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Review Article

Deep brain stimulation for tardive syndromes: Systematic review and meta-analysis

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ABSTRACT

Among the broad entity of tardive syndromes, tardive dystonia and classical tardive dyskinesia sometimes require advanced treatments like deep brain stimulation of the globus pallidus internum (Gpi-DBS) or the subthalamic nucleus (STN-DBS). This systematic review has analyzed the currently available literature reporting cases with either tardive dystonia or dyskinesia treated with DBS. The key words for the literature search included all tardive syndromes and "deep brain stimulation." Thirty-four level VI studies and one level II study with 117 patients were included. Level I studies were not identified. Only four of the patients had tardive dyskinesia. All the others had tardive dystonia. The majority had Gpi-DBS (n = 109). Patients had a mean age of 47.4 (± SD 14.7) years. The duration of follow-up was 25.6 months ± 26.2. The Abnormal Involuntary Movement Scale was reported in 51 patients with an improvement of 62 ± 15% and the Burke-Fahn-Marsden scale was reported in 67 cases with an improvement of 76 ± 21%. Reported adverse events were surgery-related in 7 patients, stimulation-induced in 12, and psychiatric in 3 patients. These reports thus suggest favorable effects of DBS and it seems to be relatively safe. DBS can be considered for patients with severe, medication-resistant symptoms. Controlled and randomized studies with blinded outcomes are needed.

1. Introduction

Tardive syndromes (TS) are a group of movement disorders that are sequelae of medications that block dopamine receptors (DRBAs) [1] Therefore, they represent an adverse effect not only related to exposure to antipsychotic medications but also to antiemetics and gastric motility medications (i.e., metoclopramide) [2]. Although the term "tardive" suggests that these syndromes are a late complication of these medications, the onset of involuntary movements is variable and may appear relatively early in the course of treatment, even after just a few doses [3]. There is no single typical phenotype of TS. The clinical presentation can be complex and a heterogenous mix of hyperkinetic symptoms such as complex repetitive movements, choreoathetosis, dystonia, and tremor [4]. In the literature it became common practice to separate classic tardive dyskinesia (consisting of repetitive and complex oral-buccal-lingual movements, as well as analogous repetitive movements in the limbs or trunk) from tardive dystonia. This seems to be justified regarding the dominant symptom but it is important to keep in mind that symptoms of the two syndromes are on a continuum. In clinical practice, the assessment of patients affected by TS is performed using different scales according to the predominant phenotypes. The Abnormal Involuntary Movement Scale (AIMS) is specifically used for tardive dyskinesia [5]. This scale aims to assess involuntary movements in several body regions and follows the severity over time. Tardive dystonia patients are commonly assessed with the Burke-Fahn-Marsden (BFM) scale, which is has two sections: a Movement Scale, based on clinical examination, and a Disability Scale, based on the patient's statements about seven activities of daily living [6]. Finally, the Extrapyramidal Symptom Rating Scale (ESRS) can be used for patients with mixed phenotypes [7].

Despite the extensive research on the pathophysiology of TS, it remains elusive and multiple hypotheses have been proposed. The hypersensitivity of dopamine D2 and possible D3 receptors after chronic blockade by DRBAs is believed to be the most important pathophysiological factor [8]. The maladaptive synaptic plasticity resulting in an abnormal balance between the direct and indirect pathways in basal ganglia has been proposed as a complementary theory [9]. The oxidative stress resulting in neurotoxicity, genetic susceptibility and GABA-insufficiency might play an important role in the development of TS [10–12].

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Dopamine-depleting agents like tetrabenazine have been studied most extensively as pharmacological treatment of TS [13]. Other therapeutic agents used for TS are amantadine [4] as well as GABA agonists like clonazepam [14]. The latter has been recommended for short-term treatment. Botulinum toxin injections have shown efficacy in the treatment of TS in several cases, especially in patients with focal or segmental tardive dystonia and in the orofacial-lingual tardive [15]. Clozapine is used as a treatment by some movement disorder specialists as an off-label medication.

Deep brain stimulation (DBS) is the surgical treatment reserved for severe medically refractory cases. In this review, we will summarize the current knowledge and state of the art DBS as treatment for TS, exploring several aspects from the surgical technique to the outcomes in this peculiar patient group.

2. Methodology

The PubMed database was searched for articles describing DBS for tardive syndromes between January 1, 1980 and June 30, 2017. Keywords were “deep brain stimulation” and “tardive dyskinesia,” “tardive dystonia,” “tardive stereotypy,” “tardive syndrome,” “akathisia,” “tardive tourettism,” “tardive myoclonus,” “tardive parkinsonism,” “tardive chorea,” “tardive hyperkinetic movements,” “tardive tremor,” and “blepharospasm/Meige syndrome.” Studies were selected if they focused primarily on DBS to treat these conditions.

Our inclusion criteria were randomized clinical controlled trials (including class IV studies), single case reports, or case series that reported the utilization of DBS in patients with tardive syndromes. Only research articles in the English language were reviewed. Our exclusion criteria were literature reviews, commentaries, and concept papers on DBS for tardive syndromes.

Fifty-six articles were identified; 35 articles fulfilled our criteria pertinent to this topic and were included for this review.

3. Results

3.1. DBS studies to date

We found 34 level IV studies and one level II study for a total of 117 cases. We report the results with respect to important clinical features. Four studies described tardive dyskinesia cases [16–19] and 30 studies were focused on tardive dystonia patients [20–49].

Kovacs [50] described the use of DBS in a patient with refractory dystonic status. This case represents a special indication and showed an excellent outcome with full persistent recovery after surgery.

The majority of the studies identified were open-label case reports or part of open-label case series of dystonia of various etiologies. Moreover, we found 4 case reports reporting an observer-blinded evaluation of the outcome after surgery [18,20,30,47]. Kefalopoulou et al. [18] performed clinical assessments of their patient with BFM and AIMS at 3 and 6 month intervals after surgery in a double-blind manner. Indeed, neither the patient, nor the rating examiner were aware of the status of stimulation (on-DBS/off-DBS) condition during the evaluation. An investigator different from the examiner was responsible to turn the stimulator on or off. However, it is well known that some patients have an immediate sensation when the stimulator is active and this could potentially unblind them. To avoid this risk, Kefalopoulou et al. placed the programmer on the patient's chest and the DBS device was switched on and off in a random way. Trottenberg et al. [20] performed a video-based, reviewer-blinded assessment. The patient was evaluated before and 6 months after the procedure by an independent neurologist reviewing videos in the on and off stimulation condition. Similarly, Damier et al. [30] performed a double-blinded evaluation in the presence and absence of stimulation at 6 months after surgery on the 10 patients included in their case series. Neither the patients nor the rating investigator was aware of which condition was being applied, and the patient was instructed not to talk to the rating investigator during the evaluation. Recently, Pouclet-Courtemanche et al. [47] provided class II evidence of the efficacy of GPi DBS on motor function in tardive dystonia using video-based double-blind assessment. At 6 months after surgery, a double-blind ESRS evaluation was performed in the stimulation “on” and stimulation “off” conditions on their case series. The two stimulation conditions were applied on two consecutive days (at the same time of day for any given patient) in a counterbalanced order across patients. The stimulator was turned on or off by a study nurse in accord with written instructions as to the order of stimulation conditions, which was supplied by the study coordinator. Neither the patient nor the rating investigator was aware of which condition was being applied, and the patient was instructed not to talk to the rating investigator during the evaluation.

Generalized dystonia followed by segmental dystonia were the most common tardive dystonia phenotypes. Indeed, we found 4 cases of focal dystonia [27,33,34,40], 14 cases of segmental dystonia [24,27,29,32,38,39,41–44] and 95 cases of generalized dystonia [20–28,30,31,33–38,44–49].

All cases of TS treated with DBS were related to the use of neuroleptics, apart from two patients treated with metoclopramide for gastritis and nausea [36,47]. The most common indications for neuroleptic prescription in our reviewed cases were depressive disorder, anxiety disorder, psychosis, and schizophrenia. We found 5 studies that included bipolar disorder patients [17,18,26,41,48], two studies describing TS in patients with Tourette's syndrome [47,49] and a case treated with neuroleptics for impulsive control disorder [49]. Of note, 10 studies did not report the underlying disease prompting the treatment with dopamine-blocking agents.

The mean age across the 117 reviewed cases was 47.4 ± 14.7 years (median: 47.4, range: 17–76). The age distribution is shown in Fig. 1.

3.2. The surgical procedure

The elective DBS target was bilateral posteroventral GPi in the majority of TS cases. Johnsen [21] et al. described a patient treated with left-sided thalamotomy plus right VIM DBS. Bilateral STN stimulation has been reported in 8 cases so far [46,49].

The stimulated electrode contact was reported in 57 of the 117 cases. Monopolar stimulation was used in the majority of the cases and bipolar stimulation was used in three studies [26,38,48]. The lowest contact followed by the second lowest contact were the most used electrodes in TS patients.

The stimulation parameters varied across patients. The mean stimulation amplitude was 3.33 ± 1.03 V (median: 3.2; range: 1–6.5). The pulse was 157.51 ± 96.57 μs (median: 130; range: 60–450).

Information about the type of anaesthesia performed was provided by 14 studies [16,23,24,27,28,30,33,35,37–39,44,48,49]. Local anaesthesia was performed in 10 out of 14 studies.

3.3. Outcomes of DBS in tardive syndromes

3.3.1. Motor effects

The AIMS was the most-used scale for the cases showing clinical features of classical tardive dyskinesia. It has been reported in 51 cases. The mean percentage of AIMS score improvement across the 51 cases was 62 ± 15% after DBS surgery (median, 58%; range, 33–90%). The distribution of % improvement of AIMS score is shown in Fig. 2.

The BFM was the most-used scale for cases with predominant tardive dystonia. It has been reported in 67 cases. Two cases were lost at follow up. Two cases showed a worsening of the motor score after surgery. The BFM motor score improvement across the 67 cases was 76 ± 21% after DBS surgery (median, 82%; range, 7–100%). The distribution of percentage improvement of BFM motor score is shown in Fig. 3.

These positive results are confirmed by the case series with