

DEEP BRAIN STIMULATION IN TOURETTE SYNDROME

Domenico Servello, Marco Sassi, Mauro Porta

Abstract

Objective: Tourette's Syndrome (TS) is a neurobehavioral disorder characterized by significant comorbidity that can cause severe social integration disability. For this reason and for the most striking motor features - the multiple motor and phonic tics - numerous attempts have been made with conventional and atypical antipsychotics, psychotherapies, invasive non-surgical treatments such as botulinum toxin infiltration, and recently with Deep Brain Stimulation (DBS).

Method: Authors report their experience with the largest series of patients affected with highly severe TS with a proved resistance to all therapeutical modalities. After a vigorous screening phase, DBS was deemed indicated for these patients, and showed during the follow-up examinations a significant improvement in all the evaluation scales considering tic manifestations and comorbid features.

Results and conclusions: The Yale Global Tic Severity Scale, in particular, documented an improvement from 41.1 ± 8.3 prior to DBS, to 28.6 ± 17.5 post-DBS ($p < 0.001$).

Along with a description of the adopted DBS technique and of the main study results, key findings related to the most important features of pre- and post-surgical management of these patients are presented in terms of (1) appropriate patient selection for DBS, (2) choice of the most indicated target for DBS on the basis of clinical manifestations, and (3) post-treatment evaluation and management, with particular regard to patient's and caregiver's compliance.

Key Words: Tourette's syndrome, tics, atypical antipsychotics, deep brain stimulation

Declaration of interest: none

Domenico Servello, MD, Marco Sassi, MD, Mauro Porta, MD
Functional Neurosurgery Unit, IRCCS Galeazzi, Via Galeazzi 4, 20161 Milano

Corresponding Author

Marco Sassi MD
Functional Neurosurgery Unit,
IRCCS Galeazzi, Via Galeazzi 4, 20161 Milano
dr.sassi@yahoo.it

Introduction

Tourette's syndrome (TS) is a chronic, neuro-behavioral disorder characterized by motor and phonic tics that persist for at least 12 months, with a waxing and waning course (Robertson 1998-2000, ICD-10, 1992, DSM-IV-TR 2000).

Another feature of the syndrome is its high comorbidity that may include attention-deficit-hyperactivity disorder (ADHD), obsessive-compulsive behavior (OCB), anxiety, and depression (Jankovic et al. 2001, Robertson 2000), to a point that it has been documented that only 12% of clinic TS patients had no comorbid psychopathology (Freeman et al. 2000). Chronic treatment is usually required if TS interferes to normal social functioning of these patients, even though TS may be self-limiting (Leckmann et al. 2002): it involves neuroleptics, adrenergic agonists, and dopamine agonists. Behavioral treatment using techniques such as habit reversal training has been shown to be effective as well. Nevertheless, symptoms

may be refractory to any conservative treatment and cause severe distress (Ackermans et al. 2006).

Conservative treatment

All patients involved in the study received a pharmacological trial under our supervision. A dopamine depletor such as Tetrabenazine was tried for all the patients (Porta et al. 2008), while a selective serotonin reuptake inhibitor (fluvoxamine up to 100 mg/day) was also administered for obsessive-compulsive comorbidity, alone or in association with clorimipramine up to 100 mg/day. Therapeutical algorithm was based on typical and atypical antipsychotics. Attention deficit-hyperactive disorder (ADHD) was treated with clonidine 75 to 150 mg per day or guanfacine 5 mg or higher per day. An informed written consent was signed by all patients concerning risks and benefits of the inclusion in the therapeutic algorithm. Indication to invasive non-surgical procedures (such

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as botulinum toxin injections) and behavioral treatment was posed on the basis of refractory tics or persistent behavioural manifestations highly interfering with quality of life.

International surgical experience

Since 1955, numerous attempts to treat these patients through various neurosurgical procedures have been made (Temel et al. 2004): a trend towards the development of guidelines for indication to DBS has been advanced, but there is still a lack of widespread agreement in the field (Mink et al. 2006). In fact, during recent years various International Centers (Van Der Linden 2002, Vandewalle et al. 1999, Shahed et al. 2007, Flaherty et al. 2005, Diederich et al. 2005, Houeto et al. 2005, Ackermann et al. 2006, Maciunas et al. 2007, Vandewalle et al. 2003) have published their experience with DBS in TS cases demonstrating refractoriness to conservative treatments. Anyway, their experience is almost solely presented on the basis of efficacy over tic manifestations, while scarce or no importance is given to behavioral comorbidities. Other authors nowadays consider Deep Brain Stimulation (DBS) in TS a possible example of surgery applied to behavioural disorder (Larson 2008), and some other experienced centers develop their own guidelines (Servello et al. 2008) considering both the behavioural and the motor features of TS.

Finally, a low but not negligible morbidity and mortality rate (Limousin et al. 1999, Beric et al. 2001, Kondziolka et al. 2002, Oh et al. 2002, Umemura et al. 2003, Lyons et al. 2004) has been documented.

The experience of the TS and Movement Disorders Center at the IRCCS Galeazzi

Starting from November 2004, 36 patients among those diagnosed with Tourette's Syndrome and documenting refractoriness to conventional and innovative treatments (refractory Tourette Syndrome, rTS) were operated for DBS at our dedicated Tourette Clinic (Table 1). Inclusion evaluation guideline is presented in Table 2. In order to be eligible for DBS, patients should demonstrate compliance with previous treatments. Compliance was assessed in terms of (1) adherence to pharmacological protocols, (2) completion of follow up visits, and (3) adherence to psycho-behavioral training programmes.

Patients were followed in an open protocol with fixed endpoint evaluations every 3 months. Among these, 8 patients were females (22%), and average age was 32 years (range 17-57, SD 10,65). Average schooling was 10 years in our sample (range 8-17, SD $\pm 2,43$). Preoperative screening included routine blood tests, chest X-rays if the patient was above 40 years old, and detailed clinical and neurologic evaluations.

Assessments were performed through a ten point scale for quality of life (VAS, Visual Analogue Scale, average value 8,88, range 5-10, SD 1.35, the patient was asked to rate the amount of influence of TS symptoms on social functioning, being 10 a complete interference with no possible social integration at all,

and 0 no influence at all), the BDI (Beck Depression Inventory, average value 27, range 15-48, SD 9.62), STAI (State-Trait Anxiety Inventory, average value 47, range 15-80, SD 12.29), Y-BOCS (Yale-Brown Obsessive-Compulsive Scale, average value 21.27, range 0-38, SD 10.39), and YGTSS (Yale Global Tic Severity Scale, average value 74.49, range 42-97, SD 12.19).

In 34 cases the thalamic intralaminar/ventralis oralis (Vo/CM-Pf) was targeted with the following coordinates: 5 mm lateral to the AC-PC line, 2 mm below the midpoint of the AC-PC line, on the AC-PC plane. One patient was treated at Vo-CM/Pf and Nucleus Accumbens- Anterior limb of the internal capsule (ALIC-NA) bilaterally during the same surgical session and finally another patient was treated solely at the ALIC-NA because of prevalent psychobehavioral comorbidities.

All cases except one received bilateral DBS: this patient, because of abnormal vasculature in the left hemisphere, was not implanted and received monolateral DBS at the right Vo/CM-Pf. One patient was treated at the posterior globus pallidus internus (Gpi) because of prevalent dystonic tic manifestations.

Rescue Surgery

In one case, we implanted the posterior "motor" Gpi in order to address the dystonic tics expressed by the patient: positive effects on tics were recorded, but considering the persistent behavioural comorbidity, a second DBS procedure for bilateral lead insertion in the ALIC-NA was accomplished after the hypotheses of Brito in 1997. Other 2 patients received this "rescue surgery" procedure after a standard Vo-CM/Pf procedure because of persistent comorbidity.

Surgical Technique

Neuronavigation-assisted (Stealthstation-Medtronic) trajectory planning was based on computed tomography (CT) – Magnetic Resonance Imaging (MRI) fusion. The Schaltenbrand-Wahren atlas was in turn fused with the contrast enhanced, 1MM sliced, 1,5 Tesla MRI.

Three-channel simultaneous micro-recording (high impedance, tungsten bipolar – Inomed MER system) was accomplished from 6 mm above the target point, ending 1.5 mm below the target at 0,5 mm steps, with the following features: 500-5000 MHz filters, cut-off 200 microV/div, 100 ms/div sweep.

Model 3387 (Medtronic, Minneapolis, MN) was implanted as definitive electrode.

Lessons Learned in Tourette Syndrome Treatment

Although DBS has shown potential in the treatment of refractory Tourette's syndrome, there are numerous issues that need to be further clarified, encompassing the fundamental moments of posing indication to DBS, choosing the proper target for the

Table 1. Demographical baseline data of the 36 patients treated with DBS

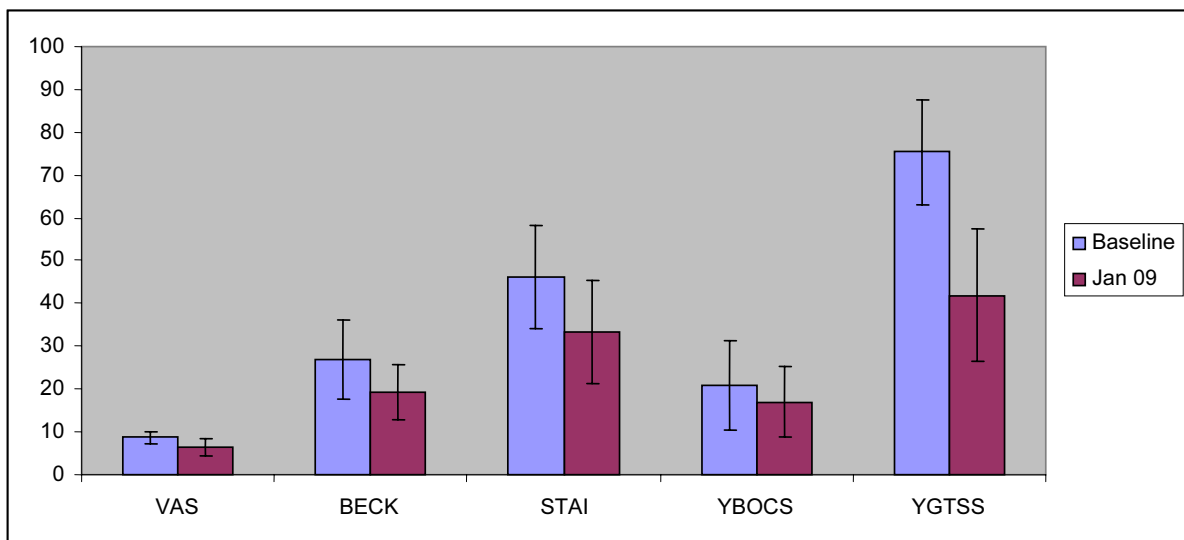
N° of pts	Sex m/f	Left/right dominance	Age at DBS	Years of schooling	First DBS date	Target of first procedure	ALIC-NA second procedure date	VAS	BDI	STAI	YBOCS	YGTSS
1	m	Right	24	10	nov-04	Vo/CM-Pf		10	31	45	32	95
2	m	Right	24	13	nov-04	Vo/CM-Pf	Sept 07	10	15	51	23	79
3	m	Right	46	12	dec 04	Vo/CM-Pf		9	28	80	31	97
4	m	Right	37	13	jan 05	Vo/CM-Pf		8,5	26	48	10	63
5	m	Right	19	10	Mar-05	Vo/CM-Pf		5	17	35	27	77
6	f	Right	28	13	apr-05	Vo/CM-Pf		6,5	48	45	28	63
7	m	Right	33	8	May 05	Vo/CM-Pf		6,5	38	43	21	89
8	m	Right	17	10	May 05	Vo/CM-Pf		8	33	43	16	91
9	m	Right	34	8	july 05	Vo/CM-Pf		8	44	52	36	91
10	m	Right	30	8	Sept 05	Vo/CM-Pf		8	36	35	17	66
11	f	Right	42	8	oct 05	Gpi	Sept 07	10	42	65	34	71
12	f	Right	31	10	oct 05	Vo/CM-Pf		8	33	48	17	66
13	m	Right	46	13	oct 05	Vo/CM-Pf		8	36	51	22	69
14	m	Right	19	11	oct 05	Vo/CM-Pf		10	25	38	28	72
15	m	Right	29	8	feb-06	Vo/CM-Pf		10	23	30	23	92
16	m	Right	31	13	feb-06	Vo/CM-Pf		10	16	15	0	42
17	m	Right	30	13	feb-06	Vo/CM-Pf		10	26	30	8	82
18	f	Right	20	8	Mar-06	Vo/CM-Pf		10	33	42	25	78
19	m	Right	18	10	Mar-06	Vo/CM-Pf		9	48	60	26	79
20	f	Right	31	8	May 06	Vo/CM-Pf	Sept 07	10	24	44	38	79
21	f	Right	45	8	Sept 06	Vo/CM-Pf		6,5	26	45	5	56
22	m	Right	37	13	dic-06	Vo/CM-Pf	dic-06	10	29	49	38	86
23	m	Right	22	8	feb-07	Vo/CM-Pf		10	29	36	13	82
24	m	Right	18	8	feb-07	Vo/CM-Pf		10	17	59	21	75
25	m	Right	39	8	apr-07	Vo/CM-Pf		8	15	47	12	75
26	m	Right	25	13	apr-07	Vo/CM-Pf		8,5	18	69	14	64
27	m	Right	24	8	lug-07	Vo/CM-Pf		8	18	41	21	70
28	f	Right	18	11	lug-07	Vo/CM-Pf		10	19	44	6	68
29	m	Right	57	8	lug-07	Vo/CM-Pf		10	24	48	31	80
30	m	Right	47	13	lug-07	ALIC-NA		10	22	54	35	94
31	m	Right	42	8	ott-07	Vo/CM-Pf		7	24	52	21	68
32	m	Right	40	8	feb-08	Vo/CM-Pf		10	16	34	3	65
33	m	Right	46	8	lug-08	Vo/CM-Pf monolat		8	16	55	20	78
34	f	Right	47	13	lug-08	Vo/CM-Pf		10	25	41	17	74
35	m	Right	25	8	nov-09	Vo/CM-Pf		10	15	48	17	68
36	m	Right	25	17	dec-09	Vo/CM-Pf		9	14	30	11	54

Legenda: Vo/CM-Pf = thalamic intralaminar/ventralis oralis target, ALIC-NA = nucleus accumbens, Gpi = posterior globus pallidus internus, monolat = monolateral DBS procedure

Table 2. Algorithm for the evaluation for indication to DBS

FEATURES	INCLUSION CRITERIA	EXCLUSION CRITERIA
Diagnosis	Diagnosis made by trained psychiatrists with DSM-IV-TR	Other DSM-IV-TR Axis 1 disorders
Clinical characters	YGTSS ≥ 35 , motor tic subscore ≥ 15	Treatment-related or iatrogenic tic disorder
	TS causing SIB distress, harm	Suicide attempts
	Compliant, able to provide informed consent	Cognitive dysfunction, dementia, or not compliant
Therapeutical issues	Medical refractory after 6 months adequate treatment for tics and comorbid features	Substance abuse
Pre-surgical evaluation	Judged able to withstand surgery after careful evaluation	Previous brain surgery
		Poor medical conditions
		Abnormal imaging examinations

Figure 1. Baseline and follow-up evaluations in main outcome measures of the sample of patients with TS treated with DBS



specific clinical manifestation exhibited by the patient, and postoperative evaluation and follow-up of the patient. These topics will be now presented in details.

Patient selection

The American Tourette’ Syndrome Association (TSA) has already published inclusion criteria guidelines (Mink et al. 2006). Nevertheless, indication to treatment is difficult, when dealing with behavioural comorbidities and poor compliance to treatment. This last issue in particular is related to the unrealistic expectations the patient devotes to DBS. What is nowadays a widespread orientation is that DBS has to be considered an adjunctive therapeutical modality, the

aim of which is to enforce the results of conservative measures of treatment. The definition of “patient refractory to conservative treatment” is still to be defined, and is to date left to the different treatment guidelines of the various groups.

Age of the patient is among the features to be discussed in inclusion guidelines. Spontaneous remission has been shown to occur in almost 50% of patients by the age of 18 years (Leckman 2002). This observation could lead to the decision to delay treatment, even though it is during these years that most of the social integration abilities are developed by the patient (Mink et al. 2006). In our Center, one patient was treated at the age of 17 (with parental consent), due to a severe uninterrupted pattern of refractory tics that we described as “status ticcosus” from its similarity

with the crises bursts of the epileptic patients in “status oepilepticus” (Servello et al. 2008).

Considering the psychobehavioral evaluation of the patient, the use of projective diagnostic tests – such as the Machover draw-a-person test (Nogueira Rivero 1960) might be helpful. This test allows to elucidate the self perception, and to evaluate how the subject feels the parts of the body. The Premonitory Urges for Tic Scale [PUTS] (Woods, Piacentini et al. 2005) is a good instrument to assess the feeling and sensations experimented before the tic. These tests could help to identify subjects with somatophobia, hypochondria, alexitimia or somatization that could require particular attention in the postoperative period, or be considered as an exclusion criteria to DBS.

Unfavourable opinions on the outcome of DBS treatment have been reported by two of our series of 36 patients (5,5%), despite statistically significant improvement in the evaluation scales, and detailed preoperative explanations of features and risks of the surgical and post-surgical evaluation. Figure 1 documents the statistically significant improvement in all the evaluation scales used at follow-up evaluation: in particular, VAS at the baseline averaged 8.83 and 6.39 at last follow-up, BDI changed from 27 to 19.25, STAI from 46.23 to 33.16, YBOCS from 20.90 to 17.06, and YGTSS from 75.35 to 41.84.

To our opinion, these negative judgements stem from excessive expectations regarding the magnitude of treatment effect.

A similar lack of satisfaction has also been reported after DBS in patients with Parkinson’s disease, despite clinical improvement (Tir et al. 2007). Psychological evaluation should specifically address this feature in the preoperative evaluation.

It has nevertheless become evident in our experience that YGTSS does not accurately describe the importance of comorbidities and the degree of social impairment and may be inadequate as a criterion for inclusion in a surgical trial. Similarly, videotaping must now be considered insufficient for the evaluation of patients with Tourette’s syndrome as potential candidates for surgery, and should no longer be used as a determining criterion for inclusion in a surgical trial. Logical next steps for the evaluation of patients with Tourette’s syndrome for DBS include defining the characteristics of the candidate patients.

The technique is in our opinion to be considered as an add-on measure over conservative pharmacological, behavioural and invasive non-surgical manoeuvres when tic severity and social impairment are high: our guidelines state a cut-off at a total YGTSS score ≥ 49 , with a YGTSS social impairment sub-item >30 .

Choice of target

The exact neuronal circuitry responsible for symptoms and comorbidities is yet to be determined, as no animal models for TS have been realized to date (Jankovic 2001, Mink, Walkup et al. 2006). An algorithm considering multiple targets could answer the wide interpatient variability in symptoms and comorbidities.

One of the most commonly used targets for DBS

in the treatment of Tourette’s syndrome, the centromedian-parafascicular complex (CM-Pf), part of the intralaminar nucleus of the thalamus, is involved in sensorimotor basal ganglia circuitry (Krauss et al. 2001, Houeto et al. 2005). The anterior CM-Pf influences cells involved in tremor generation located in a wide area including the ventral oral anterior and posterior (VoA and VoP) nuclei (Katayama et al. 2005). The intralaminar nuclei and CM-Pf convey multimodal stimulatory signals to the striatum, and are thus involved in attention and arousal in response to stimulation. Stimulation of the CM-Pf and VoA complex has proved to be effective in the treatment of behavioural aspects of Tourette’s syndrome as well as alleviation of tics (Servello et al. 2008). In our study, the mean total Yale Global Tic Severity Scale (YGTSS) scores were reduced from 41.1 ± 8.3 prior to DBS, to 28.6 ± 17.5 post-DBS ($p < 0.001$) and similar reductions were seen in YGTSS motor, phonic and social impairment scores (all $p < 0.001$ vs. baseline). In a recent case report, a woman with severe TS refractory to DBS of the anterior internal capsule achieved significant improvement in tic control at 3 months following bilateral CM-Pf stimulation (reduction in total tic score: 42% and a reduction in psychiatric side effects such as altered mood and impulse control were documented when compared with internal capsule stimulation (Shields et al. 2008).

The posterior part of the GPi acts as a relay for output pathways of the basal ganglia, and continuous high frequency stimulation of this region has been shown to ameliorate dystonia (Benabid et al. 1998, Pralong et al. 2003, Bittar et al. 2005, Vidailhet et al. 2005, Hamani and Moro 2007). Stimulation of the GPi is able to modify the neuronal activity of the VoA nucleus (Hassler and Dieckmann 1970, Pralong et al. 2003). The VoA nucleus is involved in initiating planned movement and suppressing unwanted movement, whereas the VoP nucleus plays a role in the sensations of touch, itch, temperature, taste and arousal, in addition to body position.

The nucleus accumbens is presumed to have a modulatory activity on amygdaloid basal ganglia-prefrontal cortex circuitry and, as the activity of its neurons is modulated by dopamine and a high proportion of cells have high concentrations of dopamine D1 and D3 receptors, the nucleus accumbens is believed to be involved in addiction and obsessive compulsive disorder (OCD) as well (Sturm et al. 2003). The effectiveness of DBS of the nucleus accumbens has been demonstrated in patients with severe OCD and anxiety disorder (Sturm et al. 2003).

Even though CM-Pf is often considered the preferred target for DBS (Houeto et al. 2005, Servello et al. 2008), alternative locations such as the ALIC-NA and the Gpi might be superior in addressing specific features of the clinical picture of TS, and thus be preferred over more “classical” targets when the clinical picture of the specific patient is dominated by a characteristic manifestation. Favourable outcomes in patients with Tourette’s syndrome have been reported with DBS of both the nucleus accumbens and the GPi (Vandewalle et al. 1999, Van der Linden et al. 2002, Visser-Vandewalle et al. 2003, Diederich et al. 2005, Flaherty et al. 2005, Houeto et al. 2005, Ackermans et

al. 2006, Kuhn et al. 2007, Shahed et al. 2007, Welter et al. 2008).

Recently, in a double-blind, randomized study in three patients with severe, refractory Tourette's syndrome, bilateral stimulation of the GPi produced a significant and greater reduction in tic severity (assessed using the YGTSS) than stimulation of the CM-Pf (Welter et al. 2008).

In a 37-year-old woman with severe refractory Tourette's syndrome, DBS administered to the anterior limb of the internal capsule (electrode terminating in the nucleus accumbens) provided significant reduction in tic frequency and severity at 18 months after surgery (Flaherty et al. 2005). Tic reduction was also shown following DBS of the nucleus accumbens in a 26-year-old male patient with severe tics and self-injurious behaviour (SIB); coprolalia and tics involving self-harm were almost completely resolved (Kuhn et al. 2007).

The optimal area for the final DBS electrode implantation within the chosen target nucleus was studied with intraoperative microrecordings in at least two monopolar electrode tracks, acquired at steps of 1–0.5 mm from 8–10 mm above to 1 mm below the neuroradiologically estimated position of the target nucleus. Studies are in progress in order to evaluate recognizable firing patterns which may characterize a neurophysiological target thus increasing DBS precision.

Post-operative evaluation

A complete neurological, psychiatric and neurophysiological evaluation, including a comparison between pre- and postoperative magnetic resonance imaging (MRI) to assess correct location of the definitive lead is suggested. However, Visser-Vandewalle and colleagues (Visser-Vandewalle 2007) suggest that CT should be preferred over MRI as the latter may produce unwanted effects. We performed a CT scan in the immediate postoperative period to assess immediate complications such as hemorrhagic events, while MRI has been performed in the postoperative period to all of our patients without any side-effects.

Postoperative evaluation in our protocol included the YGTSS and the Modified Rush Video Rating Scale (MRVRS) (Leckman et al. 1989) for tics. Comorbid behavioural symptoms are assessed with the YBOCS for OCD (Goodman et al. 1989 a and b), the State Trait Anxiety Inventory (STAI) for anxiety (Bertolotti 1987), the Beck Depression Inventory (BDI) for depression (Beck et al. 1987), while a ten-points Visual analogic Scale (VAS) is considered sufficient for patients to rate the extent of impairment in social functioning they consider dependent to TS (De Boer et al. 2004) along with a complete neurological and psychological evaluation at each endpoint.

Average follow-up was 29.4 months. Statistical analyses were performed using SPSS 12.0 (SPSS Inc, Chicago, Illinois).

Two-sided Student's *t* test for Gaussian distributions and Wilcoxon's non-parametric test were used to compare baseline and FU data, demonstrating statistically significant differences between baseline values and values collected two years after surgery.

These improvements in all the evaluation scales proved to be stable at latest follow-up evaluation.

Comparisons between preoperative, two years' follow-up and last follow-up were performed by generalized linear model (GLM) for repeated measurements.

Among the adverse events documented in literature on patients treated with DBS for refractory TS, there is vertical gaze palsy in one patient (Ackermans et al. 2007) and dissociation in another (Goethals et al. 2008). No reports of symptomatic intracranial hemorrhage have been made to date.

Although a monthly check for optimization of setting following DBS is accepted for the vast majority of movement disorders, it is our experience that a more elastic schedule for TS patients is required, because of the great interpatient variability concerning response to treatment, fluctuations in symptoms and patient's expectations: some patients require more frequent adjustments in order to achieve stable optimal settings. Despite clinical improvement determined by videotaping using the MRVRS (Goetz et al. 1999) and use of neurological scales such as the YGTSS, in younger patients (age <30 years) a greater trend towards dysregulation was noted in 7 out of 18 patients treated with DBS and followed for 6 months or more in our previous study (Servello et al. 2008). These patients required a more frequent adjustment of stimulator settings after surgery. The cause of this interpatient variation is not clear, but the trend towards an association between more frequent dysregulations and a younger age would represent an argument for delaying initiation of DBS in younger patients. It should nevertheless be noted that the prevalence and severity of tics and the behavioural and emotional comorbidities observed in Tourette's syndrome are both higher in younger patients (Leckman et al. 2006, Chang et al. 2008) and so this population could be deemed more likely to benefit from DBS. In addition, tics and comorbidities in young people with Tourette's syndrome have a strong association with social impairment, expressed as work/school disability and social stigma (Ohm 2006). Finally, in a disease as complex as Tourette's syndrome, the importance of a dedicated centre with an experienced multidisciplinary team for achievement of optimal outcomes with DBS cannot be overstated. The functional neurosurgeon, the neurologist, psychiatrists and psychologists should all collaborate closely in the decision-making process from appropriate selection of patients, to the choice for conservative treatment or surgery.

Conclusion

DBS is generally considered a safe technique for conservative treatment-refractory TS. Our experience demonstrates an overall efficacy in terms of the different targets adopted. Nevertheless, there are numerous issues still to be resolved: (1) first of all the delineation of precise requirements for an "ideal" Medical Center for treatment of refractory TS, (2) the establishment of reliable inclusion criteria and indication to treatment guidelines, and (3) the selection of precise DBS targets for different clinical features, along with (4) a more

precise neurophysiological characterization of the thalamic targets.

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