DBS in Dystonia and Other Hyperkinetic Movement Disorders

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Opinion statement

The diagnosis and appropriate treatment of hyperkinetic movement disorders require a work up of potentially reversible metabolic, infectious and structural disorders as well as side effects of current medication. In pharmacoresistant movement disorders with a disabling impact on quality of life, deep brain stimulation (DBS) should be considered. At different targets, DBS has become an established therapy for Parkinson's disease (GPi-STN), tremor (VIM) and primary dystonia (GPi) with reasonable perioperative risks and side effects, established guidelines and some clinical and radiological predictive factors. In contrast, for other hyperkinetic movement disorders, including secondary dystonia, Gilles de la Tourette, chorea and ballism, only few data are available. Definite targets are not well defined, and reported results are of less magnitude than those of the recognized indications. In this expanding therapeutical field without worked out recommendations, an individual approach is needed with DBS indication assessment only after rigorous multi-disciplinary scrutiny, restricted to expert centres.

Introduction

Hyperkinetic movement disorder is a heterogeneous group, including tremor, dystonia, chorea, myoclonus, tics, stereotypies, restless legs syndrome and various other disorders. Differential diagnosis of hyperkinetic movement disorders is very broad. For better

pathophysiological understanding and management, they can be classified in primary and secondary movement disorders, the latter due to hereditary degenerative diseases or secondary to known causes. Evaluation contains at first exclusion of potentially reversible causes.

After extensive laboratory investigation, workup includes always a neuroimaging (MRI) to detect possible ischemia, haemorrhage or neoplasia. Pharmacological treatment is often limited by side effects, making deep brain stimulation (DBS) an interesting alternative approach. First attempts of functional surgery as additional treatment to medical management started in the early 50s, with lesions of various anatomical targets. Preponderant limiting factors were the occurrence of irreversible side effects, particularly in bilateral approaches. In the late 1980s, Benabid et al. reported that high frequency DBS was mimicking lesion for treatment of tremor [1]. Thereafter, DBS has been shown to be as efficacious as the thalamotomy but with lesser adverse effects thanks to the advantage of adjustable stimulation parameters [2]. Since then, the potential indications of DBS have been explored in multiple fields of neurology and psychiatry. Although DBS mechanisms of action are not fully understood, it is thought to modulate the expression of dysfunctional neuronal networks. Potential risk of DBS surgery includes haemorrhage (1.9 %), infection (4.7 %), electrode breakage (0.94 %) and lead migration or misplacement (0.94 %) with an overall mortality of 0.94 % [3]. Overall, serious side effects of DBS are rare, with little impact on cognitive function and behaviour [4••].

Postoperative side effects after chronic stimulation such as muscular contractions or visual flashes, the latter due to proximity to optical tract, are mostly mild and reversible by adjusting the stimulation parameters [5]. The electrode implantation is preferably performed under local anaesthesia, as optimizing of electrode placing and consequently its therapeutical efficacy and potential side effects can be tested pre-operatively. Stereotactic neurosurgery with DBS has become an established therapy of selected movement disorders and revolutionized treatment especially in Parkinson's disease, essential tremor and dystonia after its approval by the US Food and Drug Administration in 1997 (essential tremor (ET)), respectively, in 2002 (for Parkinson's disease (PD) and dystonia) and is also used in psychiatric disorders as major depression and obsessive-compulsive disorder. An increasing number of studies suggest its efficacy in treatment of secondary dystonia and in chorea, Gilles de la Tourette's syndrome, tardive dyskinesia and ballism, turning DBS in an interesting alternative therapeutical approach, for all hyperkinetic movement disorders.

We will focus on actual state of knowledge and guidelines of DBS in following hyperkinetic movement disorders: dystonia, tardive dyskinesia, tremor, Gilles de la Tourette's syndrome, chorea and ballism.

Treatment

DBS and dystonia

Dystonia is a movement disorder characterized by sustained or intermittent agonist and antagonist muscles co-contractions, causing abnormal posture and/or movements. Dystonia may be triggered or worsened by voluntary action and associated with overflow muscle activation; sensory tricks with "gestes antagonists" can alleviate them. Their division in primary and secondary dystonia on the basis of their aetiology is essential for pathophysiological understanding and appropriate management. Further classification according to their localization (focal, segmental, multifocal, generalized, hemidystonia) and age at onset (infancy, childhood, adolescence, adulthood) can be used.

Current EFNS guidelines (2011) for diagnosis and treatment of dystonia recommend the use of DBS in primary dystonia forms, in particular primary segmental and generalized dystonia, as well as in tardive dystonia, when conservative approach failed [6••]. Before considering DBS, appropriate work up, including MRI, is mandatory to differentiate primary and secondary dystonia [6••]. By analogy to other indications, resistance to at least two different classes of medications at highest supportable dosages should be documented. Deep brain stimulation of internal globus pallidus (GPi) is considered as an

established dystonia treatment for refractory primary segmental and generalized dystonia (level A evidence) with significant improvement of quality of life starting after 3–6 months [6••, 7, 8••]. GPi is the main output of basal ganglia network. GPi-DBS influences the direct and the indirect pathways that are postulated to dysfunction in dystonia [9]. Recording oscillatory activity through implanted electrodes supports this approach, given that oscillatory theta activity is elevated in GPi, coherent to phasic dystonic muscle contraction [9]. Posteroventral GPi stimulation has the best overall effect and is superior for the arm and the trunk, whereas anterodorsal stimulation shows similar efficacy for the leg [10]. In generalised and segmental dystonia, two multicentre controlled studies showed a good risk/benefit ratio for GPi-DBS, with mean improvements of the dystonia motor score of 51 and 42 % [11, 12]. Clinical response to DBS in dystonia is typically gradually increasing over several weeks to months, and its efficacy is sustained [7] in primary dystonia up to 8 to 10 years in DT1-positive patients [4••, 13, 14]. However, only a poor or no response may occur, even in patients that are not different in clinical profile or electrode placement from those with good response [15, 16]. Predictive factors of good postoperative outcome in primary dystonia are younger age at the time of surgery (<21 years old) and shorter duration of symptoms (<15 years), while age at onset and severity of the disease seems to have little or no significant influence [4••]. Fixed skeletal deformities are associated with poorer outcome [17]. In rare cases of cervical dystonia and blepharospasm, after several years of stimulation, symptoms did not reappear after cessation of DBS, suggesting that DBS could induce plastic changes [4••]. Overall, serious side effects of bilateral GPi-DBS are rare [4••]. Nevertheless, pre- and postoperative neuropsychological and psychiatric assessment is recommended, given the high psychiatric comorbidity in the dystonia population and few reports of suicide after GPi-DBS implantation [8••]. To consider also several biases in actual studies, including highly selected patients with normal cognitive function and no mood disorders at baseline, as well as possible impact of anticholinergic co-medication [4••]. Pallidal stimulation may induce Parkinsonism as bradykinesia, freezing, postural instability and micrographism [8••]. In most cases, compromise between Parkinson symptoms and dystonia can be achieved by adapting stimulation settings and diminution of total energy delivery.

Deep brain stimulation can also be considered in cranial and cervical dystonia after failure of botulinum toxin injections (level B) [6••, 8••, 18]. Pharmacoresistant cervical dystonia may show up to 70 % improvement in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [15, 19]. Data regarding other forms of focal dystonia are limited to small series of mixed cases or individual reports, since focal dystonia are often sufficiently treatable with injection of botulinum toxin, showing encouraging but still highly variable results with mostly bilateral GPi-DBS [4••]. Some patients with severe writer's cramp have been successfully treated with unilateral DBS of the ventral oral (Vo) nucleus of the thalamus [20, 21]. There is little experience with other targets for DBS in dystonia, with scant comparative data of DBS of subthalamic nucleus versus pallidal stimulation in patients with dystonia, and in case of coexisting tremor, thalamic targets [8••].

Secondary dystonia as hemidystonia, cerebral palsy related dystonia as well as neurodegenerative forms (Wilson's disease, Lesch-Nyhan, panthotenate kinase-associated neurodegeneration (PKAN), etc.) are still being explored but

seem to respond less well to pallidal DBS than primary dystonia. Application of DBS in dystonia secondary to brain injury is also strongly debated [22]. Patients with secondary dystonia often have complex movement disorders with combination of hyperkinetic and akinetic-rigid dystonia as well as pre-existing structural brain lesions, leading to difficulties for DBS targeting [4••]. Underlying disease is often progressive, resulting at long term in DBS failure with re-emerging symptoms [4••]. A collection of case reports demonstrated very variable results in DBS treatment of dystonia symptoms in neurodegeneration with iron brain accumulation (PKAN) and its application in secondary dystonia in cerebral palsy; average improvement is around 20–25 %, bearing in mind the heterogeneity of this group of patients and the often unmodified persistence of attendant symptoms as, e.g., parkinsonism [4••, 23, 24]. Bilateral GPi-DBS has been performed in adults with dystonic-choreoathetotic cerebral palsy. Significant improvements in pain, functional disability and mental health-related quality of life have been reported [25]. In children, there is evidence to suggest better efficacy in early neurosurgical treatment before completion of motor development [26]. Considering DBS surgery in secondary dystonia as often less effective and with still limited experiences, indication should be carefully evaluated case by case by multidisciplinary team (level C) [6••].

DBS and tardive dyskinesia

Tardive dyskinesia is a hyperkinetic movement disorder that appears with a delayed onset after prolonged use of dopamine receptor blocking agents, mainly neuroleptics. Clinical manifestation of tardive dyskinesia is very heterogenic, most commonly stereotypical involuntary movement affecting the lips and tongue, that may be associated to trunk and limb involvement. Less common is tardive dystonia (1–4 %), characterized by sustained muscle contraction leading to twisting repetitive movements and abnormal postures. Remission of dyskinetic symptoms has been reported in 14 % of patients within a mean of 2.6 years after discontinuation of offending drugs and medical treatment remains often unsuccessful [5]. Tardive dystonia claims a special place among the tardive dyskinesia, because of the disability and the pain it may produce and its distinctive therapeutic options by the possibility of GPi-DBS, with similar benefit of DBS as reported in primary dystonia [8••, 6••]. In a follow-up from 3 to 76 months, more than 70 % improvement of BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) and extrapyramidal symptom rating scale (ESRS) has been reported [27]. It is likely that pathophysiology of tardive dystonia shares a common mechanism with primary dystonia, given their similar benefit of GPi-DBS [8••, 6••, 28]. Several studies reported improvement of extrapyramidal symptoms and dystonia within few hours (12–72 h) after starting GPi-high frequency stimulation, with improvement up to 80 % of axial phasic dystonic movements and oro-buccal-lingual dyskinesia [4••, 5, 28]. Benefit remains sustained on long-term follow-up of 8 years [28]. One study reports subthalamic nucleus DBS to be an effective therapy in refractory tardive dyskinesia; additional studies are needed to determine ideal stimulation target (GPi or subthalamic nucleus). Postoperative side effects after chronic stimulation are mostly mild and reversible by adjusting the stimulation parameters [5]. Even if no psychiatric or cognitive impairment after pallidal DBS in tardive dystonia reported, close psychiatric monitoring is recommended in this potentially vulnerable patient population [28].

DBS and tremor

Tremor is defined as a rhythmic and oscillatory movement of a body part with a relatively constant frequency and variable amplitude. Essential tremor has prevalence in general population ranging from 0.4 up to 6 %, with higher prevalence in people over 65 years of age [29], a 4–12 Hz postural and kinetic tremor concerning essentially upper extremities, less commonly also the lower extremities and the head. Essential tremor is improved in approximately 50 % of the patients by medication [30]. About 25–55 % of patients are refractory to medical treatment and are potential DBS candidates [29]. Target of DBS is the ventral intermediate nucleus (VIM) of thalamus [31•]. Alternative target is the posterior subthalamic area (PSA; caudal zona incerta) [30]; these findings suggest that tremor control is best with stimulation of the cerebello-thalamic afferents, which are embedded in the subthalamic area [32]. Immediate and significant improvements in upper limb tremor are obtained with sustained effect in long-term follow-up up to 10 years [30, 33]. Head tremor may also improve in bilateral thalamic stimulation [34]. Outcome for voice-tremor is mixed and often only minimal symptom reduction is reported [34, 35]. DBS failure immediately postoperative is mostly due to suboptimal electrode placement. A gradual loss of efficacy of DBS may be due to phenomena of tolerance [16] and might be prevented by overnight withdrawal from stimulation [36, 37]. Worsening of tremor over time may also be secondary to disease progression [38].

Efficacy of DBS in essential tremor and tremor of Parkinson's disease has led to apply the technique to rare secondary tremors. Tremor in MS patients has been the most studied. It has been estimated that tremor affects 26 % MS patients, most commonly a postural or intention tremor, with 3 % of patients suffering from a severe tremor [39, 40]. Effects of medication on MS tremor tend to be minor and short-lived [40, 41]. The recent review of DBS in MS patients with tremor showed in all series a tremor reduction, with variable functional improvement [41]. Long-term follow-up are scarce but point to vanishing benefit of DBS over time mainly in relation with disease progression [42]. Most common stimulation target was the VIM [41]. MS patients appeared to be less responsive to surgical intervention than those with essential tremor or secondary tremor in Parkinson's disease [43].

Holmes' tremor is characterized as a tremor present at rest, in antigravity postures and with action classically associated with midbrain lesions. It may have a levodopa-responsive component if lesion is involving the substantia nigra (pars compacta) [44]. Trials of application of DBS in Holmes' tremor have shown to be more effective in GPi than thalamic DBS [44]. There are also few cases reported of thalamic DBS in posttraumatic tremor showing tremor improvement, although there is no follow-up greater than 1 year [44].

Further randomized controlled trials comparing efficacy and security of PSA and VIM stimulation are needed. DBS in treatment of essential tremor is relatively safe; most adverse events are mild, such as paraesthesia, headache and dysarthria and can mostly be treated by adjusting stimulation settings [45]. There is no overall change in cognitive functions described in VIM stimulation [30]. In order to reduce the risk related to the material and cost related to its regular replacement, alternative approaches as gamma knife [46, 47] and focused ultrasounds [48, 49] are under investigation with promising results.

DBS and Gilles de la Tourette syndrome

Gilles de la Tourette syndrome (TS) is a disorder characterized by motor and phonic tics, often associated with other neuropsychiatric disorders, especially obsessive-compulsive disorders (OCD) and attention deficit hyperactivity disorder (ADHD). Onset is per definition before the age of 18 with a waxing and waning course of tics, with a peak of severity in early adolescence. Natural history of disease is favourable, characterized by subside of tic frequency and severity with increasing age. Treatment consists in comprehensive behavioural intervention for tics and medical treatment. In two third of patients, tics are completely regressive or only mildly persistent in early adulthood [50]. Only 5.1 % of all TS patients present malignant TS with severe disability and impairment of social psychological and intellectual development despite optimized medical and behaviour therapy [51] representing potential DBS candidates. Studies for DBS in TS are scarce and mainly targeting the ventral thalamus (70 reported cases). Second most frequent reported target (31 case reports) is the GPi [52••]. Anecdotal reports exist also for the nucleus subthalamicus (STN), the external globus pallidus (GPe) and the anterior limb of capsula interna/nucleus accumbens. Because of small number of patients, lack of controlled studies and variability in outcome measures (including comorbidities of TS), there is currently almost no data to guide target choice [52••]. GPi and thalamus appears to be the safest and most effective targets [53]. Few studies [54–57] reported higher benefit by bilateral GPi stimulation compared to bilateral thalamus stimulation. GPi-DBS seems to improve also behavioural comorbidities [54, 57, 58]. Considering particularities of this uncommon indication, involving vulnerable patients, DBS should only be offered after multidisciplinary evaluation to evaluate individual risk and benefit of operative approach by well-trained centre [52••]. Currently, the 2014 revised guidelines for DBS candidates in TS require fulfilled TS diagnostic criteria (presence of more than 1 year of multiple motor and at least one phonic tic, with onset before age of 18 years) and persistence of severe motor or vocal tics despite adequate medical and behavioural treatment, with important social, psychological or intellectual impacts. Minimal age limit is fixed at 18 years, despite theoretically possible spontaneous tic remission, given the increasing evidence of a favourable risk-benefit ratio, as delaying surgery increases psychological, intellectual and social irreparable harm, as well as bodily harm through malignant tics [52••]. Standardized assessment by videotape and validated rating scale (e.g. Yale Global Tic Severity Rating Scale (YGTSS)) should be used for tic documentation, with a total YGTSS above 35/50 for at least 1 year. At least three different pharmacological trials—an alpha-adrenergic agonist, two dopamine antagonists (one typical and one atypical) and another drug class (topiramate, clonazepam, tetrabenazine) should be documented [52••]. Psychiatric comorbidities should be carefully identified and adequately treated for at least 6 months before DBS surgery and should not be major source of functional impairment [59]. Exclusion criteria are structural lesions on brain MRI, substance abuse and risk of suicide. If deemed as good DBS candidate, a 30 to 50 % or greater improvement of motor tics is reported [52••]. No significant changes in cognition are reported after DBS application on the different targets. [57, 60]. Available data concerning effect of DBS on psychiatric comorbidities of TS patients are still limited, in part due to difficulties in their standardized evaluation, but are promising [52••, 57, 61, 62].

DBS and ballism and chorea

Ballism is a rare movement disorder consisting of non-voluntary ballistic motion of high amplitude in proximal limb, associated with a contralateral lesion of basal, most commonly due to stroke (ischemic/haemorrhagic) or to hyperglycemia. Prognosis is generally favourable with complete resolution within 3 months [63]. DBS in hemiballism should only be considered in rare cases of pharmacoresistant ballism with symptoms persisting for more than 6–12 months [63]. Choreic movements, which are defined as random brief non-stereotyped involuntary movements affecting mostly distal limbs, have a large differential diagnosis, including hereditary neurodegenerative diseases, structural lesions of basal ganglia, autoimmune, infectious and metabolic/endocrine disorders, as well as drugs and toxins.

Improvement of hemiballism—hemichorea with thalamic stimulation (VIM) has been reported [64, 65] and more favourable regarding energy consumption compared to stimulation of GPi [65]. Several case reports of DBS in Huntington disease [66, 67] and neuroacanthocytosis [68] show benefit of stimulation in GPi, although resistance exists [69]. Benefit of stimulation of the thalamus in chorea in neuroacanthocytosis is also described [70]. In contrast with the improvement of chorea, other symptoms such as gait disturbances, dysarthria and hypotonia may develop or worsen [71]. Effects on cognitive functions is controversial, some reporting stability [67] while others showing cognitive decline [66]. Despite some promising postoperative results in chorea due to neurodegenerative disorders, long-term efficacy is probably limited by progression of underlying disease, as in secondary dystonia and tremor. Nevertheless, most surgical team currently prefer approach on GPi [68]; optimal target for stimulation remains debatable and long-term outcome is still uncertain, so that an individual multidisciplinary patient approach is mandatory.

Future

Well-accepted indication in movement disorders and promising effects in other neurological and psychiatric disorders have lead to rapid expansion of DBS applications [71]. Precise mapping of functional territories of basal ganglia with their motor and non-motor functions will help to better understand behavioural and movement disorders and will permit better definition of the optimal therapeutical targets. In addition, further technical developments of hardware/electrodes will allow a better steering of the stimulation to optimize beneficial effects and reduce side effects, by directional electrodes [72] and close-loop intermittent stimulations. [73, 74]. In order to reduce the risk related to open surgery, new lesional approaches (gamma knife, focused ultrasound) are starting to emerge [46–49]. There is need of multicentric international collaboration with defined protocols for these rare and specific DBS applications. In the meantime, DBS in most of hyperkinetic movement disorders (outside primary dystonia and essential tremor) should be restricted to expert centres.

Compliance with Ethics Guidelines

Conflict of Interest

The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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