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Short communication

Deep brain stimulation for dystonia-choreoathetosis in cerebral palsy: Pallidal versus thalamic stimulation

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ABSTRACT

Introduction: Dystonia-choreoathetosis is common in patients with cerebral palsy, and medical treatment is mostly unsatisfactory. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) has shown some effect, but there is still a need to optimize treatment strategies. We aimed to assess whether the thalamic ventral intermediate nucleus (Vim) might be an alternative DBS target in dystonia-choreoathetosis.

Methods: Three patients with cerebral palsy and dystonia-choreoathetosis underwent implantation of DBS electrodes concurrently in the GPi and Vim. Final selection of stimulation site and switches during follow-up with corresponding clinical outcomes were assessed.

Results: One patient with initial GPi stimulation was switched to Vim, but likewise did not improve significantly (BFM: pre-OP 142, GPi 140, Vim 134) and stimulation was discontinued. In one patient Vim was chosen as initial target for chronic DBS. Since clinical benefit was not yet satisfying, stimulation was switched to GPi resulting in further mild clinical improvement (BFM: pre-OP 99.5, Vim 82.5, GPi 82). In one patient GPi was selected and kept on follow-up due to some therapeutic effect (BFM: pre-OP 135, GPi DBS 121).

Conclusions: The GPi still represents the most convenient DBS target in patients with dystonia-choreoathetosis. Vim DBS did not show a relevant long-term advantage in everyday life in our patients. Further alternative DBS targets need to be considered in acquired dystonia.

1. Background

Dystonia and choreoathetosis are observed in about 10–15% of patients with cerebral palsy, which might lead to approximately 2–3 cases per 10.000 subjects (the prevalence of CP being estimated with 2–3 births per 1000 [1]). Medical treatment strategies often provide insufficient symptom relief, thus deep brain stimulation (DBS) has been introduced for treatment in selected cases [2,3]. It has been recognized that the benefit of chronic DBS in such patients is much more limited than that achieved in inherited or idiopathic dystonia.

Most reports have focused on the globus pallidus internus (GPi) as a target for DBS yet with heterogeneous results and sometime negligible improvement [2,3]. Although there is limited experience with thalamic DBS in acquired dystonia, it has been discussed as an alternative target or complementary target [4–8]. No clear evidence suggests preference of a specific thalamic target e.g. ventral intermediate nucleus (Vim) corresponding to the (nucleus) ventrolateralis posterior (VLp) region according to the nomenclature of Jones [9], ventral oral anterior (V.oa) or ventral oral posterior (V.op). The optimal thalamic target in dystonia still needs to be determined. [10].

Our aim was to assess the potential impact of thalamic DBS of the Vim in patients with cerebral palsy and choreoathetosis as compared to pallidal (GPi) DBS.

2. Patients and methods

2.1. Clinical characteristics

Three patients (1 man, 2 women, age range 16–58 years) with choreoathetosis due to cerebral palsy were selected for concurrent pallidal and thalamic implantation of DBS electrodes. Patients were clinically characterized according to the Burke-Fahn-Marsden (BFM) motor score (MS) and disability score (DS) preoperatively and at a median of 14 months postoperatively (FU1; range 13–17). A long-term

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follow-up evaluation was then performed at a median of 76 months (FU2; range 30–105) after either switch or continuation of the stimulation site. A switch of active DBS target was expected to be performed when battery depletion would occur, to spare the patient an additional intervention solely dedicated to such a change. In addition, patients rated their satisfaction according to a previously outlined patient self-rating (PSR) score (4 = excellent; 3 = marked; 2 = moderate; 1 = mild; 0 = none; −1 = worse) [3].

2.2. DBS procedure

All 3 patients underwent bilateral CT-stereotactic implantation of DBS electrodes guided by microelectrode recording in the posteroventral lateral GPi and the Vim (model 3387, Medtronic®) as reported previously [11]. Implantation of DBS electrodes was performed under general anaesthesia except in patient no.2, who underwent the operation under local anaesthesia. Postoperative stereotactic CT imaging was performed to confirm appropriate placement of the DBS electrodes within the target. Extensive test stimulations of both targets were performed with externalized electrodes to select the target for chronic stimulation by assessing primarily the effect on the tonic respectively the phasic dystonic elements. This period took a few days. Both targets were equally explored with bipolar settings as used typically by our group after identifying of the appropriate contacts by testing each contact up to the threshold for side effects as recommended in the literature [12]. Both middle contacts were placed at the centre of the selected target. The electrodes were then connected to implantable pulse generators (IPG) implanted in the subclavicular subcutaneous tissue.

All patients gave their written informed consent to the operation and the follow-up examinations, which were approved by the local ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The approach with simultaneous implantation of 4 leads and potential impact on complication rates was preoperatively specifically addressed and was considered acceptable in view of the experience with multiple electrode implantation in other patients in our centre [13].

3. Results

Surgery was uneventful in all three patients. Detailed clinical data, characteristics of choreoathetosis/dystonia, outcome and stimulation settings are shown in Table 1.

3.1. Patient no. 1

The 16 year-old girl suffered from a hyperkinetic movement disorder since early childhood with involuntary movements of the head, choreoathetosis of the upper extremities and additional severe spasticity of the legs. She was permanently wheelchair-bound, the choreic movements had led to self-injury. Pre-operative BFM motor score was 112 and disability score 30 (BFM 142).

During the test phase with externalized electrodes stimulation of the GPi led to a discrete improvement of choreoathetosis whereas test stimulation of the Vim did not result in relevant short-term clinical effects. Therefore it was decided to connect the GPi electrodes with the IPG (Kinetra, Medtronic®). DBS settings are provided in Table 1C.

Chronic GPi DBS did not improve choreoathetosis significantly as reflected by the BFM motor score of 110 and a disability score of 30 (BFM 140) at FU1. Therefore a switch to Vim DBS was decided after 22 months, which likewise did not lead to a significant benefit (MS 104, DS 30; BFM 134). The multifocal DBS system was explanted after 30 months.

3.2. Patient no. 2

The 25 year-old man presented with choreoathetosis, action-induced myocloniform tremor and dystonia with additional spastic tetraparesis and ataxic gait, making a wheelchair necessary for longer distances. He was not able to drink from a glass by himself and needed assistance for eating. His speech was severely dysarthric. The pre-operative BFM motor score was 80.5 and disability score was 19 (BFM 99.5).

During the test phase with externalized electrodes Vim stimulation led to significant improvement especially of the action tremor. This was more pronounced than with GPi stimulation and therefore the Vim was chosen as the primary target to be connected to the IPG (Kinetra, Medtronic®).

Under chronic bilateral Vim DBS the patient experienced sustained improvement of dystonic tremor and fine motor skills, he was able to grip objects and could guide the glass to his mouth by himself. Furthermore his speech improved (BFM motor score 67.5, disability score 15; BFM 82.5). With the aim to optimize the therapeutic effect, stimulation was switched from Vim to GPi at 41 months post-OP when IPGs needed to be replaced because of depletion. This led to further improvement of fine motor skills and myocloniform symptoms, the tremor and dystonia remained stably improved (BFM motor score 67, disability score 15; BFM 82).

3.3. Patient no. 3

The 58 year-old woman presented with severe orofacial dyskinesia, dysphagia and anarthria as well as choreoathetotic movements of the upper extremities and pronounced spastic tetraparesis with predominance of the legs (BFM motor score 107, disability score 28; BFM 135). Symptoms existed since childhood and severe dystonic cervical movements necessitated cervical decompressive surgery due to secondary cervical spinal canal stenosis and myelopathy.

During the test phase, GPi stimulation via the externalized electrodes led to a slightly better improvement of phasic dystonic movements than Vim stimulation, therefore the GPi electrodes were finally connected to the IPG (Kinetra, Medtronic®). At FU1 there was a subjective improvement of muscle tension that, however, was not reflected by a significant improvement of the BFM motor (103) and disability score (28) (BFM 131). Nevertheless the patient opted to continue with pallidal stimulation and at FU2 there was a significant improvement after a longer stimulation period (BFM motor 94, disability score 27; BFM 121).

4. Discussion

Our study is one of the first efforts to evaluate whether thalamic DBS could yield additional benefit as compared to pallidal DBS in patients with refractory severe dystonia-choreoathetosis due to CP. Unfortunately, no such benefit could be demonstrated, with externalized electrodes, thalamic DBS was superior to pallidal DBS in only one patient who suffered from tremor. In two patients Vim stimulation was activated for several months and resulted in minimal yet not satisfying symptom improvement. At long-term follow-up, none of the patients was persistently on Vim stimulation in contrast to 2 patients who benefitted from variable improvement with GPi DBS.

Treatment of dystonia-choreoathetosis due to cerebral palsy remains a challenge. The largest series of pallidal DBS with 13 patients showed a mild but significant improvement reflected by a mean change in the BFM motor score of 24% [2], which was in line with previously reported smaller series [3]. In the present series, 2 patients finally benefitted from sustained GPi DBS with 10–20% improvement on the BFM motor score, whereas one patient had no relevant response for everyday life, neither to GPi nor to Vim stimulation and therefore the neurostimulation system was removed. Note that the subjective patients

Table 1
[A] Clinical pre- and post-operative data of 3 patients with cerebral palsy and dystonia-choreoathetosis treated with deep brain stimulation. **[B]** Classification according to the new classification system for dystonia. **[C]** Deep brain stimulation sites and settings during follow-up.

A					BFM motor score			BFM disability			PSR	
Patient	Sex	Previous medication	Age at DBS [years]	Target	Pre-OP	FU1	FU2	Pre-OP	FU1	FU2	FU1	FU2
no. 1	female	BTX, BAC, DZM, THP, VLP	16	GPi 22 months; Vim 9 months	112	110 (GPi)	104 (Vim)	30	30	30	0	0
no. 2	male	none	25	Vim 38 months; GPi 35 months	80.5	67.5 (Vim)	67 (GPi)	19	15	15	2	2
no. 3	female	BAC, NIT, OZM	58	GPi 128 months	107	103 (GPi)	94 (GPi)	28	28	27	1	2

B	Axis I: Characteristics					Axis II: Etiology	
Patient	Age at onset	Body distribution	Temporal pattern (disease course/ variability)	Other Movement Disorder	Other Neurologic Manifestation	Anatomical changes	Etiology
no. 1	Childhood	Generalized	static/persistent	Choreoathetosis	spasticity, impaired cognition	no evidence of degeneration or structural lesion	acquired: perinatal brain injury
no. 2	Childhood	Generalized	static/persistent	Choreoathetosis	spasticity, gait ataxia	no evidence of degeneration or structural lesion	acquired: perinatal brain injury
no. 3	Childhood	Generalized	static/persistent	Choreoathetosis	spasticity, dysphagia, anarthria, impaired cognition	no evidence of degeneration or structural lesion	acquired: perinatal brain injury

C	DBS target & stimulation settings (Contacts/Voltage[V]/PW[μs]/Frequency[Hz])									
Patient	VIM target coordinates[a]	initial Vim		last Vim		GPi target coordinates[a]	initial GPi	right IPG	last GPi	right IPG
		left IPG	right IPG	left IPG	right IPG		left IPG		left IPG	
no. 1	x = 14 mm lateral y = 4 mm posterior z = 0 mm below	1-2+/2.6/210/130	5-6+/2.6/210/130	1-2+/4.2/210/130	5-6+/4.2/210/130	x = 20 mm lateral y = 3 mm anterior z = 4 mm below	1-2+/4.5/210/130	1-2+/4.5/210/130	1-2+/5.0/210/130	1-2+/5.0/210/130
no. 2	x = 12 mm lateral y = 4 mm posterior z = 0 mm below	1-2+/2.5/210/130	5-6+/2.5/210/130	1-2+/4.0/210/130	5-6+/4.1/210/130	x = 20 mm lateral y = 3 mm anterior z = 4 mm below	1-2+/4.0/210/130	9-10+/4.0/210/130	1-2+/4.5/210/130	9-10+/3.9/210/130
no. 3	x = 13 mm lateral y = 4 mm posterior z = 0 mm below	NA	NA	NA	NA	x = 20 mm lateral y = 3 mm anterior z = 4 mm below	1-2+/4.0/210/130	6-7+/4.0/210/130	8-9+/2.3/210/130	0-1+/2.3/210/130

DBS = deep brain stimulation; Vim = ventral intermediate nucleus; GPi = Globus pallidus internus; BFM = Burke-Fahn-Marsden; PSR = patient satisfaction rating scale; FU = follow-up; BTX = Botulinumtoxin; BAC = Baclofen; DZM = Diazepam; THP = Trihexyphenidyl; VLP = Valproate; NIT = Nitomane; TPD = Tiaprid.
DBS = deep brain stimulation; PW = pulse width; Vim = ventral intermediate nucleus; GPi = Globus pallidus internus; IPG = implantable pulse generator.
[a] Coordinates refer to the midpoint of the intercommissural line.

ratings did not coincide with the BFM scores.

Thalamic stimulation of the Vim, the ventral oral anterior (VOA) or the ventral oral posterior nucleus (VOP) has been reported to improve choreic hyperkinesias of different etiologies in individual cases [5,6,14]. While the Vim has been established as the standard DBS target in essential tremor, it is being explored as a target for dystonic tremor [7,10]. Furthermore, some reports on improvement of various dystonic symptoms with stimulation of the “motor thalamus”, that is ventroposterolateral nucleus (VPL) or using different terminology, the Vim nucleus, have been published [8].

Overall, evidence for the efficacy of Vim DBS in dystonia remains scarce, but its efficacy on movement disorders with rapid components such as tremor could suggest a beneficial effect on dystonic or choreoathetotic movement disorders with phasic components. With that regard and considering the limited efficacy of pallidal DBS, the thalamus has been suggested an alternative and potentially promising target in choreoathetosis [4]. Notably, the thalamus has also been a frequent target for dystonia in the radiofrequency lesioning era [15]. We may not exclude that the limited improvement in our study might also be related to the selection of patients with a high degree of disability, which has been found negatively correlated with the clinical improvement after DBS [16]. Another factor might be the delay between symptom onset and DBS implantation. A longer period of life with dystonia might predict less improvement as has been shown for “primary dystonia” and in a series of children with “secondary dystonia”. Lastly chronic Vim DBS might not have been tried long enough to obtain better results, since in patient no. 3 improvement with GPi DBS as measured by the BFM was only noticeable at prolonged follow-up. This argument also applies to the initial target selection, which is done in a phase, where stimulation effects are not yet fully developed and potential neuroplastic alterations might be aborted by switching to the alternative target.

Multifocal concurrent DBS might be another option to be explored in larger trials systematically. Recently, a patient with choreic and dystonic movements in the context of neuroacanthocytosis significantly benefitted from simultaneous multifocal DBS of the GPi and Vim [4].

Another target to be explored in CP might be the cerebellum. One group has reported 4 cases of cerebellar DBS with functional improvement [17]. In particular, cerebellar DBS might be useful in the specific population of patients with dystonia but also severe spastic components. A rapid reduction of spasticity was reported with cerebellar stimulation, whereas choreoathetosis improved in a more delayed fashion [17].

Overall, DBS of the GPi still remains the most effective treatment option for patients with acquired dystonia and choreoathetosis in cerebral palsy. Further multicentre prospective trials with a double-blind design are needed to explore the value of alternative targets.

Conflicts of interest

The authors declare that they have no conflict of interest.

Disclosures

MEW, CB, AS, none. CS reports personal fees and non-financial support from AbbVie Inc. and AbbVie Deutschland, non-financial support from Merz Pharmaceuticals, personal fees from Ipsen Pharma, nonfinancial support from Allergan Inc., outside the submitted work. JKK is consultant to Medtronic and to Boston Scientific, he received honoraria from Abbvie and St. Jude.

Author roles

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AS (1) acquisition of data, (2) revising the article critically for important intellectual content, (3) final approval of the version to be submitted.

CS (1) acquisition of data, (2) revising the article critically for important intellectual content, (3) final approval of the version to be submitted.

JKK (1) conception and design of the study, acquisition of data, analysis and interpretation of data, (2) revising the article critically for important intellectual content, (3) final approval of the version to be submitted.

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