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Letter to the editor

Pallidal deep brain stimulation in Huntington's disease

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Huntington's disease (HD) is a progressive neurodegenerative disorder presenting with movement disorders, psychiatric symptoms and cognitive decline. Pharmacological therapy of chorea is often limited by side effects, particularly apathy, or has poor efficacy.

Given the effectiveness of GPi DBS to treat choreatic dyskinesias in PD it has also been tried in patients with HD and neuroacanthocytosis but experience in these patients is very limited.

Here, we report one year (case 2 and 3) and three year (case 1) follow-up assessment following GPi DBS in three HD patients with treatment-refractory chorea and provide electromyographic (EMG) findings in one of them. Neuropsychiatric symptoms were adequately controlled by pharmacological therapy. All patients had a dysexecutive syndrome but no pronounced dementia. Psychosocial support was guaranteed in all patients. Demographic and clinical data of the patients are given in Table 1.

Stereotactic bilateral MRI- and microelectrode-guided DBS electrode implantation into the posteroventral lateral portion of the GPi was performed under general anaesthesia. The surgical procedure was performed as described previously [1]. Stereotactic coordinates of the active electrodes are provided in Table 1b.

Prospective evaluation of the motor part of the Unified Huntington's Disease Rating Scale (UHDRS) was performed to assess the influence of GPi DBS on motor symptoms. To evaluate the effect of GPi DBS on chorea, dystonia and bradykinesia (consisting of items “finger tapping”, “hand pronation/supination”, “global bradykinesia”) the respective subscores were evaluated by neurologists (SZ, VT) un-blinded to the treatment condition. Motor assessment was performed at different time points up to four years preoperatively and immediately before the operation (t0). After the DBS procedure motor symptom were evaluated 3–6 months (t1) and one year postoperatively (t2) in all patients and three years postoperatively (t3) in one patient. Cognition was evaluated in two patients using the verbal fluency, Stroop, symbol digit and mini-mental state test (MMSE). Additionally, side effects of the operation or stimulation and weight were determined. Polymyographic recordings of the extremities were performed in one patient at t0 and t1 to quantify chorea.

Data are presented at a descriptive level due to the limited number of cases. Written informed consent for videos was obtained from all of the patients including a statement that the videos can be used for online publication in scientific journals.

Detailed clinical information of individual patients is given in Supplement 1 (case descriptions) including videos. Values of pre- and postoperative UHDRS total motor scores as well as chorea, bradykinesia and dystonia subscores are displayed in Fig. 1. In preoperative evaluations UHDRS total motor scores and chorea subscores deteriorated in all patients over time. Postoperatively, UHDRS total motor and chorea subscores were improved with low frequency DBS of 40 Hz (Fig. 1a, b). Reduction of chorea subscore was more pronounced in patients 1 and 2 than in patient 3. In line with clinical improvement, postoperative polymyography recordings in patient 1 at t1 showed a generalized decrease of EMG activity compared to the preoperative state (Supplement 2). Results for bradykinesia and dystonia subscores were heterogeneous (Fig. 1c, d). Bradykinesia increased and dystonia decreased in one patient. In the other two patients, bradykinesia improved but dystonia deteriorated. Adjustment of stimulation parameters including change of stimulation frequency was not associated with a further improvement. There were transient side effects with disorientation and visual hallucinations in patient 1 and reduced speech production in patient 2. We observed no persisting side effects. Anti-chorea treatment was reduced or withdrawn in all patients after DBS (Table 1a). All patients gained weight postoperatively ranging from 4 to 11 kg. Cognitive evaluation with Stroop, symbol digit and verbal fluency test was heterogeneous in the postoperative course in the two patients evaluated whereas the MMSE was stable over time.

GPi DBS markedly improved motor symptoms and activities of daily living in these HD patients with severe medically refractory chorea. Favourable effects persisted for up to three years. Improvement in chorea in our patients ranged between 40% and 58% at last follow up, which is in line with previous reports where improvements between 30% and 77.3% have been reported [2,3].

With regard to bradykinesia and dystonia results were heterogeneous. Postoperative deterioration of bradykinesia and dystonia persisted after stimulation parameters, particularly frequency, were adjusted. Differential effects on bradykinesia have also been described in PD depending on the actual site of stimulation within the internal segment of the globus pallidum [4,5]. Given the stereotactic coordinates of active contacts in our patients it is unlikely that stimulation of different sites within the GPi account for the heterogeneous effects on bradykinesia and dystonia. We

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Table 1a
Demographic variables, medication at the time of surgery and cognitive evaluation before and after the operation.

No	Age (yrs.) sex	CAG repeats	Disease duration (yrs.)	Medication pre	Medication post	Cognition before and after surgery
1	54, F	42	5	Quetiapine 75 mg Mirtazapine 45 mg Lorazepam 3 mg Tiapride 1000 mg	Olanzapine 10 mg Mirtazapine 30 mg Lorazepam 1.5 mg Flurazepam 15 mg	MMSE 20/20 VF: s-words 7/0; m-words 5/0; b-words 8/0; category 0/6 SD: 0/0 ST: colours 0/14; words 0/30; interference 0/8
2	35, F	46	4	Tiapride 800 mg Lorazepam 3.5 mg Mirtazapine 15 mg Tetrabenazine 150 mg	Tiapride 200 mg Lorazepam 0.5 mg Mirtazapine 15 mg	n.a.
3	45, M	45	7	Tiapride 600 mg Mirtazapine 15 mg Citalopram 40 mg	Tiapride 300 mg Mirtazapine 15 mg Citalopram 40 mg	MMSE 21/23 VF: s-words 2/0; m-words 0/0; b-words 2/0; category 8/8 SD: 1/6 ST: colours 37/29; words 39/35; interference 19/12

F = female; M = male; yrs. = years; n.a. = not available. MMSE = mini mental state examination; VF = verbal fluency test (category or letter in a given time is indicated); SD = symbol digit test (number of correct symbols in a given time is shown); ST = Stroop test (colours, words, interference in a given time is displayed).

hypothesize that worsening of bradykinesia and dystonia is due to disease progression rather than DBS side effects.

Of note, the right electrode in patient 3 was located more medially than the other electrodes which may explain the slightly less pronounced improvement in chorea subscore compared to the other two patients. Since the patient was satisfied with the postoperative result a revision of the electrode was not offered.

Cognitive evaluation in our patients revealed heterogeneous results. Therefore, further investigations in a larger group of patients are required to assess the influence of DBS on cognition in HD patients.

Dopamine antagonists and dopamine-depleting drugs were reduced or withdrawn in all patients which may have benefited quality of life since anti-chorea treatment often leads to impairment in activities of daily living.

Similar to the majority of previously published case reports the major limitation of the present report is that investigators were not blinded to the treatment condition. Therefore, it cannot competently be ruled out that results of the operation have been overestimated. Controlled trials with a blinded evaluation of patients are required to confirm our findings.

Low frequency GPi DBS with 40 Hz markedly improved medically refractory chorea but not dystonia or bradykinesia in these HD patients. DBS may be a treatment option for selected HD patients with severe chorea not adequately managed by pharmacotherapy.

Table 1b
Stereotactic coordinates and stimulation parameters.

Case	Stereotactic coordinates	Stimulation parameters
1	K1: x −20.8; y 2.6; z −4	K1: −2 +G, 2.7 V, 60 μsec, 40 Hz
	K2: x 19.9; y 1.4; z −4.6	K2: −9 +G, 3.0 V, 60 μsec, 40 Hz
2	K1: x −18.7; y 1.9; z −1.1	K1: −3 +G, 2.7 mA, 65 μsec, 40 Hz
	K2: x 18.9; y 2.7; z −0.7	K2: −3 +G, 3.7 mA, 65 μsec, 40 Hz
3	K1: x −20.0; y 1.0; z −1.5	K1: −1 +G, 4.7 mA, 91 μsec, 40 Hz
	K2: x 17.0; y 2.8; z 1.1	K2: −3 +G, 3.0 mA, 91 μsec, 40 Hz
	K2: x 16.8; y 3.0; z −0.9	K2: −2 +G, 3.0 mA, 91 μsec, 40 Hz

Coordinates are based on the anterior commissure − posterior commissure system with the midcommissural point as reference; x = lateral; y = anterior; z = ventral of the midcommissural point. K1 = left electrode; K2 = right electrode. mA = milliampere; μsec = microseconds; Hz = hertz; V = Volts; G = ground electrode.

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