Targets for treatment of dystonia caused by several etiologies. Meta analysis

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Resumen

Introducción: Para utilizar un meta-análisis de todos los casos reportados de la estimulación cerebral profunda (DBS) para la distonía para determinar cuáles son los factores significativos resultados influencia relacionada con el destino. La escala de movimiento Burke-Fahn-Marsden (BFM), la medida más informado, fue elegida como la principal medida de resultado para este análisis. **Material y Métodos**: Una búsqueda en MEDLINE identificaron 137 pacientes que se sometieron a DBS para la distonía en 24 estudios que tenían puntuaciones individuales BFM. Datos de los pacientes individuales, incluyendo la edad de inicio de la distonía, la edad de la cirugía, el género, la distribución de la distonía, la etiología de la distonía, la presencia de características asociadas, anormalidad de las imágenes preoperatorias, cirugías estereotáxica anteriores, el núcleo estimulado, el tipo de anestesia que se utiliza, el tiempo de respuesta a la estimulación, y el momento de la evaluación de resultados se introdujeron en una base de datos de SPSS para el análisis estadístico. **Resultados**: La media BFM cambio porcentual (mejora en la puntuación postoperatoria de la línea de base) fue 51,8% (rango - 34% a 100%). Significativamente se lograron mejores resultados con la estimulación del globo pálido interno (GPI) que con la estimulación de la parte posterior del núcleo lateral ventral (VLP) del tálamo (p = 0,0001). La etiología de la distonía también tuvo un efecto significativo en los resultados. Mejorías estadísticamente significativas en los resultados se observaron para todas las categorías etiológicos, excepto encefalitis. Distonía debido a la lesión en el parto y la encefalitis tenían significativamente peores resultados de los pacientes que eran positivos DYT1 gen, gen DYT1 negativos o tenían asociada a pantotenato quinasa-degeneración neuro (PKAN), disquinesia tardía y distonías idiopáticas y postraumático. La mayor duración de síntomas relacionados con distonía una correlación negativa con el resultado quirúrgico. Modelo de regresión utilizando el sitio tres variables-estimulación, la etiología de la distonía, y la duración de la distonía síntomas-explicó el 51% de la varianza en los resultados. **Conclusión**: La estimulación cerebral profunda de la IPG proporciona una mejoría en las puntuaciones de BFM en una variedad de condiciones distónicos.

Palabras clave: La estimulación cerebral profunda, distonía, terapia de estimulación eléctrica, mata-análisis, trastornos del movimiento, técnicas estereotáxica.

Abstract

Introduction: To use a meta-analysis on all reported cases of deep brain stimulation (DBS) for dystonia to reevaluate the good effect using the GPi as a target, which factors significant influence outcome related to the target. The Burke-Fahn-Marsden (BFM) movement scale, the most reported measure, was chosen as the primary outcome measure for this analysis. **Material and Methods**: Computerized MEDLINE searches on English literature search identified 137 patients who underwent BBS for dystonia in 24 studies that had individual BFM scores. The study was done with statistical analysis by intention to treat. Statistical analysis was made with a significant p- value of 0.05. For the comparison of pre- and postoperative scores, a test Wilcoxon signed was used. **Results**: The mean BFM percentage change (improvement in postoperative score from baseline) was 46.3%(range - 34% to 100%). At last follow-up, disease severity and the degree of disability and pain on the BFM were significantly improved by 70.4%, and 67.8%, respectively (p < 0.05, Wilcoxon signed-rank test). Significantly better outcomes

were achieved with stimulation of the globus pallidus internus (GPI) than with stimulation of the posterior portion of the ventral lateral (VLp) nucleus of the thalamus ($p < 0.05$). The etiology of the dystonia also had a significant effect on outcomes. Statistically significant improvements in outcomes were seen for all etiologic categories, except encephalitis. Dystonia due to birth injury and encephalitis had significantly worse outcomes of patients who were DYT1, or had pantothenate-kinase-associated neurodegeneration (PKAN), tardive dyskinesia, and idiopathic and posttraumatic dystonias. Longer duration of dystonia symptons correlated negatively with surgical outcome. **Conclusion**: Deep Brain stimulation of the GPi provides improvement in BFM scores in a variety of dystonic conditions.

Key words: Deep brain stimulation, dystonia, electric stimulation therapy, mata-analysis, movement disorders, stereotaxic techniques.

Introduction

The last two decades have witnessed a renaissance of functional stereotactic neurosurgery in the treatment of diseases in the movement, such Parkinson's disease, essential tremor, pure dystonia and dystonic and dyskinetic syndromes (DDS). Ablative surgery (the thalamotomies and pallidotomies) were gradually and largely replaced by chronic deep brain stimulation (DBS) applied to different target structures that are part of the basal ganglia (internal globus pallidus, subthalamic nucleus) and thalamus. The reason for this transition is the least invasive, most adaptable and possibly reversible . Since the purpose of functional neurosurgery is to relieve the symptoms of these chronic diseases (sometimes progressive) and improve the quality of life of patients, it is imperative to propose surgical procedures that do not cause complications and expect therapeutic on the disease symptoms.

When the DBS is indicated for the treatment of various dystonic syndromes, the globus pallidus internus (GPi) is most often used as a therapeutic target. His part posteroventral sensorimotor, target of Leksell and Laitinen, was recognized as the optimal target lesion surgery (pallidotomy) in the treatment of Parkinson's disease and dystonia syndromes. The volume of the sensorimotor part of the GPi is more important than other targets such as STN.

Pallidal neurons represent two subneuronal populations which differ by the presence or absence of dendritic spines (Figure 1). Neurons which presents thorns have a relatively large soma from which emerge 3-5 dendrites emitting segments secondary, tertiary or even with some veins in dendritic level (Figure 2). Neurons with thorns have a cell body smaller, however, the size and distribution of the dendritic field appears similar regardless of the type of cell. The pallidal neurons vary widely in size from 80 to 350 .mu.m and use as a neurotransmitter GABA, associated with the parvalbumin in more than 60% of the neurons. The existence of a small population of cholinergic neurons has also been described. The pallidal neurons are much less numerous than the striatal neurons, suggesting a significant convergence striato cogwheel-like mapping tridimensionnellepar reveals the significant volume reduction of a nucleus to another: the volume of the ST is estimated at 9941 mm^3, including NC: 4316 mm^3 and P: 5625 mm^3 GPe 808 mm^3 (ST / 12), the GPi 478 mm^3 (ST / 21), the SN: 412 mm^3 (ST / 25) and the STN 158 mm^3 (ST / 63) (Figure 3).

In the literature that are not many reports of these surgeries, however, the majority are single case reports and small series[1-53]. The etiologies of dystonia treated were quite varied, as were the surgical methods employed.

From these reports, it is clear that DBS can produce dramatic improvement in many, but not all, patients. From these reports, DYT1 (Table 1) patients responded better than secondary dystonias[54-58]. There is, however, significant variability within any category of the disorder, making it difficult to prognosticate for an individual patient.

The proposed of a meta-analysis besides the integration of findings to determine which factors significant influence outcome related to the target of the individual study. While often used to integrate the findings of randomized controlled trials, meta-analysis also can be applied to integrate the findings of small case series in order to create a synthesis of the literature and to answer

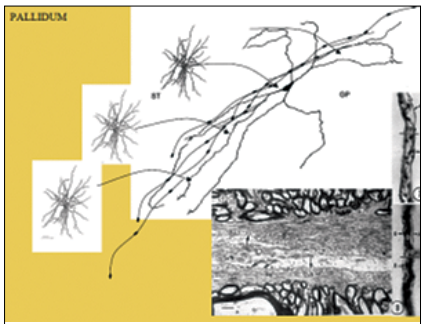

Figure 1. The dendrites of pallidal neurons (Yelnik, Francois et al. 1991).

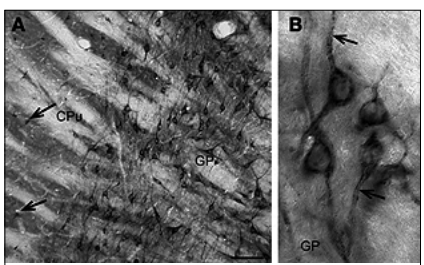

Figure 2. Neural pallidal. GP = Globus Pallidus, CPu = Caudé - putamen (Solbu, Bjorkmo et al. 2010).

questions that cannot be answered studies individually. This type of analysis necessitates certain prerequisites: 1) formulation of a purpose and specification of an outcome; 2) identification of relevant studies; 3) data analysis, and 4) dissemination of the results and conclusions[59].

Material and Methods

The study was done with statistical analysis by intention to treat. Statistical analysis was made with a significant

Table 1.
Monogenic forms of dystonia. According to Schmidt et al., 2010 (Schmidt and Klein 2010)

Designation	Dystonia type	Mode of inheritance	Gene locus	Gene	OMIM number
DYT1	Early-onset generalized torsion dystonia (TD)	Autosomal dominant	9q	GAG deletion in *DYT1*, Torsin A	128100
DYT2	Autosomal recessive TD	Autosomal recessive	Unknown	Unknown	224500
DYT3	X-linkeed dystonia parkisonism; 'lubag'	X-chromosomal recessive	Xq	Gene transcription factor *TAF1*	314250
DYT4	'Non-DYTl' TD: whispering dysphonia	Autosomal dominant	Unknown	Unknown	128101
DYT5a	Dopa-responsive dystonia. Segawa	Autosomal dominant	14q	*GTP-cyclohydrolase*	128230
DYT14	syndrome	Autosomal recessive	11p	Tyrosine hydroxylase	
DYT5b					
DYT6	Adolescent-onset TD of mixed type	Autosomal dominant	8p	*THAPI*	602629
DYT7	Adult-onset focal TD	Autosomal dominant	18p	Unknown	602124
DYT8	Paroxysmal non-kinesigenic dyskinesia	Autosomal dominant	2q	*Myofibrillogenesis regutator 1*	118800
DYT9	Paroxysmal choreoathetosis with episodic ataxia and spasticity	Autosomal dominant	1p	Unknown	601042
DYT10	Paroxysmal kinesigenic choreoathetosis	Autosomal dominant	16p-q	Unknown	128200
DYT11	*Myoclonus-dystoma*	Autosomal dominant	7q	*Epsilon-sarcoglycan*	159900
DYT12	Rapid-onset dystonia parkinsonism	Autosomal dominant	19q	*Na/K ATPase alpha 3*	128235
DYT13	Multifocal/segmental dysionia	Autosomal dominant	1p	Unknown	607671
DYT14	Dopa-responsive dystonia	Autosomal dominant	14q	*GTP-cyclohydrolase*	607195
DYT5					
DYT15	Myoclonus-dystonia	Autosomal dominant	18p	Unknown	607488
DYT16	Young-onset dystonia-(parkinsonism)	Autosomal recessive	2p	Stress-response protein *PRKRA*	603424
DYT17	Autosomal recessive primary TD	Autosomal recessive	20pq	Unknown	612406
DYT18	Paroxysmal exertion-induced dyskinesia 2	Autosomal dominant	1p	Glucose transporter *SLC2A1*	612126
DYT19	Episodie kinesigenic dyskinesia 2	Autosomal dominant	16q	Unknown	611031
DYT20	Paroxysmal non-kinesigenic dyskinesia 2	Autosomal dominant	2q	Unknown	607488

p- value of 0.05. For the comparison of pre- and postoperative scores, a test Wilcoxon signed was used.
Computerized MEDLINE searches on English literature were conducted using combination of text words: dystonic diskinetic syndrome, dystonia, stereotactic and functional neurosurgery, electric stimulation, movements disorders.
All articles describing the surgical treatment of dystonia, age at surgery, gender, distribution of the dystonia, etiology of dystonia, presence of associated features (such as tremor or myoclonus), abnormality of preoperative imaging, prior stereotactic surgeries.

Results

We reviewed 127 patients in 24 studies had individual BFM scores. The mean BFM score percentage change, or improvement in postoperative score from baseline, was 46.3% with a range of 34% to 100%. The percentage change

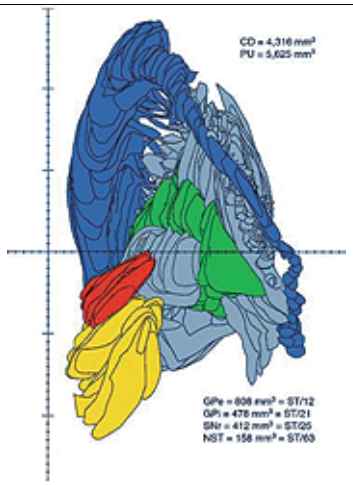

Figure 3. Rear view of NGC humans (mediolateral horizontal axis, vertical axis, dorsoventral, CD (caudate, blue ring), PU (putamen, light blue), GPe (dark green), GPi (light green), NST (red), SNr (yellow) (after Yelnik et al., 2007).

Table 2.
Comparison of Preoperative and Postoperative BFM Scores

Etiology	n	Preop	Postop	Change (%)	p value
DYT1	34	61.1	20.4	67.8	p < 0.05
Primary unspec	40	49.6	27.9	44.5	p < 0.05
Idiophatic	18	38.3	17.6	48	p < 0.05
Neonatal anoxic	8	71.7	54.5	17	p < 0.05
Tardive dystonia	11	39.4	16.5	64.7	p < 0.05
Posttraumatic	4	38	17	47	p < 0.05
PKAN	9	74.1	18.6	70.4	p < 0.05
Encephalitis	3	49	41.3	11.7	p < 0.10
Overall	127	52.6	26.7	46.3	p < 0.05

in BFM score and ranged for each etiology.

The surgery target the globus pallidum internus (GPi) in 118 Cases, the posterior portion of the ventral lateral (VLp) nucleus of the thalamus in 9 cases, and a combination of GPi and VLp in one case.

Etiology of dystonia, duration of dystonia, and nucleus stimulated were significantly correlated with percentage change in the BFM score while the following factors we assumed did not influence outcome: age on onset of dystonia, age at surgery, gender, distribution of the dystonia, presence of associated features (such as tremor or myoclonus), abnormal preoperative MRI, prior stereotactic surgeries, type of anesthesia used.

Stimulation of GPi was associated with better outcomes compared to stimulation of VLp ($p < 0.05$). The 118 subjects with GPi DBS had an average improvement in BFM scores of 67.8 ± 11.7 and the Nine patients with VLp DBS had an average improvement of 17% ± 11.7%. This between-group difference was statistically significant($p < 0.05$).

The etiology of the dystonia had a significant effect on outcome. Person with PKAN ($p < 0.05$) tardive dyskinesia ($p < 0.05$), or DYT1 ($p < 0.05$) had significantly better outcomes than inidviduals with cerebral palsy. Encephalitis was associated with significantly worse outcome than DYT1 dystonia ($p < 0.05$).

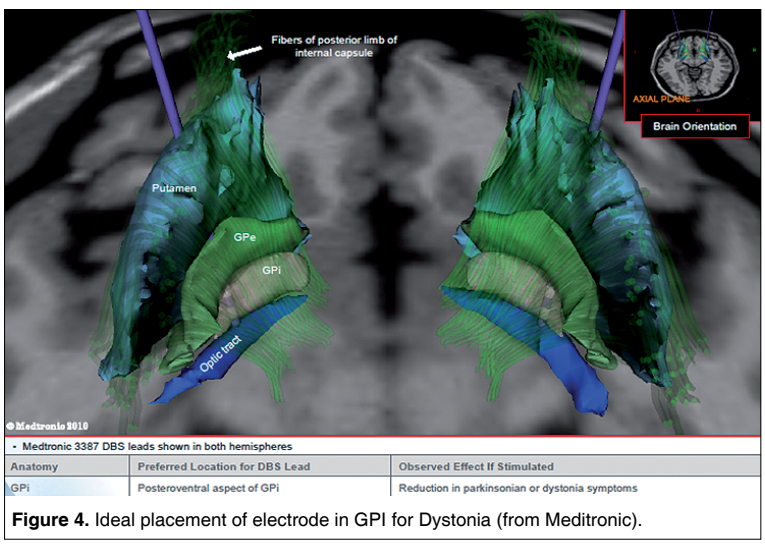

Figure 4. Ideal placement of electrode in GPI for Dystonia (from Meditronic).

There were no significant differences between inidivduals with DYT1, PKAN, idiopathic dystonia, tardive dyskinesia, or posttraumatic dystonia. Table 2.

Discussion

From a historical point of view, it should be noted that the influence of electrical stimulation of the GPi and thalamus in treating dystonia, essential tremor and Parkinson's disease had already been reported by the end Hassler 50s. Indeed, he was using electrical stimulation of target structures before lesional procedure as a measure of physiological target validation.

There have been several excellent literature reviews on the topic of DBS for dystonia[54-58]; however, one of these reviews is based on the statistical analyses of the patient data across different series.

The incorporation of individual patient characteristics and outcomes into an SPSS database has allowed us to perform stastistical analyses of patients across centers. Due to the relative rarify of these patients, several papers have noted the difficulty in any one center being able to individually incor-

porate enough patient in all etiologic categories.

This meta-analysis of existing patient data represents a means of obtaining an understanding of the effect of a complex treatment (DBS) on a rare and complex syndrome(dystonia). Using this approach, we were associated with outcomes of DBS for dystonia and etiology.

Deep brain stmulation was less effective in the birth injury group as compared to the three most favorable groups: DYT1, PKAN, and tardive dystonia. There were no significant diference betweengroup differences fro DYT1 , PKAN, idiophatic dystonia, tardive dyskinesia, or postraumatic dystonias.

Secondary dystonia had been previously considered a single entity; however, these results revealed significant differences in outcomes within this category. Patients with tardive dyskinesia demonstrated significantly better outcomes than patients with birth injury. Importantly there were poor outcomes in all groups.

Conclusion

Globus pallidus internus stimulation resulted in significant improvement in BFM outcome scores for patients with DYT1 negative or positive dystonia, PKAN, idiophatic dystonia, tardive dystonia, posttraumatic dystonias, and cerebral palsy. The degree of improvement in cerebral palsy was significantly less than the others etiologies, as the primary dystonias. For these etiologies, GPi was a better target than VLp. Because of the negative effect of prolonged duration of symptomatology on outcome, subjects should be considered for DBS as soon as surgery is medically appropriate, meaning refractory for medications and non-invasive procedures.

In view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of GPI deep brain stimulation (Figure 4) in primary and secondary dystonia and a long time follow up.

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