PRDOA 7 (2022) 100159

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Short Communications

Efficacy of deep brain stimulation of the anterior-medial globus pallidus internus in tic and non-tic related symptomatology in refractory Tourette syndrome

Raven Kisten [a], Riaan van Coller [a,*], Nafisa Cassimjee [b], Elsa Lubbe [c], Janardan Vaidyanathan [d], Pieter Slabbert [e], Nico Enslin [f], Clara Schutte [a]

[a] Department of Neurology, Faculty of Health Sciences, University of Pretoria, South Africa
[b] Department of Psychology, University of Pretoria, Pretoria, South Africa
[c] Division of Paediatric Neurology, Department of Paediatrics, Faculty of Health Sciences, University of Pretoria, South Africa
[d] Medtronic, Mumbai, India
[e] Neurosurgeon, Pretoria East Hospital, Pretoria, South Africa
[f] Department of Neurosurgery, Red Cross Children's Hospital, University of Cape Town, South Africa

ARTICLE INFO

Keywords:
Tourette syndrome
Obsessive Compulsive Disorder
Self injurious behavior
Deep brain stimulation
Antero-medial Globus pallidus

ABSTRACT

Introduction: Although refractory Tourette Syndrome (TS) is rare, it poses great challenges in clinical practice. Co-morbid psychiatric symptoms often occur, negatively impacting quality of life. Deep brain stimulation (DBS) targeting different brain structures seems effective for tics, but specific literature regarding response of psychiatric symptoms is more limited.

This study aimed to assess the outcome of tics and non-tic related symptomatology in refractory TS treated with antero-medial globus pallidus interna (amGPi) DBS.

Methods: We included all patients with refractory TS (January 2013–August 2020) from the Brain Nerve Centre and Steve Biko Academic Hospital, Pretoria, South Africa, treated with bilateral amGPi DBS; retrospective baseline, early (up to 3 months) post-DBS follow-up assessment data, as well as prospective data from the latest follow-up (mean 37.4 months) were collected using standardised scoring tools and scales.

Results: Five patients were identified. Tics decreased by 63,9% ($p = 0,002$); quality of life improved by 39,8% ($p = 0,015$); self-injurious behaviour ceased; obsessive–compulsive symptoms resolved in all but one. The number of different chronic medications used more than halved. Transient stimulation-related adverse events occurred in four patients.

Conclusion: This study contributes to the data of the efficacy of amGPi-targeted DBS in refractory TS, showing improvement in quality of life and both tic- and non-tic-related symptomatology..

1. Introduction

Tourette Syndrome (TS) is a childhood onset neuropsychiatric condition characterised by multiple tics present for more than one year [1]. The aetiology is likely multifactorial, involving complex genetic factors and environmental triggers. Patients suffering from TS frequently have comorbid behavioural and psychiatric symptoms, with an estimated lifetime prevalence of 90 % [2]. Obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD) are most common [2]. Suicide risk is higher amongst TS sufferers even after adjusting for psychiatric comorbidity [3]. These associated comorbidities often significantly affect quality of life [4].

By adulthood, >80 % will experience tic reduction, but 26–40 % will still have mild tic-related symptoms [5,6]. A minority, estimated at <5 % of all patients with TS, have refractory TS where tics are severe, cause significant functional disability and do not respond to treatment [7,8].

Deep brain stimulation (DBS) of different brain targets – most commonly the centromedian thalamus, anteromedial or posteroventral globus pallidus - may improve refractory TS [1,9,10]. While the efficacy of DBS for the reduction of severe tics is relatively well-established, the effects of DBS regarding behavioural and psychiatric comorbidity and quality of life are less often reported. A recent review reported an overall

* Corresponding author.
E-mail address: rvcoller@gmail.com (R. van Coller).

https://doi.org/10.1016/j.prdoa.2022.100159
Received 16 January 2022; Received in revised form 5 July 2022; Accepted 1 August 2022
Available online 3 August 2022

31,2% reduction of OCD and 38,9% of depression in patients irrespective of which target was used, the total number of patients studied remaining small [11,12]. Targeting the antero-medial globus pallidus internus (amGPi) for DBS in TS is currently done more frequently due to its specific limbic anatomical connections, surgical access and paucity of undesirable stimulation induced complications, yet data regarding psychiatric outcome in amGPi DBS remains limited [13]. Recently, a multi-target DBS approach in TS has been investigated, showing possible improved effect on managing tic and non-tic symptoms [14].

The aim of this study was to assess the outcome of tics and non-tic related symptomatology of refractory TS in adolescent and adult patients treated with amGPi DBS at two specialised movement disorder units in Pretoria, South Africa.

2. Methods and patients

All patients with refractory TS from the Brain Nerve Centre and Steve Biko Academic Hospital in Pretoria, who had been treated with DBS in Pretoria (patients 1-4) and at Red Cross Childrens Hospital, Cape Town (patient 5) between January 2013 and August 2020, were included; they were assessed at routine follow-up or were contacted to participate. Baseline information was collected retrospectively, whereas the latest follow-up measurements were collected prospectively and reported here. No genetic studies were performed on the patients. The data collection was mixed retrospective and prospective.

The amGPi was the target in all our patients. The choice of the amGPi as target was based on the data available, its strong limbic and associative network connections, surgical experience and the prominent non-motor co-morbidity in all 5 our patients. Non-stereotactic neuronavigation compatible target-specific sequences were acquired on a 3-Tesla GE Signa MRI scanner (Magnetic Resonance Imaging) (General Electric, Milwaukee, WI, USA). A patient specific atlas was created with minimal need for reformatting with respect to the anterior commissure (AC) - posterior commissure (PC) plane on the planning software. Target specific sequences such as the T1 and T2 weighted MRIs were done, and in addition, a double dose post-contrast T1 weighted three-dimensional multi-plane reformattable sequence was acquired, which facilitated planning of a safe trajectory. Plan-ahead paradigm was used to determine the anatomical location of the target and the orientation of the trajectory (Framelink version 5.4 & Stealth Cranial Stereotaxy 3.0, Medtronic, Minneapolis, MN, USA). The long axis of the GPi was drawn at the level of the AC-PC plane and it was divided into four quadrants. The long axis of the GPi was generally parallel to the optic tract when projected onto an inferior slice. Direct visualization was used to identify the amGPi target at the junction of the anterior two quadrants of the GPi, within the internal medullary lamina and adequately lateral from the posterior limb of the internal capsule (Fig. 1A). The optic tract was used as an internal landmark to ascertain the pallidal base. This aided in deliberating on the optimal individual electrode location and lead orientation. The stereotactic frame's base ring was applied on the day of surgery, after which a high resolution stereotactic computed tomography (CT) scan of the head was obtained which was later fused with the plan ahead data sets to transform functional/brain coordinates to stereotactic/frame coordinates. A Cosman Robert Wells (CRW) stereotactic frame (Precision model, Integra LifeSciences Corporation, Burlington, MA, USA) with a phantom base was used to perform the procedure in patients 1–4 and a Leksell frame (model G, Elekta, Stockholm, Sweden) in patient 5 under controlled general anaesthesia. Two channel simultaneous microelectrode recording (MER) using the Leadpoint 5 + 3 (Medtronic, Minneapolis, MN, USA) in the central and antero-medial trajectories of the "Ben's Gun in the 'X' configuration" were used to confirm the pallidal base (Star Drive, FHC Inc., Bowdoin, ME, USA). The pattern of MER was classified on the basis of density (high/low), frequency (high/low), regular or irregular and bursting or pausing. The inferior pallidal border of the anatomically determined amGPi target was confirmed using MER. Macroelectrode stimulation (MES) was performed 4 mm above, 2 mm above and at target to check for side-effects within the therapeutic range up to the supramaximal level (0–5 mA; 60 μsec and 130 Hz). A passive tip lead with four electrodes (3389 model [15]; Medtronic, Minneapolis, MN, USA) was implanted under intraoperative fluoroscopy guidance and after verification, a burr hole cover functioning as a lead locking device was affixed. Post-operative CT fused with the pre-operative MRI for audit of lead location was done in patients 1–4. A post-operative conditionally safe stereotactic 1.5 T MRI (Magnetom, Siemens, Erlangen, Germany) (Fig. 1 B and C) for target confirmation was done in patient 5. A primary cell neurostimulator (Activa PC, model 37601, Medtronic, Minneapolis, MN, USA) was implanted in patients 2 and 4 and, where funding allowed, a rechargeable neurostimulator (Activa RC, model 37612, Medtronic, Minneapolis, MN, USA) was implanted in patients 1,3 and 5, in the sub-clavicular region during the same procedure. After battery depletion a second Activa PC was implanted in patient 4.

The following scores were assessed and compared: Yale Global Tic Severity Scale (YGTSS); Gilles de la Tourette Quality of Life (GTS-QOL) with a visual analogue scale (GTS-QOL VAS); Yale-Brown Obsessive Compulsive Scale (Y-BOCS) or the Children's version (CY-BOCS) for participants under 18 years; Beck Depression Inventory-II (BDI-II) for patients older than 13 years; Beck Anxiety Inventory (BAI) for patients older than 17 years; Revised Children's Anxiety and Depression Scale (RCADS) and/or its parent version (RCADS-P) for children aged 8–18 years. Clinically relevant improvement regarding Y-BOCS was defined as a 35 % or more reduction in score. Chronic medication at the time of

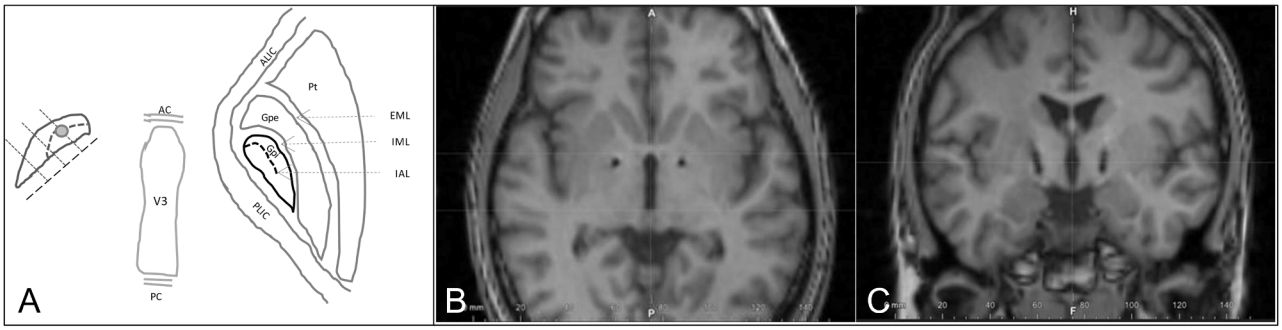

Fig. 1. Post-surgical MRI of patient 5 1A: An outline of a patient specific atlas in an axial orientation at the level of the AC-PC with the long axis of the GPi divided into four quadrants and the anatomically planned location of one electrode. Depth was determined based on the visualization of the pallidal base and optic tract. Abbreviations: AC – anterior commissure, PC – posterior commissure, V3 – third ventricle, ALIC – anterior limb of the internal capsule, PLIC – posterior limb of the internal capsule, Pt – putamen, GPe – globus pallidus externa, GPi – globus pallidus interna, EML – external medullary lamina, IML – internal medullary lamina, IAL – internal accessory lamina 1B and C: Post-operative T1 axial (Fig. 1B) and coronal (Fig. 1C) MRI images showing the position of the electrode in the amGPi in patient 5.

evaluation before and after surgery and adverse effects post-DBS were also recorded.

3. Results

The baseline characteristics of the five included patients are summarised in Table 1.

3.1. YGTSS and GTS-QOL outcome

Tic-and non-tic related outcomes for DBS are shown in detail in Table 2 and Supplementary Data Table S1. All patients showed clinically and statistically significant improvement on the YGTSS, GTS-QOL and GTS-QOL VAS scales by latest follow-up (p values 0.003, 0.015 and 0.027 respectively).

3.2. Self-injurious behaviour (SIB) characteristics and outcome

All 5 patients had experienced SIB during the course of their lives. Three of the patients had SIB at the time of surgery, and all three reported complete cessation of the SIB by the latest follow-up. No patient reported episodes of SIB post-DBS.

3.3. OCD outcome

At baseline, all patients had OCD (2 mild; 2 moderate; 1 severe), according to Y-BOCS and CY-BOCS scores, while at the latest follow-up only one patient had mild OCD symptoms. The others had scores of five or less (sub-clinical or normal range).

Two of the three patients with Y-BOCS data showed clinically relevant improvement, achieving a score less than 10. The third patient had practically reached a clinical response with 33 % reduction and a score equal to 10. Patients 1 and 5, under 18 years, were evaluated with the CY-BOCS and RCADS/RCADS-P at baseline. Patient 1 had moderate (CY-BOCS = 18) and Patient 5 mild OCD (CY-BOCS = 8), which resolved in both at follow-up: Y-BOCS = 1 and Y-BOCS = 0 respectively were recorded.

3.4. Anxiety and depression outcome

The three adult patients had baseline BDI-II and BAI data available, which improved in two after DBS (BDI-II: 25 to 14 and 17 to 2; BAI: 38 to 22 and 11 to 0), while one had worsening on both (BDI-II: 11 to 31; BAI: 3 to 23). In this patient a combination of stimulation related side-effects and medication reduction were thought to be the cause of this deterioration.

Patient 1 had marked anxiety (RCADS *t*-score = 67; RCADS-P *t*-score $\geq$ 80) and depression (RCADS-P *t*-score $\geq$ 80) at baseline but scored within normal range (Y-BOCS = 1; BDI-II = 3; BAI = 14) at follow-up; patient 5 also had anxiety (RCADS *t*-score = 69) and depression (RCADS *t*-score = 76) which normalised post-DBS (Y-BOCS = 0; RCADS *t*-scores = 43 and 39) by the last visit. This also correlates with his normal BDI-II and BAI scores of 11 and 8 at follow-up.

3.5. Medication

The medications used at the time of surgery and then at latest follow-up after DBS are shown in Table S2 in the Supplementary Data. Medications were systematically weaned after surgery, keeping co-morbid symptoms in mind. Patient 4 stopped using an SSRI on his own accord after stimulation was turned on. He subsequently reported deterioration in depression and anxiety at follow up as is shown in the follow up data. Two other patients were medication-free and the remaining two were able to reduce medication use without deterioration of co-morbidities or tics.

3.6. Stimulation parameters

The stimulation parameters of the patients before and after adjustment are shown in Table S3 in the Supplementary Data.

3.7. DBS adverse events

Apart from one patient where the pulse generator was repositioned due to poor contact with the charging device, no other surgical adverse events were found. All stimulation related side-effects were resolved with stimulation adjustments. Details of these findings are shown in Table S4 in the Supplementary Data.

4. Discussion

Tic reduction in our study was similar to the average 45–80 % improvement in YGTSS scores documented in other published studies following DBS for refractory TS, adding to the knowledge of the efficacy of DBS in this condition [9,16]. In addition, improvement of patient well-being in our study was similar to the 38.9 % and 45.7 % improvement in QOL scores seen by Kefalopoulou and Zhang [17,18].

Psychiatric comorbidity is common in TS and observational studies show that mood disorders are associated with a greater tic burden, with many patients having two or more psychiatric disorders [2,11,19,20]. Our patients had an average of four psychiatric comorbidities, including SIB and OCD in all. One study which focussed on malignant TS - severe TS needing at least one hospital admission or two emergency room visits - showed that OCD occurred in 100 % of patients; more than two co-morbid psychiatric disorders occurred in all patients and SIB was seen in 65 % [20]. An association between multiple and severe psychiatric comorbidities and refractory TS thus seems plausible with possibly common genetic risk factors. Notably, 80 % of patients in our study had a positive family history of TS, with two patients having co-transmission of OCD – an association with increased severity of OCD and likelihood of SIB has been shown in such instances. Patient 1 had bi-lineal transmission of both TS and OCD but had an unaffected twin sister. This has also been noted in twin studies for TS which showed 8 % and 53 % concordance rates in dizygotic and monozygotic twins, respectively, supporting the role of genetics, as well as epigenetic and environmental risk contributions [21]. Several candidate genes for TS have been identified over the last years, but none have yet been confirmed as major susceptibility genes. Most studies in this regard are focusing on the

Table 1
Summary of the baseline clinical characteristics of the 5 patients in the study.

Pt	Sex	Race	Family history TS	SIB	OCD	MDD	ADHD	Anxiety	Learning difficulty	YGTSS	Age at TS onset	Age at DBS (yrs)	Longest Follow-up (months)
1	F	W	+	+	+	+	–	+	–	97	3	17	33
2	M	W	+	+	+	+	+	+	–	94	10	26	55
3	M	W	+	+	+	–	–	–	–	66	11	25	48
4	M	W	–	+	+	+	–	+	–	76	6	34	27
5	M	B	+	+	+	+	+	–	+	95	12	16	24

Abbreviations: Pt: Patient, SIB: Self-injurious behaviour, OCD: Obsessive-compulsive disorder, MDD: Major depressive disorder, ADHD: Attention deficit hyperactivity disorder, YGTSS: Yale Global Tic Severity Scale, yrs: years.

Table 2
Comparison of the different measured rating scale scores before and after DBS surgery. The first number in each column is the baseline score and the number after the semicolon is the post-DBS score at last follow-up.

Pt	YGTSS			GTS-QOL		Y-BOCS	CY-BOCS	BDI-II	BAI	RCADS*	RCADS-P*	PUTS	UPS-SPS	GAF
	TTS	OIR	Total	Score	VAS									
1	47;12	50;10	97;22	70;6	30;100	-;1	18;-	-;3	-;14	64;-	>80;-	-;15	-;3	-;81–90
2	44;13	50; 0	94;13	73;26	20;78	24;5	-;-	25;14	38;22	-;-	-;-	-;21	-;2	-;71–80
3	26;13	40;10	66;23	41;8	70;75	20;0	-;-	17;2	11;0	-;-	-;-	-;16	-;0	-;81–90
4	36;12	40;30	76;42	52;46	25;50	15;10	-;-	11;31	3;23	-;-	-;-	-;29	-;8	-;61–70
5	45;19	50;20	95;39	66;17	40;80	-;0	8;-	-;11	-;8	72;41	45;48	-;18	-;0	-;81–90
Mean	39.6;13.8	46;14	85.6;27.8	60.4;20.6	37;76.6	19.7;3.2	13;-	17.7;12.2	17.3;13.4	-;-	-;-	-;19.8	-;2.6	-;-
SD	8,7;2.9	5.5;11.4	13.8;12.3	13.5;16.3	19.9;17.8	4.5;4.3	7.1;-	7.0;11.7	18.3;9.7	-;-	-;-	-;5.6	-;3.3	-;-
Min	26;12	40; 0	66;13	41;6	20;50	15;0	8;-	11;2	3;0	64;-	45;-	-;15	-;0	-;61–70
Max	47;19	50;30	97;42	73;46	70;100	24;10	18;-	25;31	38;23	72;-	>80;-	-;29	-;8	-;81–90

TTS = Total tic severity score; OIR = Overall impairment rating; *t-score. Pt = Patient number.
The first number in each column is the baseline score and the number after the semicolon is the post-DBS score at last follow-up. A dash (-) stands for score not done.

candidate pathway approach that investigates genes related to neurotransmitters of the cortico- basal ganglia- thalamo- cortical loops [22].

Risk factors for the development of refractory TS have not been conclusively identified, but we propose that OCD, possibly in combination with SIB, and a family history of TS or OCD are likely important risk factors for the development of refractory TS. If these factors are present in a patient with TS, it raises the possibility of them being used for early risk stratification and consequent treatment planning.

Evidence for outcome of behavioural and psychiatric comorbidities post-DBS surgery for refractory TS is not conclusive. Our patients had a 75 % reduction in Y-BOCS scores and none reported SIB after surgery; some improvement of OCD and SIB has also been described in previous studies [11,20]. The choice of amGPi target in all our patients may have contributed to this positive result, suggesting that personalised DBS targets should possibly be considered, according to the phenotypic presentation of the patient [9]. Depression and anxiety may respond to some extent to thalamic stimulation and improvement has also been documented in a few patients where the amGPi was targeted; we noted an improvement in 80 % of our patients [18,21].

The reduction in the pill burden achieved post-DBS in our study was noteworthy. To our knowledge, there are currently no studies investigating the effect of DBS on medication reduction, and our finding of medication-freedom in two patients and a marked reduction in one more is interesting and future studies should examine this in more detail.

Refractory TS is very rare and our study is also limited by the small number of patients and the lack of controls but aided by the long follow-up duration (mean 37.4 months) demonstrating benefit in real-world practice. Precise connectomic analysis of the anatomical target in the amGPi and stimulation parameters will also require further study to optimize outcome of DBS in Tourette syndrome in the future, and it remains to be determined whether a multi-target stimulation approach may be superior to carefully selected single target lead placing in refractory TS..

5. Conclusion

Our study contributes to the data of the efficacy of amGPi-targeted DBS in refractory TS, showing improvement in the quality of life and both tic- and non-tic-related symptomatology. The specific improvement of the non-tic related symptomatology with the use of the amGPi target is emphasised. Larger numbers of patients are needed to explain the conflicting reported outcomes in motor and non-motor symptoms in patients in blinded and open label trials of DBS in TS. Although we experienced low surgical and stimulation-induced adverse effects, clinicians should be aware of higher rates of side-effects reported in other studies, such as torsion of the extensions, secondary sepsis and skin lesions due to accidental or self-induced injuries reported in other studies [9,10].

CRediT authorship contribution statement

Raven Kisten: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Riaan van Coller:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Nafisa Cassimjee:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Elsa Lubbe:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Janardan Vaidyanathan:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Pieter Slabbert:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Nico Enslin:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Clara Schutte:** Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors appreciate the patients' co-operation and patience. We express our gratitude to Medtronic South Africa for technical support and donation of the hardware for patient 5.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2022.100159.

References

[1] K.R. Müller-Vahl, D.C. Cath, A.E. Cavanna, S. Dehning, M. Porta, M.M. Robertson, V. Visser-Vandewalle, European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: deep brain stimulation, Eur. Child Adolesc. Psychiatry 20 (4) (2011) 209–217, https://doi.org/10.1007/s00787-011-0166-4.
[2] I. Jalenques, F. Galland, L. Malet, D. Morand, G. Legrand, C. Auclair, A. Hartmann, P. Derost, F. Durif, Quality of life in adults with Gilles de la Tourette Syndrome, BMC Psychiatry 12 (2012) 109, https://doi.org/10.1186/1471-244X-12-109.
[3] L. Fernández de la Cruz, M. Rydell, B. Runeson, G. Brander, C. Rück, B. M. D'Onofrio, H. Larsson, P. Lichtenstein, D. Mataix-Cols, Suicide in Tourette's and chronic tic disorders, Biol. Psychiatry 82 (2017) 111–118, https://doi.org/10.1016/j.biopsych.2016.08.023.
[4] B.M. Kious, J. Jimenez-Shahed, D.R. Shprecher, Treatment-refractory Tourette syndrome, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 70 (2016) 227–236, https://doi.org/10.1016/j.pnpbp.2016.02.003.

[5] T.L. Lowe, M.R. Capriotti, K. McBurnett, Long-term follow-up of patients with Tourette's syndrome, Mov. Disord. Clin. Pract. 6 (2019) 40–45, https://doi.org/10.1002/mdc3.12696.
[6] E.J. Pappert, C.G. Goetz, E.D. Louis, L. Blasucci, S. Leurgans, Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome, Neurology 61 (2003) 936–940, https://doi.org/10.1212/01.WNL.0000086370.10186.7C.
[7] A. Viswanathan, J. Jimenez-Shahed, J.F. Baizabal Carvallo, J. Jankovic, Deep brain stimulation for tourette syndrome: target selection, Stereotact. Funct. Neurosurg. 90 (2012) 213–224, https://doi.org/10.1159/000337776.
[8] M. Colquhoun, J. Stern, N. Collicott, D. Williams, K. Grabecki, H. Simmons, M. Robertson, Severe refractory Tourette syndrome, J. Neurol. Neurosurg. Psychiatry 85 (2014) e3.
[9] S.C. Casagrande, R.G. Cury, E.J. Alho, E.T. Fonoff, Deep brain stimulation in Tourette's syndrome: evidence to date, Neuropsychiatr. Dis. Treat. 15 (2019) 1061–1075, https://doi.org/10.2147/NDT.S139368.
[10] R. Martínez-Fernández, L. Zrinzo, I. Aviles-Olmos, M. Hariz, I. Martinez-Torres, E. Joyce, M. Jahanshahi, P. Limousin, T. Foltynie, Deep brain stimulation for Gilles de la Tourette syndrome: a case series targeting subregions of the globus pallidus internus, Mov. Disord. 26 (2011) 1922–1930, https://doi.org/10.1002/mds.23734.
[11] D. Martino, W. Deeb, J. Jimenez-Shahed, I. Malaty, T.M. Pringsheim, A. Fasano, C. Ganos, W. Wu, M.S. Okun, The 5 pillars in Tourette syndrome deep brain stimulation patient selection, Neurology 96 (2021) 664–676, https://doi.org/10.1212/WNL.0000000000011704.
[12] J.C. Baldermann, T. Schüller, D. Huys, I. Becker, L. Timmermann, F. Jessen, V. Visser-Vandewalle, J. Kuhn, Deep brain stimulation for Tourette-syndrome: a systematic review and meta-analysis, Brain Stimul. 9 (2016) 296–304, https://doi.org/10.1016/j.brs.2015.11.005.
[13] L. Wehmeyer, T. Schüller, J. Kiess, P. Heiden, V. Visser-Vandewalle, J. C. Baldermann, P. Andrade, Target-specific effects of deep brain stimulation for Tourette syndrome: a systematic review and meta-analysis, Front. Neurol. 12 (2021), https://doi.org/10.3389/fneur.2021.769275.
[14] B. Kakusa, S. Saluja, W.J. Tate, F.M. Espil, C.H. Halpern, N.R. Williams, Robust clinical benefit of multi-target deep brain stimulation for treatment of Gilles de la Tourette syndrome and its comorbidities, Brain Stimul. 12 (2019) 816–818, https://doi.org/10.1016/j.brs.2019.02.026.
[15] P. Coubes, C. Saleh, V. Gonzalez, L. Cif, Deep brain stimulation of the globus pallidus internus and Gilles de la Tourette syndrome: toward multiple networks modulation, Surg. Neurol. Int. 3 (2012) 127, https://doi.org/10.4103/2152-7806.95424.
[16] D. Martinez-Ramirez, J. Jimenez-Shahed, J.F. Leckman, M. Porta, D. Servello, F.-G. Meng, J. Kuhn, D. Huys, J.C. Baldermann, T. Foltynie, M.I. Hariz, E.M. Joyce, L. Zrinzo, Z. Kefalopoulou, P. Silburn, T. Coyne, A.Y. Mogilner, M.H. Pourfar, S. M. Khandhar, M. Auyeung, J.L. Ostrem, V. Visser-Vandewalle, M.-L. Welter, L. Mallet, C. Karachi, J.L. Houeto, B.T. Klassen, L. Ackermans, T. Kaido, Y. Temel, R.E. Gross, H.C. Walker, A.M. Lozano, B.L. Walter, Z. Mari, W.S. Anderson, B. K. Changizi, E. Moro, S.E. Zauber, L.E. Schrock, J.-G. Zhang, W. Hu, K. Rizer, E. H. Monari, K.D. Foote, I.A. Malaty, W. Deeb, A. Gunduz, M.S. Okun, Efficacy and safety of deep brain stimulation in Tourette syndrome the international Tourette syndrome deep brain stimulation public database and registry, JAMA Neurol. 75 (3) (2018) 353.
[17] Z. Kefalopoulou, L. Zrinzo, M. Jahanshahi, J. Candelario, C. Milabo, M. Beigi, H. Akram, J. Hyam, J. Clayton, L. Kass-Iliyya, M. Silverdale, J. Evans, P. Limousin, M. Hariz, E. Joyce, T. Foltynie, Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double-blind, randomised crossover trial, Lancet Neurol. 14 (2015) 595–605, https://doi.org/10.1016/S1474-4422(15)00008-3.
[18] X.-H. Zhang, J.-Y. Li, Y.-Q. Zhang, Y.-J. Li, Deep brain stimulation of the Globus pallidus internus in patients with intractable Tourette syndrome, Chin. Med. J. (Engl) 129 (2016) 1022–1027, https://doi.org/10.4103/0366-6999.180512.
[19] B.R. Ferreira, J.L. Pio-Abreu, C. Januário, Tourette's syndrome and associated disorders: a systematic review, Trends Psychiatry Psychother. 36 (2014) 123–133, https://doi.org/10.1590/2237-6089-2014-1003.
[20] M.Y.C. Cheung, J. Shahed, J. Jankovic, Malignant Tourette syndrome, Mov. Disord. 22 (2007) 1743–1750, https://doi.org/10.1002/mds.21599.
[21] P. Richer, T.V. Fernandez, Tourette syndrome: bridging the gap between genetics and biology, Mol. Neuropsychiatry 1 (2015) 156–164, https://doi.org/10.1159/000439085.
[22] A.M. Levy, P. Paschou, Z. Tümer, Candidate genes and pathways associated with gilles de la tourette syndrome—where are we? Genes (Basel). 12 (2021) https://doi.org/10.3390/GENES12091321.