. TD treatment consists of gradual withdrawal of provoking medications and substitution of atypical neuroleptics such as clozapine or administration of tetrabenazine, dopamine agonists, and anticholinergic drugs [1]. In some cases pharmacological treatment of TD may be challenging and ineffective. Clinical similarity between TD and primary dystonia has paved the way for its neurosurgical treatment – nowadays mainly with pallidal DBS [2].

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Pallidal DBS has been shown effective in medically refractory primary generalized, segmental or even focal dystonia [2,3]. The experience of the efficacy and safety profile using pallidal DBS in TD patients is far less studied. The reasons for it may be the following facts. Patients diagnosed with secondary dystonia (such as hemidystonia or dystonia associated with cerebral palsy) fare less well after pallidal DBS than patients with primary generalized dystonia [4]. Psychiatric co-morbidity is considered a contraindication for DBS surgery by many investigators. These two main reasons may explain why the experience of DBS surgery in TD remains limited to small studies or case series [5–14]. Therefore, the main aim of this overview was to present a systematic literature review dealing with DBS for TD. We have performed the detailed discussion on the outcomes, stimulation settings, and surgical complications as well the safety profile of bilateral pallidal stimulation in TD patients. Moreover the possible underlying effects of DBS for TD using functional imaging studies have been discussed.

2. Clinical characteristics of tardive dystonia patients treated by deep brain stimulation

Since 2001, we have identified 9 original articles, in which a total of 38 patients diagnosed with TD underwent DBS procedures [5–13]. Moreover, since 2003 in another 10 published articles reporting a total of 198 patients with various types of primary or secondary dystonia we have found additional 21 patients harboring neuroleptic-induced or drug-induced TD [3,15–23]. To our knowledge, a total of 59 patients with TD have been described in literature. In 10 articles that present the series for various types of dystonia some data regarding patients' sex, disease duration, and clinical outcome are often presented as a cumulative outcome for all dystonia patients regardless of dystonia type, which considerably handicaps the clinical analysis of patient data. Nevertheless, among 59 patients there were 27 females and 20 males; in the remaining 12 individuals the patient's gender could not be identified. The mean TD duration from diagnosis to surgery was 5.5 years ranging 0.5–23 years. The mean age at surgery was 50.2 years ranging from 28 to 76 years.

In the 9 articles reporting the outcome only for TD patients the psychiatric indication for using neuroleptic drugs was stated. To the contrary, none of the 10 articles reporting the outcome for various dystonic conditions presented the underlying psychiatric indication. Among known psychiatric indications, neuroleptics subsequently developing TD were used to treat depression in 19 patients, schizophrenia in 5 patients, and in the remaining 11 patients various psychiatric disorders including bipolar disorder, psychosis, or anxiety disorder. Interestingly, out of a total of 59 patients, only 3 patients developed TD after prolonged antiemetic treatment in which metoclopramid was administered to treat gastritis [10,13,17]. In the remaining 56 patients TD developed as a consequence of neuroleptics. The most common identifiable neuroleptic was haloperidol found in 15 patients as a causative drug for inducing TD. In general, in 42 patients specific neuroleptics were identified, whereas in the remaining 14 patients no neuroleptic drug was named. The exact time of the neuroleptic exposure was provided in 23 patients and the mean time from neuroleptic exposure to TD development was 43.9 months ranging from 3 to 300 months.

Most individuals (53 patients) underwent bilateral GPi DBS [5–13,15–23]. Moreover, in 2 additional patients unilateral GPi DBS was performed to treat TD 13. In only 4 patients bilateral STN DBS was undertaken [17,18]. In 1 patient two targets GPi and ventral intermediate thalamic nucleus (Vim) were approached [5]. The mean postoperative follow-up period was 29 months ranging from 3 to 80 months.

3. Clinical outcome of pallidal deep brain stimulation for tardive dystonia

DBS for TD was first reported by Trottenberg et al. and revealed a high efficacy of bilateral GPi stimulation in a 70-year-old patient with TD decreasing the total BFMRDS scores by 73%, whereas thalamic Vim stimulation had no effect on dystonic symptoms [5]. The same study group presented additional results in 5 consecutive TD patients decreasing the BFMDRS motor and disability scores by 83% and 94% respectively, 6 months postoperatively [6]. Gruber et al. presented the largest series to date, featuring 9 patients including 3 patients reported earlier by Trottenberg et al. [10]. In this study at the mean postoperative follow-up time of 40.7 $\pm$ 20.9 months the BFMDRS motor and disability scores improved by 83% and 68% respectively [10]. Franzini at al. [7] as well Cohen et al. [8] presented 2 patients in each study, also reporting a very favorable outcome. Sako et al. [9] operated on 6 patients with TD decreasing the BFMDRS motor and disability scores by 86 $\pm$ 14% and 80 $\pm$ 12% respectively at mean follow-up of 21 $\pm$ 18 months. Capelle et al. [11] included 2 patients with craniocervical TD and 2 patients with generalized TD. At the last follow-up of 27.3 months the BFMDRS motor and disability scores improved by 77% and 84% respectively. In the last study reported by Chang et al. [12] the BFMDRS motor and disability scores improved by 71% and 48% respectively at the last follow-up ranging from 24 to 96 months. In the recent published study by Shaikh et al. 8 patients with TD were included. The total motor BFMDRS scores were improved by 85.1 $\pm$ 13.5% at the last follow-up ranging from 12 to 60 months. The outcomes of all 9 articles are summarized in Table 1 in a chronological order, by objective results based on BFMDRS scores after bilateral pallidal DBS. Some authors used additionally Abnormal Involuntary Movement Scale (AIMS) or Extrapyramidal Symptoms Rating Scale (ESRS) which may suggest that not all patients included in the study suffered from Type I – Pure Tardive Dystonia according to the recommendations provided by Adityanjee et al. [1]. Some of these patients may have exhibited Type II Tardive Dystonia with coexisting dyskinetic movements in the same or a different body part, but dystonia was the most prominent manifestation. In the study by Trottenberg et al. [6], Gruber et al. [10], and Chang et al. [12], the above-mentioned scales like AIMS or ESRS were used in addition to the BFMDRS scores in order to rate coexisting dyskinetic movements.

In the remaining 10 articles reporting series with various types of dystonia, in 2 articles the STN was the target to treat

Table 1 – Published articles presented in chronological order reporting the results of bilateral GPi DBS for patients treated for TD. 38 patients are reported in 9 articles. AIMS, Abnormal Involuntary Movement Scale; ERSR, Extrapyramidal Symptoms Rating Scale; pt, patient; pts, patients; mo, months; FU, follow-up; TD, tardive dytonia; NR, not reported.

Authors and publication years	Number of patients	Disease duration (years)	Type of DT	BFMDRS Scale Motor/disability Subscale	FU Time (mo)	Last FU Score BFMDRS Scale Motor/disability Subscale	Percentage improvement of BFMDRS
Trottenberg et al. [5] 2001	1	6	Multifocal	BFMDRS m 34.5/ AIMS 24	6	9.5 11	73% 54%
Trottenberg et al. [6]2005	5	NR	NR	BFMDRS m/d 32/8	6	NR	83%/94%
Franzini et al. [7] 2005	Pt 1	5	Generalized	BFMDRS t 36	12	5	42%
	Pt 2	3	Generalized	BFMDRS t 70	12	8	78%
Cohen et al. [8] 2007	Pt 1	4	Generalized	BFMDRS m/d 21.5/4	13	3/0	86%/100%
	Pt 2	4	Generalized	BFMDRS m/d 31.5/19	7	11.5/9	64%/53%
Sako et al. [9] 2008	6	3.1 (0.5–6)	NR Severe TD	Individual scores provided for each patient	21 ± 18	NR	86 ± 14%/ 80 ± 12%
Gruber et al. [10] 2009	9		NR	BFMDRS m/d 30.9/11.6 AIMS 23.1	40.7 ± 20.9 From 18 to 80	5.5/3.4 4.3	83%/67.7% 78.7%
Capelle et al. [11] 2010	4	6.7	2 pts generalized 2 pts craniocervical	BFMDRS m/d 43/6	27.3	7/2	77%/84%
Chang et al. [12] 2010	5	10.2	4 pts generalized dystonia 1 pt segmental dystonia	BFMDRS m/d 49.7/11.8 ESRS 10.5	24–96	14.5/6.2 2	71%/47.9% 77%
Shaikh et al. [13] 2015	8	5.4 ± 2.8	6 pts generalized dystonia 2 pts segmental dystonia	Individual scores provided for each patient BFMDRS m	6–60	NR	85.1 ± 13.5%

TD patients [17,18]. The articles by Yianni et al. [15], Pretto et al. [20], Maraginos-Ascone et al. [21], Katsokiori et al. [22], and Kim et al. [23] discuss a single TD patient in each study. All these articles indicate that bilateral GPi DBS improved the BFMDRS motor and disability scores from 28% to 77% and from 39% to 80% respectively. The largest case series among different patients with different dystonia types was provided by Egidi et al. [19]. These authors conclude that beside DYT-1 positive primary dystonia group with good clinical outcome, secondary drug-induced TD had very good results in reducing the BFMDRS motor and disability scores by 47 and 55% respectively. Starr et al. reported 3 patients with TD who benefitted from pallidal stimulation exceeding 50% on the total BFMDRS whereas 1 patient improved only slightly by 6% on the total BFMRDS [3]. In only 1 report by Krause at al. [16] 3 patients with TD were unchanged after surgery. 1 patient required internal pulse generator removal one week after surgery due to infection and was lost for follow-up. In 2 patients steady worsening of dystonia despite bilateral pallidal stimulation was noted. The clinical outcome of the 10 articles reporting TD patients within series with various dystonia types are presented in a chronological order in Table 2.

4. Clinical outcome of subthalamic deep brain stimulation for tardive dystonia

The first study reporting bilateral STN stimulation in 2 patients with TD dystonia was presented by Zhang et al. [17]. These 2 patients gained benefit from STN DBS in reducing their total BFMDRS scores at last follow-up by 92% and 91%. The authors conclude that patients with TD showed the best results among patients with secondary dystonia types. Sun et al. presented also their experience in using bilateral STN DBS for various dystonic conditions [18]. Among 14 patients with various types of dystonia, who underwent bilateral STN stimulation there were 2 patients diagnosed with TD. Unfortunately the authors presented aggregated results for all patients, irrespectively of dystonia type. The mean postoperative BFMDRS scores improved by 88.6% (range from 76% to 100%) at the mean follow-up of 28.8 months. The authors argue that STN DBS has some advantages over GPi DBS, such as immediate improvement observed once stimulation is activated, or lower stimulation settings needed for STN DBS. These 2 studies showed that STN DBS had a positive effect on various dystonia types including TD which responded favorably to STN DBS [17,18]. These studies

Table 2 – Published articles presented in chronological order reporting the results of bilateral GPi DBS for patients with various dystonia types. 21 patients with TD are reported in 10 articles. AIMS, Abnormal Involuntary Movement Scale; ERSR, Extrapyramidal Symptoms Rating scale; pt, patient; pts, patients; mo, months; FU, follow-up; TD, tardive dystonia; NR, not reported.

Authors and publication years	Number of patients	Disease duration (years)	Type of DT	Scale Subscale	FU Time (mo)	FU Score	Percentage improvement (%)
Yianni et al. [15] 2003	1 among 25 pts	12	Generalized	BFMDRS m/d/t 109/28/137	12	78/17/95	28%/39%/31%
				AIMS 24		14	41.7%
Krause et al. [16] 2005	3 pts Among 17 pt 1	23	Generalized	BFMDRS m 11	NR	NR	NR
	Pt 2	5	Generalized	BFMDRS m 62	30	63.5	Worsening
	Pt 3	17	Generalized	BFMDRS m 76	42	77.0	Worsening
Starr et al. [3] 2006	4 pts among 23 Pt 1	7	Multifocal	BFMDRS t 11	26	0	100%
	Pt 2	4	Multifocal	BFMDRS t 38	27	7.5	80%
	Pt 3	20	Multifocal	BFMDRS t 57	17	53.5	6%
	Pt 4	10	Generalized	BFMDRS t 80	9	37.5	63%
Zhang et al. [17] 2006	2 pts among 9 Pt 1	3	Generalized	NR	3	NA	92%
	Pt 2	0.5	Multifocal	NR	2	NA	91%
Sun et al. [18] 2007	2 pts among 14 Pt 1	3	Generalized	NR	28.8 for all pts	NA	88.6% for all pts
	Pt 2	12	Generalized	NR	28.8 for all pts	NA	88.6% for all pts
Egidi et al. [19] 2007	5 pts among 69 pts	3–4 years	NR	BFMDSS m/d NR	NR	NR	47.2%/54.6%
Pretto et al. [20] 2008	1 pt among 13 pts	NR	Generalized	AIMS 19	Nearly 6	2	90%
Maraginos-Ascone et al. [21] 2008	1 pt among 10	4	Trunk/Focal	BFMDRS m/d 46/16	12	24/9	48%/44%
				AIMS 23.1		4.3	78.7%
Katsokiori et al. [22] 2009	1 pt among 8 pts	3	Generalized	BFMDRS m/d 35/19	12	2/3	94%/98%
Kim et al. [23] 2011	1 pt among 10	6	NR	NR	20	NR	77%/80%

need to be replicated in larger study groups in order to provide conclusive evidence on which target (GPi or STN) would be optimal for different types of dystonia including TD.

5. Onset and duration of benefits after DBS procedures for tardive dystonia

The onset of clinical benefits in TD symptoms varies strongly between reported studies or even between patients in the same study (Tables 3 and 4). Trottenberg et al. [6] observed clinical benefits in 5 patients within 12–72 h after activation of GPi DBS. Gruber at al. [10] in reported a rapid response within minutes to hours after GPi DBS in 5 out a total of 9 patients, whereas in the remaining 4 patients the improvement was delayed to weeks or months. Most authors report that in TD patients phasic movements respond faster than tonic postures which subsequently improve over weeks to months. Capelle et al. [11] observed delayed onset of improvement after optimization of stimulation settings. The onset of response to GPi stimulation may be dependent on the initial stimulation mode. Initial bipolar stimulation mode used in the study by Capelle et al. [11] stimulates much narrower brain tissue and therefore its onset may occur later than in monopolar stimulation mode using adjunct contacts as cathodes with the ventral posterolateral part of GPi. In the recent published study by Shaikh et al. among 8 patients with TD in 4 patients there was rapid while in 4 others the response was partial with gradual resolution of residual dytonic symptoms over 48 months. In the study by Sun et al. [18] who used STN DBS for TD the observed response was immediate which according to the authors is the main advantage of STN DBS over GPi DBS in dystonic patients. Power consumption in STN DBS is much lower due to smaller functional target with coexisting immediate response to stimulation. This rapid response within minutes, hours or days in TD patients reported in independent articles is much faster than usually gradual improvement observed in primary generalized dystonia patients.

In all reported articles except for Krause et al. [16] the initial benefit was sustained at the last follow-up. The follow-up period varies considerably between reported studies ranging from 3 to 96 months but the improvement is still seen even 8 years postoperatively [12]. This improvement is stable only with an increase of stimulation voltage to maintain good clinical outcomes. In a few studies with longer follow-ups, the BFMDRS total scores tend to improve over the follow-up period when compared to the first postoperative assessment [6,12].

6. Stimulation parameters used for tardive dystonia patients

Initial DBS parameters and initial mode of stimulation were considerably different among the reports (Tables 5 and 6). Most authors used the monopolar stimulation mode activating the most ventral or two adjunct ventral contacts as cathodes [5–9,12,13,15,21]. This type of stimulation was used by Trottenberg et al. in 5 patients with rapid response to GPi stimulation [6]. Other authors followed this stimulation mode in patients with TD [9,12,13,15,21]. One exception is the study by Capelle et al. [11] in which the initial bipolar stimulation mode was chosen in 3 patients. The benefit was delayed due to optimization of stimulation settings and higher voltage needed (up to 4.5 V) rarely observed in monopolar stimulation mode. The initial bipolar stimulation mode was also used by Yianni et al. [15] in 25 dystonic patients including 1 patient with TD, which also necessitated higher stimulation voltage between 4.0 and 7.0 V. Sun et al. [18] used initial bipolar mode of stimulation with good immediate therapeutic effects but the target was STN rather than GPi and stimulation voltage was considerably lower, between 2.0 and 3.0 V. Generally, authors used most ventral contacts in monopolar fashion located in posteroventral lateral part of GPi.

Stimulation settings were highly variable among studies depending obviously on the initial mode of stimulation. Stimulation voltage ranged from 1.0 to 6.5 V and was regularly monitored in most studies to achieve a stable outcome [6,10–13,15]. Stimulation frequencies in most studies were above 130 Hz except for the study by Kim et al. [23] where low frequency below 100 Hz was used. Only one study used a constant frequency of 185 Hz [22]. Stimulation pulse widths varied between 60 μs, 90 μs, 120 μs, 210 μs or even 450 μs [5–12]. In most studies the pulse width was adjusted during the follow-up period to maintain good clinical outcome. The marked individual stimulation settings used with patients in one study or between studies may indicate that lead locations were dissimilar in individual patients, despite the similar GPi target. Despite these differences in stimulation settings that may represent different lead locations all authors reported favorable results in TD patients.

7. Safety profile of deep brain stimulation procedures in tardive dystonia patients

In a total of 59 patients after bilateral DBS procedures for TD there were two serious complications related to the operation [3,12]. In the study by Chang et al. [12] 1 patient developed intracerebral hemorrhage due to venous infarction which resulted in transient hemiparesis and aphasia. This patient recovered fully but without any mood and behavioral changes but also without response to DBS. A similar case of multifocal left frontal hemorrhage due to venous infarction causing aphasia and hemiparesis with subsequent non-response to DBS was reported by Starr et al. [3]. These 2 patients made full recovery but remained unresponsive to DBS, since the hemorrhage probably caused some misplacement of the DBS lead. There were no reported deaths related to DBS procedure in TD patients in the reviewed literature.

In the study by Capelle et al. [11] 1 patient required lead revision due to its misplacement and 1 patient experienced rapid IPG depletion without neurological complications. One patient in the study by Chang et al. [12] required battery replacement after 10 months which was complicated by a local infection. After 2 weeks of antibiotic treatment the infection resolved and the battery was replaced without complication. In the study by Krause et al. [16] 1 of the 3 patients developed a chest infection which required battery removal and therefore the patient was lost for the follow-up. Moreover, in the study by Zhang et al. [17] 1 patient who underwent bilateral subthalamic DBS for TD had transient laughter which may indicate stimulation of other than sensorimotor subthalamic subterritory. After reprogramming of stimulation settings the stimulation-induced laughter in this patient disappeared.

In general, all infections healed after antibiotics making it possible to implant new hardware. One misplaced lead was successfully replaced. Only 2 patients gained partial benefit due to intracerebral hemorrhage. Also 2 patients in the report by Krause gained no benefit from GPi stimulation for unknown reasons and their condition worsened over follow-up months. The complication rate is then similar to other studies implying GPi or STN DBS for dystonic conditions [2,3].

8. Non-motor effects of deep brain stimulation in tardive dystonia patients

Although the patients with TD are mainly handicapped by their motor disability and the associated reduced quality of life, mood as well as psychosocial functions were observed to change after surgery. In general, GPi DBS in Parkinson's disease is regarded as a safe treatment regarding cognition but some studies of GPi DBS in PD patients reported postoperative impairments of executive functions, verbal fluency and memory [24]. These observations were not confirmed in the short report by Haelbig et al. [25]. These authors performed an extensive assessment of cognitive and neuropsychiatric functions using a battery of objective tests in 15 dystonic patients including 2 patients with TD, thus demonstrating the procedure's safety. The authors conclude that no deterioration was observed in cognitive scores and neuropsychiatric measures [25]. Moreover, two patients (one reported on by Trottenberg et al. [6], and the other by Sako et al. [9]) showed significant mood improvement without objective measures presented. Gruber et al. [10] were the first to perform objective assessment of mood and neuropsychological functions in 9 consecutive patients suffering from TD after bilateral GPi. These authors showed improvement in mood scores with no

Table 3 – Stimulation settings in published articles reporting the results of bilateral GPi DBS for patients treated for tardive dystonia. The time to response as well adverse events in each of the articles are presented. M, monopolar; B, Bipolar; pt, patient; pts, patients; NR, not reported.

Author	Number of patients	Mode	Contacts	Amplitude (V) Mean SD +/− range	Frequency (Hz) Mean SD +/− range	Pulse width (us) Mean SD +/− range	Response to stimulation	Adverse events
Trottenberg et al. [5] 2001	1	M	NR	3.0 V	150 Hz	210 us	A few hours	No
Trottenberg et al. [6] 2005	5	M	One or two adjacent cathods	2.7 ± 0.8 V	144 ± 22 Hz	111 ± 57	Rapid response within 12 to 72 hours	No
Franzini et al. [7] 2005	2	M	Distal contact cathod	1 V	130	90	Good response within 3 days	No
Cohen et al. [8] 2007	2	M	Cathode contacts 1 and 5	4.0 V	130 Hz	90 in pt 1 120 in pt 2	A few hours	No
Sato et al. [9] 2008	6		One or two adjacent Ventral cathodes	2.2 ± 0.9	119 ± 28 Hz	450 us	Days to weeks	No
Gruber et al. [10] (2009)	9	M	NR	Right GPi 3.0 ± 1.0 Left GPi 2.8 ± 0.6 V	154 Hz ± 25.1	83.3 ± 13.2	In 5 pts response within minutes to hours, in 4 patients within weeks to months	No
Capelle et al. [11] 2010	4	3 pts B 1 pt M	Cathode contact 1 anode contact 2	4.5 V	130 Hz in 3 pts 160 Hz in 1 pt	210 in 3 pts 90 us in 1 pt	Response delayed due to optimization of stimulation settings	1 misplaced lead–revision 1 case of IPG depletion 16 months
Chang et al. [12] 2010	5	M	One or two adjacent cathodes	NR	Initial 145–185	Initial 210 us	NA probably delayed	Pt 4 infection 10 months after routine IPG replacement after 2 weeks of antibiotic treatment 1 pt venous infarction without behavioral and mood changes
Shaikh et al. [13] 2015	8	M	NR	3.8 ± 0.4 V	84.5 ± 30.4	141.8 ± 40.4 us	Days to months	No

Table 4 – Stimulation settings in published articles reporting the results of bilateral GPi DBS for patients treated for various dystonia types. The time to response as well adverse events in each of the articles are presented. M, monopolar; B, Bipolar; AEs, adverse events; NR, not reported; NS, not specifically reported for TD patients but for the whole dystonia group; pt, patient; pts, patients.

Author	Number of patients	Mode	Contacts	Amplitude (V) Mean SD +/− range	Frequency (Hz) Mean SD +/−range	Pulse width (us) Mean SD +/−range	Response to stimulation	Adverse events
Yianni et al. [15] 2003	1 pt among 25	B	Deepest contact cathode, superficila anode without AEs.	Initial stimulation setting for all 4.0–7.0	130 Hz–180 Hz	150–240 us	Hours to response	No
Krause et al. [16] 2004	3 pts among 17	M	Contacts above evoking phosphenes	Initial stimulation setting for all V	130 Hz	210 us	No improvement Slight worsening over follow-up	1 case of infection removal of all hardware.
Starr et al. [3] 2006	4 among 23 pts with dystonia	Mostly M	NS	NR	NR	NR	NR	Multifocal left frontal hemorrhage–venous infarction aphasia and hemiparesis. Full recovery but dystonia not responded to DBS.
Zhang et al. [17] 2006	2 pts among 9	NR	NR	NR	NR	NR	Weeks to months	1 patient persistent laughter
Sun et al. [18] 2007	2 pts among 12 pts	B	NR	2.0–3.0 V	135–185 Hz	90–120 us	Immediate response	No
Egidi et al. [19] 2007	5 pts among 69	NR	NR	NR	130 Hz	90–120 us	Days to response	No
Pretto et al. [20] 2008	1 pt among 13 pts	NS	NS	4.1 V	185 Hz	90 us	NR	No
Magarinos-Ascone et al. [21] 2008	1 pt among 10	NS	Lowest contacts	2.5 ± 0.2 NS	135–160 NS	118.5 us for all pts NS	NR	No
Katsokiori et al. [22] 2009	1 pt among 8	M	NR	2.5–4.5 V NS	185 Hz NS	210–450 us NS	Weeks to months	No
Kim et al. [23] 2011	1 pt among 10	M	NR	Initial stimulation setting for all V	88.7 Hz	165 us	Hours to response	No

change in neuropsychological functioning, moreover, a tendency for improvement in verbal fluency was observed as well [10]. Unfortunately, no cognitive impairment was noted in any of the reports describing GPi DBS for TD. To the best of our knowledge there were no suicide attempts in TD patients after DBS procedures. In contrast, in the report by Foncke et al. [26] 2 patients with preoperative periods of depression among 16 operated on for different forms of dystonia committed suicide, 3 weeks and approximately 14 months after surgery. These authors advocate extensive psychiatric and neuropsychological evaluation both pre and postoperatively [26]. The above-mentioned studies confirm the safety of GPi DBS in TD patients.

9. Possible therapeutic effects of deep brain stimulation explained by functional imaging studies

The mechanisms of action of GPi DBS in primary generalized dystonia and especially in TD are complex and not fully understood [27,28]. The GPi represents the major output nucleus of the basal ganglia, which controls supplementary motor cortex thought the ventrolateral thalamus and its thalamocortical connections. The rationale for GPi DBS is based on positive results of pallidotomy and subsequently pallidal stimulation for dystonic symptoms seen in patients with Parkinson's disease.

The pathophysiology of TD is still discussed, but the main hypothesis is that neuroleptic agents induce supersensitization of dopaminergic D1 receptors by endogenous dopamine, with subsequent neuroleptic-induced blockage of presynaptic D2 receptors causing a dysfunction of direct and indirect pathways [29,30]. This dysfunction increases D1 mediated (direct pathway) striatal output which inhibits the GPi, releasing the glumaminergic thalamocortical connections, leading to an excess of brain activation observed in different dystonia types including TD.

The results of functional imaging studies have shed some light on the pathophysiology of primary generalized dystonia and on TD as well [31,32]. These functional imaging studies revealed generally widespread brain activation to a simple motor task, a loss of cortico-cortocal inhibition, and a lack of selectivity of brain activation in dystonic patients [33]. In addition to these findings, the dysfunction of the cortical sensory system with enhanced response of the basal ganglia to sensory inputs has been shown [34]. All above-mentioned patterns of brain activation in primary generalized dystonia patients can be efficiently reversed by pallidal stimulation [31]. TD usually does not differ clinically from focal, segmental or primary generalized dystonia. The same patterns of brain activation changes due to GPi DBS in TD patients was proven in the report by Thobois et al. [31] using Positron Emission Tomography (PET) in 5 patients. The authors have shown that TD is related to an excess of brain activation in prefrontal brain areas. The GPI DBS in TD visibly reduces the activation of motor, premotor, prefrontal cortex as well as activation of cerebellum. In another report by Katsakiori et al. [22] the authors report on 8 patients with various secondary dystonia types including 1 patient with TD, who underwent a Single Photon Emission Computed Tomography (SPECT). The authors have shown widespread decrease of brain activation in response to bilateral GPI DBS. In conclusion, reducing or replacement of abnormal patterns of neuronal activity seen in GPi by DBS may normalize the thalamocortical pathways and adjust the abnormal cortical hypermetabolism in widespread motor cortical areas [35].

10. Conclusion

The rapid and long-term improvement in TD patients supports the observation that DBS is a promising treatment for patients affected by disabling TD unresponsive to pharmacological therapies and botulinum toxin injections. The safety profile and efficacy of bilateral GPi stimulation constitutes a valuable treatment solution for patients handicapped by intractable TD.

Conflict of interest

We state that all authors of this review paper declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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