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Deep brain stimulation for the treatment of cerebral palsy: A review

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KEYWORDS
deep brain stimulation (DBS), cerebral palsy, dyskinesia

1 Introduction

Cerebral palsy (CP) is a group of permanent disorders mainly involving motor impairment that results from a lesion occurring in the developing brain [1]. It is one of the most common causes of disability in children, with a prevalence in the past 40 years of 2 to 3.5 per 1000 live births [1–3]. The risk of CP may be increased by lower gestational age and birthweight, perinatal asphyxia, kernicterus, metabolic or traumatic brain injury, and vascular events [1, 4]. CP is complex, with motor impairment and abnormal postures predominating. Based on its clinical symptoms and signs, CP can be divided into four types: spastic, dyskinetic, ataxic, and mixed [5]. Spastic CP accounts for more than 80% of cases, while dyskinetic CP is observed in 4% to 17% [6, 7]. Dyskinetic CP can be further classified into three subtypes according to the nature of the involuntary movements: dystonia, chorea, and athetosis. Other classifications, such as definitions according to the lesion site (cerebral cortex, cerebellum, pyramidal system, or extrapyramidal system),
extent of injured extremities (hemiplegia, diplegia, or quadriplegia), degree of muscle tone (hypotonic, isotonic, or hypertonic), and insult timing (prepartum, intrapartum, or postneonatal), are also described in clinical practice \[8\]. Heterogeneity is a major feature of CP and makes treatment challenging. Thus, the concept of multidisciplinary and comprehensive treatment for CP patients is now widely accepted \[1\] using pharmacological interventions, neurosurgical or orthopedic treatment, and neurorehabilitation. However, pharmacological interventions are usually unsatisfactory or are only temporarily effective, especially for dyskinetic CP \[9–12\]. As for neurosurgical treatment, deep brain stimulation (DBS) has been reported as an effective neuromodulation therapy for CP \[13, 14\]. DBS has been used for treatment of various diseases, such as Parkinson’s disease, chronic pain, intractable epilepsy, depression, and Tourette syndrome \[15–20\]. Accordingly, the US Food and Drug Administration (FDA) has approved the clinical applications of DBS for a series of diseases. For CP treatment, especially the management of dyskinetic symptoms, DBS provides a plausible alternative to traditional regimens such as intrathecal baclofen \[12\]. Dyskinetic CP is the most common cause of acquired dystonia in children \[21\]. Although DBS is approved for treating dystonia, in clinical practice many CP patients presenting with predominantly dyskinetic symptoms show a hybrid of dyskinetic symptom subtypes, so called dystonia-choreoathetosis CP. They may also get a good outcome after receiving DBS treatment \[13\] but, due to a shortage of large-scale investigations, DBS is still not considered to have long-term efficacy in CP treatment \[1, 12\].

In this review we discuss the targets for DBS and mechanisms of action for the treatment of CP, and focus on presurgical assessment, efficacy for dystonia and other symptoms, safety, and risks.

2 Target selection for DBS and potential mechanisms of action

Currently, the bilateral or contralateral globus pallidus internus (GPi) is the common target selected for DBS treatment of CP and was firstly reported in dystonia treatment in the late 1990s \[22, 23\]. Similar to the subthalamic nucleus (STN) (another common target for DBS treatment), the GPi is an important part of the basal ganglia and extrapyramidal system. As there is a relationship between the GPi and disorders of movement such as CP and Tourette syndrome, the GPi has become established as the target for open resection or stereotactic surgery to relieve contralateral tremor and rigidity without paresis \[24\]. Nowadays, GPi-DBS is widely used in neuromodulation therapy of dyskinetic diseases (for instance, Parkinson’s disease), as its predominant efficacy is in ameliorating voluntary movements \[25\], and partially compensating for the shortage of treatments targeted at other basal ganglia nuclei such as the STN \[26\].

In light of its different connections and pathophysiological functions in cortical-basal ganglia-thalamocortical (C-BG-T-C) circuitry, GPi-DBS may make a contribution to treat both hypokinetic and hyperkinetic movement disorders, which could provide a benefit for patients with CP and other dyskinetic diseases. Anatomically, the globus pallidus can be mainly divided into two segments, the GPi and external globus pallidus, and is the site of convergence of a significant number of neural fibers passing through C-BG-T-C circuitry \[27\]. Histochemically, most neurons in the globus pallidus are GABAergic (\(\gamma\)-aminobutyric acid). The posterior half of the GPi (53%) has sensorimotor functions, while the intermediate part (29%) is associative, and the ventral part (18%) has limbic functions \[27\]. This functional subdivision of the GPi may have
implications for treating diseases with various manifestations of dyskinesia, or other movement disorders. Numerous experimental and clinical studies support the critical role of the GPi in motor control in dystonia [28, 29], including electrophysiological evidence supporting the movement control effects of the GPI-DBS regimen. Animal studies of levodopa-induced dyskinesia have shown that reduced activity of the STN/ GPi neurons may be a mechanism for attacking dyskinesia, while GPi modulations by DBS can be responsible for correcting movement execution, based on its complex neuronal firing pattern in coding and guiding movement information [30]. Patient studies have also shown that high frequency stimulation induced by GPI-DBS can modulate pallidal pathological low frequency activity in dystonia patients [31]. This improvement in tonic features may rely on the basal ganglia motor network. Moreover, the evidence of somatotopic organization in the GPi may also support the mechanism of GPI-DBS treatment of dyskinesia [32–34]. The fine somatotopic organization through the GPi is unraveled, with leg position dorsally, face position medioventrally, and arm position in-between [32, 33]. Correspondingly, GPI-DBS in dystonia patients supports this relationship between subregion modulation and clinical effect in certain body parts [34]. Some GPI-DBS studies in Parkinson’s disease have shown that the stimulation of the most ventral contacts can lead to amelioration of rigidity and levodopa-induced dyskinesias, and stimulation from the most dorsal contacts can lead to moderate off-drug akinesia as well as dyskinesias [35].

In addition to its predominant functional mechanisms in motor control, recently studies have also shown some nonmotor functions of the GPi [36–38]. These functions mainly include reward-related behaviors, motivation, and attentional execution. In reward-related behaviors, the increase in human GPi neuronal firing rate is associated with reward information while bilateral or unilateral lesions in the GP region can induce some pathological presentations of reward behaviors such as anhedonia and apathy. Moreover, clinical and experimental deficits in motivation and reward can be rescued after dopaminergic administration. These nonmotor roles played by the GPi could provide another approach to treat some complex syndromes such as CP via DBS neuromodulation.

There are some other targets for DBS treatment of CP (especially for dystonia), including the STN and ventral intermediate nucleus (Vim). The potential mechanism of action of these targets in CP therapy is similar to that for the GPi and is associated with motor control affected by the C-BG-T-C circuitry. Both STN and GPi stimulations have an effect on alleviating dystonia and improving life quality. While GPI-DBS produces a relatively long-term effect, STN-DBS is quick-impact and may have lower battery consumption [39, 40]. Some randomized double-blind trials and a meta-analysis also support the safety and promise of STN-DBS treatment of dystonia [41, 42]. Vim is another target for DBS and some small-sample studies have shown that compared with GPI-DBS, Vim-DBS did not show a relevant long-term advantage in CP patients. Its value in CP neuromodulation maybe investigated by further robust studies [43, 44].

3 Neuromodulation and assessment

Successful use of DBS for CP depends on suitable assessment and an appropriate modulational strategy [4]. The timing of DBS implantation and the programming of DBS are the two most important factors in this kind of neuromodulation. There is no definitive guidance on timing of DBS [14]. Theoretically, early DBS treatment may overcome maladaptive neuroplasticity in CP.
patients. However, device-related and stimulation-related long-term complications induced by DBS have raised concerns about the early implantation of DBS. A meta-analysis showed that there was a significant negative relationship between severity of dystonia and DBS outcome [45]. This may suggest early application of DBS for CP patients, based on a consideration of preventing probable aggravation in motor and other functions. Another small-sample but long-term investigation has shown that age at implant, age at onset, and disease duration do not correlate with clinical outcome in GPi-DBS treatment of CP [46]. With respect to promotion of participation and deformity prevention in children, some studies propose an early offer of DBS, preferably within 5 years of onset, to reduce the dystonic experience in childhood [47, 48].

When programming DBS, for all patients four parameters must be considered: the arrangement of electrodes (contacts), amplitude, pulse width, and frequency [14]. There are varying programming regimens according to the clinician’s experience and the actual response of patients, with amplitudes ranging from 1.0 V to 6.5 V, pulse widths ranging from 60 μs to 240 μs, and frequencies ranging from 30 Hz to 185 Hz [14]. A few studies have assessed the correlation between clinical outcome and contact location, and have proposed that the posteroventrolateral portion of the GPi may be preferable for dystonia [34, 49–51].

Preoperative and postoperative assessment is also important when considering DBS therapy, both in terms of motor control and nonmotor functions. In respect of movement assessment, the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) is a common method used in CP patients, especially for dystonia assessment [52]. Generally, the BFMDRS can be further subdivided into a motor scale (BFMDRS-M) and a disability scale (BFMDRS-D). Other motor control assessments such as the Gross Motor Functional Classification System for ambulation, and the Unified Dystonia Rating Scale are also used in clinical practice [14]. Recently, due to emphasis on the nonmotor symptoms of CP patients and the role of DBS therapy in nonmotor functions, some neuropsychological assessments are frequently applied during the postoperation period and follow-up, including the 36-Item Short Form Survey, the Symptom Check List-90, Behavioral Assessment of the Dysexecutive Syndrome, and the Goal Attainment Scaling [14]. However, whether these nonmotor functions or cognitive symptoms will be changing during a long-term follow-up after DBS still remains a source of controversy [13, 46]. It has been proposed that multidimensional assessment preoperation and postoperation is recommended to elucidate the possible effect of DBS in terms of neurofunctions, participation, care, comfort and life quality [53].

4 Efficacy for dystonia and motor function

To date, dystonia due to CP is the most acceptable indication for DBS treatment and a majority of studies on DBS efficacy focus on dystonic CP. A systematic review [12] has investigated some pharmacological and neurosurgical interventions, including oral baclofen, benzodiazepine, clonidine, gabapentin, levodopa, trihexyphenidyl, botulinum toxin, intrathecal baclofen (ITB), and DBS, for managing dystonia in CP patients and shown that only ITB and DBS may be effective. The evidence level is C for both two managements, which means it is not sufficient to make a recommendation for improving motor control, relieving pain, or easing caregiving, compared with other medical treatments. Nevertheless, DBS is still a plausible approach in clinical practice to manage generalized dystonia in CP. In future, a credible comparison is needed to evaluate the clinical choice of DBS versus ITB in CP and other
generalized dystonia patients [12]. Most class III studies have reported a positive outcome of DBS treatment in dystonia reduction [13, 46, 47, 54–56] while others have shown no support or mixed results [57–60]. There is also some conflict about the efficacy of DBS on improving motor function [13, 46, 47, 55–57, 60]. Moreover, there was an amelioration of motor function of the upper nondominant extremity but no change on the dominant side [61]. As to the applications of DBS for childhood CP, a small series study has shown an improvement in postoperative dystonia rating scales and proposed that GPI-DBS remains a viable opinion for childhood dystonic CP [59].

Although most studies have reported the efficacy of GPI-DBS in reducing dystonia and motor symptoms, the magnitude of this effect is very variable, with a mean reduction of BFMDRS-M ranging from 1.2% to 49.5% [14]. Similarly, an improvement of BFMDRS-D is also variable, ranging from 0 to 32% [14]. A slight worsening of motor function was reported in some studies [53, 60]. Reasons for this variability are still to be elucidated but predictors of a positive outcome include shorter disease duration, early surgery, higher irregular GPI neuronal firing frequency, and no fixed skeletal deformities [4, 13, 47, 62–64]. In contrast, brain lesions, severe dystonia, and concomitant spasticity may impair the therapeutic effect [4, 45, 46, 65, 66].

Compared to dystonia due to the DYT1 gene mutation, some studies have shown that dystonia due to CP may be less responsive to DBS treatment [54, 56], primarily because of ongoing efficacy in DYT1 but not CP patients during the follow-up period after DBS implantation. Control studies have shown that the improvement during the first year after DBS treatment is parallel but the overall response is more variable in CP patients [55, 56]. A long-term follow-up study is needed to investigate the exact influence of DBS treatment on dystonia and the motor symptoms of CP [14, 46]. A cohort of 15 CP patients and up to 6 years follow-up study have shown an encouraging outcome with a mean 50% improvement as assessed by the BFMDRS [46].

Some studies comparing different DBS regimens, such as bilateral GPi stimulation versus bilateral GPi plus unilateral thalamotomy, have shown no significant difference in dystonia reduction, but there may have been benefits in health-related quality of life in the group undergoing thalamotomy [57, 67].

5 Efficacy for other symptoms

Some class III studies have shown a positive effect of DBS on pain reduction and comfort improvement [46, 68], while others were negative [13, 57]. Many factors may influence these inconsistent results and patient screening is of importance. CP patients with ataxia may have a poorer outcome on improvement of functional impairment after DBS treatment [69], and a remarkable promotion of life quality can be found in studies primarily involve dyskinetic CP (e.g., dystonia or dystonia-choreoathetosis) [13, 14, 46, 56]. Some studies have reported clear benefits on speech and swallowing even in childhood CP [46, 59]. Improvement in some psychological disorders, including depression, paranoid ideation, and psychotic symptoms, have been reported [13] and some clinical studies have confirmed that there is no significant deterioration in cognition or neuropsychiatric symptoms after GPI-DBS [70–72]. A cohort study focused on children with dyskinetic CP has shown that perceptual reasoning ability, assessed by the Picture Completion subtest, improved following DBS treatment but general cognition remained stable [73].

Due to the difficulties of systematic assessment of cognition and other nonmotor symptoms in
CP patients, especially in children, there is a need to make prospective, multicenter, and age-related studies of the effects of DBS on nonmotor symptoms in CP patients, aiming to improve their quality of life [4].

6 Safety and risks

DBS is a less invasive surgical treatment and has relative low complications, which include infection, intracranial hemorrhage, mislocation of electrodes, and hardware malfunctions [74]. Although the data on complications of DBS in CP was acceptably low, it was variable and inconsistent in different studies. In a meta-analysis [45] focused on DBS treatment in dyskinetic CP, about 68 cases were identified and only a few adverse events were reported, mainly worsening of dystonia (4 cases), hemiparesis (3 cases), lead fracture (2 cases), infection (1 case), and pain (1 case) [13, 57, 75–77]. Other studies reported hardware-related infection and dysarthria [14, 46, 67]. Adverse events due to DBS treatment may be more common in pediatrics than adults, especially in children younger than 10 years old [4]. In pediatric and adolescent patients, who are the majority of dyskinetic CP cases, studies have shown that DBS treatment may having a low surgical complication rate but an increasing device or hardware complication rate, such as infections and malfunctions [78, 79]. Moreover, in order to reduce the rate of infection, a small series retrospective study has proposed a stepwise approach for bilateral GPi-DBS for childhood dystonic CP [80].

Overall, hardly any severe surgical complications have been reported for DBS treatment in CP or other dystonic disorders. Most studies have proposed that DBS treatment is beneficial for CP patients. More investigations are needed for evaluating risks relating to dystonia or other motor function severity, and life quality such as pain and caregiving [12].

7 Conclusions and future directions

DBS is an effective, safe, and recommended approach for the treatment of CP. The evidence for efficacy of DBS on dystonia, motor function and other symptoms is less robust, and is without risk elucidation so far. Some important factors, such as time of surgery, severity, and duration of dystonia or other symptoms, targets, and the modulation regimen require further research. Larger, long-term, and multicenter clinical trials may be worth considering to improve our understanding of this kind of neurosurgical intervention in patients with CP.

Conflict of interests

The authors declare no conflict of interests in this work.

References


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