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ORIGINAL COMMUNICATION

Deep brain stimulation for Meige syndrome: a meta-analysis with individual patient data

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Abstract

Background Deep brain stimulation (DBS) is an effective intervention for Meige syndrome, a type of dystonia characterized by blepharospasm, facial, and oromandibular dystonia**.** This individual patient-level data meta-analysis was to identify the potential outcome predictors, compare the stimulation targets and summarize the efficacy of DBS for Meige syndrome.

Methods Three electronic databases (PubMed, Web of Science and Embase) were searched with no publication data restriction to identify studies regarding DBS for Meige syndrome. The primary outcome was the improvement in BFMDRS-M score. Pearson's correlation coefficients and a stepwise multivariate regression analysis were used to identify the potential prognostic factors.

Results Twenty-three studies (115 patients, 94 with pallidal stimulation and 21 with subthalamic stimulation) were eligible. Patients showed significant improvement in Burke–Fahn–Marsden Dystonia Rating Scale movement (BFMDRS-M) (21.5 ± 11.0 vs 8.6 ± 6.9, $P < 0.001$) and disability (BFMDRS-D) (6.4 ± 5.1 vs 2.9 ± 2.4, $P < 0.001$) scores at the last follow-up visit (31.9 ± 30.7 months), compared with scores at baseline. Preoperative BFMDRS-M and BFMDRS-D scores were positively correlated with the relative changes in BFMDRS-M score at the last follow-up visit. On the stepwise multivariate regression, only the preoperative BFMDRS remained significant in the best predictive model.

Conclusions Based on the existing evidence, pallidal/subthalamic stimulation is an effective therapy for even the refractory Meige syndrome. Higher preoperative scores probably indicate larger improvement. Stimulation targets or other clinical factors do not constitute the outcome predictive factors.

Keywords Meige syndrome · Deep brain stimulation · Globus pallidus internus · Subthalamic nucleus · Predictive factors · Individual patient data · Meta-analysis

Abbreviations

DBS	Deep brain stimulation
GPi	Globus pallidus internus
STN	Subthalamic nucleus
BFMDRS	Burke–Fahn–Marsden Dystonia Rating Scale
BFMDRS-D	BFMDRS disability subscale
BFMDRS-M	BFMDRS movement subscale
IPD	Individual patient data

Introduction

Meige syndrome, also named blepharospasm–oromandibular dystonia, is a manifestation of segmental dystonia in which patients typically present with various degrees of blepharospasm and orofacial–cervical dystonia [1, 2]. Deep brain stimulation (DBS) has been recognized as a feasible therapy for clinically refractory Meige syndrome [3].

Publications at an earlier stage regarding DBS for Meige syndrome generally provided evidence of single case or small-sample cohort studies. Almost all of these studies preferentially chose globus pallidus internus (GPi) instead of subthalamic nucleus (STN) as the stimulation target. A literature-based analysis [3] reported treatment effects of DBS for Meige syndrome and compared the efficacy of GPi and STN stimulation. However, only 6 patients with STN-DBS in two centers [3, 4] were included, which made a direct comparison difficult to perform. Recent studies presented

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further evidence about STN-DBS and GPi-DBS for Meige syndrome [5–7], based on even larger clinical samples, which provided a better chance to comprehensively evaluate DBS targeting STN or GPi on the level of individual patient data (IPD).

In addition, studies attempting to predict the clinical outcome of DBS for Meige syndrome used different statistical method and thereby presented diverse conclusions. The previous literature-based analysis [3] found a positive correlation between disease severity at baseline and the final clinical outcomes. Horisawa et al. [7] identified no clinically significant correlations, probably due to the relatively small sample size. Wang et al. [5] binarized the outcome using the cutoff of 30% improvement in Burk–Fahn–Marsden Dystonia Rating Scale movement (BFMDRS-M) scores, and indicated that severity of the disease in the pre-surgical period served as the only independent predictors of clinical outcomes.

Based on the above-mentioned studies, a literature-based review and meta-analysis is imperative for better understanding and evaluating the stimulation targets, prognostic factors and efficacy of DBS for Meige syndrome, and therefore facilitating the intervention of this disease ultimately. In this study, IPD was extracted from all eligible publications. Clinical outcomes in the ranges of time categories, effects of stimulation targets and potential prognostic factors were evaluated based on the pooled cohort.

Methods

Search strategy and eligibility criteria

Three electronic databases (PubMed, Web of Science and Embase) were searched following PRISMA guidelines [8] to identify all case reports, case series and cohort studies reporting the demographic, surgical, and outcome data on patients with Meige syndrome treated with DBS. References of these articles were also scanned. No publication data restriction was imposed. Inclusion criteria for publications were: (1) publications written in English and reporting IPD; (2) studies reporting clinical outcomes using the BFMDRS-M and BFMDRS-disability (BFMDRS-D) sub-scores [9]; (3) studies presenting detailed information regarding stimulation targets, age at surgery, follow-up duration, the percentage improvement of the BFMDRS scores postoperatively or detailed scores at baseline and at the follow-up visit; (4) individual patient with typical symptoms such as blepharospasm, facial and oromandibular dystonia were included, and cervical dystonia or cranial–cervical dystonia could either be present or absent [3].

The following search terms were used to identify all the studies reporting on DBS for Meige syndrome: "deep brain stimulation", "DBS", "dystonia", "Meige syndrome". Two reviewers (XW and ZBZ) independently screened the title and abstract and reviewed the full text. Disagreements were resolved through negotiation. The published evidence was evaluated following the Oxford Centre for Evidence-based Medicine (OCEBM) Levels of Evidence [10].

Data extraction

The following individual participant data were extracted: (1) demographic and clinical characteristics (sex, age at onset/surgery, disease duration, BFMDRS scores at baseline); (2) surgical items (stimulation targets, programming parameters); (3) clinical outcomes (BFMDRS scores at each follow-up visit, follow-up length, adverse events or complications, and quality of life). WebPlotDigitizer 3.9 (Austin, TX; https://arohatgi.info/WebPlotDigitizer) was used to extracted data displayed only graphically.

We removed all the duplicate studies or patients and included the studies with larger cohort or longer follow-up duration when we identified reports about duplicate patient data.

Statistical analysis

The individual patient data were pooled and analyzed together. The primary outcome was the relative change in the BFMDRS-M scores at the follow-up visit. The safety of DBS for Meige syndrome was evaluated mainly based on adverse events of particular interest such as intracranial hematoma, infections, lead misplacement and death. Comparisons between scores at baseline (0 months) and in different time categories (0 to ≤ 6, >6 to ≤ 12, >12 to ≤ 24, >24 to ≤ 36, and >36 months) postoperatively were performed using Paired Student *t* test. Mann–Whitney *U* test and Fisher's exact test were used to compare characteristics and clinical outcomes between patients who underwent GPi-DBS and STN-DBS. In addition, potential predictive factors for relative improvement (%) in BFMDRS-M were tested using Pearson's correlation coefficients and a stepwise multivariate regression analysis. $P \leq 0.05$ was defined as statistically significant. All the statistical analyses were performed with SPSS 23.0 (IBM, Armonk, NY).

Results

Search results

37 studies were assessed for eligibility by full-text reviewing. After excluding articles without using BFMDRS ($n=2$), reporting repeated data ($n=1$), without complete data (such as follow-up duration) or detailed individual preoperative

and postoperative BFMDRS-M/D scores ($n=11$), 23 studies involving 115 patients from 23 centers were identified (Table 1, Fig. 1). The median number of patients included in these studies were 3 (range 1–20). Based on the OCEBM, all the 23 studies were qualified as level 4 evidence.

Demographics of the patients and targets for DBS

As is shown in Table 2, 115 patients were included in our analysis (52 men, 61 women, and 2 unknown). These patients had a mean ± SD (range) age at surgery of 49.4 ± 12 (14–72) years. Their age at surgery was 58.3 ± 10.1 (26–77) years and they had a disease duration of 8.7 ± 6.6 (0.25–38) years. Patients received GPi-DBS ($n=94$) largely outnumbered patients underwent STN-DBS ($n=21$). STN-DBS were performed in only three centers [3–5], most of which were performed in recent years. There were no differences in the sex composition between the two groups. On the whole, compared with patients in the STN group, patients in the GPi group were younger at the onset of symptoms (48.1 ± 12.7 vs 54.7 ± 6.3, $P=0.028$), had more severe movement (BFMDRS-M, 23.1 ± 11.2 vs 14.5 ± 6.7, $P<0.001$) and disability (BFMDRS-D, 8.0 ± 5.0 vs 3.1 ± 3.7, $P<0.001$) symptoms.

Programming and follow-up

In general, GPi stimulation amplitudes were 3.3 ± 1.0 (range 1–6.7) V on the left and 3.2 ± 0.9 (1–5.2) V on the right, with a pulse width ranging from 60–450 μs and a frequency ranging from 40–235 Hz. With regard to STN stimulation, the amplitudes were 2.3 ± 0.8 (1.1–4.0) V on the left and 2.4 ± 0.9 (1.1–4.5) V on the right, with frequency ranging from 90–185 Hz. The pulse width were 73.3 ± 18.5 (60–120) μs for the left side and 71.4 ± 15.3 (60–120) μs for the right side. Statistical between-group differences existed in the bilateral amplitude and pulse width ($P<0.001$).

The follow-up length after surgery was 31.9 ± 30.7 (2–150) months, and patients underwent GPi-DBS had a significant longer follow-up duration than those who received STN-DBS (34.4 ± 31.0 vs 19.5 ± 26.4, $P=0.003$).

Outcome of DBS

Considering the heterogeneity in the length of the follow-up, clinical outcomes were assessed at the following five postoperative time categories: 0 to ≤ 6, > 6 to ≤ 12, > 12 to ≤ 24, > 24 to ≤ 36, and > 36 months. As shown in Table 3, The BFMDRS-M scores evaluated during these five time categories were 7.0 ± 4.9 (0.5–19, $n=54$), 6.6 ± 4.8 (0–18.5, $n=35$), 9.0 ± 7.6 (0–29, $n=23$), 11.9 ± 8.3 (0.5–30, $n=22$) and 7.3 ± 6.6 (1–33, $n=33$), corresponding to the mean improvement of 64.8%, 71.1%, 51.9%, 56.1% and 67.6% relative to the baseline scores, respectively ($P\leq0.001$ for all the 5 time categories). Overall, at the last follow-up visit, scores of BFMDRS-M improved significantly, compared with baseline scores (21.5 ± 11 vs 8.6 ± 6.9, $P<0.001$).

With regard to the BFMDRS-D scores ($n=66$), there was significant improvement at the last follow-up visit relative to the baseline (6.4 ± 5.1 vs 2.9 ± 2.4, $P<0.001$). The BFMDRS-D scores assessed in the above-mentioned 5 time categories were: 3.6 ± 2.5 (0–8, $n=27$), 2.4 ± 2.2 (0–6, $n=16$), 2.1 ± 1.8 (0–6, $n=15$), 3.4 ± 2.8 (0–12, $n=17$) and 3.5 ± 2.6 (0–8, $n=11$), respectively, all of which represented significant improvement ($P<0.05$ for all).

At the last follow-up visit, improvement (%) in BFMDRS-M score of GPi and STN group were 57.4 ± 40.5 and 46.4 ± 39.0, respectively. Most of the cases in these two groups showed various ranges of improvement. There were significant improvement in the BFMDRS-M scores postoperatively at the last follow-up visit both in the GPi group (23.1 ± 11.2 vs 8.6 ± 6.8, $P<0.001$) and STN group (14.5 ± 6.7 vs 8.3 ± 7.7, $P<0.001$). As mentioned above, however, there were significant between-group differences in some of the baseline characteristics, such as age at onset, preoperative movement and disability severity, and follow-up visit, which made direct comparisons of these two targets difficult. Nevertheless, considering that significant differences in the dystonia severity (BFMDRS-M and BFMDRS-D, patients in the GPi group seemed to have more severe symptoms) at baseline as well as the insignificant relative changes (%) in the BFMDRS-M at the last follow-up visit (57.4 ± 40.5 vs 46.4 ± 39.0, $P=0.169$), GPi probably served as a better stimulation target than STN.

In addition, there is a positive linear correlation between the relative change (%) of BFMDRS-M and BFMDRS-D (Pearson $r=0.630$, $P<0.001$) at the last follow-up visit (Fig. 2).

Outcome predictive factors of DBS

To identify the potential predictive factors of the outcome (relative improvement of BFMDRS-M at the last follow-up visit). Each clinical and demographical factors were tested separately. There were no significant differences in the clinical outcomes between the binary variables such as sex and stimulation targets. As is shown in Fig. 3, the BFMDRS-M ($r=0.212$, $P=0.024$) and BFMDRS-D ($r=0.344$, $P=0.005$) at baseline were significantly positively correlated with the clinical outcomes. There were no significant positive correlations between the outcomes and other continuous clinical variables such as age at onset of symptoms ($r=-0.185$, $P=0.051$), age at surgery ($r=-0.215$, $P=0.183$), disease duration ($r=0.121$, $P=0.205$) and follow-up period ($r=0.057$, $P=0.545$).

Table 1 Characteristics of the included 23 studies

Study	Number of patients	Mean age at onset, ± SD	Mean disease duration, ± SD	Mean age at surgery, ± SD	Stimulation target	Mean months after surgery at the last FU ± SD	Mean preoperative BFMDRS-M score ± SD	Mean postoperative BFMDRS-M score ± SD	Improvement (%) in BFMDRS-M score[a]
Vercueil et al. [35]	1	44	15	59	GPi	6	NA	NA	66
Capelle et al. [12]	1	55	5	60	GPi	24	18	6	66.7
Houser et al. [1]	1	44	2	46	GPi	6	44	10	73.3
Ostrem et al. [36]	6	54 ± 10.7	8.2 ± 6.3	62.2 ± 6.7	GPi	6.7 ± 1.6	21.8 ± 8.3	6.1 ± 4.2	72.0
Blomstedt et al. [37]	1	26	18	44	GPi	18	24.5	7	71.4
Loher et al. [38]	1	55	5	60	GPi	36	18	6	66.7
Berman et al. [39]	7	45.1 ± 11	13.7 ± 11.8	58.9 ± 7.1	GPi	7.6 ± 3.6	16.9 ± 8.4	7.1 ± 4.3	58.0
Sensi et al. [13]	9	28.9 ± 13.6	16.1 ± 5.1	45 ± 12.9	GPi	36 ± 0	37.5 ± 14.1	15.8 ± 9.1	57.9
Woehrle et al. [14]	1	72	5	77	GPi	16	22	11	50
Ghang et al. [40]	11	49.5 ± 9.8	8.7 ± 7.6	58.2 ± 7.7	GPi	12 ± 0	24.5 ± 5.9	6.3 ± 5.6	74.3
Inoue et al. [41]	1	43	18	61	GPi	120	35	5	85.7
Lyons et al. [42]	3	NA	NA	64 ± 8.5	GPi	48 ± 6	27.3 ± 1.2	8 ± 4.4	70.7
Markaki et al. [43]	1	42	7	49	GPi	6	10	3	70
Romito et al. [44]	1	56	12	68	GPi	38	66	4	93.9
Reese et al. [45]	12	55.9 ± 5.8	8.6 ± 4.4	64.5 ± 4.4	GPi	36.1 ± 22.7	21.4 ± 3.1	10.1 ± 4.1	52.8
Sako et al. [20]	5	51.6 ± 8.9	13.0 ± 4.5	64.6 ± 7.2	GPi	49.4 ± 43.7	22.2 ± 12.4	3.1 ± 1.4	86.0
Tai et al. [46]	1	63	3	66	GPi	60	32	8	75
Ostrem et al. [4]	4	55.3 ± 6.6	10 ± 5.4	65.3 ± 2.2	STN	6 ± 0	17 ± 3.9	8.6 ± 3.4	49.4
Wang et al. [3]	4	48.8 ± 9.7	4.8 ± 3.3	53.5 ± 12.7	GPi/STN	68.8 ± 39.2	16.9 ± 5.0	6.4 ± 5.3	62.1
Sobstyl et al. [47]	6	46 ± 12	12.5 ± 4.8	58.5 ± 8.5	GPi	31 ± 20.9	23.7 ± 6.7	11.0 ± 3.0	53.6
Aires et al. [11]	2	59 ± 12.7	11 ± 8.5	70 ± 4.2	GPi	24 ± 0	32.5 ± 30.4	2.8 ± 1.1	91.4
Horisawa et al. [7]	16	45.8 ± 11	5.7 ± 4.4	51.4 ± 11.6	GPi	66.6 ± 42.1	16.3 ± 5.7	6.7 ± 7.6	58.9
Wang et al. [5]	20	55.6 ± 7.1	4.6 ± 4.4	60.1 ± 7.1	GPi/STN	18.2 ± 12.5	13.7 ± 6.5	11 ± 9.8	19.7

[a]Percentage improvement (%) was calculated based on the mean BFMDRS-M scores

GPi globus pallidus internus, *STN* subthalamic nucleus, *BFMDRS* Burke–Fahn–Marsden Dystonia Rating Scale, *BFMDRS-D* BFMDRS disability subscale, *BFMDRS-M* BFMDRS movement subscale

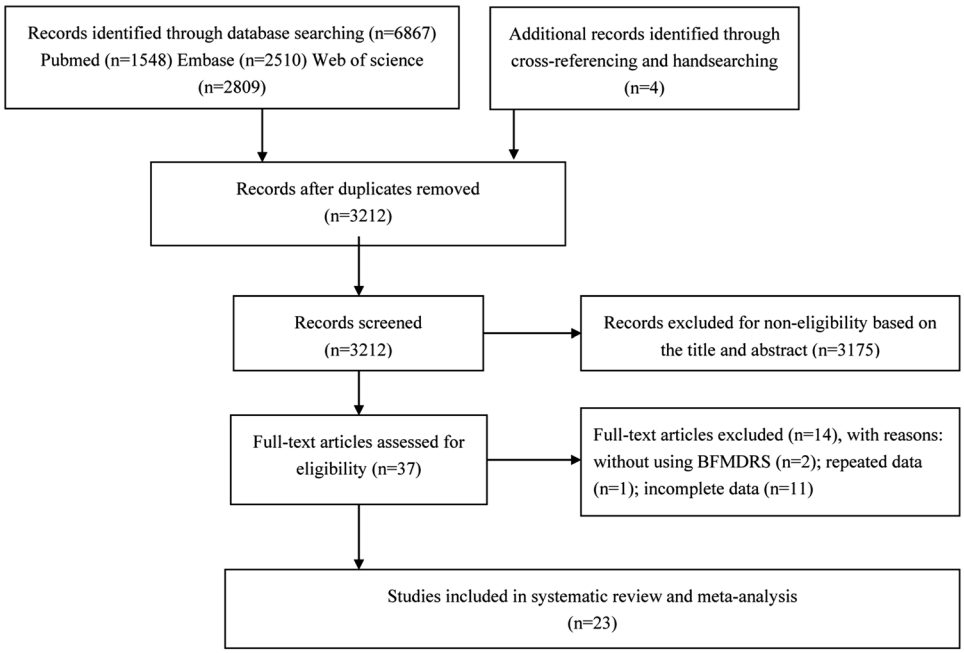

Fig. 1 Flow diagram based on PRISMA statement (www.prisma-statement.org)

Furthermore, in the stepwise multivariate regression analysis, percent improvement (%) of BFMDRS-M was defined as dependent variables; sex, age at onset, age at surgery, disease duration, follow-up length, stimulation targets and BFMDRS-M at baseline were included as independent variables. The best predictive model contains only the preoperative BFMDRS-M ($\beta = 0.214$, $P = 0.024$).

Adverse event, complications, and qualities of life

Postoperative hematoma was reported in one patient. Besides, one study reported an infection of the electrode in a patient 2 years after surgery. No deaths or severe adverse events were reported in these patients. Complications or side effects of stimulations were reported in 14 of the 23 studies. Severe and permanent complications owing to procedures or chronic stimulations were rare. Most of the complications were mild and transient side effects induced by stimulation, including slowness in motor functions, worsening of balance, perioral tightness, stiffening, transient worsening of dysarthria, most of which could be reversed or alleviated through proper adjustment in stimulation parameters. In addition, the hardware-related problems included battery exhaustion, migration of the lead, and bowstringing.

Some of the patients had psychological comorbidities such as depression. Alleviation of the symptoms could improve the mental status of the patients, thus improving their quality of life. However, very few studies have reported the changes of life quality or mental status [4, 11–14]. In one patient, Individual Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) [15] scores improved from 62 at baseline to 83 at the last follow-up visit. In addition, in another patient, the score of Hamilton Depression Scale improved from 17 points pre-operatively to 13 points 24 months after surgery. On the whole, objective evidence of improvement in qualities of life and mental status after DBS was lacking.

Discussion

Our study provided the most comprehensive summary of the publications regarding patients with Meige syndrome treated with DBS based on individual patient-level data meta-analysis. It has been recognized that conservative therapies, such as oral medications and botulinum toxin injections maybe ineffective for patients with refractory dystonia. Our meta-analysis provided evidence that DBS, targeting at either STN or GPi, is effective in the treatment of this kind of dystonia, with a high level of efficacy. In addition, our Pearson's correlation coefficients and a stepwise multivariate regression analysis indicated that only the disease severity at baseline predicated the clinical outcome. Therefore, our study enriched the previous literature and further validated the role of DBS in the treatment of Meige syndrome, which may improve the clinical procedures ultimately.

Target for DBS

Studies indicate that dystonia is a network disorder involving a basal ganglia-cerebello-thalamo-cortical circuit, which is composed of the direct, indirect and hyperdirect pathways

Table 2 Patient characteristics, outcomes and programming parameters at the last follow-up visit

	All patients ($n=115$)	GPi Group ($n=94$)	STN Group ($n=21$)	Significance of difference between GPi and STN group
Male/female/unknown	52/61/2	42/50/2	10/11/0	1.000
Mean age at onset ± SD (range), years	49.4 ± 12 (14–72)	48.1 ± 12.7 (14–72)	54.7 ± 6.3 (43–66)	**0.028**
Mean age at surgery ± SD (range), years	58.3 ± 10.1 (26–77)	57.6 ± 10.7 (26–77)	61.2 ± 6.4 (44–71)	0.217
Mean disease duration ± SD (range), years	8.7 ± 6.6 (0.25–38)	9.2 ± 6.9 (0.33–38)	6.6 ± 4.8 (0.25–17)	0.116
Mean preoperative BFMDRS-M score ± SD (range)	21.5 ± 11.0 (3–66)	23.1 ± 11.2 (7–66)	14.5 ± 6.7 (3–26)	**0.000**
Mean postoperative BFMDRS-M score ± SD (range)	8.6 ± 6.9 (0–33)	8.6 ± 6.8 (0–33)	8.3 ± 7.7 (0–25)	0.578
Mean preoperative BFMDRS-D score ± SD (range)	6.4 ± 5.1 (0–23)	8.0 ± 5.0 (0–23)	3.1 ± 3.7 (0–10)	**0.000**
Mean postoperative BFMDRS-D score ± SD (range)	2.9 ± 2.4 (0–12)	3.4 ± 2.2 (0–12)	2.0 ± 2.7 (0–8)	**0.006**
Mean FU ± SD (range), mos	31.9 ± 30.7 (2–150)	34.4 ± 31.0 (2–150)	19.5 ± 26.4 (3–125)	**0.003**
Mean improvement (%) in BFMDRS-M score ± SD (range)	55.4 ± 40.3 (− 214.3–100)	57.4 ± 40.5 (− 214.3–100.0)	46.4 ± 39.0 (− 43.3–100)	0.169
Mean DBS programming parameters ± SD (range)				
Voltage (V) Lt	3.1 ± 1.0 (1–6.7)	3.3 ± 1.0 (1–6.7)	2.3 ± 0.8 (1.1–4.0)	**0.000**
PW (μs) Lt	159.1 ± 93.1 (60–450)	182.2 ± 91.6 (60–450)	73.3 ± 18.5 (60–120)	**0.000**
Frequency (Hz) Lt	145.5 ± 35.0 (40–235)	147.5 ± 37.3 (40–235)	138.1 ± 24.1 (90–185)	0.13
Voltage (V) Rt	3.1 ± 0.9 (1–5.2)	3.2 ± 0.9 (1–5.2)	2.4 ± 0.9 (1.1–4.5)	**0.000**
PW (μs) Rt	161.2 ± 94.2 (60–450)	185.0 ± 92.0 (60–450)	71.4 ± 15.3 (60–120)	**0.000**
Frequency (Hz) Rt	144.3 ± 35.2 (40–235)	146.6 ± 37.7 (40–235)	135.7 ± 22.2 (90–185)	0.086

Boldface type indicates statistical significance

GPi globus pallidus internus, *STN* subthalamic nucleus, *BFMDRS* Burke–Fahn–Marsden Dystonia Rating Scale, *BFMDRS-D* BFMDRS disability subscale, *BFMDRS-M* BFMDRS movement subscale, *FU* follow-up

Table 3 Clinical outcomes in different time categories

Time categorical (months)	Mean BFMDRS-M score	Improvement (%) in BFMDRS-M score*	*P* value	Mean BFMDRS-D score	Improvement (%) in BFMDRS-D score[a]	*P* value
> 0 and ≤ 6	7.0 ± 4.9 (0.5–19)	64.8	**0.000**	3.6 ± 2.5 (0–8)	52.0	**0.000**
> 6 and ≤ 12	6.6 ± 4.8 (0–18.5)	71.1	**0.000**	2.4 ± 2.2 (0–6)	57.9	**0.004**
> 12 and ≤ 24	9.0 ± 7.6 (0–29)	51.9	**0.001**	2.1 ± 1.8 (0–6)	61.8	**0.006**
> 24 and ≤ 36	11.9 ± 8.3 (0.5–30)	56.1	**0.000**	3.4 ± 2.8 (0–12)	58.0	**0.001**
> 36	7.3 ± 6.6 (1–33)	67.6	**0.000**	3.5 ± 2.6 (0–8)	65.7	**0.014**

Boldface type indicates statistical significance

BFMDRS Burke–Fahn–Marsden Dystonia Rating Scale, *BFMDRS-D* BFMDRS disability subscale, *BFMDRS-M* BFMDRS movement subscale

[a]Percentage improvement (%) was calculated based on the mean BFMDRS-M scores

where both GPi and STN are situated [16–18]. In addition, voluntary motor controlling dysfunction and unbalanced neurotransmitters in the basal ganglia and thalamus are also involved in patients with Meige syndrome, resulting in imbalances of excitatory and inhibitory pathways [19, 20]. Mechanisms of DBS are multifactorial, and long-term

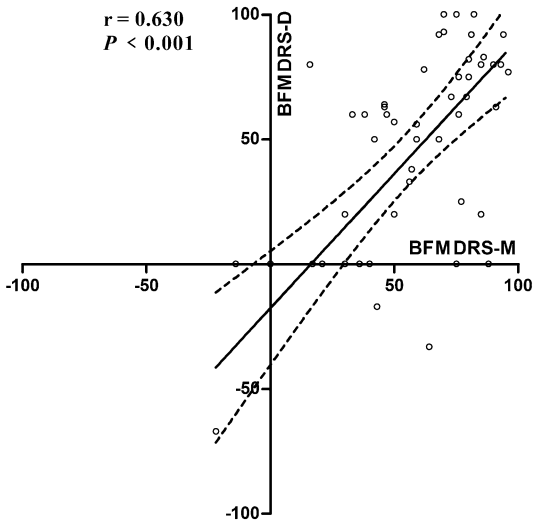

Fig. 2 Correlation between relative improvement (%) in BFMDRS-M and BFMDRS-D at the last follow-up visit. There is a positive linear correlation between the relative improvement of BFMDRS-M and BFMDRS-D (Pearson $r=0.630$, $P<0.001$). dots, individual patient values; black solid line, linear regression line; area between the dotted line, 95% confidence interval; BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; BFMDRS-D, BFMDRS disability subscale; BFMDRS-M, BFMDRS movement subscale

neuronal reorganizations, transient neuromodulatory effects and synaptic plasticity are involved in this procedure [21]. DBS has been recognized as the most effective intervention for intractable generalized, segmental and focal dystonia [22]. The GPi and in recent stages, the STN are the two main stimulation targets in the treatment of dystonia owing to their involvement in the motor circuit [23].

Previous published studies at an earlier stage were more likely to choose GPi than STN as the stimulation target for Meige syndrome, and only six patients underwent STN-DBS were included in the literature-based analysis of Wang et.al [3]. However, further evidence of Meige syndrome treated with STN-DBS was provided in some recent larger scale studies [5, 6, 24]. In a randomized double-blind crossover trial comparing STN DBS and GPi DBS for refractory dystonia, STN seems to be an effective and safe, stimulation target; however, optimal target could not be concluded due to factors such as the heterogeneity of the patients and the relatively small sample size [25]. Moreover, Liu et al. [26] made a comparison of the outcomes of GPi-DBS and STN-DBS in the treatment of primary dystonia, and the result suggested that both of them improved movement symptoms in the short-term, whereas STN-DBS was associated with

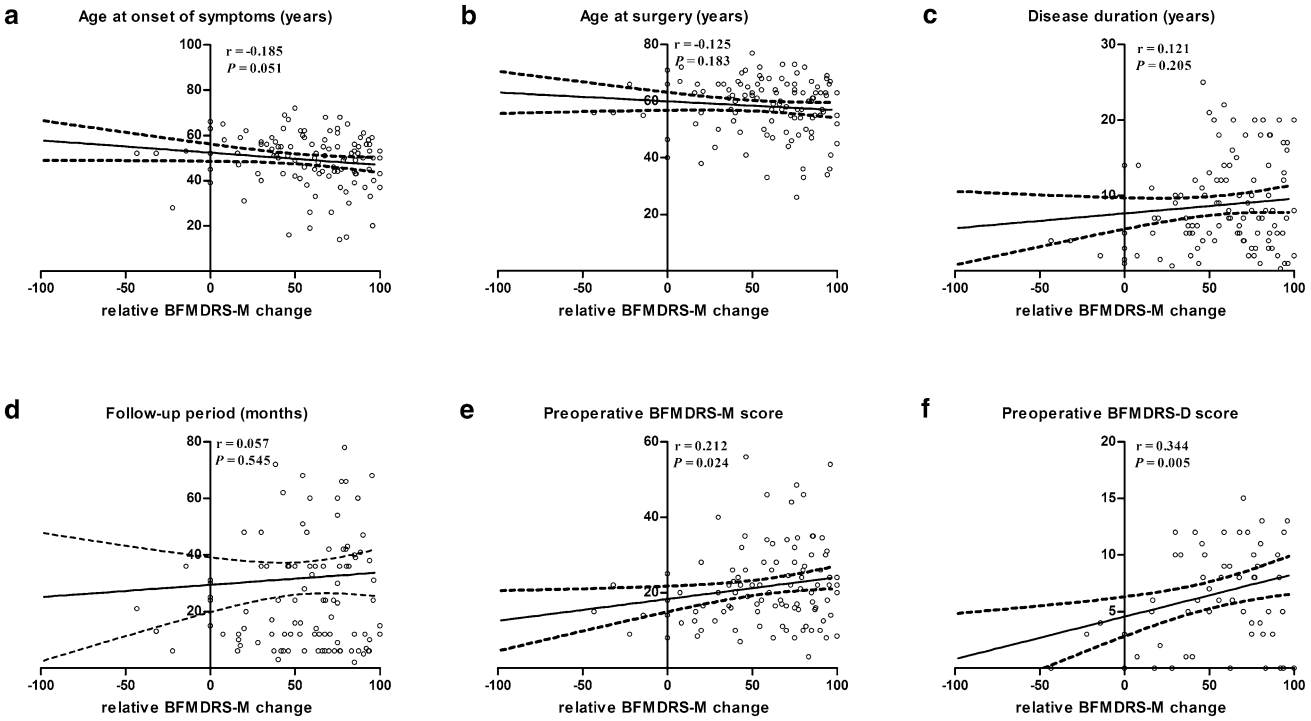

Fig. 3 Potential predictive factors for relative improvement (%) in BFMDRS-M at the last follow-up visit. There were no significant correlations between **a** age at onset (Pearson $r=-0.185$, $P=0.051$) **b** age at surgery ($r=-0.125$, $P=0.183$) **c** disease duration ($r=1.121$, $P=0.205$) **d** follow-up period ($r=0.057$, $P=0.545$) with the relative improvement (%) in BFMDRS-M at the last follow-up visit. There were significant positive correlations between **e** preoperative BFMDRS-M score ($r=0.212$, $P=0.024$) **f** preoperative BFMDRS-D score ($r=0.344$, $P=0.005$) and the relative improvement (%) in BFMDRS-M at the last follow-up visit. dots, individual patient values; black solid line, linear regression line; area between the dotted line, 95% confidence interval; *BFMDRS* Burke–Fahn–Marsden Dystonia Rating Scale, *BFMDRS-D* BFMDRS disability subscale, *BFMDRS-M* BFMDRS movement subscale

more side effects. In our analysis, patients in the both of the GPi-DBS cohort and STN-DBS cohort showed statistically significant improvement in the BFMDRS-M scores at the last follow-up visit (62.8% and 42.8%). There were some significant between-group differences in their demographic, clinical factors and baseline severity, so direct comparisons between these two targets were hard to perform, thus making identification of the best target difficult. However, our multivariate regression model indicated that the choice of the stimulation target did not predict the clinical outcome, which was in accordance with the study of Wang et al. [3].

Clinical outcomes and predictive factors

In our study, almost all of the included patients failed in the conservative therapies (oral medications, botulinum toxin injections, etc.) before receiving the functional neurosurgery. The improvements (%) of BFMDRS-M at the last follow-up visit was 55.4 ± 40.3, and results of the individual patients were variable [5, 7]. On the whole, these patients showed significant improvement in BFMDRS-M and BFMDRS-D in all of the five time categories, which indicates that DBS, targeting at either GPi or STN, is a feasible surgical therapy in the treatment of even the medically intractable Meige syndrome, and could alleviate the symptoms and improve the functional status of the patients. Besides, Zhan et al. suggested that STN-DBS could also improve the quality of life in addition to decreasing the severity of the disease without causing severe adverse event [6].

Many studies attempted to identify the potential prognostic factors of the DBS in the treatment of generalized, segmental, cervical dystonia and secondary dystonia. A previous study retrospectively analyzed 28 patients with cervical dystonia, and identified no particular clinical predictive outcomes of the response [27]. Besides, evidence of outcome predictors of the generalized dystonia was controversial: some studies found no definite factors [28, 29], whereas age at surgery [30, 31], disease duration [30], or DYT-1 status [31] were associated with the final response in other studies. Moreover, a study of Koy et al. [32] identified a significant negative correlation between the outcome of dyskinetic cerebral palsy and dystonia severity. For the pediatric dystonia, an IPD-level meta-analysis [33] suggested that older age at onset, idiopathic dystonia, inherited dystonia without nervous system pathology and truncal involvement were the predictors of a better outcome using the multivariable hierarchical regression. With regard to the outcome of DBS for Meige syndrome, the literature-based analysis [3] revealed that preoperative higher BFMDRS score indicated higher improvement. In the studies of Horisawa et al. [7] and Wang et al. [5], the outcomes were binarized with a cutoff of 30% improvement in the BFMDRS-M: Horisawa found no predictive factors and Wang indicated that severity of the disease in the pre-surgical stage predicted a poor outcome.

Our study used a stepwise multivariable regression model to analyze the pooled IPD from 94 patients that underwent GPi-DBS and 21 patients received STN-DBS, and suggested that severity of the disease was the only factor predicting the outcome. Our findings were in accordance with a recent meta-analysis of pantothenate kinase-associated neurodegeneration [34] and the study of Wang et al. [3]. These findings may further validate the high efficacy of pallidal and subthalamic stimulation for even the serious and refractory Meige syndrome. Moreover, there is a possibility of the floor effect, which means patients with less severe dystonia have less room of improvement, as suggested by Wang et al. [3]. Thus, the greater improvement shown by the patients that underwent GPi-DBS than those received STN-DBS in our analysis maybe attribute to the floor effect. Many patients had difficulty in speaking, walking or functional blindness due to the movement deficits such as blepharospasm, facial and oromandibular dystonia, as a result, these patients had various degrees of disability, as indicated by BFMDRS-D. In our cohort, the improvement in BFMDRS-D positively correlated with the percent change in the BFMDRS-M, which further validated that DBS could improve the symptoms as well as decrease the extent of disability.

Furthermore, Yao et al. [24] retrospectively explored the correlations of electrode contact location in bilateral STN-DBS with the response of patients with Meige syndrome, and found that volume of activated tissue within the STN could significantly predict the BFMDRS improvement. However, pooled analysis could not be performed due to the lack of available IPD.

Complications

Most of the complications in our study were mild and transient, which did not affect the long-term effects of DBS. Side effects induced by stimulation included worsening of balance, motor functions or dysarthria. Hardware-related side effects included bowstringing, battery exhaustion and migration of the lead. Most of these complications could be reversed or alleviated through stimulation parameters adjustment or proper surgical procedures. Besides, some studies did not specify the exact patients with complications, thus the insufficient data were not be included in the stepwise regression model.

Level of evidence

Unlike in many other movement disorders such as Parkinson disease and cervical dystonia, large randomized clinical trials are not available in Meige syndrome. Slow recruitment due to the small number of patients may be an essential

reason, in which condition, evidence for DBS in the treatment of Meige syndrome is limited to nonrandomized studies including case report and case series. Larger randomized control clinical trials are needed for a higher level of evidence.

Strengths and limitations

The present analysis included the recently published large-scale studies and made a more comprehensive comparison of GPi and STN as the stimulation targets. Besides, considering the heterogeneity of the follow-up length in the study, we divided the follow-up duration into five time categories and validated the efficacy of GPi/STN DBS in the long term. Moreover, the regression model in our study excluded factors such as stimulation target and age at onset/surgery as predictors of the outcome and recognized the severity of the disease at baseline as the only prognostic factors. Our study has the potential to identify the patients who were most likely to benefit from this surgical procedure and improve the life qualities of patients ultimately.

There were several limitations in our study. First, almost all of the articles included in our analysis were observational, so inherent limitations in methodology and patient selection could not be avoided. As a result, bias-risk assessment was not performed and the level of evidence was limited in our study. Second, only BFMDRS was chosen as the criterion of outcomes in our study, quality of life and mental status were not evaluated owing to the insufficient data. Thus, to evaluate the effects of DBS in a more comprehensive manner, quantitative evaluations of health-related quality of life and mental status using specialized scales such as SF-36 are needed in the further studies. Finally, all the included studies were clinical studies focusing on clinical scores, as a result, the present study did not include the microelectrode recordings and neuro-radiological analysis.

Conclusion

Based on the existing evidence, GPi/STN DBS is an effective, safe, and feasible surgical method for even the intractable Meige syndrome in the long stage. Stimulation target, age at onset/surgery or disease duration does not predict the clinical outcome. Large scale, prospective, randomized clinical trials and electrophysiological or neuro-radiological studies are warranted in the future.

Compliance with ethical standards

Conflicts of interest The authors have no conflict of interest to report.

Ethical standards All studies in this review have been approved by the local ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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