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PARKINSONISM AFTER INTERNAL *GLOBUS PALLIDUS* DEEP BRAIN STIMULATION IN DYSTONIA

TÂNIA SOFIA MENESES LAMPREIA

ORIENTADOR: PROFESSOR DOUTOR MIGUEL VILHENA SOARES COELHO

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Tese especialmente elaborada para obtenção
do grau de Mestre em Neurociências

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RESUMO

Introdução: A distonia é uma doença do movimento caracterizada por posturas e movimentos involuntários, frequentemente repetitivos e padronizados, com uma importante heterogeneidade fenotípica e etiológica. Apesar de classicamente considerada uma doença dos gânglios da base, os modelos fisiopatológicos mais recentes sugerem um envolvimento mais abrangente de redes neuronais implicadas no controlo do movimento. A cirurgia de estimulação cerebral profunda (DBS) no *globus pallidus* interno (GPi) é um tratamento bem estabelecido para a distonia quando a terapêutica médica não se mostra suficiente, embora os seus mecanismos de ação não estejam, ainda, totalmente esclarecidos. Alguns doentes desenvolvem sinais parkinsónicos meses após GPi-DBS para a distonia, incluindo alterações da marcha com *freezing* (FOG), mas não há estudos que tenham abordado as características cirúrgicas e da estimulação nestes casos e o mecanismo subjacente permanece desconhecido.

Objetivo: Avaliar a frequência e os fatores preditores de parkinsonismo após DBS do GPi numa coorte de doentes com distonia; descrever as características clínicas e as alterações aos parâmetros de estimulação realizadas para melhoria do parkinsonismo.

Métodos: Foi realizado um estudo observacional, retrospetivo, longitudinal de doentes com distonia submetidos a DBS bilateral no GPi no Departamento de Neurociências do Hospital de Santa Maria (HSM) entre 2010 e 2021. Foram excluídos os doentes intervencionados antes dos 18 anos, os doentes com DBS unilateral ou em localizações diferentes do GPi. Os processos clínicos foram revistos para recolha de dados demográficos, clínicos e cirúrgicos.

Resultados: Um total de 43 doentes com distonia submetidos a DBS bilateral do GPi foram incluídos. 22 (55.1%) eram mulheres, a idade média de início da distonia foi de 26.33 (±22.29) anos, idade média à data da DBS de 45.35 (±16.97) anos e tempo médio de duração da distonia à data da DBS de 19.12 (±15.14) anos. O tempo médio de seguimento pós-operatório foi de 83.6 (±41.25) meses. 28 (68.1%) tinham distonia generalizada, 5 (11.6%) segmentar e 4 (9.3%) focal cervical. A maioria (n=24, 55.8%) tinha distonia isolada, 9 (20.9%) combinada e em 10 (23.3%) a distonia associava-se a outros sinais neurológicos ou sistémicos. Em 21 (48.8%) a distonia era idiopática esporádica, em 15 (34.9%) adquirida, 6 (14%) tinham distonia hereditária e 1 idiopática familiar. Sete (16.28%) desenvolveram parkinsonismo numa média de 30.43 (±28.66) meses pós DBS. A bradicinésia foi o sinal mais frequente à apresentação, mas nunca isoladamente. Os

sinais parkinsónicos progrediram ao longo de meses e, quando plenamente manifesto, o FOG era o sinal mais comum, seguido de alterações da marcha e bradicinésia. Não foram identificadas diferenças estatisticamente significativas entre o grupo com e o grupo sem parkinsonismo quanto à idade de início da distonia (p=.31), ao tipo de distonia (p=1, p=.87 e p=.55), à idade à data da DBS (p=.50), ao tempo de evolução da distonia à data da DBS (p=.84), à medicação (p=.32, p=.42, p=.65 e p=1) ou ao benefício da distonia com a DBS (p=.74). Em relação aos parâmetros cirúrgicos, nos doentes que desenvolveram parkinsonismo o valor do anel no hemisfério direito foi significativamente inferior (mediana 71.30 vs 77.80, p=.03) e a profundidade da ponta do elétrodo no hemisfério esquerdo significativamente superior (mediana 42 vs 41.5, p=.04) quando comparado com o grupo sem parkinsonismo. Não foram encontradas diferenças estatisticamente significativas entre os dois grupos em relação às coordenadas funcionais (hemisfério direito X p=.18, Y p=.21, Z p=.61, hemisfério esquerdo X p=.49, Y p=.13, Z p=.75), elétrodo final (p=.07 e p=.85), valor do anel no hemisfério esquerdo (p=.14), valor do arco (p=.25 e p=.93), profundidade do elétrodo no hemisfério direito (p=.11) e parâmetros de estimulação (hemisfério direito: tipo de estimulação p=.31, cátodo p=.89, voltagem p=.47, frequência p=.30, largura de pulso p=.32, hemisfério esquerdo: tipo de estimulação p=.71, cátodo p=1, voltagem p=.19, frequência p=.30, largura de pulso p=.53). Ao longo de 34.71 (±21.21) meses foi realizada uma média de 11.43 (±11.03) alterações aos parâmetros de estimulação por cada doente, com o objetivo de melhorar o parkinsonismo. A alteração de monopolar para bipolar foi realizada um total de 4 vezes, sempre com melhoria do parkinsonismo, mas agravamento da distonia em 50% das vezes. A seleção de contactos mais dorsais foi realizada 4 vezes, com melhoria do parkinsonismo numa das vezes, sem agravamento da distonia. A redução da voltagem, tentada 11 vezes, melhorou os sinais parkinsónicos 27% das vezes, mas com agravamento da distonia em 2/3 desses e o aumento da voltagem, realizado 13 vezes, melhorou o parkinsonismo 23% das vezes, sem agravamento da distonia. Das 9 reduções da largura de pulso, 33% beneficiaram o parkinsonismo mas com agravamento da distonia em 2/3 desses. Alteração para estimulação monopolar dupla, *interleaving,* contactos mais ventrais e alterações à frequência de estimulação foram realizadas apenas 1 a 2 vezes e sem benefício. A largura de pulso foi aumentada 17 vezes, mas em apenas 1 vez com benefício no parkinsonismo. Em 4 dos 7 doentes o parkinsonismo melhorou, num destes com resolução. Não foram encontradas diferenças estatisticamente significativas entre os parâmetros de estimulação no início do parkinsonismo e após as alterações realizadas. Nos doentes que melhoraram, 1 passou a estimulação bipolar, 2 a cátodos mais dorsais e 3 reduziram a voltagem. Não foram encontradas diferenças significativas na avaliação da distonia antes e após as alterações (p=.75).

Discussão: Este é o primeiro estudo em que é feita uma comparação entre as características clínicas e cirúrgicas dos doentes com e sem parkinsonismo pós GPi-DBS. Nesta coorte de doentes com distonia submetidos a DBS bilateral no GPi, 16.28% dos doentes desenvolveram parkinsonismo em média 30.43 (±28.66) meses após DBS. Comparativamente com outras séries, nesta coorte houve uma maior frequência de parkinsonismo e o seu diagnóstico foi mais tardio, o que pode estar relacionado com diferenças entre as populações e metodologia. À apresentação do parkinsonismo a bradicinésia foi o sinal mais frequente, mas sempre associado a outros sinais e verificando-se um agravamento ao longo dos meses seguintes, o que torna improvável que esta alteração represente apenas a lentidão de movimentos alternados que se pode objetivar na distonia. Quando plenamente manifesto, o sinal mais comum foi o FOG, seguido de alteração da marcha e bradicinésia. Três doentes cumpriram critérios formais para parkinsonismo e em apenas 1 doente se registou tremor de repouso. Estes aspetos vão ao encontro do que está reportado na literatura. Não foram encontradas diferenças clínicas, nomeadamente em relação à distonia, entre os doentes com e sem parkinsonismo. Na maioria dos parâmetros cirúrgicos não foram, também, encontradas diferenças. Os doentes com parkinsonismo apresentam valores de ângulo do anel no hemisfério direito inferiores aos doentes sem parkinsonismo. O ângulo do anel é responsável por uma rotação no plano sagital e, neste caso, condiciona uma deslocação do volume de tecido ativado (VTA) para áreas mais anteriores e ventrais. Nos doentes com parkinsonismo foi também identificado uma maior profundidade do elétrodo do hemisfério esquerdo em relação aos doentes sem parkinsonismo, o que pode traduzir uma deslocação da VTA para regiões inferiores ou mais ventrais. Diversos estudos mostram que a área posteroventral lateral do GPi é o alvo preferencial para o tratamento da distonia. Adicionalmente, há evidência de efeitos opostos com a estimulação de regiões mais ventrais ou mais dorsais no GPi, com agravamento da acinésia e da marcha mas melhoria da distonia e discinésias quando a estimulação é na zona ventral e melhoria da acinésia mas agravamento da distonia e discinésias com estimulação em regiões mais dorsais. Nos doentes que desenvolveram parkinsonismo nesta coorte, é possível que a VTA englobe regiões mais ventrais do GPi e/ou estruturas adjacentes no plano sagital, como o *Globus Pallidus* externo (mais anterior e posterior, para além de mais lateral) e a região subpalidal. O fenótipo dos doentes que desenvolveram parkinsonismo é o de um parkinsonismo com alterações precoces da marcha, em particular, com FOG. Admite-se que a estimulação do GPi possa inibir a atividade do núcleo pedunculopôntico (PPN), uma estrutura do tronco cerebral implicada na fisiopatologia do *freezing.* Esta relação entre estimulação do GPi e modulação da atividade do PPN com impacto no parkinsonismo foi já mostrada em estudos com macacos 1-metil-4-fenil-1,2,3,6-tetrahidropiridina (MPTP). Nos doentes que obtiveram

benefício no parkinsonismo, uma modificação da VTA induzida pela estimulação bipolar e redução da voltagem ou deslocação por contactos mais dorsais, poderá ter contribuído para a melhoria clínica, embora a ausência de diferenças significativas entre os parâmetros antes e após as alterações, não nos permita conclusões definitivas.

Conclusão: O aparecimento de sinais parkinsónicos após DBS do GPi para tratamento da distonia pode ocorrer anos após a cirurgia e caracteriza-se por um fenótipo predominantemente acinético com alterações da marcha e FOG. As características da distonia e a maioria dos aspetos relacionados com a cirurgia não parecem determinar o aparecimento do parkinsonismo. Diferenças na localização da VTA podem estar na génese deste efeito adverso, eventualmente por estimulação de estruturas adjacentes ou diferentes redes neuronais. Estudos de análise de VTA e de mapas de conectividade poderão ajudar a caracterizar as estruturas implicadas no parkinsonismo pós DBS no GPi e na fisiopatologia do FOG.

Palavras-chave: distonia, parkinsonismo, *freezing* da marcha, estimulação cerebral profunda, *globus pallidus* interno.

ABSTRACT

Introduction: Dystonia is a movement disorder characterized by involuntary movements and postures for which deep brain stimulation (DBS) in the internal Globus pallidus (GPi) is an established treatment. Some patients are known to develop parkinsonism after GPi-DBS for dystonia, but no studies have addressed the baseline clinical and DBS-related features in these patients.

Objective: To evaluate the frequency and predictors of parkinsonism after GPi-DBS in dystonia; to describe the clinical characteristics and stimulation changes performed to improve parkinsonism.

Methods: In this retrospective longitudinal study, adult dystonia patients submitted to bilateral GPi-DBS between 2010 and 2021 at the Neuroscience Department of the HSM were included and the medical records reviewed.

Results: A total of 43 patients were included, 22 (51.2%) females, with a mean age of dystonia onset of 26.33 (±22.29) years old and mean age at DBS of 45.35 (±16.97) years old. 28 (68.1%) had generalized dystonia, most commonly idiopathic sporadic (48.8%). Seven patients (16.28%) developed parkinsonism at a mean of 30.43 (±28.66) months after DBS. When fully-blown, FOG was the most frequent sign. In the parkinsonism group, the right ring and the left lead depth were significantly different from the non-parkinsonism group (median 71.30 vs 77.80, p=.03 and median 42 vs 41.5, p=.04, respectively). Each patient was submitted to a mean of 11.43 (±11.03) stimulation changes to improve parkinsonism, which was achieved in 4.

Discussion: Differences in ring angle and electrode depth may induce a shift in the volume of tissue activated (VTA), involving different GPi areas and neighbor structures. More ventral GPi activation is known to worsen akinesia and gait and GPi stimulation can alter pedunculopontine (PPN) function and cause FOG.

Conclusions: VTA analysis and connectivity maps studies could further explore our hypothesis and add knowledge to FOG pathophysiology.

Key-words: dystonia, parkinsonism, freezing of gait, deep brain stimulation, internal globus pallidus.

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TABLE ÍNDEX

ABBREVIATIONS LIST

ACDY5	Adenylate cyclase 5
BFMRS	Burke-Fahn-Marsden Dystonia Rating scale
CGIC	Clinical Global Impression of change
CNS	Central Nervous System
CRF	Case report forms
DBS	Deep brain stimulation
DYT	Dystonia
FOG	Freezing of gait
GPe	Globus Pallidus externus or external Globus Pallidus
GPi	Globus Pallidus internus or internal Globus Pallidus
Hz	Hertz
HSM	Hospital de Santa Maria
L	Left hemisphere
MPTP	1-metil-4-fenil-1,2,3,6-tetrahidropiridina
N	Sample size (number)
NoPark	Group without parkinsonism
PANK2	Pantothenate kinase 2 gene
Park	Group with parkinsonism
PD	Parkinson disease
PKAN	Pantothenate kinase associated neurodegeneration
PPN	Pedunculopontine nucleus
PW	Pulse width
R	Right hemisphere
SD	Standard deviation
STN	Subthalamic nucleus

TOR1A	Torsin family 1 member A gene
TWSTRS	Toronto Western Spasmodic Torticollis Rating scale
V	Volt
VPS13A	Vacuolar protein sorting 13 homolog A gene
VTA	Volume Tissue Activated
μs	microsecond

INTRODUCTION

Dystonia is a movement disorder characterized by involuntary movements and postures, often repetitive and patterned, with an important clinical and etiologic heterogeneity [Albanese et al. 2013]. Albeit classically described as a basal ganglia disorder, recent pathophysiologic studies support a wider model including changes in sensorimotor integration, inhibitory dysfunction at several levels of the central nervous system (CNS) and maladaptive plasticity [Bruggemann 2021] involving the basal ganglia, thalamus, cerebellum and different cortical areas.

Bilateral internal *globus pallidus* (GPi) deep brain stimulation (DBS) surgery is an established treatment for generalized, segmental and focal cervical dystonia, when medical treatment is not effective [Krack et al. 2016, Vidailhet et al. 2005, Kupsch et al. 2006], being associated with motor and quality of life improvement [Loher et al. 2008, Mehrkens et al. 2009]. Response to DBS is, nevertheless, variable, and although some dystonia subtypes seem to benefit more than others, the reasons for this clinical response variability are not yet fully understood [Fox and Alterman, 2015].

The main target for dystonia treatment is the sensorimotor region of the GPi, the lateral posteroventral area. Several pathophysiological mechanisms have been proposed to explain the clinical effect of DBS in dystonia, namely the possibility of electrical stimulation modulating the pathological neuronal activation patterns, such as the neuronal discharges in the 4-12 Hz band [Barow et al. 2014], modifications of the pallidal output and subsequent modulation of motor neuronal circuits and networks, as the pallidal-thalamic-cortical pathway [Herrington et al. 2016].

The clinical effect of GPi-DBS in dystonia develops over days, weeks or even months, especially for the more tonic (rather than phasic) postures [Krauss et al. 2004], which adds more complexity to the stimulation adjustments during follow-up. Along with the symptomatic improvement, some authors have reported the emergence of parkinsonian features as a side effect, such as hypokinesia and gait changes [Zauber et al. 2009, Schrader et al. 2011]. These features have been described in generalized, segmental and focal dystonia, involving regions not affected by the dystonia itself and are characterized by difficulty in alternating movements [Huebl et al. 2015], micrography [Blahak et al. 2011, Schrader et al. 2011], gait change with step size reduction [Jakob et al. 2015] and increased cadence [Wolf et al. 2016], postural reflex changes [Jakob et al. 2015] and freezing of gait (FOG) [Schrader et al. 2011]. Although considered a rare side effect [Volkmann et al. 2012], post-DBS gait changes were seen in 6 of 71 patients (8.5%). Albeit being referred as mild,

these motor changes have functional impact [Berman et al. 2009], potentially causing serious morbidity due to falls [Schrader at al. 2011].

The relationship between the occurrence of parkinsonism after GPi-DBS and dystonia or DBS features is not yet well established. Ostrem (2007) showed a trend towards an association between motor complications and post-DBS dystonia improvement [Ostrem et al. 2007]. Remission of parkinsonism is seen when stimulation is turned OFF, gradually recurring when ON [Jakob et al. 2015, Schrader et al. 2011] and improving when frequency is reduced, at the cost of dystonia worsening [Huebl et al, 2015]. No association was found between parkinsonism and other stimulation parameters [Schrader et al. 2011] or proximity to the internal capsule [Berman et al. 2009]. Specific contact localization in the sensorimotor GPi may be relevant for clinical heterogeneity regarding dystonia outcomes [Horn et al. 2022] but also adverse events. In Parkinson Disease (PD) patients, stimulation of more ventral regions of the GPi improved dyskinesias while worsening gait and akinesia, and more dorsal stimulations had an opposite clinical effect [Bejjani et al. 1998]. Schrader (2011) also suggested that GPi stimulation may influence the pedunculopontine nucleus (PPN) activity, a central structure for gait and FOG [Schrader et al. 2011].

Overall, data regarding parkinsonism after GPi-DBS in dystonia in scarse and the pathophysiological mechanisms unknown.

RESEARCH PURPOSE

To study the frequency, clinical features and predictors of parkinsonism after GPi-DBS in dystonia, as well as treatments performed to improve this side effect.

OBJECTIVE

The primary objective was to evaluate the frequency and predictors (clinical and DBS-related) of parkinsonism after bilateral GPi-DBS in a dystonia population.

Secondary objectives were to characterize the clinical features of the parkinsonism and to analyze the stimulation parameters changes performed in order to reach clinical improvement.

METHODS

Study type and population

An observational, retrospective, longitudinal study was conducted. All patients submitted to DBS for dystonia treatment, at the Neurosciences department of Hospital de Santa Maria (HSM) between 2010 and 2021, were considered for inclusion and their medical records reviewed. Inclusion criteria were the presence of dystonia accordingly to the 2013 consensus update in phenomenology and classification of dystonia [Albanese et al. 2013], bilateral GPi-DBS, post-DBS follow-up of at least 6 months and age at DBS $\geq$ 18 years old. Patients were excluded if DBS was unilateral or not in the GPi, if age at DBS was less than 18 years old, if follow-up after DBS was less than 6 months or if parkinsonian signs were present before DBS.

DBS procedure

Bilateral GPi-DBS was performed between 2010 and 2021 accordingly to the Neurosciences Department DBS protocol. All patients were followed by a Movement Disorders specialist, at the Movement Disorders outpatient clinic of the Neurological Department of HSM. Patients were considered for GPi-DBS if dystonia was insufficiently controlled with medical treatment [Kupsch et al. 2006, Volkmann et al. 2012, Volkmann et al. 2014]. Pre-operatively all patients were submitted to a psychiatric evaluation, a neuropsychological study and brain magnetic resonance (MRI) and were excluded from surgery if there was evidence of major psychiatric disorders, dementia and brain imaging with signs of significant atrophy and vascular changes. A head computed tomography (CT scan) with DBS protocol was performed 2 days before surgery and a new head CT with a stereotactic frame was performed at the day of the surgery, both with contrast. For stablishing the target coordinates, GPi standard coordinates (20-22 mm lateral to and 4 mm below the intercommissural line, and 2-3 mm anterior to the intercommissural midpoint) [Schrader et al. 2011] were used and adjusted to patient's brain imaging from CT and MRI using a fusion software (Medtronic® StealthStatins and Boston® Elements). At the day of the surgery a head CT scan with stereotactic frame was performed. Patients underwent bilateral stereotactic surgery under local anesthesia and sedation. Intraoperative

microelectrode recording and macroelectrode stimulation were used to locate the optimal site for implanting the DBS lead, with the patient awaken. Medtronic quadripolar leads or Boston directional lead with 8 contacts were used. A neurostimulator was implanted in an infraclavicular pocket on the same day after lead implantation. After surgery a CT scan was performed for lead placement confirmation and stimulation parameters were progressively adjusted in order to achieve the best clinical response.

Demographic, clinical and surgical variables

All medical records were reviewed to extract the following demographic, clinical and surgical data: age at dystonia onset, gender, age at DBS, duration of dystonia at DBS, time of follow-up after DBS, dystonia classification regarding body distribution, temporal pattern, associated clinical features and etiology [Albanese et al. 2013], psychiatric comorbidities, neuropsychologic evaluation results, dystonia evaluation pre and post DBS (Burke-Fahn-Marsden Dystonia Rating scale (BFMDRS) [Burke R et al 1985] and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [Consky ES et al 1990]), surgical adverse events, DBS stimulator brand, final lead and plastic tip depth of the lead for each hemisphere, functional and stereotactic coordinates, arc and ring angle values for each hemisphere. Contact position scheme here represented following the classic Medtronic® scheme: right hemisphere P0, P1, P2 and P3 (from inferior/ventral to superior/dorsal position) and left hemisphere P8, P9, P10 and P11 (from inferior/ventral to superior/dorsal). When Boston® directional electrodes were used, to the same scheme above we added 3 contacts in P1 and P9 and 3 contacts in P2 and P10: P1C1, P1C2, P1C3, P2C1, P2C2, P2C3 in the right hemisphere and P9C1, P9C2, P9C3, P10C1, P10C2 and P10C3 in the left hemisphere. Stimulation parameters (stimulation type, active contact, voltage, frequency and pulse width) and retrieved at specific time points: at the diagnosis of parkinsonism (for those who developed parkinsonism), 3 to 9 months after DBS (for those who did not develop parkinsonism), at the end of follow up and when changes were performed in order to improve parkinsonism. Stimulation parameters were considered when present for at least 8 weeks during the 6 months preceding these time points [Huebl et al. 2015, Wolf et al. 2016].

The presence of parkinsonism was considered when characteristic clinical features were described in clinical records. Clinical criteria of parkinsonism demand the presence of bradykinesia plus rigidity and or rest tremor [Postuma et al. 2015]. Apart from these core signs, other clinical features such as gait disturbance, freezing of gait (FOG) and postural instability are common in parkinsonian syndromes. As previously reported [Schrader et al.

2011], some patients after GPi-DBS develop a gait disturbance with or without FOG, which is frequently present in patients with parkinsonian syndromes, but that is not sufficient for the diagnosis of parkinsonism if the core clinical features are absent. For simplicity reasons, from now on in this manuscript, the term parkinsonism will be used for those patients who fulfil clinical criteria of parkinsonism and also for those who have characteristic clinical features, as gait disturbance and FOG, although may not entirely fulfill the clinical criteria.

Data regarding parkinsonism after DBS was retrieved, including date of onset, clinical features at presentation, clinical features when fully-blown and clinical features at the end of follow-up. The number and type of stimulation changes for clinical improvement in those with parkinsonism and information regarding the clinical benefit for each change were also collected, along with stimulation parameters at the diagnosis of parkinsonism, after the stimulation changes for parkinsonism improvement (in those who developed parkinsonism) and at the end of follow-up for every patient.

We used the Clinical Global Impression of Change Scale (CGIC) to evaluate dystonia improvement after DBS: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse. For this purpose, we selected two time points in medical records: T1 (time 1): at the diagnosis of parkinsonism in those with parkinsonism and at 3-9 months after surgery in those without parkinsonism; T2 (time 2): at the end of follow-up for all. In those without parkinsonism T1 was chosen based on data from previous studies having shown that parkinsonism after GPi-DBS usually emerges 3-9 months after surgery [Schrader et al. 2011, Wolf et al. 2016].

CGIC was also used to evaluate parkinsonism improvement at the end of follow-up.

In those who developed parkinsonism, an additional qualitative dichotomic evaluation of parkinsonism and or dystonia was performed after each stimulation parameters change: parkinsonism improved yes or no; dystonia worsened yes or no.

The study protocol and case report forms (CRF's) were approved by the Centro Academico de Medicina de Lisboa (CAML) Ethical Committee.

Statistical analysis

Data from the CRF's were transferred for an electronic data base in SPSS (version 24). A descriptive analysis was performed to characterize demographic and clinical aspects of the population as well as DBS related features. The group of patients who developed parkinsonism was also characterized separately. For comparison between the two groups (patients with parkinsonism and patients without parkinsonism) we used non-parametric tests. Fisher Exact test was used for categorical variables (gender, dystonia classification,

neuropsychologic evaluation, psychiatric comorbidities, final lead, stimulation type and active contacts) and Mann-Whitney for numeric variables (age at dystonia onset, age at DBS, time from dystonia onset to DBS, functional coordinates, ring, arc and plastic tip depth, stimulation parameters (voltage, frequency and pulse width), dystonia improvement (CGIC)). For comparison of numeric variables of dependent samples (dystonia evaluation at T1 and T2 and stimulation parameters before and after parkinsonism) we used the Wilcoxon signed-rank test and the sign test. For comparisons of categorial variables of dependent samples (stimulation type and contacts) we used the Marginal Homogeneity test. For categorial dichotomic variables of dependent samples, McNemar test was used. A *p* value of <.05 was considered to be significant.

RESULTS

A total of 55 patients with dystonia submitted to DBS between 2010 and 2021 were identified. 12 patients were excluded from the study: 1 had Subthalamic Nucleus (STN) stimulation, 1 and GPi+Ventral Intermedial Nucleus of the thalamus (VIM) stimulation, 2 had unilateral GPi stimulation and 8 were pediatric patients (DBS performed before age 18).

Clinical and demographic characteristics

A total of 43 patients were included for analysis. Clinical and demographic characteristics of these patients are presented in Table 1.

22 were female and 21 males. The mean age at dystonia onset was 26.23 (±22.29) years old, with a minimum of 0 (during the first year) and a maximum of 68 years old. 28 patients (68.1%) had generalized dystonia, 20 of them with lower limb involvement, 14 (6%) had segmental dystonia, 5 (11.6%) multifocal and 4 (9.3%) focal (cervical). Apart from 1 patient with paroxysmal dystonia, all the other patients had a persistent pattern. Dystonia was isolated in 24 cases (55.8%), associated with other movement disorder (combined) in 9 (20.9%) and associated with other neurological or systemic signs in 10 (23.3%). In the combined dystonia group, 9 patients had chorea, 5 had myoclonus, 3 had parkinsonism, 2 had tics and 2 had ataxia (4 patients had more than one additional movement disorder). Regarding the 10 patients with other associated features, 5 had pyramidal signs, 2 had epilepsy and 2 had deafness. Idiopathic sporadic was the most common etiology (n=21, 48.8%), whereas 15 (34.9%) had acquired dystonia, 6 patients (14%) had inherited dystonia

and 1 had idiopathic familial dystonia. Among the cases of acquired dystonia, 8 had hypoxic-anoxic encephalopathy at birth, 5 had tardive dystonia (post neuroleptics), 1 was post-traumatic and in 1 patient was due to kernicterus. In the group of inherited dystonia, 2 had DYT 1/DYT-TOR1A gene mutations, 2 had PKAN-PANK2 mutations, 1 ADCY5 mutation and 1 chorea-acanthocytosis (VPS13A mutation).

BFMRS before DBS was available in 26 patients (motility score) and 17 patients (disability score). In these, the mean motility score was 39.21 (±22.97) and the mean disability score was 10.06 (±7.49).

Neuropsychological evaluation was normal in 15 cases (34.9%), 14 patients (32.6%) had a multiple domain Mild Cognitive Deficit (MCI) and 9 (20.9%) a one domain MCI. Most patients (n=23, 53.5%) had no psychiatric comorbidity, 10 (23.3%) had depression, 4 (9.3%) had depression and anxiety, 3 (7%) had anxiety, 2 had the diagnosis of Bipolar disease and 1 had psychosis.

Table 1: clinical and demographic characteristics of the study population

Sex (F) *(%, N)*	51.2 (22)
Age at dystonia onset (years) *(mean ± SD)*	26.23 (±22.29) [0-68]
Body distribution – *n* (%)	
Focal	4 (9.3)
Segmental	6 (14)
Multifocal	5 (11.6)
Generalized	28 (65.1)
With lower limb	20
Without lower limb	8
Temporal pattern – *n* (%)	
Persistent	42 (97.7)
Paroxysmal	1 (2.3)
Associated features – *n* (%)	
Isolated	24 (55.8)
Combined	9 (20.9)
Myoclonus	5
Parkinsonism	3
Chorea	9
Tics	2
Ataxia	2
Other neurological or system signs	10 (23.3)
Pyramidal	5
Epilepsy	2
Deafness	2
Aetiology – *n* (%)	
Inherited	6 (14)
(2 DYT-TOR1A, 2 PKAN-PANK2, 1 ADCY5, 1 VPS13A)	
Acquired	15 (34.9)
Hypoxic-anoxic	8
Tardive	5
Kernicterus	1
Post-traumatic	1
Idiopathic sporadic	21 (48.8)
Idiopathic familial	1 (2.3)
BFMRS preDBS *(mean ± SD)*	
Motility (n=26)	39.21 (±22.97)
Disability (n=17)	10,06 (±7.49)
Neuropsychology - *n (%) (n=38)*	
Normal	15 (34.9)
MCI - 1 domain	9 (20.9)
MCI – multidomain	14 (32.6)
Psychiatric comorbidity – *n* (%)	
Normal	23 (53.5)
Anxiety	3 (7)
Depression	10 (23.3)
Anxiety + depression	4 (9.3)
Bipolar	2 (4.7)
Psychosis	1 (2.3)

ADCY5= adenylate cyclase 5, BFMRS= Burke-Fahn-Marsden Dystonia Rating scale, DBS= deep brain stimulation, DYT= dystonia, F= female, n=sample size, PANK2= pantothenate kinase 2, PKAN= Pantothenate kinase associated neurodegeneration, SD= standard deviation, TOR1A= torsin family 1 member A, VPS13A= Vacuolar protein sorting 13 homolog A, %= percentage

DBS aspects and follow-up

Patients were submitted to DBS at a mean age of 45.35 (±16.97), the youngest with 18 years old and the eldest at 77 years of age (Table 2), with a mean disease duration of 19.12 (±15.14) years.

In the right hemisphere, the most frequent final lead was central, in 53.5% (23) of the patients, followed by lateral (23.3% (10)) and anterior (20.9% (9)). The lead tip was positioned at a mean of 1.1 (±2.04) mm deep from the target (as the target is set at 40mm). The mean values of the functional coordinates were: X: 20.67 (±1.83), Y: 2.0 (±1.55) and Z: -1.86 (±1.41). The mean ring value was 76.68 (±8.58)° and the arc 82.16 (±4.99)°.

In the left hemisphere the central electrode was also the most frequent (72.1% (31)), followed by the anterior (14% (6)) and the lateral (11.6% (5)). The lead tip was introduced at a mean of 1.3 (±1.28)) mm deeper to the target. Functional coordinates mean values were: X: -20.61 (±1.57), Y: 1.56 (±1.30) and Z: -2.17 (±1.73). Left ring mean was 75.43 (±9.86)° and left arc 96.37 (±5.26)°.

No surgical related adverse events were reported in 86% of patients. 6 patients had surgery adverse events: 1 case of system infection leading to lead reimplantation, 1 case of reimplantation of the right lead due to absent clinical effect, 1 case of asymptomatic subarachnoid haemorrhage, 1 case of asymptomatic caudate ischemia, 1 case of delirium and 1 late symptomatic oedema with aphasia, who improved after dexamethasone and speech therapy.

After DBS, patients were followed up during a mean of 83.6 (±41.25) months during which each patient had a mean of 23.86 (±11.97) movement disorders clinical appointments. Post-DBS BFMRS was performed 9.71 (±7.41) months after surgery, with a mean motility score of 24.95 (±22.0) (total of 10 patients) and a mean disability score of 7.38 (±5.32) (total of 8 patients). In a total of 9 patients, BFMRS motility score pre and after DBS was available, showing a mean reduction of 17.78 (±15.48) points, representing an improvement of 48.6 (±25.88) %.

The mean dystonia improvement at 13.02 (±15.04) months after DBS, using the CGIC, was 1.58 (±0.76).

Table 2: DBS related clinical and surgical features

Age at surgery *(mean ± SD) [min - max]*		45.35 (±16.97) [18-77]
Disease duration *(mean ± SD)*		19.12 (±15.14)
DBS system brand.	Medtronic® Boston®	41 2
R lead position - *n (%).*	Central Anterior Medial Lateral Posterior	23 (53.5) 9 (20.9) 1 (2.3) 10 (23.3) 0
L lead position – *n (%)*	Central Anterior Medial Lateral Posterior	31 (72.1) 6 (14) 0 5 (11,6) 1 (2.3)
R lead depth *(mean ± SD)*		41.1 (±2.04)
L lead depth *(mean ± SD)*		41.3 (±1.28)
R functional coordinates *(mean ± SD)*	X Y Z	20.67 (±1.83) 2.0 (±1.55) -1.86 (±1.41)
L functional coordinates *(mean ± SD*)	X Y Z	-20.61 (±1.57) 1.56 (±1.30) -2.17 (±1.73)
R Arc *(mean ± SD)*		82.16 (±4.99)
R Ring *(mean ± SD)*		76.68 (±8.58)
L Arc *(mean ± SD)*		96.37 (±5.26)
L Ring *(mean ± SD)*		75.43 (±9.86)
Surgical adverse events (AE) – *n* (%)		
	No AE System infection (with reimplantation) Reimplantation (unilateral) Brain haemorrhage (asymptomatic) Ischaemic lesion (asymptomatic) Delirium Late symptomatic oedema	37 (86) 1 (2.3) 1 (2.3) 1 (2.3) 1 (2.3) 1 (2.3) 1 (2.3)
Follow-up duration (months) *(mean ±SD)*		83.6 (±41.25)
Nºclinical appointments *(mean ±SD)*		23.86 (±11.97)
BFMRS post-DBS	Motility (n=10) Disability (n=8) Time after DBS (months)	24.95 (±22.0) 7.38 (±5.32) 9.71 (±7.41)
Dystonia evaluation CGIC *(mean ±SD)*		1,58 (±0.76)
Evaluation time *(months post-DBS) (mean ±SD)*		13.02 (±15.04) [2-84] Median: 7,0

AE= adverse events, CGIC= clinical global impression of change scale, max= maximum, min= minimum, n= sample size, Nº= number, L= left hemisphere, R= right hemisphere, SD=standard deviation, %= percentage

Patients with parkinsonism: clinical and DBS features

Seven patients (16.28%) developed parkinsonism during follow-up. Clinical and surgical characteristics of these 7 patients are presented in tables 3 and 4, respectively.

5 patients were female. The age of dystonia onset was 32 **(**±23.71) years old, age at DBS was 49 (± 13.65) years old and time from dystonia onset and DBS was 17 (±12.38) years. 5 patients had generalized dystonia, 4 of them with lower limb involvement, 1 had multifocal and 1 segmental dystonia. There were no patients with focal dystonia. Dystonia was isolated in 5, combined in 1 (with myoclonus) and associated with epilepsy in another patient. 5 patients and idiopathic sporadic dystonia, 1 patient with DYT1/DYT-TOR1A generalized dystonia and 1 had tardive dystonia. The diagnosis of parkinsonism was made at a mean of 30.43 (±28.66) months after DBS, from 2 months in 2 cases to 84 months in 1 case. At the diagnosis of parkinsonism, dystonia improvement (CGIC) was 1.43 (±0.53). At the presentation of parkinsonism, appendicular bradykinesia was present in 5 patients, micrography in 3, FOG, hypophonia and rigidity in 2 each (table 3). Parkinsonism was symmetric in 3, unilateral (left side) in one, asymmetric (more on the right side) in one and of unknown symmetry in 2.

Regarding the DBS features (table 4), in the right hemisphere all the patients had the central lead implanted, the lead tip depth was 1.85 (±0.94) mm from the target, the mean ring value was 70.04 (±7.29), the mean arc value was 84.44 (±4.47) and the mean values of the functional coordinates were: X: 19.95 (±1.16), Y: 2.74 (±1.53) and Z: -2.41 (±1.25).

In the left hemisphere, the central lead was implanted in 6 and the anterior lead in 1, the lead tip was implanted at 2.29 (±1.52) mm deep from the target, the mean ring value was 69.16 (±9.32), the mean arc was 95.59 (±1.69) and the functional coordinates had the following mean values: X: -20.16 (±0.65), Y: 2.29 (±0.89) and Z: -2.44 (±1.43).

At the diagnosis of parkinsonism, the stimulation parameters (which were the selected parameters during the 6 months period before parkinsonism diagnosis) were right monopolar stimulation in all, 6 of whom in the P0 contact and 1 in P1 contact, with a mean voltage of 3.21 (±0.66) Volts (V), a mean frequency of 132.86 (±7.56) Hz and a mean pulse width (PW) of 88.57 (±33.38) μs. In the left hemisphere, stimulation was monopolar in all but one patient who had bipolar stimulation. The P8 was the chosen negative contact in 5 and P9 in 2 patients. The patient with bipolar stimulation had the cathode in P8 and the anode in P9 (P8-/P9+). The mean left voltage was 3.33 (±0.6) V, the mean frequency 132.86 (±7.56) Hz and the mean PW 97.14 (±50.57) μs.

Table 3: Clinical features of the 7 patients who developed parkinsonism

N=7	
Sex (F) – *n* (%)	5 (71.4)
Age at dystonia onset *(mean ±SD)*	32 (±23.71)
Age at DBS *(mean ±SD)*	49 (±13.65)
Dystonia duration (at DBS) (years) *(mean ±SD)*	17 (±12.38)
Dystonia classification	
Body distribution	
Focal	0
Segmental	1
Multifocal	1
Generalized	5
with lower limb	4
without lower limb	1
Associated features	
Isolated	5
Combined (myoclonus)	1
With other features (epilepsy)	1
Etiology	
Inherited (DYT1/DYT-TOR1A)	1
Acquired (Tardive syndrome)	1
Idiopathic sporadic	5
Dystonia evaluation (CGIC)* *(mean ±STD)*	1.43 (±0.53)
Parkinsonism diagnosis	
Time from DBS *(months) (mean ±SD)*	30.43 (±28.66) [2-84]; median 28
Clinical presentation	
Bradykinesia *1	5
Micrography	3
FOG	2
Hypophonia	2
Rigidity	2
Freezing (non-FOG)	1
Gait	1
Falls	1
Postural Instability	0
Rest tremor	0

CGIC= Clinical Global Impression of change, DBS= Deep Brain Stimulation, DYT1= DYT1 Dystonia caused by TOR1A mutations, F=females, FOG= freezing of gait, SD=standard deviation, TOR1A= torsin family 1 member A

Table 4: DBS features and last stimulation parameters before parkinsonism in patients who developed parkinsonism

Right hemisphere	
Final lead	
Central	7
Lead tip depth *(mean ± SD)*	41.85 (±0.94)
Functional coordinates *(mean ± SD)*	
X	19.95 (±1.16)
Y	2.74 (±1.53)
Z	-2.41 (±1.25)
R Ring *(mean ± SD)*	70.04 (±7.29)
R Arc *(mean ± SD)*	84.44 (±4.47)
Stimulation parameters	
Type	
Monopolar	7
Negative contact	
P0	6
P1	1
Voltage (V)	3.21 (±0.66)
Freq (Hz)	132.86 (±7.56)
PW (μs)	88.57 (± 33.38)
Left hemisphere	
Final lead	
Central	6
Anterior	1
Lead tip depth *(mean ± SD)*	42.29 (±1.52)
Functional coordinates *(mean ± SD)*	
X	-20.16 (±0.65)
Y	2.29 (±0.89)
Z	-2.44 (±1.43)
L Ring *(mean ± SD)*	69.16 (±9.32)
L Arc *(mean ± SD)*	95.59 (±1.69)
Stimulation parameters	
Type	
Monopolar	6
Bipolar	1
Negative contact	
P8	5
P9	2
Positive Contact	
P9	1
Voltage (V)	3.33 (±0.6)
Freq (Hz)	132.86 (±7.56)
PW (μs)	97.14 (±50.57)

L= left hemisphere, Hz= hertz, PW= pulse width, R= right hemisphere, SD= standard deviation, V=Volts, μs= microseconds.

Comparisons between patients with and without parkinsonism

When comparing patients who developed parkinsonism (Park) with those who did not developed parkinsonism (NoPark), we find no significant differences in age at dystonia onset (median 18 vs 17.50, U= 94.5, z= -1.04, p=.31), gender (5 vs 17 females, two-tailed p=.41), age at DBS (median 46 vs 43, U=105.00, z=-0.69, p=.50) and dystonia duration at DBS (median 18 vs 16.85, U=119.5, z=-1.37, p=.84). No differences were found in medication (anticholinergics, tetrabenazine, baclofen, botulinum toxin injections, levodopa, antidepressants and benzodiazepines) between the two groups (table 5). Surgical adverse events were, also, similar between the two groups (p=.68).

There were also no differences regarding dystonia subtypes, namely body distribution of dystonia (two-tailed p=1), dystonia associated features (two-tailed p=.87) and etiology (two-tailed p=.55). No differences were found in dystonia benefit (CGIC) after DBS (median 1 vs 1.5, U=113.00, z=-0.47, p=.74) and its time of evaluation after surgery (median 27 vs 7, p=.09).

In what concerns surgical aspects, we found no significant differences between the lead position (right hemisphere p=.07, left hemisphere p=.84), right lead tip depth (median 42 vs 41.5, U=78.00, z=-1.62, p=.11), right functional coordinates (X: median 19.99 vs 20.96, U=84.00, z=-1.37, p=.18; Y: median 2.75 vs 2.07, U=87.50, z=-1.27, p=.21; Z: median -2.20 vs -1.97, U=110.00, Z=-0.53, p=.61), right arc (median 85.30 vs 81.05, U=90.50, z=-1.17, p=.25), left functional coordinates (X: median -20.08 vs -20.79, U= 104.5, z=-0.71, p=.49; Y: median 2.75 vs 2.07, U=79.00, z=-1.55, p=.13; Z: median -2.20 vs -1.75, U=116.00, z=-33, p=.75), left ring (median 75.7 vs 75.85, U=80.00, z=-1.5, p=.14) and left arc (median 96.10 vs 95.25, U=123, z=-0.10, p=.93). Significant differences between the two groups were found in the left lead tip depth (median 42 vs 41.5, U=65,00, z=-2.06, p=.04) and the right ring (median 71.30 vs 77.80, U=62.50, z=-2.09, p=.03).

When comparing the stimulation parameters at T1 (meaning at the diagnosis of parkinsonism in Park group and a time point of chronic stimulation between 3 and 9 months after DBS in NoPark group) we found no significant differences between stimulation type (right hemisphere p=.31, left hemisphere p=.71), the selected cathode (right hemisphere p=.89, left hemisphere p=1) voltage (right hemisphere: median 3.4 vs 3, U=103.50, z=-0.75, p=.47; left hemisphere: median 3.5 vs 3, U=86, z=-1.32, p=.19), frequency (right hemisphere: median 130 vs 130, U=112.00, z=-1.23, p=.30; left hemisphere: median 130 vs 130, U=112.00, z=-1.26, p=.30) or pulse width (right hemisphere: median 90 vs 60, U=94.00, z=-1.2, p=.25; left hemisphere: median 60 vs 60, U=106.00, z=-0.74, p=.47). A

further analysis transforming the categorical variables stimulation type and cathode into categorical dichotomic variables (having monopolar stimulation vs not having monopolar stimulation and cathode at the most ventral position (P0/P8) versus cathode at a more dorsal position) did not find any significant differences either (right hemisphere monopolar vs not monopolar, p=.31, left hemisphere monopolar vs not monopolar, p=.65, any hemisphere bipolar vs not bipolar, p=.39, right hemisphere P0 vs not P0, p=.39, left hemisphere P8 vs not P8, p=.69, any hemisphere having any contact not P0/P8 vs not, p=.68).

Table 5: Clinical, DBS and stimulation parameters comparisons between patients with and without parkinsonism

	With Parkinsonism	No Parkinsonism	p
Age at dystonia onset (y) *(mean±SD)*	32 (±23.71) Mdn: 18	25.11(±22.18) Mdn: 17.50	p=.31*
Sex (F) *(mean±SD)*	(71.4) 5	(47.2) 17	p=.41*[1]
Age at DBS (y) *(mean±SD)*	49 (±13.65) Mdn: 46	44.64(±17.62) Mdn:43	p=.50*
Dystonia duration at DBS (y) *(mean±SD)*	17 (±12.38) Mdn: 18	19.53(±15.74) Mdn 16,85	p=.84*
Dystonia – body distribution (n) Focal Segmentar Multifocal generalizada	 0 1 1 5	 4 5 4 23	p=1*[1]
Dystonia subtype – associated features Isoladed Combined With other neurological/systemic features	 5 1 1	 19 8 9	p=.87*[1]
Dystonia etiology Inherited Acquired Idiopathic sporadic Idiopathic familial	 1 1 5 0	 5 14 16 1	p=.55*[1]
Dystonia benefit *(mean±SD)*	1.43 (±0.53) Med 1	1.61 (±0.80) Med 1.5	p=.74*
Dystonia evaluation – months from DBS *(mean±SD)*	30.43 (±28.66) Median 28	8.56 (±5.54) Median 7	p=.09*
R Functional coordinates *(mean±SD)* X Y Z	 19.95 (±1.16) Mdn 19.99 2.74 (±1.53) Mdn 2.75 -2.41 (±1.25) Mdn -2.20	 20.81 (±1.91) Mdn 20.96 1.86 (±1.53) Mdn 2.07 -1.75 (±1.43) Mdn -1.97	 p=.18* p=.21 p=.61
L Functional coordinates *(mean±SD)* X	 -20.16 (±0.65) Mdn -20.08	 -20.69 (±1.69) Mdn -20.79	 p=.49* p=.13

Y Z	2.29 (±0.89) Mdn 2.49 -2.44 (±1.14) Mdn -2.01	1.42 (±1.33) Mdn 1.46 -2.11 (±1.83) Mdn -2.05	p=.75
R Arc *(mean±SD)*	84.44 (±4.47) Mdn 85.30	81.71 (±5.02) Mdn 81.05	p=.25*
R Ring *(mean±SD)*	**70.04 (±7.29)** **Mdn 71.30**	**77.97 (±8.29)** **Mdn 77.80**	**p=.03***
L Arc *(mean±SD)*	95.59 (±1.69) Mdn 96.1	96.52 (±5.71) Mdn 95.25	p=.93*
L Ring *(mean±SD)*	69.16 (±9.32) Mdn 75.7	76.65 (±9.60) Mdn 75.85	p=.14*
R electrode (n) Central Lateral Anterior Medial Posterior	 7 0 0 0 0	 16 10 9 1 0	p=.07*[1]
L electrode Central Lateral Anterior Medial Posterior	 6 0 1 0 0	 25 5 5 0 1	p=.84
R electrode depth *(mean±SD)*	41.86 (±0.94) Mdn 42	40.95 (±2.18) Mdn 41.5	p=.11*
L electrode depth *(mean±SD)*	**42.29 (±1.52)** **Mdn 42**	**41.10 (±1.15)** **Mdn 41.5**	**p=.04***
<u>R stimulation parameters</u> <u>Type</u> Monopolar Bipolar <u>Negative contact</u> P0 P1 P2 P3 <u>Positive contact</u> P0 P1 P2 Voltage *(mean±SD) (V)* Frequency *(mean±SD) (Hz)* Pulse width *(mean±SD) (μs)*	 7 0 6 1 0 0 0 3.21 (±0.66) Mdn 3,4 132.86(±7.56) Mdn 130 88.57(±33.38) Mdn 90	 27 9 22 8 3 3 2 6 1 3.01 (±0.78) Mdn 3 133.33 (±20) Mdn 130 73.89 (±19.46) Mdn 60	 p=.31*[1] p=.89 p=.47* p=.30* p=.31*
<u>L stimulation parameters</u> <u>Type</u> Monopolar Bipolar Bipolar with double cathode <u>Negative contact</u> P8 P9 P10 P11 <u>Positive contact</u> P8	 6 1 0 5 2 0 0 1	 25 10 1 21 9 4 2 2	 p=.71*[1] p=1

P9	0	7	
P10	0	2	
Voltage *(mean±SD) (V)*	3.33 (±0.60) Mdn 3.5	3.08 (±0.63) Mdn 3	p=.19*
Frequency *(mean±SD) (Hz)*	132.86 (±7.56) Mdn 130	133.33 (±20) Mdn 130	p=.30*
Pulse width *(mean±SD) (μs)*	97.14 (±50.57) Mdn 60	75.56 (±21.44) Mdn 60	p=.53*
Oral medications	1	11	p=.65*[1]
Anticholinergics	5	18	p=.42
Benzodiazepines	0	4	p=1
Tetrabenazine	0	3	p=1
Baclofen	2	5	p=.32
Botulinum toxin	0	2	p=1
Levodopa	4	20	p=1
Antidepressants			

F= Female, *[1]Fisher Exact Test, L= left, Mdn= median, R= right, SD=standard deviation, y= years, *Mann-Whitney test, *[2] Significant difference p<.05

Patients with parkinsonism: clinical evolution and stimulation parameters changes

After the diagnosis of parkinsonism, patients were followed up during 44.57 (±18.14) months. During this period, new clinical features were added, progressing to a fully-blown parkinsonism. At this point, each patient had a mean of 4.14 (±1.06) different symptoms (among the ten symptoms in table 6), FOG being the most frequent, present in 5 patients, followed by gait disturbance (apart from FOG) in 4 and bradykinesia in 4 (table 6). Only one patient had rest tremor.

Table 6: Clinical characteristics at full-blown parkinsonism

Clinical features	Total nº of patients	Nº of cases with new clinical features (not present at presentation)
FOG	5	3
Gait	4	3
Bradykinesia	4	2
Postural instability	3	3
Hypophonia	3	3
Rigidity	3	3
Falls	2	1
Freezing (non-FOG)	2	1
Micrography	2	1
Rest tremor	1	1
Nº of symptoms per patient *(mean±SD)*	4.14 (±1.06)	

SD= standard deviation

Stimulation parameters changes were performed in order to improve parkinsonism. These changes took place until parkinsonism had sufficiently improved or, in patients in whom parkinsonism did not respond, up to the end of the study follow-up. For practical reasons, this time point will be designated here as the end of parkinsonism and occurred 34.71 (±21.21) months after parkinsonism diagnosis. During this period, a total mean of 11.43 (±11.03) changes were tried for each patient. Changes involving multiple parameters (increasing voltage + PW, increasing voltage + decreasing PW, decreasing voltage + increasing PW, decreasing voltage + PW) occurred in 21% of changes, 2.43 (±3.05) times in each patient.

Table 7 shows the type of stimulations changes and its effect in parkinsonism. In those improving parkinsonism, information about eventual worsening of dystonia is presented. In what concerns stimulation type, a change from monopolar to bipolar was tried 4 times, improving parkinsonism in all of these but worsening dystonia in a half. A change to double monopolar was tried once without benefit and a change to interleaving in 2, also without a positive impact in parkinsonism.

Contacts were changed to more ventral in 1, without benefit, and to more dorsal in 4, with benefit of parkinsonism in one of these (25%), without worsening dystonia.

Voltage was changed 24 times, in 11 of these it was decreased and in 13 increased. When it was decreased, parkinsonism improved 3 times (27.27%), in 2 of them (66.66%) worsening dystonia. When increasing voltage, in 3 times parkinsonism improved (23.07%), without worsening of dystonia.

Only one change of frequency was performed (increased) without impact of parkinsonism.

Pulse width was changed 26 times, decreased in 9 and increased in 17. After decreasing PW, parkinsonism improved 3 times (33.33%), but with worsening of dystonia in 2 (66.66%). Of the 17 times of PW increasing, only 1 (5.8%) improved parkinsonism but worsened dystonia. In two cases, stimulation was turned OFF during a period of a few weeks, improving parkinsonism but worsening dystonia.

Table 7: Nº of stimulation changes per patient (and in total), and its effect in parkinsonism and dystonia

Nº of total changes *(mean±SD)*	11.43 (±11.03) [3-33]	Improved parkinsonism	Worsed dystonia
Nº of multiple changes*	2.43 (±3.05)		
Stimulation type *(mean±SD)*			
Bipolar	4	4	2
Double monopolar	1	0	
Interleaving	2	0	
Contact changes *(mean±SD)*			
More ventral	1	0	
More dorsal	4	1	0
Voltage *(mean±SD)*			
Decreased	11	3	2
Increased	13	3	0
Frequency *(mean±SD)*			
Decreased	0		
Increased	1	0	
Pulse width *(mean±SD)*			
Decreased	9	3	2
Increased	17	1	1

SD= standard deviation

After the stimulation changes, at the end of parkinsonism, mean parkinsonism improvement with CGIC was 3 (minimally improved) (±2.52). 4 of the 7 patients improved (including 1 considered as resolved) and 3 worsened. 3 patients still had FOG and gait impairment (table 8). One of these 3 patients preferred not to try to improve parkinsonism further in order to maintain dystonia benefit.

Evaluation of dystonia (with CGIC) at the end of the study (T2) follow-up in these 7 patients was 1.86 (±1.07) (median 2), not significantly different from its evaluation before parkinsonism (T1) (median 2 vs 1, z=-0.82, p=.75). This was also the case for the NoPark group, with not differences regarding dystonia improvement between T2 and T1 (median 2 vs median 1, p=.75).

Table 8 shows the stimulation parameters before and after parkinsonism.

Table 8: Stimulation parameters before and after parkinsonism and degree of parkinsonism improvement (CGIC) after stimulation changes

n=7	At the diagnosis of parkinsonim	At the end of parkinsonism	CGIC
1	R: Monopolar P1 3,5V 150Hz 150us L: Monopolar P9 3,5V 150Hz 150us	R: Monopolar P1 3V 130Hz 90us L: Monopolar P9 3V 130Hz 70us	6
2	R: Monopolar P0 4,1V 130Hz 90us L: Monopolar P8 3,9V 130Hz 60us	R: Monopolar P0 3,5V 130Hz 120us L: Monopolar P8 3,5V 130Hz 120us	1
3	R: Monopolar P0 2,7V 130Hz 60us L: Bipolar P8- /P9+ 3,7V 130Hz 180us	R: Monopolar P1 1,7V 130Hz 60us L: Bipolar P8-/P9+ 3,5V 130Hz 100us	1
4	R: Monopolar P0 3,8V 130Hz 90us L: Monopolar P8 3,8V 130Hz 60us	R: Monopolar P1 3,2V 150Hz 90us L: Monopolar P9 3,1V 150Hz 80us	1
5	R: Monopolar P0 2,7V 130Hz 60us L: Monopolar P9 2,7V 130Hz 60us	R: Bipolar P1-/P0+ 3V 130Hz 200us L:Bipolar P10-/P9+ 2,6V 130Hz 200us	1
6	R: Monopolar P0 3,4V 130Hz 110 us L: Monopolar P8 3,4V 130Hz 110us	R: Monopolar P0 3,5V 130Hz 110us L: Monopolar P8 3,6V 130Hz 110us	5
7	R: Monopolar P0 2,3V 130Hz 60us L: Monopolar P8 2,3V 130Hz 60us	R: Monopolar P0 3V 130Hz 60us L: Monopolar P9 1V 130Hz 120us	6

CGIC= clinical global impression of change, L=left, R= right, V=volts, Hz=hertz, μs=microseconds

No differences were found between the stimulation type (monopolar vs other or bipolar vs other, p=1), contact position (P0 vs other and P8 vs other, right hemisphere p=.25, left hemisphere p=.5), voltage (right hemisphere p=.45, left hemisphere p=.06), frequency (right and left hemisphere, p=1) and pulse width (right hemisphere p=.75, left hemisphere p=.78) between before and after parkinsonism (table 9).

Table 9: Stimulation differences between before and after changes to improve parkinsonism, in patients with parkinsonism

	At the diagnosis of parkinsonism	At the end of stimulation changes	
R Stimlulation			
Type			
Monopolar	7	6	p=1*
Bipolar	0	1	
Contact			
Negative			
P0	6	3	p=.25*
P1	1	4	
Positive			
P0	0	1	
Voltage (V)	3.21 (±0.66)	2.99 (±0.61)	p=.45*[1]
Frequency (Hz)	132.86 (±7.56)	132.86 (±7.56)	p=1*[1]
PW (*μs*)	88.57 (±33.38)	104.29 (±47.91)	p=.75*[1]

L stimulation			
Type			
Monopolar	6	5	p=1*
Bipolar	1	2	
Contact			
Negative			
P8	5	3	p=.5*
P9	2	3	
P10	0	1	
Positive			
P9	1	2	
Voltage (V)	3.33 (±0.60)	2.9(±0.91)	p=.06*[1]
Frequency (Hz)	132.86 (±7.56)	132.86 (±7.56)	p=1
PW (*μs)*	97.14 (±50.57)	114.29 (±42.37)	p=.78

Hz= Hertz, L= Left, R= right, V= Volts, μs= microseconds, *McNemar, *[1] Wilcoxon

DBS features in patients who improved and who did not improve are presented in table 10. No comparisons were performed between those who improved and those who did not improve due to the small sample size.

Table 10: Functional coordinates, ring, arc, electrode and catheter depth in patients with and without improvement

	Functional coordinates	Arc	Ring	Electrode	Catheter depth
Improved n=4	R: X 21.71; Y 0.77; Z -1.2 L: X -20.08; Y 1.15; Z -1.87	R: 79.90 L: 96.80	R: 71.30 L: 76.80	R: central L: central	R: 42 L 42
	R: X 20.92; Y 3.24; Z -2.02 L: -21.36; Y2.49; Z -2.30	R: 79.70 L: 96.10	R: 77.80 L: 75.70	R: central L: central	R: 42 L: 42
	R: X 19.99; Y 2.31; Z -2.31 L: -20.30; Y 2.50; Z -2.17	R: 86.60 L: 97.20	R: 66.80 L: 60.50	R: central L: central	R: 42 L: 45
	R: X 19.07; Y 3.82; Z -1.45 L: X -19.43; Y 3.73; Z -1.74	R: 90.90 L: 94.40	R: 72.20 L: 76.70	R: central L: central	R: 43 L: 43
Not improved n=3	R: X 20.50; Y 2.75; Z -5 L: X -20.43; Y 2.75; Z - 5	R: 88.20 L: 96.90	R: 57.60 L: 56.70	R: central L: central	R: 40 L: 40
	R: X 18.68; Y 5.16; Z -2.44 L: X -20; Y 2.20; Z -2	R: 80.50 L: 92.50	R: 66.10 L: 60.70	R: central L: central	R: 41.50 L: 41.50
	R: X 18.78; Y 1.11, Z -2.20 L: X -19.52; Y 1.23; Z -2.01	R: 85.30 L: 95.20	R: 78.50 L: 77.00	R: central L: anterior	R: 42.50 L: 42.50

L= left hemisphere, R= right hemisphere

DISCUSSION

In this retrospective longitudinal study of a cohort of 43 patients submitted to bilateral GPi-DBS for dystonia with a mean of 83,6 months of follow-up, 16.28% developed parkinsonism. This group of patients had a significantly lower right ring angle value and a significantly deeper left electrode, comparing with those without parkinsonism. No differences were found regarding clinical aspects and other surgical and stimulation features.

The study cohort

Different dystonia subtypes are encompassed in this cohort reflecting the disease heterogeneity and the recognized clinical benefit of GPi-DBS in different types of dystonia, including generalized [Holloway et al., 2006] and focal or segmental types [Vidailhet et al., 2005, Volkmann et al., 2014]; isolated [Andrews et al., 2010] combined [Welter at al., 2010] and associated with other clinical features [Vidailhet et al., 2009, Timmermann et al., 2010]; as well as hereditary [Kupsch et al., 2006], idiopathic and acquired forms [Damier et al., 2007]. Benefit from DBS is, nevertheless, variable and expected to be more pronounced in those with isolated dystonia or specific genetic forms [Fan et al., 2021]. Our patients had a significant clinical improvement after DBS, in line with what is known from the literature [Fan et al., 2021]. Although information driven by BFMRS results was limited, dystonia evaluation with a validated Likert-7 point scale, the CGIC, was consistent with benefit up to the end of follow-up. Disease duration and age at DBS were also similar to other studies [Bruggemann et al., 2015, Kupsch et al., 2011] although others have reported lower [Fan et al., 2021] or higher [Schrader et al., 2011] ages at surgery, probably reflecting differences in dystonia populations, as focal dystonia onset is usually later than generalized forms. The frequency of surgical adverse events was comparable [Fan et al., 2021] or lower [Kupsch et al. 2006] to what others have published in GPi DBS in dystonia, generally inferior to what is observed in Parkinson's Disease, possibly explained by a lower age at surgery in dystonia patients [Kupsch et al., 2011]. A long follow-up period is worth to be highlighted in our series (mean of more than 6 years), as only few studies have 5 or more years of follow-up [Tagliati et al., 2010]. This aspect allowed us to confirm the benefit in dystonia during a long period of time and increased the possibility of identifying patients developing parkinsonian features later in course of follow-up.

Parkinsonism after GPi-DBS: clinical features

Parkinsonism after DBS occurred in 7 (16.28%) of our patients. Schrader et al. [Schrader et al. 2011] have reported this adverse event in 8.5% of a series of 71 patients occurring after 3 to 6 months after surgery. Methodologic issues may explain some of the differences between the two studies. In Schrader's cohort, acquired causes of dystonia apart from tardive as well as patients with gait disturbance caused by dystonia in lower limbs were not included, meaning that it was a purer group of dystonia. It is possible that in our series, patients with previous gait disturbance due to dystonia might have contributed to a delayed identification of parkinsonian features, explaining our later diagnosis of parkinsonism at around 30 months after DBS. On the other hand, Schrader et al. have systematically evaluated patients using videotaping of MDS-UPDRS gait assessment, possibly allowing an early recognition of subtle clinical changes. On the other hand, this study had a shorter period of follow-up after DBS (mean of 27.7 months) comparing to ours (mean 83.6 months), possibly preventing the identification of parkinsonian features emerging later. The higher frequency of parkinsonism in our cohort is more difficult to explain by population differences, but the longer follow-up may have contributed to this higher frequency. Although more complex forms of dystonia were included in our study, we cannot speculate that these patients were more prone to develop parkinsonism, as the 7 patients with parkinsonism had mostly isolated forms of dystonia, except in one case of combined dystonia with myoclonus and one case with epilepsy. In addition, no differences were found between the group with and without parkinsonism regarding dystonia subtypes and etiology. In line with other authors [Berman et al, 2009, Schrader et al. 2011], we have found parkinsonism to emerge in patients with generalized and segmental types of dystonia. Although parkinsonism after focal forms of dystonia has been described [Berman et al. 2009], no focal forms of dystonia were found in our patients with parkinsonism, possibly reflecting the low frequency of focal dystonia in our cohort.

The problem of parkinsonism after GPi-DBS has been addressed by Berman et al. using a questionnaire to analyze motor function compromise in several daily tasks as handwriting, lifting objects or getting out of the car, among others [Berman et al. 2009]. This group concluded that the most frequent clinical change was bradykinesia, which was also the case in our 7 patients at the moment of parkinsonism diagnosis. Bradykinesia, addressed by finger tapping, has been reported to be present in some patients with dystonia, reflecting a slowness of movements probably due to a disturbed motor command. We might question if bradykinesia identified in our patients could represent this slowness of movements caused by dystonia and not a true decrement of velocity and amplitude.

Although we cannot entirely exclude this possibility, those patients considered to have bradykinesia did not have only this clinical sign at the diagnosis of parkinsonism, meaning that the diagnosis of parkinsonism was not based only on the presence of appendicular bradykinesia. FOG, gait disturbance apart from FOG, appendicular freezing, rigidity, hypophonia and micrography were additional clinical features present in these patients. Bradykinesia was addressed in patients with dystonia after GPi-DBS under an experimental design of a tapping maneuver and a reduction of the tapping frequency was confirmed after high frequency stimulation (≥ 130Hz) [Huebl et al. 2015]. All our patients with parkinsonism had a stimulation frequency of 130 Hz or more in each hemisphere before parkinsonism. Nevertheless, we found no significant differences between stimulation frequency between these patients and those without parkinsonism to draw more conclusions.

After bradykinesia, micrography was the second most frequent symptom at presentation, followed by FOG, hypophonia and rigidity. Others have addressed micrography [Blahak et al. 2011] and gait disturbance [Wolf et al. 2016] in dystonia patients submitted to GPi-DBS. Handwriting was shown to be significantly affected after DBS with decreased character height and width at 4 to 10 months after DBS when comparing to pre-DBS. Using gait analysis Wolf et al. have registered the emergence of parkinsonian gait features and decreased gait variability at a mean of 7 months after DBS.

In the months following parkinsonism diagnosis, a fully-blown clinical picture developed. At this stage, FOG was the most frequent sign, followed by gait disturbance and bradykinesia, postural instability, rigidity and hypophonia. In Schrader's case series, FOG was present in all the affected patients and was associated with the stimulation status, resolving immediately after stimulation was turned OFF (stim OFF) and remerging during the 24h after stimulation was turned ON (stim ON). This was also the case in two of our patients who tried a period of stim OFF in order to improve gait. Postural instability, sometimes with falls, were also frequent. In fact, in a study analyzing postural stability in stim OFF and stim ON conditions in thirteen patients with dystonia, velocity and amplitude of postural reactions was showed to be compromised [Jakob G et al. 2015]. These findings suggest a gait disturbance, with FOG and postural instability, as the most frequent clinical picture of parkinsonism after GPi-DBS and leads us to speculate about the pathophysiologic mechanisms underneath. Neurophysiology data from animal [Garcia-Rill et al, 1991] and human [Thevathasan et al 2012] studies point out the pedunculopontine nucleus (PPN), in brainstem, as central in locomotion and, particularly, FOG pathophysiology. PPN is a neurochemical heterogeneous nucleus with gabaergic, cholingeric and glutamatergic neurons, receiving afferents from the motor cortex and basal ganglia, namely the GPi, and with ascending and descending efferents to the basal ganglia, brainstem and spinal cord [Stein et al, 2012]. Loss of PPN cholinergic neurons has been shown in PD and atypical

parkinsonism, such as Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA), all diseases in which FOG is a clinical feature. Animal studies have shown that bilateral PPN lesions induce akinesia and that local injections of GABA agonists or high frequency stimulation of the PPN in monkeys produce contralateral parkinsonism [Benarroch et al, 2013]. Also, low-frequency stimulation of the PPN has treated akinesia in MPTP monkeys [Jenkinson et al, 2004] but PPN-DBS in human PD patients with FOG had mixed results [Ferray et al 2009, Stefani 2007, Moro 2010]. GABAergic projections from the most posterior and ventral region of the GPi, the target of GPi-DBS, to the PPN are recognized [Munro-Davies et al. 1999]. In PD, an hyperactivated GPi may inhibit PPN causing gait disturbance and akinesia and, indeed, GPi-DBS in monkeys was accompanied by an increase of theta and alfa power in PPN neurons [Zhang et al 2011]. We can hypothesize that GPi stimulation in dystonia patients could increase GABAergic output from the GPi to the PPN, inhibiting this nucleus and inducing FOG. Nevertheless, this hypothesis deserves further studies.

Formal criteria of parkinsonism were present in 3 patients. A case report of parkinsonism with full clinical criteria was reported in one patient immediately after GPi-DBS [Zauber et al. 2009]. Nevertheless, this seems to represent an exception rather than the typical case. Only one of our patients had rest tremor and, as far as we are aware, no other cases with rest tremor have been reported.

No clinical features differentiated those who developed and those who did not developed parkinsonism. This is in line to what have been reported about parkinsonism emerging after focal [Berman et al. 2009], segmental and generalized forms of dystonia [Schrader et al. 2011]. In most series dystonia was isolated, with one case of combined dystonia (with chorea) in Schrader series of 2011 [Schrader et al. 2011] and in Wolf study [Wolf. et al. 2016]. Most cases reported were idiopathic forms of dystonia [Schrader et al. 2011, Berman et al, 2009, Blahak et al 2011, Huebl et al 2015], one DYT1 and two tardive [Schrader et al. 2011], also overlapping with our own results. Although the most common cause of acquired dystonia in our series was hypoxic-anoxic encephalopathy, none of these developed parkinsonism. Our patients with parkinsonism were also similar to those without, regarding age at dystonia onset, dystonia duration at DBS and age at DBS. To our knowledge no other studies have compared clinical features between patients who develop and who did not developed this adverse event. The 6 patients reported by Schrader et al have an older age at disease onset (mean 46) and a higher age at DBS (mean 61.3) than ours. No differences in medication between both groups were found in our study and no medications able to induce parkinsonism were identified.

Parkinsonism after GPi-DBS: DBS related features

Dystonia benefit from DBS was similar between those with and without parkinsonism. We found no differences between the two groups regarding functional coordinates, final lead, arc angle values, left ring angle value, right lead tip depth relative to the target or stimulation parameters. To our knowledge there are no previous studies describing DBS features in these patients. In Schrader study, stimulation parameters before parkinsonism are reported, showing mostly bipolar stimulation with high voltages and pulse width [Schrader et al 2011].

Our patients with parkinsonism had a significantly lower right ring angle and a significantly deeper left lead tip. No previous studies have addressed these features in patients with parkinsonism following GPi-DBS. Ring angle is a rotation along the sagittal plane and defines the electrode trajectory through the brain in this plane. For a given lead tip position, different ring angle values determine different contact positions within this plane, more anterior versus more posterior and more ventral vs more dorsal. It is known that DBS induces an area of tissue activation around the contact, namely the volume of tissue activated (VTA), whose shape and volume depends on the type of stimulation and stimulation parameters [Krauss et al 2020]. Depending on the VTA, GPi-DBS can activate different areas within the GPi and neighboring structures, including the external globus pallidus (GPe) (more anterior, posterior and lateral) and the subpallidal area (inferiorly), [Koeglsperger et al 2019]. In our cohort, parkinsonian patients have lower right ring values, probably inducing a sagittal shift of the VTA, to a more anterior and ventral location. This finding is interesting because stimulation of different regions within the sensorimotor GPi is recognized as having different clinical effects. In PD patients, Bejjani et al have reported that more dorsal stimulation of the sensorimotor GPi improved parkinsonism but induced dyskinesias while a more ventral stimulation improved dyskinesias but worsened akinesia and gait [Bejjani B et al 1998]. A more ventral stimulation of the GPi, and even the subpallidal area possibly including palidothalamic fibers, has been recognized as an ideal target for dystonia [Zittel et al, 2020]. We can speculate that, in our parkinsonian patients, VTA involving a more ventral pallidal region, while improving dystonia, could account for this adverse event. A deeper lead tip, which we found in the left hemisphere in the parkinsonian group, are in line we this hypothesis of a more ventral GPi stimulation inducing parkinsonism in these patients.

The unilaterality of these finding (right ring and left lead depth) is difficult to comment. Only five out of the seven patients had information regarding clinical symmetry. Of these,

three had symmetric findings, one had left parkinsonism and one had an asymmetric parkinsonism worse in the right side. The small group size prevents further conclusions about this issue.

Stimulation changes to improve parkinsonism

In order to improve parkinsonism, movement disorders specialists changed the stimulation parameters several times throughout a period of 34 months, trying to find a balance between parkinsonism improvement and worsening of dystonia. This highlights the difficulty in reaching an improvement of parkinsonism without compromising dystonia, which has already been suggested by Schrader [Schrader et al 2011]. A mean of 11.43 changes per patient were performed based on the specialist experience. 21% of these changes involved multiple parameters at the same time, not allowing us to draw conclusions on the effect of specific parameter changes. Regarding the other modifications, changing from monopolar to bipolar stimulation always improved parkinsonism, although with dystonia worsening in 50% of the changes. Altering to more dorsal contacts had a positive impact on parkinsonism in 25% of the attempts, not worsening dystonia. Decreasing voltage improved parkinsonism in 27% of the changes but worsening dystonia in two thirds, while increasing voltage improved parkinsonism in 23% not worsening dystonia. Pulse width decreased improved parkinsonism in 33% while worsening dystonia in two thirds of these cases. Double monopolar, interleaving stimulation, more ventral contacts and frequency changes were tried very few times and without benefit of parkinsonism. Increasing pulse width was tried very frequently (in 17 times), possibly when trying to compensate for dystonia worsening after previous stimulation changes, having no significant impact on parkinsonism. Although we were not able to identify statistically significant differences between stimulation parameters before and after the entire period of changes, possibly due to the small sample size, those who improved parkinsonism (table 8) changed to more dorsal contacts (patients 3 and 4), to bipolar stimulation (patient 5) and decreased voltage (patients 2,3 and 4). Bipolar stimulation induces a change of the VTA shape, from a spheric current typical of monopolar stimulation [Krauss et al 2020], to an oval form, which can reduce the involvement of neighboring structures and reduce side effects. Capsular side effects are commonly improved by this strategy but are probably not involved in parkinsonian symptoms [Berman et al 2009, Schrader et al 2011] as the former emerge immediately after stimulation is turned ON and the latter take 24h to reemerge after a specific stimulation in turned ON [Schrader et al. 2011]. Nevertheless, other structures such

as the GPe or other regions in the GPi could be implicated. Changing to more dorsal contacts could possibly improve parkinsonism by shifting away from the more ventral region of the sensorimotor GPi, a region known to induce parkinsonian features when stimulated [Bejjani B et al 1998].

Dystonia is more than a basal ganglia disease, it is a network disease encompassing basal ganglia, cerebellar and cortical connections [Horn et al 2022, Reese et al 2017]. VTA itself may not account for the response variability to GPi-DBS in dystonia [Zittel et al 2020] and functional and structural connectivity with other brain structures may underline clinical outcomes [Okromelidze L, et al 2020]. Similarly, adverse events after GPi-DBS, as parkinsonism and FOG, may be caused by network modifications rather that more focal stimulation changes. To further test these hypothesis, VTA analysis using modern imaging software and connectivity studies would be tempting.

Limitations

This study has some limitations. First, its retrospective nature accounts for medical records data being not standardized and homogenous, which could prevent a correct identification of parkinsonism in some patients. Nevertheless, parkinsonism was always diagnosed by a movement disorders specialist, all clinical appointments were reviewed more than once and, whenever doubts regarding the description of parkinsonian signs were present, data was further analyzed and discussed with a second investigator. In all patients considered to have parkinsonism, parkinsonian signs worsened in the following months after presentation. Those patients with isolated descriptions of subtle parkinsonian signs in one clinical appointment without a consistent worsening in the following months were not considered as cases. Second, as we included patients submitted to DBS through a long period of time (from 2010 to 2021), we admit that differences in scientific knowledge may have influenced neurologist's perception of specific clinical features, namely parkinsonism, and the neurologist's management of stimulation parameters. Third, the missing data regarding dystonia evaluation before and after DBS with BFMRS and neuropsychological evaluation, which is probably a result of the retrospective nature of the study. Nevertheless, we do not consider it to have an impact in our results. Dystonia benefit from DBS was very clear from medical records and a 7-point Likert scale allowed us to classify this response. Fourth, the small sample size limited the identification of eventual differences between the two groups and, mostly, between the cases before and after parkinsonism.

CONCLUSIONS

GPi-DBS is an established treatment for dystonia but well-defined orientations and protocols regarding stimulation type and parameters are still lacking and many questions related to clinical heterogeneity, variable response to DBS and side effects are still unanswered. A percentage of patients are known to develop parkinsonian features after GPi-DBS, mainly involving gait disturbance, with FOG and akinesia. In this study, 16% of adult dystonia patients treated with bilateral GPi-DBS developed parkinsonian features around 2,5 years after DBS. We have found that patients developing parkinsonism have a lower right ring angle and deeper left lead tip, which we hypothesize may underlie this adverse event by shifting the VTA and, consequently, stimulating areas involved in parkinsonism. Future research using VTA analysis and connectivity maps could further clarify our hypothesis if differences in VTA and connectivity networks between patients with and without parkinsonism after GPi-DBS are found. This can bring us additional knowledge on the pathophysiology of FOG and the mechanisms underneath DBS.

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