REVIEW

Bilateral Pallidotomy for Dystonia: A Systematic Review

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ABSTRACT: Stereotactic lesioning of the bilateral globus pallidus (GPi) was one of the first surgical treatments for medication-refractory dystonia but has largely been abandoned in clinical practice after the introduction of deep brain stimulation (DBS). However, some patients with dystonia are not eligible for DBS. Therefore, we reviewed the efficacy, safety, and sustainability of bilateral pallidotomy by conducting a systematic review of individual patient data (IPD). Guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and IPD were followed. In May 2020, Medline, Embase, Web of Science, and Cochrane Library were searched for studies reporting on outcome of bilateral pallidotomy for dystonia. If available, IPD were collected. In this systematic review, 100 patients from 33 articles were evaluated. Adverse events were reported in 20 patients (20%), of which 8 were permanent (8%). Pre- and postoperative Burke-Fahn-Marsden Dystonia Rating Movement Scale scores were available for 53 patients. A clinically relevant improvement (>20%) of this score was found in 42 of 53 patients (79%). Twenty-five patients with status dystonicus (SD) were described. In all but 2 the SD resolved after bilateral pallidotomy. Seven patients experienced a relapse of SD. Median-reported follow-up was 12 months (n = 83; range: 2–180 months). Based on the current literature, bilateral pallidotomy is an effective and relatively safe procedure for certain types of dystonia, particularly in medication-refractory SD. Although due to publication bias the underreporting of negative outcomes is very likely, bilateral pallidotomy is a reasonable alternative to DBS in selected dystonia patients.

Key Words: pallidotomy; dystonia; safety; efficacy; sustainability

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive movements, postures, or both.[1] It is a debilitating disorder with a high burden of disease.[2] If pharmacological treatment fails, stereotactic functional neurosurgery is an established next step in the treatment algorithm. It is considered the most successful strategy in life-threatening, medication-refractory status dystonicus (SD).[3]

Nowadays, deep brain stimulation (DBS) is preferred over lesioning techniques for dystonia.[4-7] However, from the 1950s to the 1980s, thalamotomy and pallidotomy were the cornerstones of stereotactic neurosurgical treatment for dystonia.[8,9] Although DBS of the pallidum has important advantages over ablative procedures, including its reversibility and the ability to adjust stimulation parameters, it also has its limitations. Adverse events such as infection, skin erosion, and hardware malfunction, but also lifelong follow-up and neurological side effects, for example, long-term akinesia and gait disorder, are well known. In fact, hardware-related issues are more common in patients with dystonia than in patients with other

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movement disorders.[10] Furthermore, DBS is expensive, and reimbursement and availability vary among countries.[11]

Cognitive impairment, young age, cachectic state, and inability to comply with follow-up visits are recognized as valid reasons to refrain from DBS.[12] Severe medical-refractory dystonia and SD often coincide with impaired cognition and cachectic state, particularly in the case of neurometabolic or neurodegenerative diseases. In these patients bilateral pallidotomy is a valid treatment, but this step is not easily taken. The literature on this topic is limited to case reports and case series. Therefore, we performed this systematic review and collected the individual patient data (IPD) to assess the efficacy, safety, and sustainability of bilateral pallidotomy in patients with dystonia.

Patients and Methods

A systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Fig. 1).[13] A systematic search for relevant studies was performed up to May 2020, based on electronic databases Cochrane Library, Medline, Embase, and Web of Science. The search strategy was designed using the Medical Subject Headings terms "pallidotomy" and "dystonia." The references of the included articles were scrutinized for other relevant studies.

Study Selection

Three authors independently made the study selection. Disagreements were solved in a consensus meeting. Peer-reviewed full-text papers that reported on motor outcome were selected. The initial selection was based on screening of titles and abstracts. Further selection was made after reading and cross-reading of the full text. Patients with dystonia in the context of Parkinson's disease were excluded. Studies with overlapping patients were also excluded, except when additional IPD could be obtained by including both articles. In case of missing data, an attempt to contact the corresponding author was made twice by e-mail.

Data Extraction

The following data were extracted: (1) Patient characteristics: age, gender, diagnosis, and dystonia type; (2) efficacy of pallidotomy, as expressed by an improvement in motor performance (Burke-Fahn-Marsden Dystonia Rating Scale [BFMDRS],[14] Unified Dystonia Rating Scale [UDRS], or any other qualitative or quantitative description); (3) safety in terms of reported

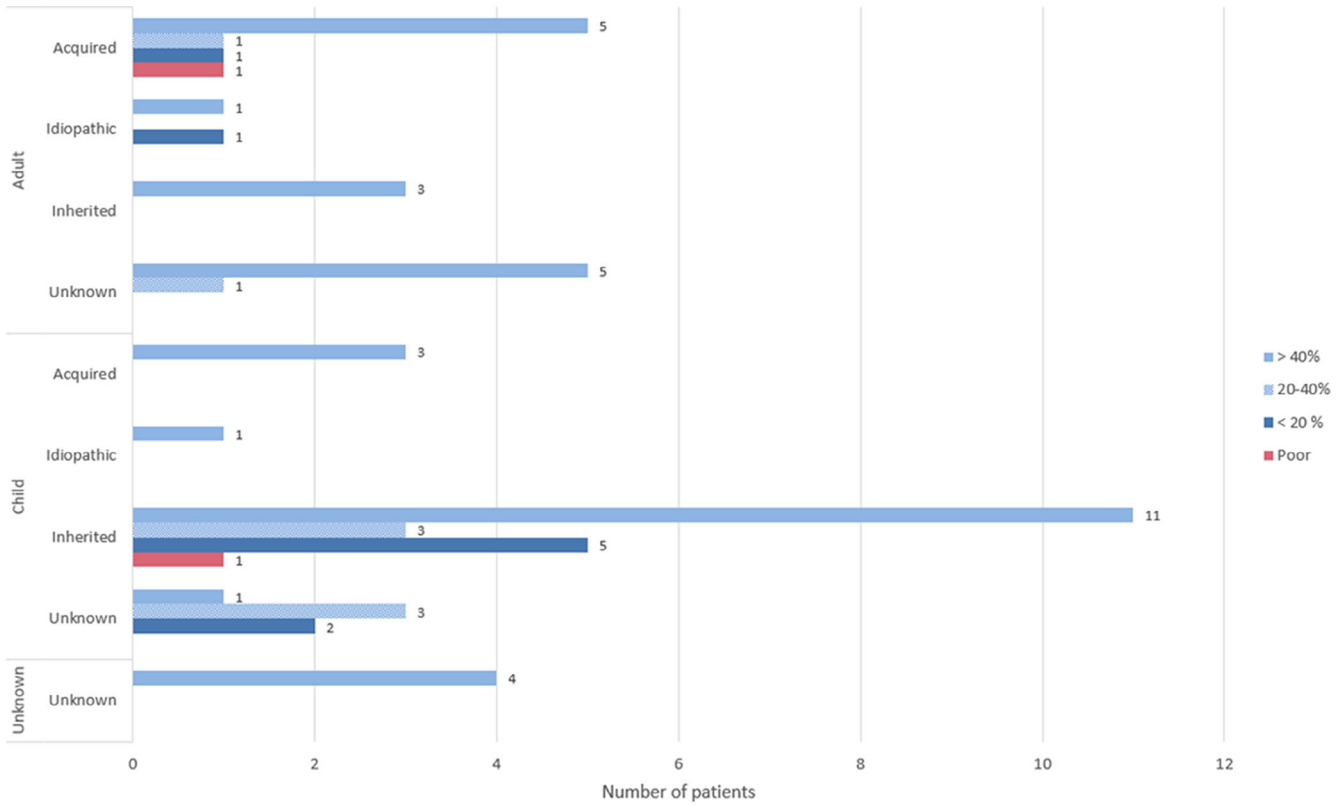

FIG. 1. Improvement Burke-Fahn-Marsden Dystonia Rating Scale movement score at the end of reported follow-up (n = 53). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1. Overview of studies on bilateral pallidotomy for dystonia

Author	Gender (M/F)	Age at start of disease	Age at surgery	Symptoms pre-op	Diagnosis	Dystonia type	BFMDRS movement	BFMDRS disability	Staged/simultaneous	Other scores	Score	Follow-up	Child/adult	Complications	Part of case report/case series	Aftereffects	Relapse/no improvement
Levi et al (2019) *Italy*	F	2 y	10 y	Status dystonicus	PKAN classic	Inherited	–	–	Simultaneous	BAD	SD: 32, postop: 32, last: NA	–	Child	–	Series	Ineffective, death due to SD after 35 days	Death
	F	4 y	7 y	Status dystonicus	Post-infective SD	Acquired	–	–	Simultaneous	BAD	SD: 32, post-op: 29, last: 31	12 mo	Child	–	Series	1 day	SD resolution
	M	1 y	9 y	Status dystonicus	–	–	–	–	Staged	BAD	SD: 30, post-op: 14, last: 15	12 mo	Child	–	Series	35 days	SD resolution
	M	2 y	8 y	Status dystonicus	PKAN atypical	Inherited	–	–	Simultaneous	BAD	SD: 31, post-op: 30, last: 30	12 mo	Child	–	Series	15 days	SD resolution
	F	1 y	19 y	Status dystonicus	Cerebral palsy	Acquired	–	–	Simultaneous	BAD	SD: 31, post-op: 24, last: 28	38 mo	Adult	–	Series	50 days	Death due to complications unrelated to baseline dystonia
	F	1 y	10 y	Status dystonicus	GNAO1	Inherited	–	–	Simultaneous, after failed DBS	BAD	SD: 32, post-op: 28, last: 28	180 mo	Child	–	Series	60 days	SD resolution
	M	2 y	16 y	Status dystonicus	Cerebral palsy	Acquired	–	–	Simultaneous	BAD	SD: 30, post-op: 28, last: 28	30 mo	Child	–	Series	8 days	Death due to complications unrelated to baseline dystonia
Garone et al (2019) *Italy*	M = 7, F = 1, unknown = 1			Status dystonicus	–	Both acquired and inherited	–	–	–	DSAP	DSAP4 = 1, DSAP5 = 6, unknown = 2	–	Child		Series	–	SD resolution in all but 1 patient; dystonia relapse in 7 of 9 patients
Franzini et al (2018)[a] *Italy*	F	4 y	6 y	Status dystonicus	Tuberculous meningoencephalitis	Acquired	Pre-op: 110, 3 mo: 50	Pre-op: 30, 3 mo: 30	Simultaneous	–	–	3 mo	Child	–	Report	Second day after surgery: dramatic reduction of dystonic movements	Unknown
Horisawa et al (2018)[a] *Japan*	M	36 y	38 y	Camptocormia	Tardive dystonic camptocormia	Acquired	Pre-op: 3, post-op: 0	Pre-op: 3, post-op: 0	Staged	–	–	18 mo	Adult	–	Report	Complete resolution of symptoms after unknown time parameter	Unknown
Horisawa et al (2018)[a] *Japan*	M	43 y	47 y	Embouchure dystonia	Embouchure dystonia	Acquired	–	–	Staged: 6-mo interval	–	–	12 mo	Adult	–	Report	Complete resolution of symptoms after unknown time parameter	Unknown
Kohara et al (2017) *Japan*	M	–	32 y	Trunk and upper extremity dystonia	Tardive dystonia	Acquired	Pre-op: 28.5, post-op: 1.5, 9 mo: 0		Simultaneous	–	–	9 mo	Adult	–	Report	Immediately post-surgery	Unknown
Franzini et al (2017)[a] *Italy*	M	–	9 y	Status dystonicus	–	Idiopathic	–	–	Staged, 2-week interval	UDRS	Pre-op: 110, post-op: 41	6 mo	Child	–	Report	Gradual improvement over 2 mo	Unknown
Minkin et al (2017)[a] *Bulgaria*	M	45 y	68 y	Focal dystonia	Meige syndrome	Idiopathic	Pre-op: 26, 6 mo: 3, 24 mo: 3	–	Staged: 6-mo interval	–	–	24 mo	Adult	–	Report	Immediately	Unknown
Horisawa et al (2016)[a] *Japan*	M	27 y	36 y	Cervical dystonia	–	Idiopathic	–	–	Simultaneous	TWSTRS and Tsui score	Pre-op: 12 and 6, 1 week: 1 (both)	12 mo	Adult	Transient aggressive behavior	Report	Day after surgery	Unknown
Franzini et al (2015)[a] *Italy*	F	Birth	15 y	Generalized dystonia	Hypoxic event	Idiopathic	Pre-op: 56, 12 mo: 28	–	Staged interval unspecified	–	–	12 mo	Child	–	Report	Few weeks after lesions	Unknown
Marras et al (2014)[a] *Italy*	M	3 y	15 y	Status dystonicus	Chromosomopathy	Inherited	Pre-op: 101, 22 mo: 16	Pre-op: 30, post-op: 30	Simultaneous	–	–	22 mo	Child	–	Series	40 days	Unknown
	M	1 mo	19 y	Status dystonicus	Epileptic encephalopathy		Pre-op: 84, 21 mo: 4	Pre-op: 30, post-op: 30	Simultaneous	–	–	21 mo	Adult	–	Series	30 days	Unknown
	M	4 mo	6.5 y	Status dystonicus	Bilateral striatal necrosis	Inherited	Pre-op: 60, 15 mo: 57	Pre-op: 30, post-op: 30	Simultaneous	–	–	15 mo	Child	–	Series	21 days	Unknown
	M	8 mo	12 y	Status dystonicus	Hypoxic event	Acquired	Pre-op: 77, 15 mo: 44	Pre-op: 26, latest follow-up: 28	Simultaneous	–	–	15 mo	Child	–	Series	60 days	Unknown
Fonoff et al (2012)[a] *Brazil*	F	2 y	23 y	Generalized dystonia	–	Idiopathic	–	–	–	–	–	24 mo	Unknown	Severe hypophonia	Series	–	Relapse after 2 y
	M	11 y	41 y	Generalized dystonia	–	Idiopathic	–	–	–	–	–	24 mo	Unknown	–	Series	–	Relapse
	F	40 y	58 y	Generalized dystonia	–	Acquired	–	–	–	–	–	24 mo	Unknown	Speech impairment	Series	–	Relapse after 2.5 y
	M	10 y	20 y	Generalized dystonia	–	Idiopathic	–	–	–	–	–	24 mo	Unknown	–	Series	–	Relapse after 4.5 y
Zirn et al (2011)[a] *Germany*	F	7 y	15 y	–	*TOR1A* gene mutation	Inherited	–	–	–	–	–	–	Child	Mutism, dysarthria, dysphagia, hyperhidrosis	Letter to the editor	Immediately, cessation of hyperkinesia	Needs assistance in all aspects of life, however, may be due to disease progression
Hashimoto et al (2010)[a] *Japan*	M	–	56 y	Tardive jaw-opening dystonia	Tardive dystonia	Acquired	Motor speech and eating pre-op: 8, post-op: 1	Pre-op: 8, post-op: 2	Simultaneous	–		24 mo	Adult	–	Report	Immediately	Unknown
Elkay et al (2009)[a] *United States*	F	–	21 y	Status dystonicus	Batten disease	Inherited	Pre-op: 120, 5 mo: 65	–	Simultaneous	–	–	6 y	Adult	–	Report	10 days	Slight opisthotonus but never to prepallidotomy level
	F	–	19 y	Generalized dystonia	Batten disease	Inherited	–	–	–	–	–	6 y	Child	–	Report	Immediately	Relapse after 3 weeks
Cersosimo et al (2007)[a] *Argentina*	F	6 y	19 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 108, 3 mo: 70, 1 y: 42, 8 y: 21	Pre-op: 26, 3 mo: 15, 1 y: 9, 8 y: 8	Simultaneous	–	–	96 mo	Adult	–	Series	–	Unknown

(Continues)

TABLE 1. Continued

Author	Gender (M/F)	Age at start of disease	Age at surgery	Symptoms pre-op	Diagnosis	Dystonia type	BFMDRS movement	BFMDRS disability	Staged/simultaneous	Other scores	Score	Follow-up	Child/adult	Complications	Part of case report/case series	Aftereffects	Relapse/no improvement
	M	10 y	14 y	Focal dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 42, 3 mo: 10, 5 y: 11, 6 y: 32, 8 y: 50	Pre-op: 12, 3 mo: 8, 5 y: 8, 6 y 12, 8 y: 15	Simultaneous	–	–	96 mo	Child	Anarthria	Series	–	Relapse after 60 mo
Teive et al (2005)[a] *Brazil*	M	–	8 y	Status dystonicus	Cerebral palsy	Acquired		–	–	–	–	–	Child	–	Series	–	Unknown
Hwang et al (2005)[a] *United States*	M	6 mo	6 y	Generalized dystonia	Glutaric aciduria type 1	Inherited	Pre-op: 115, 6 mo 98	–	Staged, 3-mo interval	Global Dystonia Rating Score	Pre-op: 98, post op: 78	6 mo	Child	–	Report	Immediately	Unknown
Rakocevic et al (2004)[a] *United States*	M	10 mo	18 mo	Generalized dystonia	Glutaric aciduria type 1	Inherited	–	–	Staged	–	–	24 mo	Child	Left horizontal gaze preference	Report	–	Unknown
Kyriagis et al (2004)[a] *United States*	M	16 mo	9 y	Status dystonicus	Hallervorden-Spatz disease	Inherited	–	–	Simultaneous	–	–	12 mo	Child	–	Report	6 mo, with intrathecal baclofen	Alleviation of spasms with bilateral pallidotomy and baclofen
Hutchison et al (2003)[a] *Canada*	–	4 y	13 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 70.5, post-op: 48	–	–	–	–	–	Child	–	Series	–	Unknown
	–	7 y	14 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 53.5, post-op: 13.5	–	–	–	–	–	Child	–	Series	–	Unknown
	–	7 y	9 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 75, post-op: 52	–	–	–	–	–	Child	–	Series	–	Unknown
	–	9 y	9 y	Generalized dystonia	–	–	Pre–op: 113.5, post–op: not available	–	–	–	–	–	Child	–	Series	–	Unknown
	–	5 y	16 y	Generalized dystonia	–	Idiopathic	Pre-op: 49, post-op: 45, 5 mo: 56	–	–	–	–	–	Child	–	Series	–	Relapse at 5 mo
Eltahawy et al (2004)[a]	M	7 y	14 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 75, 6 mo: 25	–	Simultaneous	Global Outcome Score	6 mo: 4	6 mo	Child	Hypophonia	Series	–	Unknown
	M	8 y	15 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 71, 6 mo: 38	–	Simultaneous	Global Outcome Score	6 mo: 3	6 mo	Child	Dysphonia	Series	–	Unknown
	F	7 y	17 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 53, 6 mo: 13	–	Simultaneous	Global Outcome Score	6 mo: 4	6 mo	Child	–	Series	–	Unknown
	M	5 y	19 y	Generalized dystonia	Idiopathic	Idiopathic	Pre-op: 49, 6 mo: 40	–	Simultaneous	Global Outcome Score	6 mo: 1	6 mo	Adult	–	Series	–	Unknown
	M	1 y	12 y	Generalized dystonia	Glutaric aciduria	Inherited	Pre-op: 113, 6 mo: 99	–	Simultaneous	Global Outcome Score	6 mo: 1	6 mo	Child	–	Series	–	Unknown
Sanghera et al (2003)[a] *United States*	–	7 y	15 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 50, post-op: 12	–	Simultaneous	UDRS	Pre-op: 68, post-op: 12	12 mo	Child	–	Series	–	Unknown
	–	8 y	10 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 26, post-op: 19	–	Staged	UDRS	Pre-op: 36, post-op: 21	12 mo	Child	–	Series	–	Unknown
	–	9 y	51 y	Generalized dystonia			Pre-op: 57, post-op: 15	–	Staged	UDRS	Pre-op: 83, post-op: 26	12 mo	Adult	–	Series	–	Unknown
	–	8 y	13 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 48, post-op: 17	–	Simultaneous	UDRS	Pre-op: 81, post-op: 20	12 mo	Child	–	Series	–	Unknown
	–	12 y	16 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 27, post-op: 10	–	Simultaneous	UDRS	Pre-op: 41, post-op: 2	12 mo	Child	–	Series	–	Unknown
	–	7 y	17 y	Generalized dystonia	–	–	Pre-op: 59, post-op: 17	–	Simultaneous	UDRS	Pre-op: 101, post-op: 27	12 mo	Child	–	Series	–	Unknown
	–	6 y	15 y	Generalized dystonia	–	–	Pre-op: 56, post-op: 45	–	Simultaneous	UDRS	Pre-op: 82, post-op: 74	12 mo	Child	–	Series	–	Unknown
	–	9 y	19 y	Generalized dystonia	–	–	Pre-op: 56, post-op: 43	–	Simultaneous	UDRS	Pre-op: 86, post-op: 63	12 mo	Adult	–	Series	–	Unknown
	–	5 y	15 y	Generalized dystonia	–	–	Pre-op: 49, post-op: 46	–	Simultaneous	UDRS	Pre-op: 78, post-op: 66	12 mo	Child	–	Series	–	Unknown
	–	2 y	11 y	Generalized dystonia	–	–	Pre-op: 58, post-op: 36	–	Simultaneous	UDRS	Pre-op: 88, post-op: 54	12 mo	Child	–	Series	–	Unknown
	–	0.4 y	8 y	Generalized dystonia	–	–	Pre-op: 31, post-op: 25	–	Staged	UDRS	Pre-op: 51, post-op: 34	12 mo	Child	–	Series	–	Unknown
Anca et al (2003)[a] *Israel*	F	7 y	15 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 78, 1 y: 42, 2 y: 52	Pre-op: 28, 1 y: 22, 2 y: 22	–	–	–	24 mo	Child	1 patient of these aphonia after 1 y	Series	–	Significant motor improvement over first 3–4 mo but progressive worsening after 1 y
	M	8 y	11 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: unknown, 1 y: 14, 2 y: 14, 3 y: 23, 4 y: 38	Pre-op: unknown, 1 y: 4, 2 y: 4, 3 y: 6, 4 y: 9	–	–	–	24 mo	Child	1 patient of these aphonia after 1 y	Series	–	Relapse after 3 y
	M	9 y	13 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 68, 1 y: 15, 2 y: 25	Pre-op: 26, 1 y: 3.5, 2 y: 9	–	–	–	48 mo	Child	1 patient of these aphonia after 1 y	Series	–	Significant motor improvement over first 3–4 mo but progressive worsening after 1 y
Teive et al (2001)[a] *Brazil*	M	37 y	40 y	Generalized dystonia	Trauma	Acquired	Pre-op: 51, 3 days: 15, 3 m: 51, 6 mo: 51	–	Simultaneous	–	–	6 mo	Adult	Track hemorrhages: motor seizure, hemiparesis	Series	Immediately but relapse 3 mo later	Relapse after 3 mo
	M	16 y	35 y	Generalized dystonia	–	–	Pre-op: 60, 3 days: 52 (stage1) /46	–	Staged	–	–	6 mo	Adult	–	Series	Progressive improvement up to 3 mo	Unknown

(Continues)

TABLE 1. Continued

Author	Gender (M/F)	Age at start of disease	Age at surgery	Symptoms pre-op	Diagnosis	Dystonia type	BFMDRS movement	BFMDRS disability	Staged/simultaneous	Other scores	Score	Follow-up	Child/adult	Complications	Part of case report/case series	Aftereffects	Relapse/no improvement
							(stage 2), 3 mo: 18, 6 mo: 18										
	–	5 y	–	–	–	–	Pre-op: 50, 3 days: 50, 3 mo: 28, 6 mo: 28	–	Simultaneous	–	–	6 mo	Child	–	Series	Progressive improvement up to 3 mo	Unknown
	M	23 y	28 y	Generalized dystonia	–	–	Pre-op: 48, 3 days: 40, 3 mo: 6, 6 mo: 4	–	Simultaneous	–	–	6 mo	Adult	Transient lethargy	Series	Progressive improvement over 6 mo	Unknown
	-	21 y	–	–	–	–	Pre-op: 28, 3 days: 24, 3 mo: 12, 6 mo: 12	–	Simultaneous	–	–	6 mo	Adult	–	Series	Progressive improvement up to 3 mo	Unknown
Cubo et al (2000)[a] *United States*	F	4 y	13 y	Generalized dystonia	Westphal variant of Huntington's disease	Inherited	Pre-op: 56, 3 mo post-op: 49	–	Simultaneous	–	–	3 mo	Child	Edema on the right capsule: seizures	Report	Little improvement over 3 mo	Disease progression
Iacono et al (1996)[a] *United States*	M	8 y	17 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	–	–	Simultaneous	–	–	12 mo	Child	–	Report	Immediately	Unknown
Vitek et al (1998)[a] *United States*	–	–	–	Generalized dystonia	–	–	Pre-op: 34, 1 mo: 10	Pre-op: 10, 1 mo: 3	–	–	–	2 mo	Unknown	–	Series	–	Unknown
	–	–	–	Generalized dystonia	–	–	Pre-op: 31, 2 mo: 5	Pre-op: 8, 2 mo: 0	–	–	–	2 mo	Unknown	–	Series	–	Unknown
	–	–	–	Generalized dystonia	–	–	Pre-op: 41, 1 week: 6	Pre-op: 8.5, 1 week: 2	–	–	–	2 mo	Unknown	–	Series	–	Unknown
Ondo et al (1998)[a] *United states*	M	10 y	51 y	Generalized dystonia	–	–	Pre-op: 57, post-op: 9	Pre-op: 16, post-op: 8	Staged	UDRS, ADL	Pre-op: 83, post-op: 20, ADL = pre-op: 16, post-op: 8	6 mo	Adult	–	Series	–	Unknown
	–	13 y	18 y	Generalized dystonia	Trauma	Acquired	Pre-op: 56, post-op: 46	Pre-op: 18, post-op: 16	Simultaneous	UDRS, ADL	Pre-op: 86, post-op: 58, ADL = pre-op: 18, post-op: 16	6 mo	Adult	–	Series	–	Unknown
	M	10 y	16 y	Generalized dystonia	Hypoxic event	Acquired	Pre-op: 59, post-op: 17	Pre-op: 19, post-op: 9	Simultaneous	UDRS, ADL	Pre-op: 101, post-op: 27, ADL = pre-op: 19, post-op: 9	6 mo	Child	–	Series	2 days	Unknown
	F	7 y	14 y	Generalized dystonia	Genetic	Inherited	Pre-op: 50, post-op: 17	Pre-op: 18, post-op: 7	Simultaneous	UDRS, ADL	Pre-op: 68, post-op: 21, ADL = pre-op: 18, post-op: 7	6 mo	Child	Transient lethargy	Series	Gradual improvement over 3 mo	Partial recurrence after 6 mo
	F	8 y	13 y	Generalized dystonia	*TOR1A* gene mutation	Inherited	Pre-op: 48, post-op: 17	Pre-op: 17, post-op: 6	Simultaneous	UDRS, ADL	Pre-op: 81, post-op: 20, ADL = pre-op: 17, post-op: 6	6 mo	Child	–	Series	Within 3 weeks	Unknown
Weetman et al (1997)[a] *United Kingdom*	M	–	31 y	Generalized dystonia	Tardive dystonia	Acquired	Pre-op: 76, 8 mo: 21	Pre-op: 22, 8 mo: 4	Simultaneous	Obeso scale	Grade 2	8 mo	Adult	–	Report	Immediately	Slight recurrence
Lin et al (1999)[a,b] *Taiwan*	M	–	29 y	Generalized dystonia	Perinatal asphyxia	Acquired	Pre-op: 51, 3 mo: 37, 6 mo: 33.5, 1 y: 33.5	–	–	–	–	12 mo	Adult	–	Report	Improvement over 6 mo	Unknown
Lin et al (1998)[a,b] *Taiwan*	F	30 y	36 y	Generalized dystonia	Dystonia due to hypovolemic shock	Acquired	Pre-op: 74, 1 mo: 47, 3 mo: 34, 6 mo: 28, 9 mo: 28	Pre-op: 20, 1 mo: 12, 3 mo: 10, 6 mo: 9, 9 mo: 9	–	–	–	9 mo	Adult	Transient right facial weakness	Report	Improvement over 9 mo	Unknown
Lin et al (2001)[b] *Taiwan*	n = 18, 8 men, 10 women	Average = 24.8 y	BFMDRS movement	Generalized dystonia	–	–	13% decrease	9% decrease	14 simultaneous, 4 staged	–	–	12 mo	–	Transient adverse effects in 7 of 18: urinary incontinence (2), visual field defects (2), hemiparesis (2), unsteady gait (1), fever (1)	Series	–	Unknown
Khandelwal et al (2018)	M	–	48 y	Cervical dystonia	Cervical dystonia	–	–	–	Simultaneous	–	–	–	Adult	Transient bilateral mydriasis and visual field defects	Report	–	Unknown

[a]Included in meta-analysis.
[b]Overlapping patient.
Abbreviations: BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; DBS, deep brain stimulation; ADL, activities of daily living; UDRS, Unified Dystonia Rating Scale; BAD, Barry Albright Dystonia; SD, status dystonicus; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; PKAN, Pantothenate Kinase-Associated Neurodegeneration; DSAP, Dystonia Severity Action Plan.

adverse events, which were categorized as transient or permanent; and (4) sustainability of the lesion effect and duration of follow-up. Ten corresponding authors were contacted to retrieve supplementary IPD. Four authors responded, which led to additional IPD of one patient.[15]

Methodological Quality Assessment

Methodological quality of case series was assessed using the tool of Moga et al.[16] Case reports were assessed using an adapted version of the same tool (Table APPENDIX S1). To assess the methodological quality of the included case series and case reports, the overall percentage of agreement was calculated. Subsequently, two separate Cohen's kappas were calculated for both the case reports and the case series assessment to assess interrater agreement.

Data Analysis

Data were analyzed using SPSS version 22. Descriptive statistics were used for analysis of IPD. To describe age and duration of follow-up, means and standard deviations were used. For categorical variables (gender, type of dystonia, diagnosis, UDRS, and side effects), frequencies with percentages were used. The BFMDRS movement score was assessed separately, if available. For this score, the relative change percentage was subdivided into four categories: >40%, 20–40%, <20%, and worsening (relative to baseline).

Results

Study Selection

The electronic search yielded 1149 papers (Medline: 296, Embase: 452, Web of Science: 401, and Cochrane Library: 0). No randomized clinical trials were found. After duplicates were removed, 764 papers remained. Titles and abstracts were screened for eligibility. Subsequently, 166 full-text papers were read and assessed for eligibility. Initially non-English articles were excluded. However, due to scarcity of literature, non-English papers were also assessed. Finally, 33 papers met our inclusion criteria and were included in this review.[15,17-48] The reasons to exclude the other 133 articles were the following: congress abstracts (n = 37), described no patients (n = 25), full text not available (n = 18), unilateral pallidotomy (n = 15), Parkinson's disease (n = 12), no (motor) outcomes (n = 9), patients described before (n = 7), thalamotomy or other lesions (n = 6), no dystonia patients (n = 2), and DBS only (n = 2) (FIGURE S1).

TABLE 2. Individual patient data group characteristics

Characteristic	Total population
Sex (n = 75)	
Men	35/75 (46%)
Women	18/75 (24%)
Unknown	22/75 (30%)
Mean age at surgery ± SD (y), n = 70	20 ± 13.9
Type of dystonia (n = 72)	
Generalized	49/72 (68%)
Status dystonicus	16/72 (22%)
Focal	6/72 (8%)
Camptocormia	1/72 (1%)
Mean duration of follow-up ± SD (mo), n = 67	19.7 ± 27.7
Diagnosis (n = 55)	
Idiopathic	9/56 (16%)
Acquired	17/56 (30%)
Inherited	30/56 (54%)
BFMDRS improvement (n = 53)	
>40%	34/53 (64%)
20–40%	8/53 (15%)
<20%	9/53 (17%)
Worsening	2/53 (4%)
UDRS (n = 17)	
Improvement ≥20%	11/17 (65%)
Score decrease <20%	4/17 (24%)
No change or worsening	2/17 (12%)
Side effects (n = 75)	
Transient	6/75 (8%)
Permanent	8/75 (11%)

Abbreviations: BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; UDRS, Unified Dystonia Rating Scale.

Patient and Study Characteristics

The 33 included studies were published between 1996 and 2020, describing 100 patients (Table 1). If sufficient data were available, IPD were collected (Table 2). The included studies were case series (n = 14), case reports (n = 18), and a letter to the editor (n = 1). The number of enrolled patients per study varied from 1 to 18. The majority of patients suffered from generalized dystonia before surgery (65%); 25 patients (25%) had SD. Seven patients (7%) had focal or other forms of dystonia. Thirty-one patients (31%) had a confirmed genetic diagnosis, 18 of whom had DYT1 dystonia, caused by a mutation in the *TOR1A* gene. Table 1 presents additional information on etiology and clinical presentation. The median age at surgery was 17 years (n = 85).

Methodological Quality Assessment

The overall agreement between raters was 91% (190/209) for case reports and 86% (216/252) for case series. Both Cohen's kappas were substantial (case reports: 0.76, case series: 0.67). Therefore, the interrater variability is low (APPENDIX S1).

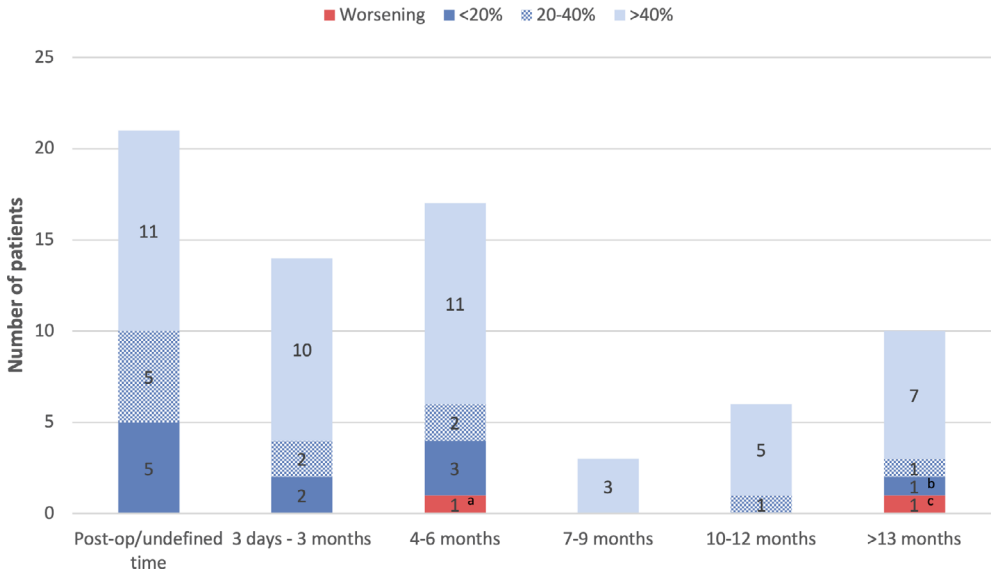

FIG. 2. Improvement BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) movement score, categorized by percentage decrease in score at latest-reported follow-up. Some studies report multiple follow-up moments. Letters a–c represent relapsing patients. For exact scores of patients see Table 1. a: Hutchison et al (2003). 8.2% improvement immediately postoperatively and relapsed at 5-month follow-up to a level 14.3% worse than baseline. b: Anca et al (2003), maximal improvement of 46.2% at 12-month follow-up, but the score had dropped to 33.3% improvement at 24-month follow-up. c: Cersosimo et al (2008). Maximal improvement of 76.2% at 3-month follow-up and showed relapsing at 60-month follow-up. At 96-month follow-up, the BFMDRS score had dropped to 19.1% worse than baseline. [Color figure can be viewed at wileyonlinelibrary.com]

Efficacy

Of 100 patients, BFMDRS scores were assessed for 53 patients pre- and postoperatively. One paper presented improvement percentage for 18 patients on a group level instead of individual scores.[34] The outcome for patients lacking a BFMDRS score was quantified by the UDRS (n = 17), a qualitative description of motor results (n = 12), or another scale (n = 3). Of note, a variety of other scales were used, and some patients were scored twice on separate scoring systems: Barry Albright Dystonia scale (n = 7), Activity of Daily Living scale (n = 5), Gross Outcome Score (n = 5), Obeso scale (n = 1), Toronto Western Spasmodic Torticollis Rating Scale (n = 1), Tsui score (n = 1), and the Global Dystonia Rating Scale (n = 1).

Motor Performance

BFMDRS scores were available for 53 of 100 (53%) patients, showing improvement after pallidotomy in 51 of 53 patients (96%). Forty-two patients (79%) showed improvement of 20% or more. In 34 patients (64%) improvement was >40% at the end of reported follow-up (Fig. 1). Improvement typically did not occur in the early postoperative phase but became apparent after several weeks to months (Fig. 2). Lin et al reported a mean 13% improvement at 1-year follow-up in a group of 18 patients with generalized dystonia (no individual scores available).[34] Cersosimo et al reported on a patient with a maximum improvement of 76.2% at 3 months followed by a secondary deterioration of 19% at 96 months.[18] Another patient experienced a temporary postoperative deterioration for a few weeks but returned to preoperative level at 3 months.

Disability

A disability score was available for 21 patients (21%). Fifteen patients showed an improvement (14 patients >20%). Four patients showed no improvement. The scores of 2 patients worsened, 1 of whom had an initial improvement of 33% at 60 months that dropped to –25% at 72 months. Lin et al also scored the disability scale and reported a mean improvement of 9% (no individual scores are available).[34]

In 17 other patients, the UDRS score was used. Of those, the vast majority improved more than 20% (n = 15; 88.2%), 1 patient improved 15%, and 1 patient improved 10%.[40] On the remaining reported scales, all patients improved (Table 1).

Sustainability

The mean follow-up was 18.2 months (range 2–180 months; n = 83). In 17 patients, the follow-up duration was not (individually) reported. In most patients, the beneficial effect lasted through follow-up. In 19 of 100 patients, a relapse of dystonic symptoms was reported (Table 1). One study reported relapsing SD.[45] Six patients were treated with DBS after bilateral pallidotomy, because their dystonic symptoms reappeared after temporary benefit.[24,38,49] The relapse

TABLE 3. Reported adverse events in all studies mentioned in this review

Article	Patients	Permanent adverse events	Transient adverse events
Khandelwal et al (2018)	1		Bilateral mydriasis and visual field defects (n = 1)
Horisawa et al (2016)	1		Transient aggressive behavior (n = 1)
Fonoff et al (2012)	2	Severe hypophonia (n = 1), speech impairment (n = 1)	
Zirn et al (2011)	1	Mutism, dysarthria, dysphagia, and hyperhidrosis (n = 1)	
Cersosimo et al (2008)	1	Anarthria (n = 1)	
Rakocevic et al (2004)	1	Left horizontal gaze preference (n = 1)	
Eltahawy et al (2004)	2	Hypophonia (n = 1), dysphonia (n = 1)	
Teive et al (2001)	2		Transient lethargy (n = 1), track hemorrhages (n = 1)
Cubo et al (2000)	1		Right capsule edema (n = 1)
Ondo et al (1998)	1		Transient lethargy (n = 1)
Anca et al (2003)	1	Aphonia (n = 1)	
Lin et al (1998)[a]	1		Transient right facial weakness (n = 1)
Lin et al (2001)	7		Urinary incontinence (n = 2), visual field defects (n = 2), hemiparesis (n = 2), unsteady gait (n = 1), fever (n = 1)

[a]Also mentioned in Lin et al (2001).

time of dystonic symptoms after pallidotomy varied between 3 weeks and 4.5 years.

Safety

Adverse events were reported in 20 of 100 patients (entire data set). Of note, adverse effects were sometimes reported in case series and therefore not analyzed as adverse effects in individually reported patients. The adverse effects in individually reported patients are presented in Table 3. Twelve patients (60%) had a variety of transient side effects (lethargy, edema, subgaleal effusion, urinary incontinence, visual field defects, hemiparesis, unsteady gait, and fever). Eight patients (40%) experienced permanent deficits (mutism, hypophonia, dysphonia, anarthria, aphonia, dysarthria, dysphagia, hyperhidrosis, and limitation of left horizontal gaze). Surgical track hemorrhages were reported in 1 patient. In most cases (n = 19), adverse effects were noticed shortly after surgery. One patient reported development of aphonia at 1-year follow-up.[17] No deaths due to bilateral pallidotomy were registered.

Staged pallidotomy was reported in 12 of 48 patients and simultaneous bilateral pallidotomy in 35 of 48 patients. For the remaining 52 cases, these data were not reported. In the "staged" group, a case of unilateral horizontal gaze impairment and a case of transient lethargy were reported. The other adverse events occurred either in the "simultaneous" group or in the "unreported" group.

One paper by Khandelwal et al was not included in the overall analysis because of a lack of clinical outcome data. Nevertheless, the paper is mentioned in Table 3 because of a transient adverse effect of bilateral mydriasis and visual field defects.[50]

Discussion

This systematic review evaluated the efficacy, safety, and sustainability of bilateral pallidotomy for dystonia. In 2008, Gross stated that improvement after pallidotomy was similar to DBS and that complications appeared to be rare.[51] Although this statement was based on studies of unequal levels of scientific evidence, it provides food for thought regarding whether the abandonment of bilateral pallidotomy as a treatment option in selected patients is justified. In the reviewed papers, the rationale for choosing pallidotomy over DBS is generally not mentioned. A few exceptions were as follows: patients decided against implantation of material inside their head, higher costs of DBS, and in one case DBS was ineffective for SD and it was decided to perform bilateral pallidotomy.

Efficacy and Sustainability

Bilateral pallidotomy was shown to lead to improvement in the majority of patients with a reported BFMDRS score (96%). BFMDRS score as the most relevant outcome measure revealed an improvement of 20% or more in 42 of 53 patients (79%). Of these, 34 (64%) patients had an improvement of more than 40%. Three patients experienced secondary worsening of the BFMDRS score, 2 of which returned to baseline (Fig. 2).[17,29] Although in some cases immediate effects were reported, the beneficial effect of bilateral

pallidotomy typically took weeks or months to occur. The cause for heterogeneity in response time is unknown. After bilateral pallidotomy, the disability scale (maximal 30 points) showed overall a mean improvement of 6.5 points (22%) but was observed only in a minority of patients. Stewart and colleagues concluded that the disability score is less responsive to change in dystonic symptoms.[52] There can be a meaningful change in functioning in the absence of a disability score improvement.[53] All these aspects of pallidotomy should be mentioned in counseling patients.

No conclusions can be drawn concerning long-term efficacy of bilateral pallidotomy in the treatment of dystonia as the median-reported follow-up time was only 18 months.

In medication-refractory SD, bilateral pallidotomy initially terminated in 23 of 25 reported cases (92%). Remarkably, in a single study by Garone and colleagues after initial benefit, relapse of symptoms was reported in 7 patients.[45] Unfortunately, the (possible) explanations for these relapses are not mentioned, nor the duration of the relapse nor the type of dystonia. In combination with the fact that this is the only study that reports the recurrence of SD after bilateral pallidotomy, conclusions cannot be drawn on the risk of relapse after SD. Of note, an additional search for cases describing unilateral pallidotomy for SD was performed, but such cases were not identified.

Safety

In the literature, adverse events of bilateral pallidotomy include hemiparesis, visual field defects, and neuropsychological changes. The latter often disappear within 6 months after pallidotomy but are reported permanent if lesions encroach the anteromedial (nonmotor) portion of the pallidum. Facial paresis is also frequently reported. Limb paresis (up to 4%) and visual field deficits (up to 14%) are less common. Of note, most data on side effects of pallidotomy are from patients with Parkinson's disease.[54]

In this review, transient and permanent adverse events were reported after bilateral pallidotomy. Temporary lethargy and permanent speech disorders (eg, hypophonia) were most frequently reported. Adverse events were less reported after staged bilateral pallidotomy, but in 45 patients adverse events were not specified to be related to either a staged or a simultaneous procedure, so these data should be interpreted with caution. Also, some adverse events reported in a simultaneous procedure were the result of a unilateral complication, for example, seizures by a hemorrhagic track. Therefore, the safety benefits of staging the procedure should be weighed carefully in individual cases. Based on this review, the marginal safety gain of staging, barely, if at all, outweighs the discomfort of two surgeries and the delayed relief of dystonic symptoms.

Five patients (5%) had permanent speech disorders after bilateral pallidotomy. Transient or stimulation-dependent speech disorders are also reported after DBS.[12] On the contrary, the same authors state that DBS-hardware problems are very common (36.1%). The adverse event profiles of both lesioning and DBS are to be kept in mind when considering surgical treatment, but as the profiles do not match, this should be done with caution.

Finally, we identified 5 patients with DBS after bilateral pallidotomy. DBS in both the internal globus pallidus and subthalamic nucleus has been reported to be successful. Although this is encouraging evidence, we cannot draw conclusions from these data. The reported cases in literature on this matter are scarce, requiring further validation in future studies.

Limitations

The main limitation of this review is that only case reports and case series on bilateral pallidotomy in dystonia were available. This comes with a high probability of underreporting of negative outcomes, leading to inevitable publication bias in this review. The second limitation of this study is that not all included patients were evaluated using standardized assessment tools (eg, BFMDRS, UDRS).

We recommend the application of standardized tools such as BFMDRS for clinical assessment in future reports on pallidotomy for dystonia. In addition, we recommend the use of personalized goals.[55,56] Finally, the 12-month follow-up sample size was considerably smaller than that at 3 and 6 months. As such, no definite conclusions can be drawn on long-term sustainability of bilateral pallidotomy nor the risk of relapsing in the long term. Data on specifics of surgical techniques were too sparsely reported to consider in this analysis. For future reports we suggest to provide at least the following points: general anesthesia or awake surgery, use of micro-electrode recording, target localization, probe type and diameter, lesioning duration and temperature, and number of lesions per side and preferably postoperative evaluation of lesion size and location.

The next step, a controlled trial of pallidotomy in dystonia, is worth exploring, as this review shows not only that pallidotomies in dystonia are currently being performed and reported but also that there is at least some equipoise in the field. The potential factors complicating a controlled trial include the establishment of DBS as the standard surgical treatment for dystonia in most centers and the lack of proper neurosurgical training and expertise in ablative surgeries for movement disorders.

Conclusion

Based on this systematic literature review, bilateral pallidotomy is in the short term an effective treatment for dystonia, particularly in treating medication-refractory SD and despite a considerable number of adverse events. Given the burden of dystonia, bilateral pallidotomy should be regarded a viable tool in the armamentarium of the neurosurgeon in the treatment of dystonia, particularly for patients with contraindications for DBS or if the severity of the dystonic symptoms outweighs the risk of permanent speech disorders.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.