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REVIEW ARTICLE

Pallidus Stimulation for Chorea-Acanthocytosis: A Systematic Review and Meta-Analysis of Individual Data

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ABSTRACT

A significant proportion of patients with chorea-acanthocytosis (ChAc) fail to respond to standard therapies. Recent evidence suggests that globus pallidus internus (GPi) deep brain stimulation (DBS) is a promising treatment option; however, reports are few and limited by sample sizes. We conducted a systematic literature review to evaluate the clinical outcome of GPi-DBS for ChAc. PubMed, Embase, and Cochrane Library databases were searched for relevant articles published before August 2021. The improvement of multiple motor and nonmotor symptoms was qualitatively presented. Improvements in the Unified Huntington's Disease Rating Scale motor score (UHDRS-MS) were also analyzed during different follow-up periods. A multivariate linear regression analysis was conducted to identify potential predictors of clinical outcomes. Twenty articles, including 27 patients, were eligible. Ninety-six percent of patients with oromandibular dystonia reported significant improvement. GPi-DBS significantly improved the UHDRS-motor score at < 6 months ($p < 0.001$) and ≥ 6 months ($p < 0.001$). The UHDRS-motor score improvement rate was over 25% in 75% (15/20 cases) of patients at long-term follow-up (≥ 6 months). The multiple linear regression analysis showed that sex, age at onset, course of disease, and preoperative movement score had no linear relationship with motor improvement at long-term follow-up ($p > 0.05$). GPi-DBS is an effective and safe treatment in most patients with ChAc, but no reliable predictor of efficacy has been found. Oromandibular dystonia-dominant patients might be the best candidates for GPi-DBS.

Keywords Chorea; Chorea-acanthocytosis; Deep brain stimulation; Dystonia; Globus pallidus internus; Individual patient data.

INTRODUCTION

Chorea-acanthocytosis (ChAc), an autosomal recessive neuroacanthocytosis associated with VSP13A mutations in the chorein gene, classically causes oromandibular chorea with lip and tongue biting, tongue protrusion or feeding dystonia, and paroxysmal head/neck and trunk movements.[1-4] ChAc is a chronic progressive disease. Currently, the management of ChAc is purely symptomatic and includes botulinum toxin for oral-oro-facio-lingual dystonia; phenytoin, lorazepam, and levetiracetam for seizure management; antidepressants or antipsychotics; and dopamine antagonists. However, medications and botulinum toxin injections have limited efficacy in treating various motor symptoms (such as limb chorea and dystonia) in patients with ChAc.[5]

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Many studies have confirmed that deep brain stimulation (DBS) is an effective treatment modality for various movement disorders such as Parkinson's disease (PD), essential tremor, dystonia, and Huntington's chorea. Primary stimulation targets include the globus pallidus internus (GPi) and subthalamic nucleus (STN).[6-9] ChAc has clinical features similar to Huntington's disease. In 2013, Miquel et al.[10] reported that bilateral GPi-DBS could effectively reduce motor symptom severity and improve functional capacity in patients with ChAc (chorea-acanthocytosis mechanism and pallidus stimulation) (Figure 1). However, the study was limited by sample size (n = 15). In recent years, cases with good results after DBS in patients with ChAc have been reported. Therefore, we need to summarize recently reported cases of ChAc to more comprehensively and reliably evaluate the efficacy of DBS in treating ChAc.

Current studies (mostly case reports or small case series) can only provide level III or IV evidence to confirm the efficacy of DBS in ChAc treatment. Three basic questions regarding the application of DBS to ChAc remain unanswered. First, what are the short-term and long-term effects of GPi-DBS on ChAc? Second, how should GPi-DBS be programmed to achieve the best clinical outcome, i.e., is there a difference in the efficacy of high- and low-frequency stimulations of each target? Third, what factors are correlated with postoperative motor improvements? As no large-scale randomized study has provided evidence to answer these questions, we collected available published patient data to perform an individual patient analysis and discuss the feasibility of DBS for ChAc treatment.

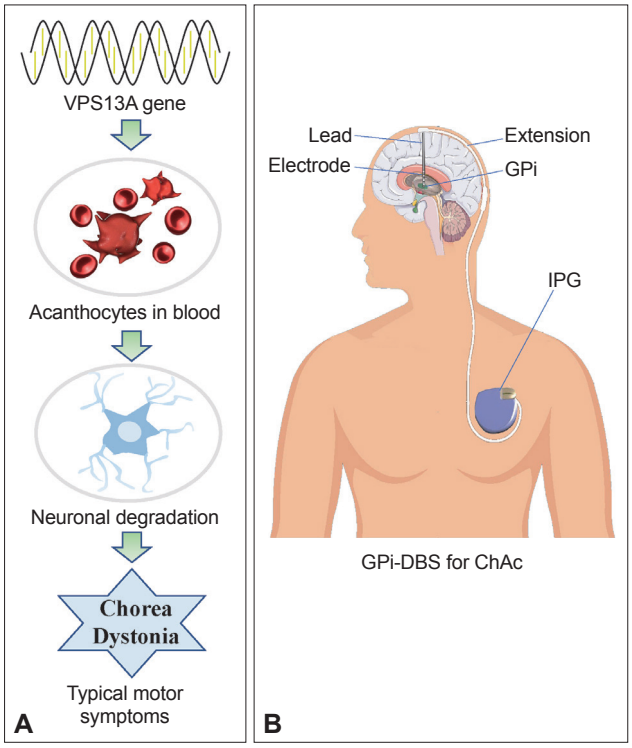

Figure 1. The ChAc mechanism and pallidus stimulation. A: ChAc, a neurodegenerative disease caused by a mutation in the VPS13A gene, is marked by the presence of acanthocytes in blood and choreiform movements. B: GPi-DBS for the treatment of ChAc. GPi-DBS, deep brain stimulation of globus pallidus interna; IPG, implanted pulse generator; ChAc, chorea-acanthocytosis.

METHODS

Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the PubMed, Embase, and Cochrane Library databases for studies published before August 1, 2021. We used the following keywords in the standard search: "chorea," "acanthocytosis," "chorea-acanthocytosis," "pallidal stimulation," "deep brain stimulation," and "DBS"; 237 studies were retrieved.

Inclusion and exclusion criteria

The inclusion criteria were as follows: articles comprising patients 1) diagnosed with ChAc and 2) who underwent bilateral GPi-DBS surgery. The diagnosis was based on the clinical neurological manifestation, the presence of acanthocytes, and the molecular analysis of VPS13A mutations. The diagnosis of ChAc in some patients without Western blotting (absence of the chorein/VPS13A protein) and genetic testing is based on the patient's medical history, clinical manifestations, the presence of acanthocytes, neurological examination, and cranial MRI findings. The exclusion criteria were as follows: 1) articles with cases reported elsewhere, 2) articles with unilateral surgical procedures or no reported laterality, 3) articles with no reported baseline features or postoperative symptom improvement, and 4) non-English articles, conference articles, and abstract-only articles. For a more comprehensive analysis of the effect of surgery, case series with missing individual patient data regarding nonmotor symptoms were included.

Data extraction

Two reviewers (H.W.B. and L.C.H.) independently extracted the data using custom data extraction tables to identify the baseline characteristics of patients, including age at the time of surgery and disease onset, sex, follow-up period, and disease course. In addition, the surgical process included the surgical target and stimulation parameters; postoperative improvement results, including the Unified Huntington's Disease Rating Scale motor score (UHDRS-MS), UHDRS chorea score (UHDRS-CS), Abnormal Involuntary Movement Scale (AIMS), and Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) score; and changes

in nonmotor symptoms (cognitive and psychiatric symptoms). The follow-up period was categorized as early follow-up (EFU, < 6 months) and long-term follow-up (LFU, ≥ 6 months).

Analysis strategy

The percent improvement in UHDRS-MS and UHDRS-CS was quantitatively analyzed. The changes in ChAc motor symptoms (chorea, bradykinesia, dystonia, and gait balance) and nonmotor symptoms (cognitive and psychiatric symptoms) were qualitatively analyzed. The stimulation parameters were placed in bins as follows: amplitude was binned by 0.5 mV/bin, frequency by 12.5 Hz/bin, and pulse width by 12.5 μs/bin. Finally, stimulation and hardware-related adverse events were analyzed qualitatively.

Statistical analyses

IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The changes in UHDRS-MS and UHDRS-CS scores were analyzed using a paired Student's *t*-test or an independent sample *t*-test. A multivariate linear regression was performed to evaluate the association between clinical/demographic characteristics and percent change in UHDRS-MS at LFU. The latter was regarded as the dependent variable. Independent variables included sex (a binary variable, where male = 0 and female = 1), age at surgery (years), preoperative UHDRS-MS, time interval after surgery (months), stimulus frequency, and the UHDRS-MS improvement rate at EFU. All continuous data are presented as the mean ± standard deviation and range. We reported two-tailed *p* values and 95% confidence intervals (CIs). A significance threshold of $p = 0.05$ was selected, and the significance levels for multivariate linear regression were adjusted using the Benjamini–Hochberg procedure to account for multiple testing.

RESULTS

Search results and baseline features

Based on the inclusion and exclusion criteria, 20 articles, including 27 patients, were considered in the final analysis. The PRISMA flowchart is shown in Figure 2.

Patient clinical features

The characteristics of the patients receiving bilateral GPi-DBS are shown in Table 1. Twenty-seven patients (18 male and 9 female, mean age 37.37 years) underwent follow-up after an average duration of 22.77 months. Detailed information on the 27 patients is presented in Table 1.

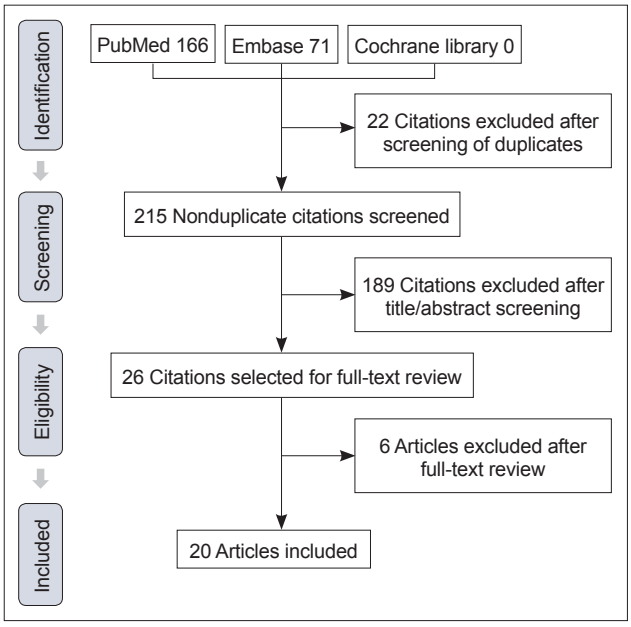

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the included studies.

Stimulation parameters

The program parameters of the 27 patients receiving bilateral GPi-DBS are shown in the Supplementary Table 1 (in the online-only Data Supplement). DBS treatment failed for one patient;[11] seven patients received low-frequency GPi stimulation, and the rest received high-frequency GPi stimulation. Symptoms in three low-frequency stimulation patients worsened with high-frequency stimulation. The other four patients reported optimal symptom improvement with low-frequency stimulation. The respective average stimulation parameters for patients with low- and high-frequency stimulations were as follows: amplitude, 3.1 ± 0.4 V; frequency, 55 ± 16 Hz; pulse width, 90 ± 36 μs and amplitude, 2.7 ± 0.8 V; frequency, 135 ± 18 Hz; and pulse width, 85 ± 35 μs. The average stimulation parameters of the 52 electrodes were amplitude, 3.1 ± 0.81 V; frequency, 128.1 ± 43.29 Hz; and pulse width, 89.5 ± 27.11 μs. Frequency histograms of the stimulation parameters are shown in Figure 3.

Therapeutic effects

Outcomes by scale evaluations

The UHDRS-MS data are listed in Table 2. The UHDRS-MS scores of patients receiving GPi-DBS were significantly reduced at EFU and LFU (mean improvement rates, 51.75% ± 15.15% [$n = 20$] and 43.68% ± 35.42% [$n = 21$], respectively). The UHDRS-MS improvement rate showed a decreasing trend at LFU, but the difference in the improvement rate between the EFU and LFU periods was not statistically significant ($p = 0.104$). Addi-

Table 1. An overview of the 27 patients with chorea-acanthocytosis

Patient number	Sex	Chorea in Western blot of red cells membranes	VPS13A mutations	CK (U/L)	MRI	Acanthocytes (%)	Age at disease onset (yr)	Age at the time of surgery (yr)	LFU (mo)
P1[20]	F	AB	ND	Inc	Ca	20	25	33	60
P2[21]	F	ND	Present	× 1.59	NA	20	35	39	13
P3[22]	M	AB	ND	NA	Ca	+	30	54	5
P4[23]	M	ND	Present	Inc	NA	21	33	36	24
P5[4]	M	ND	Present	586	NA	20	32	35	12
P6[4]	M	ND	Present	815	Stri	Many	30	37	12
P7[4]	M	ND	Present	2,601	NA	Many	32	37	12
P8[4]	M	ND	Present	688	NA	Many	29	35	12
P9[4]	F	ND	Present	1,014	NA	Many	33	36	12
P10[4]	F	ND	Present	233	NA	5	29	33	12
P11[24]	F	ND	ND	NA	Ca	30	38	43	12
P12[25]	M	ND	Present	× 32.6	Nor	+	22	31	6
P13[26]	F	ND	ND	NA	NA	NA	22	31	45
P14[13,27]	M	ND	Present	× 18.8	Nor	10	24	32	84
P15[12]	M	ND	ND	× 2.22	Ca	6	17	40	9
P16[12]	M	ND	ND	Normal	Ca	+	18	30	21
P17[28]	M	ND	ND	NA	Ca; Pu	NA	26	32	8
P18[29]	M	ND	Present	Inc	Nor	7	30	43	12
P19[30]	F	AB	ND	× 4	Ca	NA	31	38	36
P20[10]	F	Present	Present	NA	Ca	NA	35	41	36
P21[10]	F	Present	ND	NA	Nor	NA	25	32	6
P22[11]	M	ND	Present	× 4.18	Ca	20–25	35	38	1 week microlesioning effect; stop DBS at 3 weeks, ineffective
P23[22]	M	AB	ND	NA	Ca	+	32	43	3
P24[31,32]	M	AB	Present	× 2.6	Nor	NA	48	49	41
P25[33]	M	AB	Present	NA	NA	NA	29	48	24
P26[33]	M	AB	Present	NA	NA	NA	30	32	36
P27[34]	M	ND	Present	NA	Ca; Pu	NA	22	31	39
Mean ± SD	5 F (33%), 10 M (67%)	/	/	/	/	/	29.3 ± 6.48	37.37 ± 6.17	22.77 ± 19.45

SD, standard deviation; F, female; M, male; LFU, long-term follow-up; AB, absent; NA, not assessed/not reported; ND, not done; CK, creatine kinase; Ca, caudate; Pu, putamen; Stri, striatal; Nor, normal; Inc, increase; DBS, deep brain stimulation.

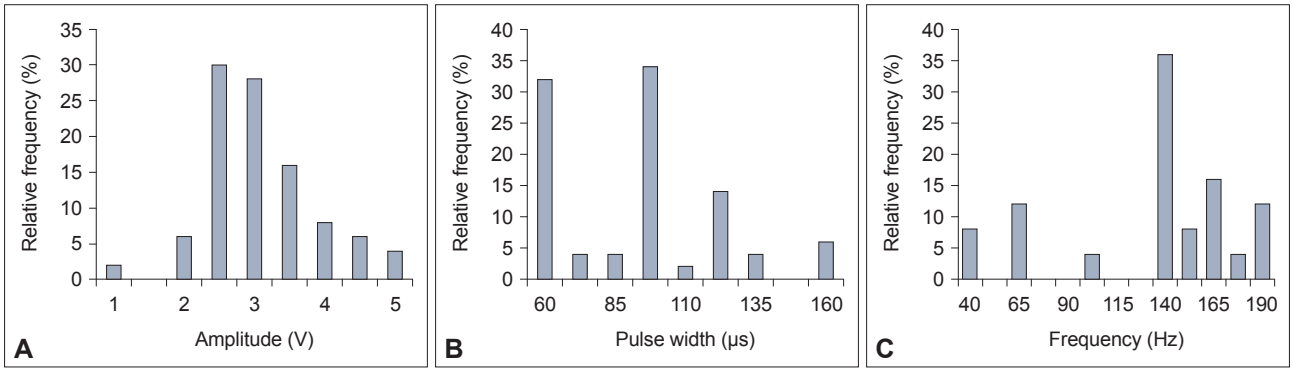

Figure 3. Frequency histograms of stimulation parameters. A: Relative frequency as a percentage of deep brain stimulation amplitude in volts from 52 electrodes. B: Relative frequency as a percentage of pulse widths in microseconds from 52 electrodes. C: Relative frequency as a percentage of frequencies utilized in Herz from 52 electrodes.

tionally, the UHDRS-CS of patients receiving GPi-DBS was also reduced significantly at EFU and LFU (mean improvement rates, 65.32% ± 14.64% and 69.73% ± 17.55% [n = 8], respectively). The mean percent change of the UHDRS-MS was greater in the low- than in the high-frequency stimulation group (mean improvement rates at EFU, 62.21% ± 11.46% [n = 3] and 49.91% ± 15.70% [n = 17], respectively; mean improvement rates at LFU, 54.58% ± 16.70% [n = 4] and 41.12% ± 39.47% [n = 17], respectively).

The total AIMS scores of the 17th patient improved by 40% (5 months after the surgery) and 50% (8 months after the surgery). The BFMDRS motor score (BFMDRS-MS) of the 13th patient improved by 75% at 1 year after the surgery.

Outcome by symptoms

Motor symptoms

Table 2 shows the motor effects of GPi-DBS. Among the 19 patients who received high-frequency stimulation, the chorea (trunk and limbs) of 16 (three did not report chorea) slightly improved, and the trunk spasm symptoms of five improved. The oromandibular dystonia of 18 (one patient did not report oromandibular dystonia) almost disappeared after bilateral high-frequency GPi stimulation. As their oromandibular dystonia was relieved, the patients' symptoms of dysphagia also improved. The trunk and limb dystonia symptoms in eight patients improved after bilateral high-frequency GPi-DBS. The unstable standing posture and gait of four patients significantly improved under high-frequency GPi stimulation. One patient occasionally developed gait freezing after high-frequency GPi-DBS, which may have resulted from disease progression or stimulus-related side effects. There were 8 patients with dysarthria before surgery; 2 with complete remission, 1 with partial improvement, and the rest presented with no significant improvement.

Seven patients received low-frequency GPi-DBS. The chorea of the remaining patients slightly improved except for one patient who did not report chorea. Trunk spasm symptoms completely improved in one patient and were partially relieved in two patients. After bilateral low-frequency GPi stimulation, the oromandibular dystonia almost disappeared in two patients, and the other five were partially relieved. Three of four patients had partly improved dystonia of the trunk and limbs, and one showed no such improvement. The unstable standing posture and gait of three patients significantly improved after the surgery, except for one without change. After low-frequency GPi stimulation, two of the six patients (four did not report dysarthria) showed a slight improvement in symptoms, whereas the remaining four showed no significant change in dysarthria. The burping symptoms in one patient significantly improved after low-frequency GPi-DBS.

DBS can reduce disabling motor symptoms. In some patients with dystonia, the effect of microdamage can temporarily improve motor symptoms after DBS. Chronic stimulation significantly improves dyskinesia in patients with ChAc. At present, it is difficult to evaluate whether the initial symptoms reappear after the power of the pulse generator has been exhausted. However, the clinical symptoms reappear in some patients after the stimulator is turned off.

Nonmotor (cognitive and psychiatric) symptoms

Five patients had cognitive impairment before surgery; two had no change in cognitive function after GPi-DBS, and results regarding the postoperative cognition of the other patients were not reported. Eight patients had mental symptoms before surgery such as depression, anxiety, obsessive-compulsive disorder, and impulsive behavior. After the surgery, one patient's anxiety and depression improved significantly, one patient's mood and behavior did not change, and the results of the mental symptoms of the other patients were not reported. Therefore, there was insufficient evidence to draw conclusions about cognitive or neuropsychiatric changes in patients with ChAc after GPi-DBS.

Adverse events

There were two postoperative hardware-related side effects, three surgery-related side effects, and nine stimulation-induced side effects. The details of these adverse events are shown in Table 3.

Factors associated with Unified Huntington's Disease Rating Scale motor score change

In the univariate linear regression analysis, sex, age at the time of surgery, DBS duration, baseline UHDRS-MS, and stimulus frequency were not associated with the percent change in UHDRS-MS at LFU in patients receiving bilateral GPi-DBS (p > 0.05) (Table 4).

DISCUSSION

Our study shows that GPi-DBS effectively alleviates chorea and dystonia (including the limbs and trunk) in patients with ChAc. The UHDRS-MS improvement rate was over 25% in 75% (15/20 cases) of patients at LFU (≥ 6 months). The average improvement rate of UHDRS-MS was 43.68% at the final phase. Moreover, this study showed no significant difference between high- and low-frequency GPi-DBS in improving UHDRS-MS under the optimal parameter stimulation state. Therefore, our study is the first to explore the short- and long-term efficacy of DBS and the safety in treating ChAc in a relatively large cohort

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Table 2. Motor outcome by scale evaluation

Patient	UHDRS-MS			UHDRS-CS			Symptom							
	UHDRS-MS at baseline	UHDRS-MS at EFU (imp%)	UHDRS-MS at LFU (imp%)	UHDRS-CS at baseline	UHDRS-CS at EFU (imp%)	UHDRS-CS at LFU (imp%)	Chorea	Dystonia	Feeding difficulties	Dysarthria	Oromandibular dystonia	Trunk spasm	Gait balance	Involuntary movement
P1	24	14 (41.7)	21 (12.5)	24	14 (41.67)	NA	↑	↑	NA	→	↑	↑	NA	NA
P2	44	13 (70.45)	12 (72.73)	13	2 (84.62)	2 (84.62)	↑	↑	↑	↑	↑	↑	NA	NA
P3	40	23 (42.5)	NA	8	1 (87.5)	NA	↑	NA	↑	NA	↑	↑	NA	↑
P4	59	36 (38.98)	35 (40.68)	NA	NA	NA	↑	NA	NA	→	↑	↑	↑	NA
P5	62	20 (67.74)	18 (70.97)	20	7 (65)	5 (75)	↑	↑	↑	→	↑	NA	↑	NA
P6	42	16 (61.9)	12 (71.4)	12	5 (58)	3 (75)	↑	↑	↑	→	↑	NA	↑	NA
P7	24	11 (54.17)	10 (58.33)	8	4 (50)	2 (75)	↑	↑	↑	→	↑	NA	↑	NA
P8	22	11 (50)	10 (55)	8	2 (75)	2 (75)	↑	↑	↑	→	↑	NA	↑	NA
P9	48	26 (45.83)	24 (50)	14	4 (71.43)	2 (85.71)	↑	↑	↑	→	↑	NA	↑	NA
P10	16	7 (56.25)	7 (56.25)	6	3 (50)	4 (33)	↑	↑	↑	→	↑	NA	↑	NA
P11	61	NA	31 (49.18)	24	NA	11 (54.17)	↑	NA	NA	↑	↑	NA	↑	NA
P12	NA	NA	NA	13	NA	4 (69.23)	↑	NA	↑	↑	↑	NA	↑	NA
P13	NA	NA	NA	14*	NA	3.5 (75)	↑	NA	→	→	↑	NA	NA	NA
P14	34	26 (23.53)	54 (-58.82)	NA	NA	NA	↑	→	NA	↑	↑	NA	→	NA
P15	36	13 (63.89)	13 (63.89)	14	3 (78.57)	4 (71.43)	↑	↑	↑	→	↑	↑	↑	NA
P16	53	26.5 (50)	37 (30)	20	9 (55)	NA	↑	↑	↑	NA	↑	↑	NA	NA
P17	NA	NA	NA	20†	12 (40)	10 (50)	↑	↑	↑	↑	↑	NA	↑	↑
P18	39	NA	13 (66.67)	NA	NA	NA	↑	NA	↑	→	↑	↑	↑	NA
P19	32	12 (62.5)	13 (59.4)	NA	NA	NA	NA	NA	NA	→	↑	NA	NA	NA
P20	35	27 (22.86)	32 (8.57)	NA	NA	NA	NA	NA	NA	→	↑	NA	NA	NA
P21	55	33 (40)	31 (44)	NA	NA	NA	NA	NA	NA	→	↑	NA	NA	NA
P22	NA	NA	NA	NA	NA	NA	→	NA	→	NA	→	→	NA	NA
P23	74	50 (32.43)	NA	24	8 (66.67)	NA	↑	NA	NA	→	NA	↑	↑	NA
P24	33	9 (72.73)	14 (57.58)	NA	NA	NA	↑	NA	NA	→	↑	NA	NA	NA
P25	67	18 (73.13)	10 (85.07)	NA	NA	NA	↑	NA	NA	→	↑	NA	↑	NA
P26	31	11 (64.52)	11 (64.52)	NA	NA	NA	↑	NA	NA	→	↑	NA	↑	NA
P27	15	NA	21 (-40)	14	9 (35.71)	22 (-57.14)	↑	NA	NA	→	↑	NA	NA	NA
Number of patents with improvement/ no change/ worsening/NA	/	/	/	/	/	/	23/1/0/3	12/1/0/15	13/2/0/12	5/19/0/3	25/1/0/1	8/1/0/18	15/1/0/11	2/0/0/25

*BFMDRS-MS; †AIMS. UHDRS-MS, Unified Huntington's Disease Rating Scale motor score; EFU, early follow-up (< 6 months); LFU, long-term follow-up (≥ 6 months); UHDRS-CS, UHDRS chorea score; NA, not assessed/not reported; BFMDRS-MS, Burke–Fahn–Marsden Dystonia Rating Scale Score motor score; AIMS, Abnormal Involuntary Movement Scale; ↑, improvements; →, no change.

Table 3. The relationship between motor improvement and clinical features

Side effects	No. of cases
Hardware-related side effects	
Twiddler syndrome	1
Implanted pulse generator infection	1
Surgery-related side effects	
Misplaced right electrode	1
Generalized seizure	2
Stimulus-related side effects	
Dysarthria	1
Abnormal pulling at over 60 Hz stimulation	1
Worsening of chorea and dysarthria at 130 Hz	1
Blurred vision in the lowest plots and using high amplitude	1
Freezing of gait	1
Exacerbation of both chorea and dystonia at high-frequency (130 Hz) stimulation	1
Worsening of trunk spasms at 40–50 Hz stimulation	1
Experienced increased chorea and side effects (facial hemi-spasms, visual disturbances, and vegetative changes) regardless of the bipolar stimulation parameters used at a high frequency	1
Low-frequency stimulation led to the deterioration of speech and gait	1
Total	14

Table 4. The relationship between motor improvement and clinical features

Parameter	Coefficient	Standard error	Beta	*t*	*p*
Sex	-0.636	17.771	-0.008	-0.036	0.972
Age at onset (yr)	2.806	1.702	0.47	1.649	0.121
Duration (yr)	1.133	2.496	0.131	0.454	0.657
Baseline UHDRS-MS	0.625	0.586	0.262	1.066	0.304

UHDRS-MS, Unified Huntington's Disease Rating Scale motor score.

of patients with ChAc. Moreover, our study is the first to explore the UHDRS-MS improvement rates between high- and low-frequency GPi-DBS. In summary, our study has enriched the previous literature and has further validated the role of GPi-DBS in the treatment of ChAc, which may ultimately improve clinical procedures.

Overall, these patients showed significant improvement in UHDRS-MS at EFU and LFU, indicating that GPi-DBS is a feasible surgical therapy in medically intractable ChAc treatment. Furthermore, it may alleviate motor symptoms and improve the functional status of patients. Contrary to other research,[10] we could not find a correlation between surgical outcome and age at surgery, course of disease, or preoperative movement score. The heterogeneity of the diseases, wide age range of our population, and small sample size could explain these negative findings. Interestingly, it was shown that most patients benefited from stimulation of the ventral side of the GPi in the early phase of stimulation. In contrast, in the late stimulation phase, the electric field was larger and closer to the dorsal side of the GPi.[10] However, the pooled analysis could not be performed due to the unavailability of data.

The DBS parameters of ChAc are inconsistent across various research centers. Interestingly, this study showed that the mean percent change of the UHDRS-MS improved more in the low-than high-frequency stimulation group under the optimal parameter stimulation state. Moreover, in some cases of ChAc, improvement was only achieved with low-frequency stimulation (40 Hz) with worsening of symptoms at high-frequency stimulation (130 Hz).[12,13] According to previous studies, the therapeutic mechanism of DBS in movement disorders is unclear, and the mechanism by which different stimulation frequencies induce different therapeutic effects remains to be elucidated.[14] The cause of these antagonistic stimulatory effects remains unclear and requires further study.

Given the heterogeneity and complexity of ChAc symptoms and the significant interindividual differences in the clinical response to DBS treatment, a single target stimulation is insufficient to manage all of the patient's clinical symptoms (such as various involuntary movements). Using multiple targets rather than a single target may be more effective or produce long-term effects on some symptoms. A recent case report demonstrated the feasibility and effectiveness of combined complex stimulation. The trunk spasm and chorea symptoms in two patients improved significantly after combined stimulation of GPi and the ventralis oralis complex of the thalamus.[15] However, this strategy may result in a higher complication risk than using a single target. Therefore, the benefits and risks of using multiple targets must be clearly understood. Moreover, Wu et al.[16] reported that BFMDRS-MS and UHDRS-MS improved rapidly after STN-DBS in two siblings with ChAc. STN-DBS appears to provide effective, long-lasting, and more rapid-acting treatment for ChAc and shows potential economic advantages because it uses less electrical energy.[17,18] Although STN-DBS can quickly improve patients' motor symptoms, its potential risks of causing or aggravating cognitive impairment, insufficient improvement of axial symptoms, and declines in verbal fluency tasks, in particular, should also be considered.[16]

In the present review, oromandibular dystonia significantly improved in 25 of the 26 patients postsurgery. In cases where oromandibular dystonia affects a patient's voice, the voice becomes clearer as the condition improves. In this study, the dysarthria of five patients receiving GPi-DBS improved postoperatively. However, nine patients showed no improvement in postoperative dysarthria. The nonreactivity or deterioration of dysarthria symptoms may be related to disease progression or adverse re-

actions to DBS. Generally, DBS improves dysarthria, as seen in patients with PD after STN-DBS.[19]

Standard antiepileptic drugs can control epileptic symptoms before surgery, and DBS does not aggravate these symptoms. Moreover, there are limited reports on seizures in patients with other movement disorders caused by GPi or STN stimulation. Because most studies have not systematically reported the changes in nonmotor symptoms after DBS, there is insufficient evidence to make conclusions regarding the changes in nonmotor symptoms (cognitive and neuropsychic) after DBS in patients with ChAc.

The adverse reactions reported in this study also deserve attention. Hardware-related complications can occur even 1 year after surgery. Implantable pulse generator protrusion or lead/wire fracture can occur, particularly in patients with ChAc presenting with chorea, which can be violent. Furthermore, in some patients, the main motor symptoms of chorea improved, whereas other symptoms such as dysarthria or gait problems often developed or worsened. Future studies should preferably involve a random division of patients into surgical and nonsurgical control groups to evaluate effects that may occur independently of DBS due to the natural progression of the disease. Fundamentally, DBS may be chosen when the patient has a relatively slow progression. For example, all the subjects who underwent DBS had an atypical presentation that indicated a milder disease course than the typical presentation from childhood. Therefore, DBS can be recommended in some but not all cases, although clinical symptoms are disabling even with many medications.

In the context of these overall positive findings, some limitations must be highlighted in the published case reports. First, the data come from case reports or case series studies and articles involving operations performed by different surgeons and evaluations performed by different doctors (Table 1[4,10-13,20-34]), which may affect surgical efficacy evaluation. The majority of the reported cases did not use blind methods to evaluate symptoms, which could bias results. Moreover, in some patients, neither western blotting nor VPS13A mutation tests were performed. Therefore, it is essential to establish a professional medical center to systematically evaluate and treat patients with ChAc. Second, publication bias (the publication of positive results) may exaggerate the real benefits of surgery in patients with ChAc. Moreover, the final follow-up of most reported cases was one year. Undoubtedly, a LFU study is needed to evaluate the effect of DBS on activities of daily living and quality of life. Third, there are no images to determine the electrode placement position for comparison between different studies. Due to the unavailability of data on the stimulation area, the correlation between symptoms and the stimulation area in patients with ChAc was not analyzed. Due to the limited data, the outcomes of GPi-DBS on cognition and behavior of patients with ChAc deserve further study. Currently, the GPi is the target of most DBS for ChAc; however, the best target is still unknown. Therefore, more extensive clinical and basic studies are needed to better understand the mechanism of ChAc and discover ideal targets and treatment modalities.

In conclusion, this study demonstrated that GPi-DBS is an effective and safe treatment in most patients with ChAc, but no reliable predictor of efficacy has been found. Chorea and dystonia can be adequately and consistently controlled via GPi-DBS. Despite disease progression, oromandibular dystonia-dominant patients might be the best candidates for GPi-DBS surgery. Moreover, the optimal stimulation program remains unknown; stimulation frequency, pulse width, and amplitude should be adjusted according to the principle of individualization.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22003.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Supplementary Table 1. Detailed information on the stimulation parameters in the chorea-acanthocytosis

Patient number	Lead and IPG models	Contact settings in evolution	L pulse amplitude (V)	R pulse amplitude (V)	L pulse width (μs)	R pulse width (μs)	L pulse frequency (Hz)	R pulse frequency (Hz)
P1[20]	3387 Medtronic®; IPG: ND	R5-, L2-	4.5	4.5	120	120	180	180
P2[21]	3387 Medtronic®; Soletra®	0-, 4-	3	2.9	90	90	130	130
P3[22]	3389 Medtronic®; Activa PC®	R1-, L9-	2.5	2.5	60	60	130	130
P4[23]	Model 3387, Medtronic; Soletra, Medtronic	NA	2.9	2.3	60	60	130	130
P5[4]	L302 DBS lead; dual-channel PINS DBS implanted pulse generator, PINS	NA	2.6–3.5	2.6–3.6	70–100	70–100	150–165	150–165
P6[4]	L302 DBS lead; dual-channel PINS DBS implanted pulse generator, PINS	NA	2.5–3.8	2.5–3.3	80–140	80–110	150–175	150–175
P7[4]	L302 DBS lead; dual-channel PINS DBS implanted pulse generator, PINS	NA	2.0–3.0	2.0–3.0	60–80	60–80	135–165	135–165
P8[4]	L302 DBS lead; dual-channel PINS DBS implanted pulse generator, PINS	NA	2.5	2.5	90	90	160	160
P9[4]	L302 DBS lead; dual-channel PINS DBS implanted pulse generator, PINS	NA	2.0–2.7	2.0–2.7	90–100	90–100	150	150
P10[4]	L302 DBS lead; dual-channel PINS DBS implanted pulse generator, PINS	NA	0.0–1.6	1.8–2.5	60	60	130–145	130–145
P11[24]	Quadripolar electrodes (L302, PINS; Medical, China); implanted pulse generator, NA	Left, case (+) and contact-1 (-); right, case (+) and contact-5 (-)	2.2	2.2	60	60	130	130
P12[25]	3387 Medtronic®; Activa PC®	Right case (+), contact 1 (-)	2.6	2.6	60	60	100	100
P13[24]	NA	R 1- C +, L 5- C +	3.5	2.5	130	130	60	60
P14[13,27]	3387 Medtronic®, Kinetra®	R6-, L2-	3	2	90	90	130	130
P15[12]	3387 Medtronic®; Kinetra®	R0- 1-, L5- C+	4	3.6	90	90	40	40
P16[12]	3387 Metronic®; Kinetra®	L1-2-, R5-6-	4.8	4.5	90	90	60	60
P17[28]	3387 Medtronic®; IPG, NA	R9-, L1-	3	3.2	60	60	60	60
P18[29]	Lead, NA; auto-recharge stimulator, St Jude Medical	R1-, L1-	4	4	212	212	60	60
P19[30]	3387 Medtronic®, Activa PC®	R9-11+, L1-3+	5	4	90	120	180	180
P20[30]	3387 Medtronic®, Kinetra®	R 4-5-6-, L 0-1-2-	2	2	60	60	130	130
P21[30]	3389, Medtronic®, Kinetra PC®	R1-, L5-	2.6	2.6	90	120	140	140
P22[11]	3387 Medtronic®, Itrel II®			Ineffective				
P23[22]	3389 Medtronic®, Activa PC®	R0-, L9-	2.5	2.5	90	90	130	130
P24[31,32]	3387 Medtronic®, Soletra®	R1-, L3-	2.8	2.8	150	150	40	40
P25[33]	3387 Medtronic®, Itrel II®	R0+1-2-, L0-1-2+	3.3	3.5	120	150	160	160
P26[33]	3387 Medtronic®, Itrel II®	R1-, L2-	2.9	3.3	120	120	170	170
P27[34]	3387 Medtronic®, Kinetra®	R2-, L5-	4	2.9	60	60	185	185

The "–" symbols demonstrate the minimum to the maximum values during programming. NA, not assessed/not reported; L, left; R, right; IPG, implanted pulse generator; ND, not done; DBS, deep brain stimulation.