Thalamic deep brain stimulation for Tourette syndrome

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1. Introduction

Tourette syndrome (TS) is a complex chronic neuropsychiatric disorder characterized by motor and vocal tics. Motor tics are sudden, repetitive, stereotyped movements such as eye blinking, facial twitching, and head or shoulder movements, whereas vocal or phonic tics are sounds produced by moving air through the nose, mouth, or throat (e.g. coughing and throat clearing) as well as repeating syllables, words, or phrases \cite{1}. TS typically has an onset in early childhood, and boys are more commonly affected than girls. Symptoms usually start with transient bouts of simple motor tics. Tics can become more “complex” in nature and appear to be purposeful. A fleeting feeling of relief often follows performance of a tic or a series of tics \cite{2,3}. Tics typically follow a waxing and waning pattern of severity, intensity, and frequency \cite{4}. Tic severity usually peaks between 8 and 12 years of age, with many patients showing a marked reduction in severity by the end of adolescence \cite{5–7}. Approximately 20% of children with TS continue to experience a moderate level of impairment of global functioning by the age of 20 years \cite{7}. TS alone is the exception rather than the rule. Attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive behaviour (OCB) are the most common co-morbidities. The presence of these co-morbidities can add another layer of complexity, which may make it more difficult to develop a treatment plan that not only addresses the tics, but also the co-occurring disorders.

TS might be interpreted as an overactive abnormal neural activity of both the sensimotor and the limbic circuits, involving multiple outputs, of the basal ganglia \cite{8}.

2. Treatment of TS

Frequently, TS is found to be a self-limiting disorder, whereas in a small proportion of patients the tics continue into adult life and require long-term behavioural or drug treatment. Behavioural and drug treatment may provide temporary control of symptoms but certain patients prove to be medically untreatable or experience unbearable side effects from the medication. For these patients, surgery may be an option.

In the past, various attempts have been made to treat patients suffering from TS through neurosurgical ablation...
tive procedures [9]. The target sites have been diverse including the frontal lobe (prefrontal lobotomy and bimedial frontal leucotomy), the limbic system (limbic leucotomy and anterior cingulotomy), the thalamus and the cerebellum. The results have often been unsatisfactory or major side effects have occurred such as hemiplegia or dystonia. Hassler and Dieckmann reported on the beneficial effects of lesioning the intralaminar and midline thalamic nuclei in patients suffering from TS, and, in patients with facial tics, also the nucleus ventro-oralis internus (Voi) [10].

Deep brain stimulation (DBS) has been introduced in the field of neuropsychiatry to modulate neuronal activity in the same areas as those targeted for lesioning in the past, but in a reversible way. The difficulty was that Hassler made up to ten coagulations in the intralaminar and medial thalamic nuclei, so a strategic point had to be found so that as many of the nuclei targeted by Hassler could be stimulated by one electrode for each hemisphere. This strategic point was found, studying the Schaltenbrand-Wahren atlas [11], on a coronary slice at 4 mm posterior to the midpoint of the line connecting the anterior commissure (AC) with the posterior commissure (PC) and 5 mm lateral to the AC-PC line, and the dorsolateral plane, at the level of AC-PC. The first target for DBS, the medial part of the thalamus at the crosspoint of the centromedian nucleus (Cm), the substantia periventricularis (SPv) and the nucleus ventro-oralis internus (Voi), has been described by Vandewalle in 1999 [12]. The results of thalamic DBS in the first 3 Tourette patients have been described in 2003 [13].

3. Targets

In the last ten years, more than 90 patients with TS have been reported to be treated with DBS in the literature, with ten different brain targets, including the Cm-Spv-Voi cross point of the thalamus [12–19]. The group of Servello and Porta [20–22] targeted the same area but at a point 2 mm more anteriorly. And one case is described with DBS of the dorsomedial thalamus [23,24]. Besides the thalamus, the globus pallidus externus (GPe) [25] and both the ventroposterolateral motor, as well as the anteromedial limbic part of the globus pallidus internus (GPI) have been targeted for DBS in refractory TS [26–33]. Also the nucleus accumbens [34–38], and internal capsule [16,37,38], have been described, mostly in TS patients also suffering from OCs. Finally, in a patient suffering from both Parkinson’s disease and tics, there was an improvement of tics after DBS of the subthalamic nucleus [39].

More detailed information about the targets and results are described in an excellent review by Piedad et al. [40]. The general rationale for modulating these areas is based on the assumption that tics and associated behavioural disorders are related to a dysfunction of the cortico-basal ganglia-thalamocortical circuitry. Focal disruption of different functional striatal territories results in abnormal activation of neocortical motor and non-motor areas, producing repeated stereotyped movements and abnormal behaviour [41].

3.1. Thalamic DBS

After the promising results of DBS in the first TS patient described by Vandewalle et al. [12], the same group reported on the beneficial effects of DBS of the same target in three patients in [13]. The authors stated that stimulation of the nucleus ventro-oralis internus would lead to diminished motor and vocal tics through inhibiting projections to the facial parts of the premotor (and motor) cortex. Stimulation of the intralaminar nuclei would reduce the activity of the dorsal, sensorimotor parts of the striatum, while stimulation of the midline thalamic nuclei would reduce activity in the ventral, limbic striatum. Almost 80 patients received thalamic DBS for intractable TS, although within the thalamic target there has been some variety. However, sample sizes are small, with the majority of studies being single case reports, there have only been a limited number of studies of thalamic DBS in TS with an accurate methodological design [15,19].

Visser-Vandewalle reported in [12,13] the results of the first three Tourette patients. There was not only a good effect on tics but also on associated behavioural disorders, like obsessive-compulsive behaviour (OCB) and self-injurious behaviour (SIB). With a follow-up period of respectively 5 years, 1 year and 8 months, there was not only a good effect on tics (with a tic reduction of resp. 90%, 72% and 83% with stimulation on compared with the stimulation off condition), but also on associated behavioural disorders such as obsessive-compulsive disorder (OCD) or self-injurious behavior (SIB). Stimulation induced side effects consisted of drowsiness, and changes in sexual functioning. The long-term outcomes of the first and second patient were described in a recent report by the same authors [42]. Tic improvement observed at 5 years in patient 1 (90.1%) was maintained at 10 years (92.6%).
In patient 2, the tic improvement at 8 months (82%) was slightly decreased at 6 years (78%).

Maciunas et al. described in [15] the effects of DBS in five patients with intractable TS, with a follow-up of three months. They used the same target as described by Vandewalle et al. in 1999. After the first four weeks postoperatively, randomized double-blinded assessments showed a statistically significant reduction in motor and vocal tics. At three months, open label assessments showed in three out of five patients an average tic reduction of 50%. The secondary outcome measures anxiety, depression and OCD showed a trend towards improvement. In one patient, a psychotic event was described as an unwanted stimulation-related effect. Bajwa et al. [16] found a good effect of DBS of this thalamic target in a 50 years old patient suffering from TS with OCD and SIB. After 24 months, stimulation resulted in a 66% improvement on the Yale Global Tic Severity Scale (YGTSS), and a 76% reduction of the YBOCS. Idris presented one case with bilateral cortical hematomas after thalamic DBS, with a short note that complex motor and vocal tics improved [17]. In one patient only mild improvement was seen after DBS of the CM/SPv/VOi crosspoint [18]. Most recently, Ackermans et al. presented a double-blind randomized clinical trial of six TS patients with 49% improvement on tics and no significant difference in associated behavior [19].

In 2008, Servello et al. [20] reported on the beneficial effects of DBS in 18 patients with TS, with the target being located 2 mm more anteriorly than the one from Vandewalle et al. After an unblinded follow up from 3–17 months, there was a tic improvement varying between 24 and 79% in 15 out of 18 patients. The authors also described a good effect on behavioural disorders. As a stimulation-induced negative side effect, temporary disturbances of oculomotion were mentioned. Fifteen of these 18 patients were followed for 2 years and showed 52% tic improvement at this long-term follow-up [21].

Additionally, this same group of Servello et al. reported on 36 Tourette patients with different brain targets. In total 19 patients were followed for two years after thalamic stimulation of the CM-Pf/Vo with a 54.2% tic reduction [22].

Finally, the beneficial effect of DBS of the dorsomedial nucleus of the thalamus has been described by Vernalen et al. [24,25] in one patient. After unsuccessful DBS of the GPi, the electrodes were removed and two electrodes were implanted in the Cm-Pf complex of the thalamus. The patient showed the highest benefit with stimulation of the most dorsal contacts, which were located in the dorsomedial nucleus, with a 36% improvement of tics.

4. Clinical and surgical evaluation

4.1. Patient selection and surgical procedure

Careful patient selection is absolutely mandatory for DBS in TS [43]. The TS patients considered for DBS should comprise only very severe cases in whom tics are life threatening, result in physical disability or lead to functional impairment and cause significant impairment in quality of life. And in who have already fruitlessly received standard therapies. Several papers providing guidelines for DBS in TS [43–45] have addressed this.

Surgeons should have substantial experience in DBS treatment of movement disorders to enhance efficacy and minimize complications. The technique of DBS applied to TS is in broad lines similar to the one used for more classic indications. The target for TS, such as the nuclei of the medial part of the thalamus, is mostly invisible with current imaging techniques. Moreover, TS patients might pull themselves out of the stereotactic frame because of the high ratio of motor tics occurring in the head region. One solution would be to operate with the patient being under general anaesthesia. Because of the uncertainty of the ideal target and the importance of intra-operative findings, the patient should be cooperative during surgery. Sedating the patient to obtain tic suppression with maintenance of the possibility to communicate with the patients is preferable. The patients can be sedated with a combination of lorazepam and clonidine [12], or with a Propofol Target Controlled Infusion [42], sufficiently reducing the tics and their implications for the stereotactic procedure.

At the same time the patient can be interrogated so that acute negative stimulation-induced side effects can be detected and the position of the electrode adapted.

4.2. Peri- and post-operative evaluation

It is of paramount importance that for all TS patients treated with DBS, the exact location of the electrode is precisely determined and all effects are meticulously described. A more comprehensive survey of guidelines for the peri-operative assessment of the effects of DBS in TS can be found elsewhere [43].
First, the execution of DBS should be restricted to neurosurgical units experienced in the DBS treatment of movement disorders with established collaborations with neurological and psychiatric departments specialized in the diagnosis and treatment of TS. For the assessment of clinical effects, a description of the effect on tics, on associated behavioural disorders, the stimulation-induced side effects, and complications, are mandatory. The most commonly used scale for tic rating is the Yale Global Tic Severity Scale (YGTSS) [46]. For a more objective evaluation, the patient should also be recorded on videotape with and without stimulation. The tics should be rated on these tapes by two independent investigators. Ideally the patient and investigator are blinded to the status of the stimulation. A careful psychiatric and neuropsychological evaluation should be performed at regular intervals. The clinical effects should be correlated to the exact position of the electrode. The most prudent approach is to perform a CT-scan postoperatively, and fuse these images with preoperative MR-images. Only if these prerequisites are fulfilled and a maximum of data is exchanged between centres, the optimal target can be established.

5. Complications and side effects after thalamic DBS

Two major complications have been described, consisting of a small intracranial haemorrhage in one patient resulting in vertical gaze palsy during six months and subjective changes in the velocity of upward gaze afterwards [47]. One patient had intracerebral hematomas located around both electrodes [17].

The group of Servello [22] reported on the need for repositioning of the two leads in one patient and removal of the DBS implant due to an infection along the extension cables and pulsgenerator in another patient. Two other patients required revision of surgical wounds along the extension cables because of diastasis, and two patients required surgical revision of the pulsgenerator because of infection. Finally hardware failure with monolateral extension cable rupture was documented in one patient.

Six Tourette patients have been extensively followed and described by Ackermans et al. [19]. Some side effects were noticed, especially lack of energy resulting in restriction in their daily activities and visual changes. One patient of the randomized controlled trial reported vertical gaze difficulty after thalamic DBS due to a haemorrhage at the end of the left electrode [47]. Because the thalamic target for DBS is located near the nuclei responsible for vertical gaze, trajectory planning and electrode positioning should be performed with a special focus on vertical eye movements and with extreme accuracy and caution. Aside from the proven vertical gaze disturbances, all the other included patients reported visual problems. This may not be due to ocular abnormalities but to visual processing problems. Visual processing difficulties are frequently present in TS and are thought to be most reflective of the underlying frontostriatal dysfunction [48]. Previous studies examining saccades in TS have reported however conflicting results [48]. Servello et al. [20] also reported on stimulation induced subjective vertigo, blurring of vision and upward ocular deviation after thalamic DBS. In this study however these symptoms appeared to be transient.

6. Conclusion

Given the many different targets used for DBS in TS, and the small number of patients suffering from the intractable syndrome, continuous exchange of clinical experience, and an on-going evaluation is important. A uniform approach with standard inclusion criteria and outcome measures is warranted to find out which is the most optimal target, or whether “tailored” targeting is needed, with a specific target for a specific subtype of patients, as also suggested by Porta et al. [49].

Given the consequences of TS for social, familial and professional life, patients have to deal with many challenges after surgery. Anticipating on these postoperative changes prior to surgery will be helpful to assist patients and their families in benefiting from tic reduction and maximizing the overall outcome and success of surgery.

The results of thalamic DBS in TS prove that the technique is effective in the treatment of carefully selected patients. Because of the occurrence of stimulation related side effects the search for the most optimal target is still going on. Patients treated with DBS will need long-term follow-up in order to answer questions regarding long-term efficacy, and outcome. In addition, the phenotypic variability of TS patients and various co-morbidities make it even more difficult to evaluate exactly what circuits should be modulated depending on the predominant clinical features. Given the complexity of TS and difficulties adhering to crossover protocols, future studies should consider delayed therapy
or randomization to ‘off’ or ‘on’ groups rather than a crossover design.

Determination of the optimal surgical target and stimulation parameters will require close multicentre collaboration and standardized methods for postoperative evaluations. Other questions still to be addressed are whether tolerance or hardware failure would play a role. Therefore a prospective, multicenter double-blinded study to evaluate the effects of DBS in selected Tourette patients would be the most ideal approach.

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