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REVIEW ARTICLE

Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up

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Abstract
Background Eighteen patients with severe and refractory Tourette Syndrome underwent bilateral thalamic deep brain stimulation. The surgical procedures and stimulation processes of the cohort were reported in 2008; the 2 year follow-up was reported in 2009. The aim of the research is the assessment of long-term outcome (5–6 years) on tics, obsessional behaviours, anxiety, mood, and on the overall general health of the patients and their general satisfaction.
Method In this study, all 18 of the original patients will be discussed, pre- and post-DBS, according to our protocol using standardized objective schedules, as well as the clinical impressions of both clinicians and patients. As there were no substantial nor statistical differences on measures of cognitive functioning between pre-DBS and 2 year follow-up, we decided not to continue this aspect of the formal assessment, particularly as there were also no clinical indications.
Results At 5–6 year follow-up, there was a significant reduction in tic severity ($p<0.001$), and significant improvements in obsessive compulsive behaviours ($p=0.003$), anxiety ($p<0.001$) and depressive ($p<0.001$) symptoms. Patients, in general, required less medication for tics, co-morbid conditions and/or co-existent psychopathologies. The long-term outcome/satisfaction were not unanimous between patients and the medical team.
Conclusions At long-term follow-up, DBS was very successful in terms of a significant improvement in tics and also a significant reduction in the potentially disabling symptoms of obsessionality, anxiety and depression. However, compared with our more positive overall results at 2 years, these later results demonstrate long-term difficulties as follows: non-compliance, long-term complications , and the differences in the opinions between the (a) medical, (b) the surgical teams and (c) the post-DBS patients as to their outcome/satisfaction with the procedures. Our experience highlights the need for controlled studies, for long-term follow up, and the need to improve the selection of patients for DBS.

Keywords Deep brain stimulation · Tourette syndrome · Follow-up · Psychopathologies

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Introduction

Gilles de la Tourette syndrome (GTS) is a childhood onset neuropsychiatric movement disorder, characterized by multiple motor and one or more vocal (phonic) tics lasting longer than a year. Associated co-morbid conditions are obsessive-compulsive behaviors (OCB) and disorder (OCD) and attention deficit hyperactivity disorder (ADHD), whilst co-existent psychopathologies including anxiety and depression which occur in approximately 90 % of clinical and community cohorts [35, 36]. For the majority of moderate to severely affected patients, medications are the mainstay of treatment and these include both "typical" and "atypical" neuroleptics (e.g. haloperidol, pimozide, sulpiride, tiapride, aripiprazole),

clonidine, guanfacine and tetrabenazine. For the OCB/OCD and depression, the antidepressants (particularly the selective serotonin reuptake inhibitors—SSRIs) are used; whilst for ADHD symptoms, clonidine, guanfacine, stimulants (e.g. methylphenidate) and atomoxetine are prescribed [34, 35, 36, 44]. Comprehensive Behavioural Intervention for Tics (CBIT) has also been shown to significantly reduce symptoms [30], which includes Habit Reversal Training (HRT) [61].

In severe adult GTS, deep brain stimulation (DBS) is currently being used and investigated for patients who are refractory to medication and other therapies. In the 13 years since the first GTS DBS report from the pioneering Dutch Flemish Group [55], there have been numerous papers, including many reviews. Summarising from two recent and comprehensive reviews [12, 28], and three subsequent case reports [13, 42, 43], there have been approximately 104 GTS patients who have received DBS in over 20 centres worldwide. We are stating that *approximately* 104 GTS patients have been stimulated, as Hariz & Robertson [12] noted that some centres have reported what seemed to be the same/similar cases more than once.

Nine different brain targets for DBS, including the thalamus [medial portion at the cross point of the centromedian nucleus (CM)] with the ventralis oralis pars intermedia (Voi), the medial portion of the thalamus [CM-parafasicularis (Pf)], the globus pallidus pars interna (GPi), the posteroventrolateral GPi, the anteromedial GPi, the nucleus accumbens (Nac) and the ventral caudate and anterior internal capsule, have been stimulated [12, 28, 32]. With regards to targets in DBS for GTS, an interesting paper was that of Martinez-Fernandez et al. [24], who documented their experiences using DBS on five patients with GTS targeting *subregions* of the globus pallidus internus (GPi). They reported a reduction in tic severity overall, but noted that the response was variable. In addition, their results suggested that the anteromedial GPi was superior to the posteroventral area. However, Pansaon Piedad et al. [28] noted that the most common and promising targets were the globus pallidum and the thalamus. Hariz & Robertson [12] were unconvinced about recommending a unanimously agreed upon specific DBS target in GTS.

There are only three papers which have published double blind trials (DBT) and used evidence based criteria, with the first two including a total of eight patients [22, 59], included in the third one by Hariz & Robertson [12]. Subsequently, the pioneers in GTS DBS (the Dutch Flemish Group) had also published a long-term outcome paper (6–10 years), and their general conclusions were that bilateral thalamic DBS may provide sustained tic benefit after at least 6 years, but they were cautious as to overall outcome. They highlight the need for improved preoperative assessment and selection procedures, as well as postoperative psychosocial adaptation. The same group [3] then published results of a DBS crossover trial using thalamic stimulation in six patients (eight enrolled but two were not included in the study). The primary outcome measure was a change in tic severity using the Yale Global Tic Severity Scale (YGTSS): the effect of stimulation after surgery showed significant improvement (49 %) on the YGTSS ($p=0.028$) when compared with pre-operative assessments. The secondary outcome measure did not show any group effect between ON and OFF stimulation at 1 year postoperatively. Of interest is that tic severity was significantly lower *during* ON stimulation when compared to OFF stimulation. Cognitive re-assessment at 1 year after surgery showed that patients required more time to complete the Stroop Colour Word Card Test (which measures selective attention and response inhibition). Side effects included one small haemorrhage ventral to the tip of the electrode, one infection of the pulse, subjective gaze disturbances and reduction of energy levels in all patients. The authors felt that the DBS was successful (tic severity reduced), but highlighted the substantial side effects, and thus recommended further DBT of DBS using different targets.

Despite a debate over the definition of "refractoriness" and a recommendation of the need for a final definition [28], there have been general clinical sensible practices advocated [32], as well as suggested treatment algorithms [15]. Finally, with regards DBS in GTS patients, there have even been at least five "guideline" papers [6, 25, 26, 33, 57], targeting potentially different audiences, e.g. European [26]. Overall, it appears that the target selection is still under debate.

In summary, since the first DBS in patients with GTS was documented in 1999 (that is, at least 13 years ago) a plethora of single case reports, small series, short term outcome papers, and three DBS have been published (patients numbering a total of approximately 104 GTS patients receiving DBS), as have numerous reviews and "guidelines". We decided, as we have a large cohort of patients ($n=18$), to document our experiences with a 5–6 year follow-up which will be the longest on a substantial number of patients.

Methods and materials

Eighteen patients were recruited from our Milan-Bergamo based dedicated GTS clinic (see Table 1), satisfying DSM-IV-TR [4] and ICD-10 [62] criteria. The results of the original study, describing the surgery and stimulation of the 18 GTS patients, were documented fully by Servello et al. [46]. Subsequently, we reported a 2 year follow-up, in which 15 patients were described [31], highlighting the reduction in tic severity, as well as significant improvements in obsessive-compulsive symptoms/behaviours (OCS/OCB), reductions in anxiety and depressive symptoms,

Table 1 Demographic, clinical and medication data on the long-term follow-up of DBS GTS patients

N°	Sex	Age (years)	Age (years) at tic onset	Date of DBS	Assoc features (Pre DBS)	Date of most recent assessment post DBS	Pharm treatment pre DBS (ever)	Pharm treatment post DBS
1	M	24	5	Nov 2004	OCB aggr SIB ADHD	May 2011	Tetra; Pim; Fluvox	NIL
2	M	24	4	Nov 2004	OCB aggr SIB	Jun 2011	Tetra; Pim; Sulp; Clon	Pim; Aripip; Sertraline
3	M	47	7	Dec 2004	OCB aggr SIB	Jan 2010	Tetra; Pim; Sulp; Fluvox	NIL
4	M	37	10	Jan 2005	Depr	Jan 2011	Pim; Fluvox	Pim
5	M	19	10	Mar 2005	NIL	Jul 2011	Tetra; Pim; Tiapr; Fluvox; Clon	NIL
6	F	28	12	Apr 2005	NIL	Feb 2011	Tetra; Hal; Fluvox	Sulp
7	M	33	10	May 2005	OCB aggr SIB	Mar 2011	Pim; Fluvox	Pim
8	M	17	6	May 2005	NIL	Jan 2011	Tetra; Pim; Fluphen; Fluvox; Guan	NIL
9	M	34	4	Jul 2005	OCB aggr SIB	Nov 2010	Tetra; Pim; Fluphen; Fluvox	Pim; Aripip
10	M	30	9	Sep 2005	OCB aggr SIB	Jan 2007	Tetra; Pim; Fluvox; Clon	NIL
11	F	31	8	Oct 2005	OCB aggr	May 2011	Tetra; Pim; Fluvox	Tiapr
12	M	46	10	Oct 2005	OCB	Jan 2011	Pim; Tia; Fluvox	Pim
13	M	19	10	Oct 2005	NIL	May 2011	Tetra; Pim; Hal; Fluphen; Fluvox	NIL
14	M	23	6	Feb 2006	SIB	Mar 2011	Tetra; Pim; Fluphen; Fluvox	Pim; SSRI; Baclofen
15	M	31	7	Feb 2006	SIB depr	Mar 2011	Tetra; Pim; Hal; Fluphen; Fluvox	Pim; Aripip
16	M	30	10	Feb 2006	Depr	Feb 2011	Tetra; Sulp; Tia; Fluphen; Fluvox	Pim; Aripip
17	F	20	7	Mar 2006	OCB	Apr 2011	Tetra; Pim; Hal; Fluphen; Fluvox	NIL
18	M	18	6	Mar 2006	SIB aggr	Mar 2011	Tetra; Pim; Sulp; Fluphen	Pim; Tiapr

In particular, pharmacologic treatment of GTS patients is reported before DBS (PRE DBS) and in the most recent assessment (POST DBS)

OCB (Obsessive Compulsive Behaviours); ADHD (Attention Deficit Hyperactivity Disorder); SIB (Self-Injurious Behaviours); aggr (aggression); depr (depression); Tetra (Tetrabenazine); Pim (Pimozide), Sulp (Sulpiride), Tiapr (Tiapride), Aripip (Aripiprazole), Fluphen (Fluphenazine); Hal (Haloperidol); SSRI (Selective Serotonin Reuptake Inhibitor); Fluvox (Fluvoxamine); Clon (Clonidine)

*Patient N° 3 died in March 2010 of DBS-unrelated causes

**DBS explantation: patient N° 6 in November 2009; patient N° 13 in November 2008; patient N° 18 in December 2009

and a subjective perception of improved social functioning and quality of life. Finally, there were no substantial differences in cognitive functioning before and after DBS.

In the 2 year follow-up, three patients were excluded, but, as they are included in this report, they deserve mention in the methods. The first two patients, who were not included in the 2 year follow-up, were numbers 6 and 13 (see Table 1): they had both asked to withdraw from the study at the time, because they requested switching off/removal of the device. Both of these patients subsequently returned to the clinic, and thus to the study and the follow-up protocol. In our 2-year follow-up we also did not include patient number 16 (see Table 1), as both the patient and ourselves were dissatisfied with his DBS results. Thus, after verifying the correct position of the thalamic electrodes, we concluded that the thalamic DBS had not worked, and so we had recommended further DBS intervention targeting the anterior (limbic) GPi. In fact, he refused the GPi DBS, then requested we switch off the device, and he left our hospital to explore further interventions. The other hospital did not pursue the DBS, but gave him more medication without success. He subsequently returned to our clinic and rejoined the DBS programme.

In this long-term (5–6 years) prospective follow-up study, all 18 of the original patients will be discussed, pre and post DBS according to a protocol using standardized objective schedules, as well as global clinical impressions of both clinicians and patients. As there were no substantial differences on measures of cognitive function between pre DBS and 2 year follow-up, we decided not to continue this aspect, particularly as there were no clinical indications.

For the overall global assessment of improvement (See Table 3, columns 1–5) we collected data as follows. An expert (MMR) "eyeballed" *each patient's improvement* on the YGTSS and YBOCS (blind to the patient) and gave an opinion as to how the patient had responded at the assessment at the end of long-term follow-up (columns 5, 6). The two clinicians (MP & DS, once again blind to the scores) assessed the patients using global clinical impressions (Table 3, columns 7,8). In addition, the patients were asked separately how they felt they had responded (Table 3, column 9). It must be borne in mind, however, that the impressions of both MP and DS may well also have been influenced by their contact with the patients.

The patients were followed up regularly by us, from both clinical and research perspectives. The standardized rating

scales and schedules by which we assessed the patients were as follows: Yale Global Tic Severity Scale (YGTSS) [19], Yale Brown Obsessive Compulsive Scale (YBOCS) [11], the Stait Trait Anxiety Inventory (STAI) [51], and the Beck Depression Inventory (BDI) [5].

For the initial DBS procedure, patients were admitted to the neurological Department and checked 1 week after discharge. Then they were monitored monthly and no worsening of the clinical picture occurred. Over the long-term, and for those included in this report, the patients were subsequently followed up 3–4 times a year by senior medical and surgical staff; others were seen in addition, on demand.

Standard protocol approvals, registrations, and patient consents

As stated before, but we feel it important to reiterate in this communication, ethical approval was received from our institutional ethical standards committee on human experimentation, and written informed consent was obtained from all patients participating in the study.

As our population was not normally distributed, we used nonparametric statistics. We used one way repeated measures ANOVA, Holm-Sidak method [SigmaPlot 11.0 (2008) Systat Software Inc., San Jose, CA, USA]. Values of $p<0.05$ were considered significant.

Results

The demographic details of our 18 patients are shown in Table 1. The cohort included three women and 15 men. The age range was 17–47 years (mean=28.39; SD=8.93). The age at tic onset was 4–12 years (mean=7.83; SD=2.38). Other demographic data such as the education level of the patients, the duration of tics of GTS prior to DBS, the pre DBS Diagnostic Confidence Index [40] scores, the age at DBS and neuropsychological assessments were all clearly documented in our previous papers [31, 46].

With regards to the co-morbid conditions (OCB, ADHD, SIB) and co-existent psychopathologies and behaviours (depression ,aggression), it can be seen (Table 1, column 6) that only four patients (numbers 5, 6, 8, 13) had “pure GTS” (ie “ tics only”). The dates of DBS (column 5) and the final follow-up assessment are also given (Table 1, column 7). Any medications the patients had taken prior to the DBS are shown (column 8), as are the medications taken at the final assessment post DBS (column 9).

The results of the standardized neuropsychiatric rating scales at baseline (pre DBS) versus the 5–6 year follow-up (post DBS), as well as percentage differences (Δ %), are shown in Table 2 and Fig. 1. In addition to a significant reduction in tic severity using the YGTSS ($p<0.001$), it can be seen that ratings also showed significant improvements in obsessive–compulsive behaviours ($p=0.003$) using the YBOCS, anxiety ($p<0.001$) symptoms using the STAI, and depressive symptoms ($p<0.001$) using the BDI. In addition, it can be seen that out of the 72 result-instances, that, apart from the YBOCS in one instance in each of four patients (5, 6, 13, 14) and STAI in two instances in two patients (13, 14). *all* patients improved in their symptoms using all the rating scales (negative percentage differences: Δ %). In other words, 66/72 patients' results improved. Finally, the patients, in general, required less medication for tics and/or co-morbid conditions and co-existent psychopathologies (Table 1, column 9). Of importance and unexpectedly, the long-term outcomes/satisfactions as assessed by the medical and surgical teams and the patients' opinions were not unanimous.

With regards to the overall global assessment of improvement on tics after DBS (See Table 3, columns 5), (MMR’s “eyeballing" of YGTSS scores) it can be seen that all patients improved on the YGTSS (i.e. all patients improved with regards to their tics). However, four patients had worsened with regards to their YBOCS (obsessive compulsive behaviours; Table 3, column 6). The two neurological and neurosurgical clinicians (MP see Table 3, column 7; DS see Table 3, column 8) both thought that, overall, patients had improved, but they differed in their opinions as to how much each patient had improved, and in as many as 11/15 patients, their overall improvement impressions were different (Table 3, columns 7,8). Finally, when the patients were asked separately how they felt they had responded to DBS (Table 3, column 9), their results were once again different to all three of the clinicians’ scores. In fact, in only 7/15 patients' assessments the three clinicians (MMR, MP, DS) and the patients concur that the patients had improved, albeit to differing degrees.

The results shown in Fig. 1 also demonstrate how the GTS patients responded to the DBS with improved scores on the YGTSS (measuring tic severity), YBOCS (measuring obsessionality), BDI (measuring depression) and STAI (measuring anxiety symptomatology).

Finally, four of the original cohort of 18 will be mentioned separately. One had DBS at age 47 years, the patient was assessed at 5 years (aged 52 years), and then died of non-related causes (number 3, cancer-related death). Two patients (numbers 6 and 13) had their last assessments at 4 and 3 years post DBS, respectively, and then requested DBS cessation for personal reasons. The final patient (number 18) was advised to discontinue DBS as he had experienced numerous medical complications of DBS (e.g. infection, rejection of the pouch, probably as a result of excessive "self-grooming”). This was proposed despite the fact that when he was last assessed at 3 years, he had done very well in all of the severity ratings.

Table 2 Clinical data of GTS patients before DBS and in the most recent assessment POST DBS

N°	YGTSS Pre DBS	YGTSS Post DBS	YGTSS Δ %	YBOCS Pre DBS	YBOCS Post DBS	YBOCS Δ %	STAI pre DBS	STAI post DBS	STAI Δ %	BDI pre DBS	BDI post DBS	BDI Δ %	Total Δ %
1	92	25	−67	32	8	−60.0	45	20	−31.3	31	11	−31.7	−47.5
2	79	10	−69	23	10	−32.5	51	20	−38.8	15	4	−17.5	−39.4
3	97	25	−72	31	15	−40.0	80	20	−75.0	28	11	−27.0	−53.5
4	63	5	−58	10	4	−15.0	48	23	−31.3	26	35	14.3	−22.5
5	77	30	−47	27	28	2.5	35	20	−18.8	17	15	−3.2	−16.6
6	63	58	−5	28	35	17.5	45	28	−21.3	48	35	−20.6	−7.3
7	89	12	−77	21	8	−32.5	43	29	−17.5	38	10	−44.4	−42.9
8	88	6	−82	16	5	−27.5	43	20	−28.8	33	7	−41.3	−44.9
9	91	3	−88	36	0	−90.0	52	20	−40.0	44	3	−65.1	−70.8
10	66	15	−51	17	14	−7.5	35	33	−2.5	36	22	−22.2	−20.8
11	79	15	−64	17	5	−30.0	48	20	−35.0	33	9	−38.1	−41.8
12	59	28	−31	22	3	−47.5	51	30	−26.3	36	10	−41.3	−36.5
13	83	45	−38	28	39	27.5	38	39	1.3	25	17	−12.7	−5.5
14	95	15	−80	0	5	12.5	20	20	0.0	16	10	−9.5	−19.3
15	79	32	−47	8	1	−17.5	30	20	−12.5	26	14	−19.0	−24.0
16	92	19	−73	23	6	−42.5	30	20	−12.5	23	11	−19.0	−36.8
17	73	30	−43	25	19	−15.0	42	20	−27.5	33	16	−27.0	−28.1
18	90	25	−65	26	20	−15	60	25	−43.8	48	10	−60.3	−46.0

The Δ % is the difference in percentage between the POST DBS score and the PRE DBS score: the negative value stand for a decrease and, therefore, an improvement of the score. The TOTAL Δ % is the resultant improvement (negative value) or worsening (positive value) of the clinical assessment in the most recent assessment compared to the PRE DBS condition

STATISTICAL ANALYSIS One Way Repeated Measures Analysis of Variance, Holm-Sidak method [SigmaPlot 11.0 (2008) Systat Software Inc., San Jose, CA, USA]

YGTSS mean ± standard deviation

PRE DBS 80.83±11.98 (range 59–97) vs POST DBS 22.11±14.19 (range 3–22); ***P*<0.001**

YBOCS mean ± standard deviation

PRE DBS 21.67±9.11 (range 0–36) vs POST DBS 12.50±11.54 (range 0–39); ***P*=0.003**

STAI mean ± standard deviation

PRE DBS 44.22±13.10 (range 22–80) vs POST DBS 23.72±5.74 (range 20–39); ***P*<0.001**

BDI mean ± standard deviation

PRE DBS 30.89±9.98 (range 15–48) vs POST DBS 13.89±8.90 (range 3–35); ***P*<0.001**

Discussion

As can be seen from our data, the relevant Tables and Figure, at long-term follow-up (15 patients at 5–6 years, three patients at 3–4 years), DBS was successful in terms of a significant improvement in tics, and also a significant reduction in the disabling symptoms of obsessionality, anxiety and depression, all measured using standardised procedures/scales.

However, compared with our more positive overall results at 2 years [31], these later results demonstrate long-term difficulties as follows: (i) non-compliance with treatment, (ii) long-term complications , and (iii) the obvious differences in the opinions between the (a) medical staff, (b) the surgical team and (c) the post-DBS patients, as to their assessments/ opinions of the outcome/satisfaction with the procedures. In order that our discussion is comprehensive, yet easily understandable, we have decided to use sub-headings.

Overall long-term results of DBS on tics, co-morbid conditions and co-existent psychopathologies

Our long-term (5–6 years) follow-up results show an overall significant reduction in tic severity, as well as significant improvements in the co-morbid obsessive compulsive behaviours (OCB), and co-existing psychopathologies, such as anxiety and depressive symptomatology. With regards to the co-morbid conditions (OCB) and co-existent psychopathologies and behaviours (depression, aggression), it can be seen that the majority of our patients had a range of co-morbid conditions and co-existent psychopathologies. In

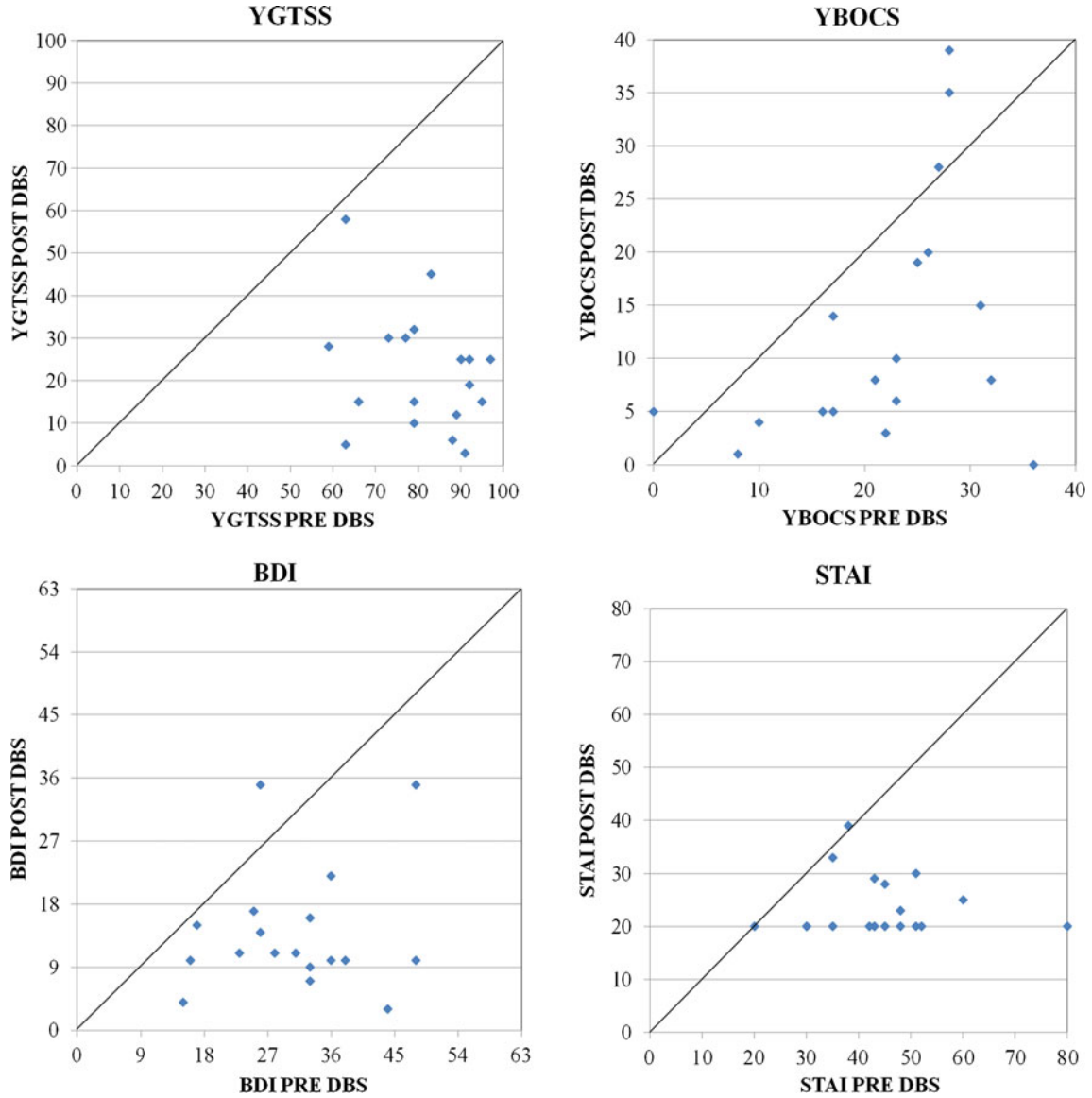

Fig. 1 Graphical representation of clinical data: the most recent assessment of the POST DBS score (vertical axis) is compared to the PRE DBS score (horizontal axis). The black line represents the unaltered condition; points over the black line stand for a score worsening; points under the black line stand for a score improvement

addition, the patients in general required less medication for their tics, co-morbid conditions and/or co-existing psychopathologies. These results are almost certainly due to the DBS, but one must also be aware of the natural progression of the disorder (improving with age and requiring less medication) [29].

Results in patients with tics only (i.e. “pure GTS”)

In fact, only four patients (numbers 5, 6, 8, 13) had only tics (i.e. “pure GTS”), which is known to be one factor or phenotype [37], and which has been shown to occur in approximately only 10 % of both clinical [9] and community samples [16, 17].

Of importance is that all our patients with "pure GTS" (4/18) improved with regards to their tics as judged by their YGTSS scores (see Table 2), and as many as three quarters (3/4) required no medication at 5-year follow-up (see Table 1), and the one who did require medication (number 6) required only sulpiride monotherapy (Table 1). Of these "pure GTS", only two responded very well (patients numbers 5 & 8). Thus, patient number 5 (see Tables 1, 2, 3) did very well with regards to his improvements in tics and the YGTSS, his overall change/improvement and his requiring no medication post DBS; however, he seems to have become a little obsessional after DBS (increase in YBOCS score) and disagreed with the clinician's evaluations of his status; possibly the

Table 3 Surgical complications of the GTS patients and most recent outcome POST DBS. The outcome POST DBS was evaluated by three different clinician (MMR, MP and DS); the same overall evaluation was made also by the patient himself

N°	Surgical complications of our DBS cohort [46]	Follow up post DBS	Most recent outcome comment	Pre & Post DBS YGTSS SCORES TABLE 2 (& MMR comments e.g. VG, G)	Pre & Post DBS YBOCS SCORES TABLE 2 (& MMR comments e.g. VG, G)	Overall success doctor (MP)	Overall success doctor (DS)	Overall success (PATIENT)
1		6 years, 6 months	Well	92-25 VG	32-8 VG	VG	VG	SB
2		6 years, 7 months	Rescue DBS for poor control [47] SIB, Rage, aggression	79-10 VG	23-10 G	SB	G	G
3		5 years, 1 month	Died unrelated causes (ca) 2010	97-25 VG	31-15 G	G	VG	-
4		6 years	Well Smoking excessively ISQ To pre-DBS	63-5 VG	10-4 G	SB	VG	SB
5		6 years, 3 months	Mild Occ FT & body MT	77-30 G	27-28 W	G	VG	SB
6		5 years,10 months	Pt requested device removal 25/09/2009	63-58 S	28-35 W	SB	-	-
7		5 years, 10 months	Mild Occ FT	89-12 VG	21-8 G	G	VG	VG
8		5 years, 8 months	Mild Occ FT	88-6 VG	16-5 VG	VG	VG	VG
9	Surgical wound healing diff – patient picking at wound	5 years, 4 months	Aggr Occ rage	91-3 VG	36-0 G	G	G	SB
10		1 year, 4 months	Mild Occ FT	66-15 VG	17-14 G	G	VG	VG
11		5 years, 7 months	V occ Mild FT & VC	79-15 VG	17-5 VG	G	VG	G
12	Abdominal wall haematoma (x % all DBS)	5 years, 3 months	Occ mild OCB	59-28 G	22-3 VG	SB	VG	G
13		5 years, 7 months	Pt requested device removal 12/11/2008	83-45 G	28-39 W	SB	G	-
14		5 years, 1 month	Mild Occ FT & OCB	95-15 VG	0-5 W	SB	-	G
15		5 years, 1 month	Mild Occ FT & mild spitting	69-32 G	8-1 VG	G	G	SB
16		5 years	Mild OCB & mild body MT	92-19 VG	23-6 VG	G	VG	G
17		5 years, 1 month	Rare mild body MT	73-30 G	25-19 SB	VG	-	G
18		5 years	Infection/rejection of DBS pouch (See text)	90-25 G	26-20 SB	G	VG	G

VG = very good. G = Good. SB = Slightly better. S = same. W = worse

emerging obsessionality may account for this. Patient number 8 (see Tables 1, 2, 3) did very well according to his rating scales, his overall improvement, the clinicians' and his own assessments, and he also required no medication post DBS. The other two patients failed to do well in general; obsessionality (as measured by the YBOCS) increased and, moreover, they requested device removal. It can be seen (Table 3) that one patient (number 6) had requested the device removal (5 years and 10 months after DBS), and of importance in this regard is that the two clinicians evaluating his scores (MMR & MP, eyeballing rather than statistically) commented that with regards to his tics, he was only the same or slightly better after DBS. Although it was felt clinically that he had no OCB diagnosis, his OC symptoms (as measured by the YBOCS) were thought to have worsened after DBS and requiring sulpiride. The last "pure GTS" (patient number 13; see Tables 1, 2, 3) also requested removal of the device (5 years and 7 months after DBS) and also seemed to increase in obsessionality and anxiety after DBS. His two treating clinicians (MP & DS) also disagreed as to how well he had done after DBS (MP = slightly better; DS = good). These four patients highlight the fact that, despite their diagnosis of "pure GTS" (i.e. tics only), only 2/4 did very well and the two who failed to respond requested device removal and had increased obsessionality after DBS.

Patients and clinicians varying views on the long-term results

Importantly and also unexpectedly, the long-term outcome/satisfaction was not unanimous between patients and the medical team. With regards to the overall global assessment of improvement (see Table 3, columns 5–9), in only 7/15 patients did the three clinicians (MMR, MP, DS) and the patients all concur that the patients had improved, albeit to different degrees. This highlights the importance of taking the patients' views into account, and differentiating the spoken views (impressions) from the results which they score on the various self rating scales and the objective rating schedules (e.g. YGTSS).

Compliance/adherence

We have already mentioned that in the 2 year follow-up, three patients were excluded and it may be argued that all three were non-compliant with treatment, as they did not follow our advice and in the end requested device switch off/removal. One may, however, also invoke psychosocial issues in the area of compliance, but these are far too complex to discuss in this paper [37].

Adverse side effects and events complicating DBS

As in our earlier reports, there were relatively few serious adverse side effects and events complicating DBS, we would like to reiterate that immediately after surgery only 2/18 patients had side effects (wound healing problems immediately after surgery, and abdominal wall (pouch haematoma) [46]. In our 2 year follow-up [31] no serious side effects were noted.

With regards to infection in this long-term cohort, only one patient (number 18) had an infection, but he also had a very complicated and difficult course and so we feel that he needs special mention. In brief, he was implanted in March 2006 (first Pulse & first Generator, P1G1). In July 2007, the battery of his pulse generator was "exhausted" (had "died") and so our surgeon (DS) replaced it with a new one (G2). The patient's first pouch (P1) was in the abdomen. He remained well until October 2007; at that stage his pouch scar separated, the wound opened spontaneously and the skin flap broke. The surgeon (DS) repaired the pouch (P1) and suspected an infection and, according to the protocol, took a sample of the fluids for culture and microbiology. The culture was, in fact, reported to be "normal"; the wound then healed spontaneously. In March 2008 the patient was admitted on an elective basis to the plastic surgery department for bariatric abdominoplasty (as he had become very obese). Our surgeon (DS) participated in the surgery because when the abdominoplasty occurred (and wall removed) the pouch was also removed. A week later the plastic surgeon reviewed the patient again and noted the presence of post-operative fluid and an unpleasant odour; the wound material was once again sent off for a blood culture which was negative for bacteria. In June 2008, 1 month later, the healing process remained difficult and so our surgeon (DS) changed the pouch site from the abdomen to the subclavicular region (P2). DS also gave the patient a new pulse generator (G3) as the previous one needed to be changed, and a new one would also decrease the chance of any possible infection. A year later (in June 2009) the patient had a further retroauricular scar separation (behind the ear) where there are connections between the leads and extension cable (the cable is larger than the lead and to protect the "joining area" there is a silicon cap behind the ear). Three years after the DBS, probably due to his recommencing his excessive grooming (which included the site of pouch/stimulator, as well as skull and neck entries), he began a cycle of infections and what were also felt to be rejections. This unacceptable cycle for this patient continued for 2 months.

We observed no evidence of hemorrhages or ischaemia as complications and only one infection (patient number 18). This is in contrast to the findings of Servello et al. [49] who retrospectively reviewed 531 DBS procedures on 272 patients with a variety of movement disorders (e.g. Parkinson's disease, essential tremor and dystonia) and among which there were 39 GTS patients. Servello et al. [48] reported a statistically significant association of infective complications in the GTS sub-group when compared to the other disorders.

It has been suggested that lesional surgery in the thalamus resulted in dementia/cognitive impairment in patients with PD, whereas in our paper, and many others targeting the thalamus in GTS, cognitive decline was not observed [31], and this is particularly true after 5 years of follow-up. This may of course be because the natural progression of GTS does not usually result in dementia anyway [35, 36], whilst in PD, dementia is a fairly common endpoint [45]. In addition, there have been no cases of mortality with DBS in patients with GTS (our series and our reviews of the literature). Instead, in patients with PD, for example, Servello et al. [49] reported three patients with PD who died (aged 68, 67, and 72 years), but it should be noted that they were a much older group and also the target was different.

In our group of 18 patients we encountered no instances of repositioning after migration of stimulator and only one case of revision surgery as a result of infection (patient number 18).

We also feel it appropriate that we mention adverse side effects/events in DBS as a whole (e.g. Parkinson's disease, tremor, dystonia, cluster headache, as comprehensively reviewed by Starr & Sillay) [52], in GTS [12, 26, 60], and individual case series/reports (see Table 4). It can be seen from Table 4 that DBS in general is a relatively safe procedure, and this appears to be even more so in patients with GTS. By and large GTS patients are young and healthy (e.g. when compared to the older PD population). Our data over a 5–6 year period would also concur with this. In particular, there have been no reports in GTS post-DBS patients of suicides, psychosis, nor major depressive illnesses. In addition, in our group, we encountered no instances of our GTS patients having sedation, anxiety, altered mood, reduced energy, increased or decreased sexual drives or function, vertical gaze palsy, transient apathy or hypomania, dissociative states, or bradykinesia (for individual references and details see Table 4), as has been reported in other GTS cases or cohorts.

In our cohort two patients had blurring vision (implanted with thalamic target and over 4 V).

It should also be pointed out that whilst the side effects of DBS surgery in patients with GTS are minor, the patients nevertheless require general anaesthesia, which always carries a risk.

In the Milan series of DBS in all patients, Servello et al. (2011 Berlin-personal communication) examined data on 348 patients and 670 DBS procedures from 1997 to 2011 and documented adverse events as follows: *five (1.4 %)* cases of infection-culture positive for Staphylococcus aureus; *12 (3.4 %)* cases of cutaneous erosions; *12* implant removal (3.4 % by patient); *seven* implant removal in 45 patients with GTS (15.5 %); *five* implant removal in other pathologies (1.6 %); and *139* patients with external extension. In this follow-up study, there were no instances of implant removal. Infection complications were higher in GTS patients than in the rest of diseases requiring DBS [47]. We feel strongly that compliance in general is reduced in patients with GTS when compared with other DBS patients.

Starr and Sillay [52] summarised their peri-operative and device-related complications using Medtronic DBS hardware as provided in Table 4. The results are based on a series of 637 new DBS leads in 358 patients implanted by a single surgeon (Starr over the period 1998–2006). The procedures were performed with frame-based stereotaxy using MRI and microelectrode recording. The total incidence of unexpected returns to the operating room for management of a complication was 59 surgical cases in 50 of the 358 operated patients, or 14 %. Most of these re-operations were on the subcutaneous rather than intracranial parts of the hardware. The risk of requiring further intracranial surgery to replace a broken, misplaced, or infected lead was 5.9 % per patient (see Table 4).

In the international experience most of the DBS repeat operations are due to subcutaneous complications rather than intracranial parts of the hardware [52]. In the general DBS literature, the rates of reported infection vary from 0.4 to 12.7 % [27, 58]. It must be noted however that a low value (0.4 %) refers to cases of infection during the first 30 postoperative days, and it should be pointed out that this is the period of when effective surgery-related infections occur.

Practical aspects of long-term DBS surgical follow-up

The position of pulse, pouch and stimulator might need changing by the surgeon, and indeed it occurred in one of the cases (patient number 18) following complications. In addition there may be a spontaneous change of the position of the stimulator; this may happen in activities of daily living such as when a person moves (e.g. when driving a car, a patient's pectoral muscles will move a lot). In addition, there may be tethering, and thus fibrosis of the extension cable. Finally, our surgeon (DS) initially placed the pouch in the sub-clavicular position (n=5), but for the latter 13 patients he placed the pouch on the abdomen predominantly for cosmetic and practical reasons.

Other issues

One is tempted to ask whether or not lessons have been learned from our personal experience and reviewing the literature. For example, an initial lesional effect has been noticed in all the patients, but is the initial lesional effect a predictor of outcome? Unfortunately, we are unable to answer this either from our data or reviewing the literature.

In addition, one may ask whether or not it is justified to use low intensity initially for programming sessions or not

Table 4 Complications in 637 DBS interventions in 358 patients implanted 1998–2006

Complication	Number of occurrences	Number of patients	Implanted leads (%)	Patients (%)	Main Complications with DBS for GTS patients [references]
Hemorrhagic stroke (arterial or venous)	8	8	1.3	2.2	Nil [12, 26, 60]
Ischemic stroke (capsular infarction)	1	1	0.2	0.3	Nil [12, 26, 60]
Asymptomatic hemorrhage*	15	15	2.4	4.2	Nil [12, 26, 60]
Stroke with permanent neurologic deficit	4	4	0.6	1.1	Nil [12, 26, 60]
Chronic subdural hematoma	1	1	0.2	0.3	[14] (patient also had low factor X111A activity). *N*=1
DBS lead fracture	5	4	1.4	1.1	Nil [12, 26, 60]
Lead extender fracture	3	3	0.5	0.8	Electrode connections perm damaged by retrocollic tics/jerks [50]
Poor initial lead position resulting in re-operation	11	10	1.7	2.8	Nil [12, 26, 60]
Lead migration resulting in re-operation	2	2	0.3	0.6	Nil [12, 26, 60]
Infection requiring removal of IPG and lead extender, and IV antibiotics	8	8	1.6†	2.2	One: patient number 18 [current paper]
Infection requiring removal of all hardware including brain leads	7	7	1.6†	2.0	Nil [12, 26, 60]
Return to operating room for other exploration/repair of subcutaneous hardware⊥	22	19	3.5	5.3	Nil [12, 26, 60]
Infection requiring IV antibiotics without hardware removal (both at frontal incision)	2	2	0.3	0.6	Nil [12, 26, 60]
Major air embolus (prolonging the procedure or requiring its abandonment)	3	3	0.5	0.8	Nil [12, 26, 60]
Intra-operative seizure (focal)	1	1	0.2	0.3	Nil [12, 26, 60]
Postoperative seizures	4	4	0.6	1.4	Nil [12, 26, 60]
Tense cerebrospinal fluid collection around IPG, not surgically treated	2	2	0.3	0.6	Nil [12, 26, 60]
Postoperative aspiration pneumonia	3	3	0.5	0.8	Nil [12, 26, 60]
Suicide attempt or psychiatric hospitalization within 6 months of surgery	4	4	0.6	1.1	Nil [12, 26, 60 and subsequent case series/reports]
DBS in GTS side effects (below) - case reports & reviews					
1. Reduced energy (almost all cases). 2. Increased and/or reduced sexual drives (*n*=1 & *n*=1) 3. Vertical gaze palsy					[55, 56] & [1, 2] (Dutch Flemish Group)
Small haemorrhage at target site & persistent bradykinesia of left hand (well tolerated by patient)	1				[7]
Transient apathy & hypomania	2	2		n/a	[8, 18, 50]
Difficulties with penile erection	1	1		Na	[54]
Dissociative State	1	1		Na	[10]
1. Surgery related - bleeding & infection - rare 2. Stimulation related, e.g. sedation, anxiety, altered mood, change in sexual function = rare/few	Hardly any serious adverse effects at all	Few		Na	[12, 26, 60]
TOTAL UNPLANNED INTRACRANIAL RE-OPERATIONS (all DBS patients 1998–2006) [52]	26	21	4.1	5.9	
TOTAL UNPLANNED RE-OPERATIONS (all DBS patients 1998–2006) [52]	59	50	9.3	14.0	

The mean follow-up time was 54 months; modified from Starr and Sillay [52]

‡ The number of occurrences is greater than the number of patients affected for certain types of complications because there were multiple occurrences in one patient

† To calculate a "per lead implant" infection rate, an infection involving a dual-channel IPG (Kinetra) was counted as affecting two leads, while an infection of a single-channel IPG was counted as affecting one lead

* Threshold of detection was volume > 0.2 cc

⊥ Problems included: sterile seroma around IPG, *N*=2; hematoma around IPG, *N*=1; hardware disconnection, *N*=3; failure of wound to heal, *N*=1; IPG malfunction, *N*=1; elective repositioning of connector from cervical to cranial position, *N*=8; lead extender replacement to address patient discomfort, *N*=2; connector or IPG repositioning for threatened erosion, *N*=3; repair DBS anchoring system, *N*=1

and once again, it is unclear. Should one make an analogy to drug treatment, especially in children and adolescents, and "start low and go slow"? If a response lasts longer, one should, therefore, use the stimulator for 5 rather than 3 years. Actually, if the stimulator is programmed with a low intensity the battery lasts longer, but there is not a precise protocol of programming the stimulator in advance.

Other unanswered potential questions include whether or not there are predictors of how frequently patients require stimulation parameter control. Actually, only some of our patients required close control and it was for brief periods of time only (possibly the waxing periods characteristic of GTS), whereas the other patients attend follow-up clinic just for the periodic scheduled visits; this may be explained either by the operation either by the waxing and waning course of the syndrome itself.

It may also be asked whether or not the local field potential activity is altered during DBS. For example, Marceglia et al. [23] described the neurophysiological aspects of the VO during DBS in seven patients with GTS. They recorded single unit activity and local field potentials (LFPs) a few days after DBS. Single unit recordings showed that the VO complex is characterised by a localised pattern of bursting neuronal activity. LFP spectra demonstrated that the VO of GTS patients has a prominent oscillatory activity at low level frequency (2–7 Hz) and in the alpha band (8–13 Hz), whilst this was virtually absent during beta activity. In each patient the mean LFP frequency significantly correlated with single-unit interburst frequency [23]. Whether or not this can be generalised to similar activity targeting other areas of the brain is as yet unknown. One may pose the question, how can one distinguish the potential role of the syndrome on this aspect?

Finally, there are other potential problems which are pertinent to GTS only as a result of the phenomenology, comorbidity and co-existent psychopathologies. For example tics can be very jerky and strong and can result in damage. With regards to surgery, this could mean, for example, dislodging of the DBS device. In addition, patients with GTS frequently indulge in self-injurious behaviours (SIB) with a predominantly obsessional flavor [39], and thus patients may have to literally "pick" at scars (they acknowledge that they do not want to do this, but they "have to"; i.e. it is obsessional). Frequently, patients with GTS touch themselves or other people in an obsessional way [38] and this may be similar to "self - grooming" (e.g. "excessively shaping one's hair style"); or if they actually hurt themselves, it may be SIB. In either event, this is a potential difficulty which may be encountered with DBS.

Other arguments for long-term follow-up

Three of the original 18 patients were not included in the 2 year follow-up [31], but are included in this communication, and thus in this longer term follow-up. We suggest that this indicates the usefulness of long-term follow-up, particularly in a syndrome such as GTS which has waxing and waning, suppressible and suggestible symptoms [40], but symptoms are also influenced by age [29], and possibly by life stressors and life events. Actually, several studies have invoked a role of psychosocial stress in the prediction of severity, and thus in the prognosis of GTS in a case report [53], and then in a controlled study [20] in which youngsters with GTS experienced significantly more psychosocial stress than did the controls; the estimates of psychosocial stress were predictive of future depressive symptoms. Thereafter, Lin et al. [21] undertook a longitudinal study during which they examined both Group A beta-hemolytic streptococcal (GABHS) upper respiratory infections as well as psychosocial stress in children and adolescents with GTS and compared them to healthy controls. Results first showed that a minority of children with GTS were sensitive to previous GABHS infections. Secondly and importantly, the GTS youngsters had significantly more psychosocial stress than did the control group. In summary, it seems that psychosocial stress is indeed a factor which makes tics worse at the time of the stress, but that also GTS subjects experience more stress than does a control group.

Limitations of the study and our long-term follow-up

In the first instance, the obvious limitation is that the study was not a controlled study (i.e. was not double-blind) and it is, therefore, open to criticism. Secondly, we failed to measure the ADHD and aggressive symptomatology with standardised scales, and limited our impressions of the improvements to clinical opinion only. We also did not measure or take psychosocial stress into account. Finally, although we took videos of the patients, this was not according to a strict video-protocol and thus we feel it inappropriate to publish this aspect of the study.

In our defense, ours is one of the longest and the largest follow-up studies of DBS in GTS patients, the other being by Ackermans et al. [3], which also followed up six patients for 6 years, after a randomised controlled double-blind DBS study.

Conclusions

At the long-term follow-up of 18 patients (15 patients at 5–6 years: three patients at 3–4 years), DBS was successful in terms of a significant improvement in tics as well as a significant reduction in the disabling symptoms of obsessionality, anxiety and depression. However, as evidenced by our more positive overall results at 2 years, compared with those later on presented in this communication, difficulties have been encountered: (i) non-compliance, (ii) long-term complications, and (iii) the obvious differences in the

opinions between the medical and surgical teams and the post-DBS patients as to their outcome/satisfaction with the procedures. Our experience highlights the need for not only controlled studies but also for long-term follow-up, and the need to improve the selection of patients for DBS.

Conflicts of interest None.

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