Neurol Sci (2012) 33:269–274
DOI 10.1007/s10072-011-0741-y

ORIGINAL ARTICLE

Deep brain stimulation of the globus pallidus internal improves symptoms of chorea-acanthocytosis

Peng Li · Rui Huang · Wei Song · Jie Ji · Jean-Marc Burgunder · Xing Wang · Qi Zhong · Alain Kaelin-Lang · Wei Wang · Hui-Fang Shang

Received: 9 April 2011 / Accepted: 30 July 2011 / Published online: 24 August 2011

Abstract Chorea-acanthocytosis is a rare autosomal recessive disorder. To date, treatment is only symptomatic and supportive. Results from the few reports of chorea-acanthocytosis patients treated with deep brain stimulation (DBS) have been inconsistent. We present case reports for two patients with chorea-acanthocytosis who received DBS treatment and compare the outcomes with results from the literature. Both patients showed the typical clinical features of chorea-acanthocytosis with motor symptoms resistant to medical treatment. Chorea was significantly improved following low-frequency DBS treatment in both patients. However, dystonia was only mildly improved. Four chorea-acanthocytosis patients treated with DBS treatment have been reported in the literature. One patient had improvement with low-frequency DBS stimulation, while another two had improvement with higher-frequency DBS. One patient, however, did not improve with either low-frequency or high-frequency DBS. Bilateral DBS to the GPi can improve chorea and dystonia in some patients with intractable chorea-acanthocytosis. However, selection criteria for the most promising candidates must be defined, and the long-term benefits evaluated in clinical studies.

Keywords Chorea-acanthocytosis · Deep brain stimulation

P. Li · X. Wang · Q. Zhong · W. Wang (✉)
Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu 610041, SiChuan, China
e-mail: wwang126@yahoo.cn

R. Huang · W. Song · J.-M. Burgunder · H.-F. Shang (✉)
Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, SiChuan, China
e-mail: hfshang@yahoo.com

J. Ji
Department of Hematology, West China Hospital, Sichuan University, Chengdu 610041, SiChuan, China

J.-M. Burgunder · A. Kaelin-Lang
Department of Neurology, Inselsptial, Bern University, 3010 Bern, Switzerland

Introduction

Chorea-acanthocytosis is a rare autosomal recessive neurodegenerative movement disorder characterized by chorea and dystonia with onset in young adulthood [1]. With disease progression, a hypokinetic state and epilepsy may develop. Mutations in the gene encoding chorein (*VPS13A)* may account for at least some cases of chorea-acanthocytosis [2]. The prognosis for this disease is poor, and current treatments are only symptomatic and supportive. Most patients are intractable to medical treatment, however, based on our and other's experience in treating L-dopa induced dyskinesia in patients with Parkinson's disease [3] and with other types of dyskinesia [4], we reasoned, that bilateral deep brain stimulation (DBS) of the internal segment globus pallidus would be helpful in decreasing chorea in patients affected by the disease. Here, we present two male chorea-acanthocytosis patients treated in this way and compare the effects with previously published reports [5–8].

Materials and methods

Case reports

Patient 1

A 39-year-old Chinese man from a consanguineous family developed tic-like orofacial movements, shoulder

shrugging, neck stretching and slight gait instability at the age of 17 years. His symptoms gradually progressed and he developed orofacial and lingual dyskinesia, with tongue biting at the age of 27 years. His symptoms were improved by tiapride (100 mg, three times per day). He later developed difficulty in writing, speaking, and swallowing. By the age of 36 years, walking was significantly impaired due to chorea of the lower limbs and trunk. These symptoms were not improved by higher doses of tiapride, nor by haloperidol and clonazepam. One generalized tonic–clonic seizure occurred at the age of 37 years. His older sister died of a similar condition at the age of 40 years. Total motor score before DBS treatment was 36, as determined by the Unified Huntington's Disease Rating Scale (UHDRS).

Patient 2

A 30-year-old Chinese man from a non-consanguineous family had developed mild tic-like orofacial movements, shoulder shrugging and neck stretching at the age of 18 years. He also had orofacial and lingual dyskinesia with tongue biting at the age of 26 years; these symptoms were improved by tiapride (100 mg, three times per day). His symptoms gradually worsened over the next 4 years, with generalized chorea and trunk spasms by the age of 30 years. He also experienced difficulties in writing, speaking, swallowing, and walking. No improvements

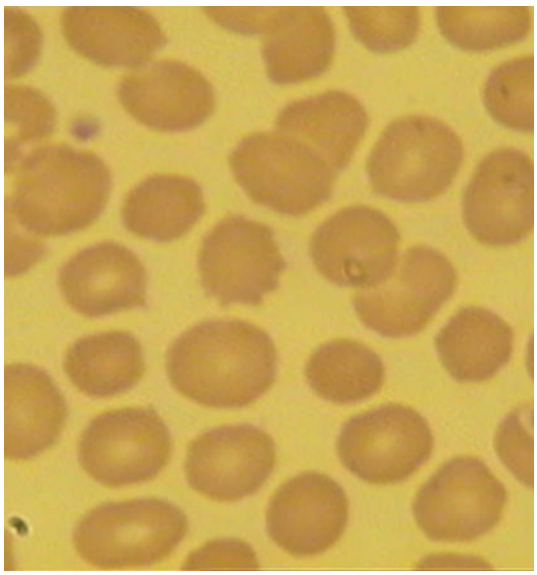

Fig. 1 Acanthocytes in the blood smears of Patients 1 and 2. Note the numerous spicules on the red blood cells

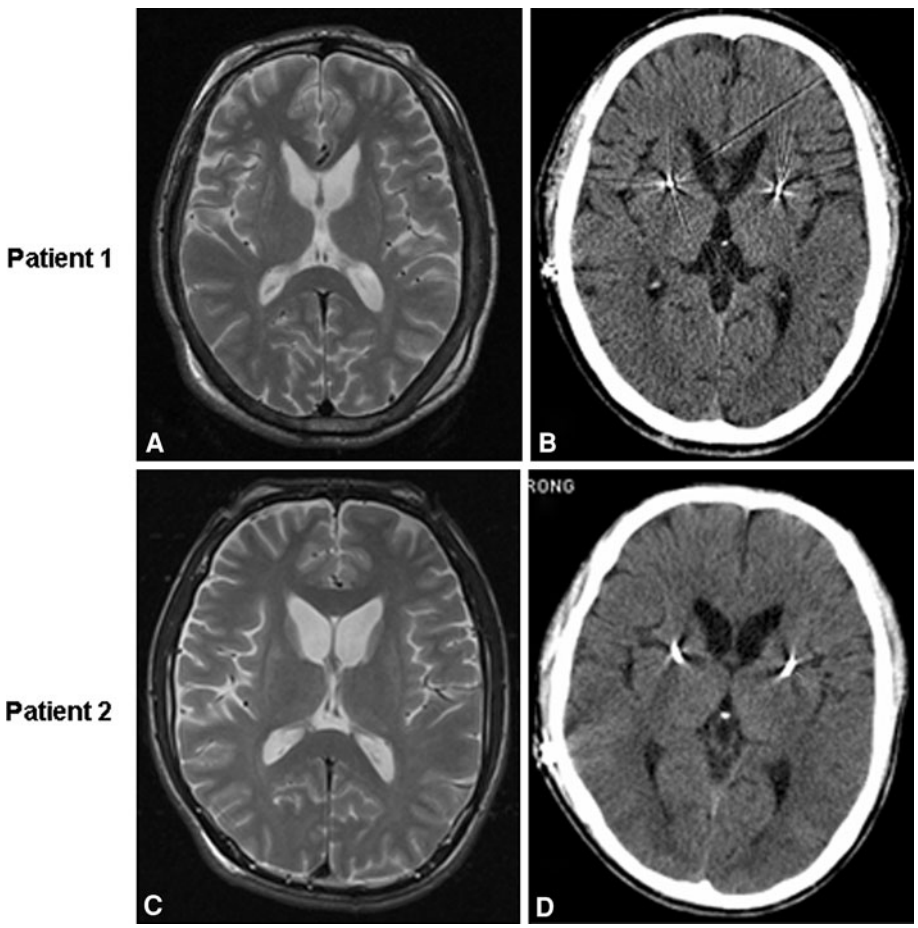

Fig. 2 Conventional MRI scan of these two patients revealed atrophy of the basal ganglia and abnormal intensity of T2-weighted images from the basal ganglia (**a** Patient 1, **c** Patient 2). These images indicate hypometabolism and atrophy. Brain CT scans of patients after electrodes were implanted in GPi (**b** Patient 1, **d** Patient 2)

were observed with higher dose of tiapride, nor with clonazepam and haloperidol. He lost weight (15 kg in the year before DBS treatment). There was no known family history of progressive motor disorders. The total UHDRS score was 53 before DBS treatment.

Acanthocytes were detected in peripheral blood smears from both patients (around 6% of the RBC count, Fig. 1). Blood creatine kinase was slightly elevated in Patient 1 (502 IU, reference range: 19–226), but normal in Patient 2. The EMG showed bilateral neurogenic changes in the anterior tibial muscles in Patient 1, but no abnormalities in several muscle groups of both the upper and lower extremities were observed in Patient 2. The EEG revealed no abnormalities in either patient. In both patients, brain

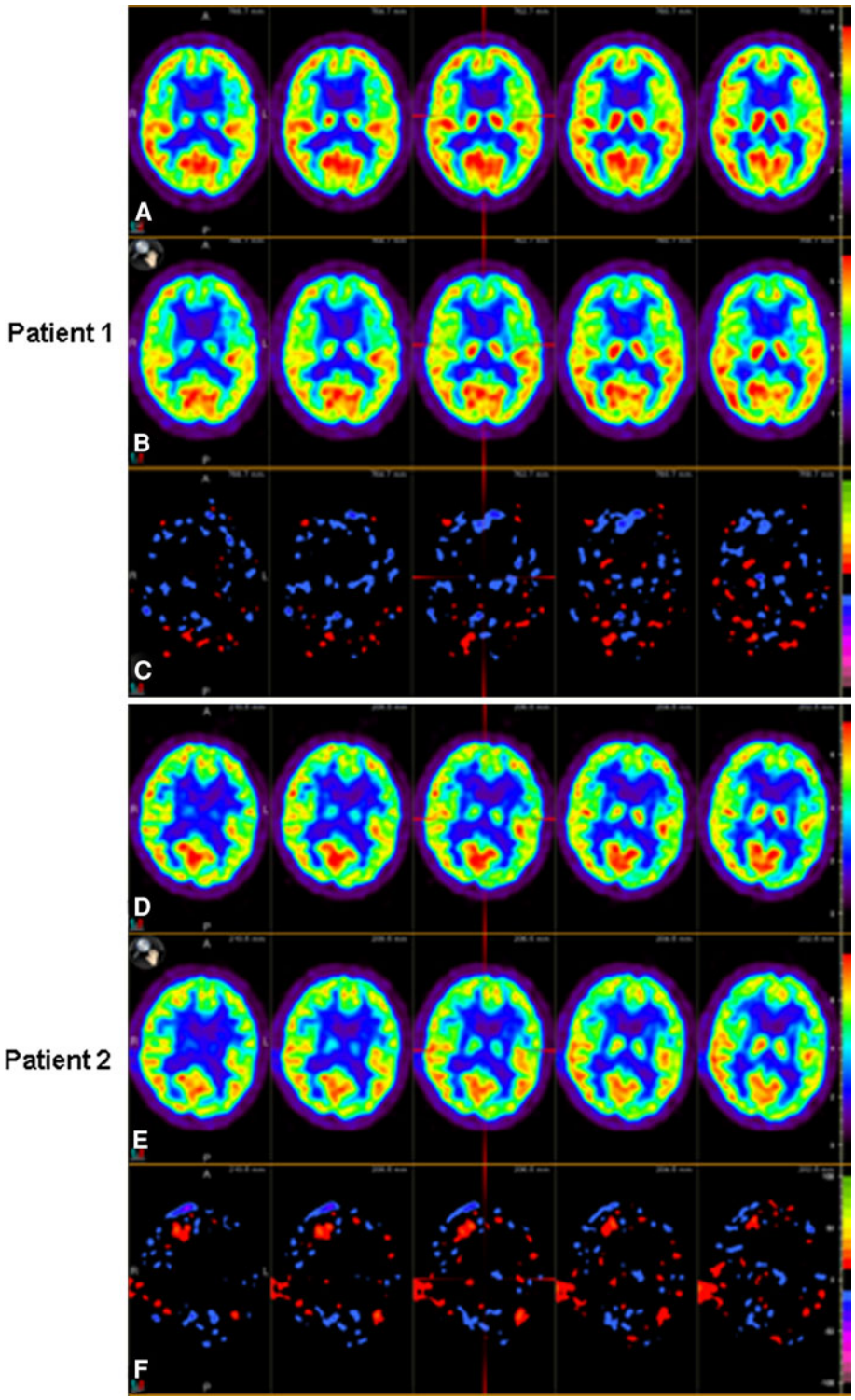

Fig. 3 18F-FDG PET scans taken from Patients 1 and 2 before and after electrode implantation. **a** Pre-operative PET scan from Patient 1. **b** Post-operative PET scan from Patient 1 taken 9 months after surgery. **c** Subtraction analysis of both scans from Patient 1. **d** Pre-operative PET scan from Patient 2. **e** Post-operative PET scan from Patient 2 taken 1 month after surgery. **f** Subtraction analysis of both scans from Patient 2

MRIs revealed atrophy of the basal ganglia, particularly in the caudate nucleus, as well as bilateral increases in the signal intensity of T2-weighted images from the striatum (Patient 1: Fig. 2a; Patient 2: Fig. 2c). Positron emission tomography using ^{18}F-fluorodeoxyglucose (18F-FDG) revealed bilateral hypometabolic regions in the caudate nucleus and putamen in both patients (Patient 1: Fig. 3a; Patient 2: Fig. 3d). Huntington's disease was excluded in both patients by the demonstration of normal CAG triplet repeat numbers in both alleles of the *IT15* gene. Extensive laboratory tests showed no evidence of autoimmune or metabolic disorders in either patient. Finally, no cognitive impairments were detected in either patient; MMSE scores were in the lower normal range (26).

Informed consent was obtained from both patients before surgery.

Results

Under general anesthesia and electrophysiologic guidance, electrodes for chronic stimulation (7,428 electrodes, Medtronic) were positioned within the GPi (Fig. 2b). Chorea movements were markedly improved 4 weeks after the operation by low-frequency stimulation (40 Hz at 3.5 V and 60 μs pulse width). Dystonia was mildly improved with low-frequency stimulation. In both patients, however, symptoms were worsened by high-frequency stimulation (130 Hz) to the GPi. The total UHDRS motor score of Patient 1 was 13 at the 1-month follow-up and 13 at the 9-month follow-up (Table 1). The total UHDRS motor score of Patient 2 was 26 at the 1-month follow-up and 27 at the 5-month follow-up (Table 1). Dysphagia was significantly improved in both patients. An 18F-FDG PET scan from Patient 1 at 9 months post-surgery revealed sustained bilateral hypometabolism in the caudate and putamen. Similarly, bilateral hypometabolism in the caudate and putamen was still observed in Patient 2 at the 1-month follow-up examination (Fig. 3b). Subtraction analysis showed no difference between pre-operative and post-operative 18F-FDG PET signals in either patient (Patient 1: Fig. 3c; Patient 2: Fig. 3f). Similarly, MMSE scores showed no change after surgery.

Discussion

We treated two male patients suffering from chorea, dystonia and trunk spasms. These are the typical motor features of choreo-acanthocytosis. Indeed, acanthocytes were detected in the blood of both patients. Magnetic resonance imaging and 18F-FGD PET scans revealed bilateral atrophy of the caudate nucleus and putamen in both patients. In contrast, CAG triplet repeats in the *IT15* gene were within the normal range, excluding Huntington's disease. These symptoms are consistent with the diagnosis of choreo-

Table 1 Unified Huntington's Disease Rating Scale evaluation

UHDRS	Patient 1			Patient 2		
	Prior to surgery	GPi 40 Hz (1 month)	GPi 40 Hz (9 months)	Prior to surgery	GPi 40 Hz (1 month)	GPi 40 Hz (5 months)
Ocular pursuit	0	0	0			0
Saccade initiation	0	0	0			0
Saccade velocity	0	0	0	0	0	0
Dysarthria	1	1	1	1	0	1
Tongue protrusion	2	0	0	2	0	0
Finger taps	2	2	2	5	4	4
Pronate/supine	1	1	1	4	3	3
Luria	1	0	0	2	0	0
Rigidity	0	0	0	1	1	1
Bradykinesia	1	1	1	1	1	1
Limb dystonia	5	3	3	7	4	4
Trunk dystonia	2	1	1	3	2	2
Face/BOL chorea	4	0	1	6	4	4
Limb chorea	8	2	2	11	4	4
Trunk chorea	2	1	1	3	1	1
Gait	2	0	0	2	1	1
Tandem walking	3	0	0	3	1	1
Retropulsion	2	1	0	2	0	0
Total	36	13	13	53	26	27

Table 2 Previous case reports of chorea-acanthocytosis treated with DBS

Age	Sex	Family history	Age of onset	Clinical history	Epilepsy	Cognitive function	Neuropsychological assessment	Duration to DBS	DBS implantation site	Outcome	Reference
38	M	(−)	35	Obvious gait disturbance due to hyperkinesia of the lower limbs. Generalized chorea, eating difficulty at the age of 35 years. Involuntary vocalizations, comprising grunting and whistling occurred at the age of 17 years	No attack	Normal	Obsessive–compulsive features, moderate distractibility, marked reactive depression	3	Bilateral GPi external pulse generator, bipolar stimulation	20 days follow-up; high-or low-frequency stimulation: failure	Wihl et al. [8]
43	M	(−)	31	Oromandibular dyskinesia, dysarthria. Trunk spasms appeared obvious at the age of 43 years	General epileptic seizure	Normal	Not available	12	Bilateral ventral oral part of the motor thalamus (Vop)	2-year follow-up: 160 Hz, improvement of choreic movements and axial truncal spasms	Burbaud et al. [5]
32	M	(−)	24	Choreatic-dystonia syndrome, dysarthria with recurrent distressing tasteless belching and dramatic tongue biting and walking difficulty	No attack	Impairment	Not available	8	Bilateral GPi internal pulse generator, monopolar stimulation on two adjacent contacts	3-month follow-up: 40 Hz, improvement of chorea, blenching and dysarthria; 130 Hz, slight improvement of dystonia; chorea and dysarthria worsening; 10 Hz, no effect	Guehl et al. [7]
35	F	(+)	25	At 25 years, she developed tongue and lip biting, movement disorders and mild loss of postural reflexes. On examination, she had dysarthria, oromandibular dystonia, mild chorea and irregular choreic gait with occasional flexor truncal spasms	No attack	Normal	Not available	8	Bilateral GPi	2 years follow-up: 130 Hz, improvement of chorea-dystonia; 40–50 Hz. worsening of truncal spasms	Ruiz et al. [6]

acanthocytosis, although patients were not screened for mutations in *VPS13A*, the only known causative gene [2]. Patient 1 had slightly increased creatine kinase, neurogenic impairment of the muscles of the distal extremities and seizure attacks in addition to abnormal involuntary movements (chorea). Patient 1 also had a similarly afflicted sister, suggesting an autosomal recessive inheritance and consistent with the usual inherited pattern of choreo-acanthocytosis. McLeod syndrome, another syndrome with acanthocytes in the peripheral blood smear, was improbable in Patient 2, since he lacked the common McLeod syndrome features of peripheral neuropathy, cardiomyopathy and hemolytic anemia. However, neither XK gene mutations nor the presence of the kell antigen was analyzed. Patient 2 had no known familial history, which suggests that he may be a sporadic case. However, he had only sibling (an unaffected younger sister), and so the inheritance pattern could not be analyzed.

Both patients were intractable to traditional medicine with the disease progression, although tetrabenazine was not tried since it was not available in China. However, both patients showed an obvious improvement in chorea symptoms and mild improvements in dystonia movements with low-frequency (40 Hz) stimulation of the GPi. Both chorea and dystonia were exacerbated by high-frequency (130 Hz) GPi stimulation. Guehl et al. [7] observed similar clinical results in a 32-year-old male patient with the disease under GPi stimulation (Table 2). In contrast to our findings, Burbaud et al. [5] found improved trunk spasm and chorea using high-frequency (130 Hz) DBS of the Vop of the thalamus. Ruiz et al. [6] observed improved dystonia and chorea using high-frequency (130 Hz) DBS of the GPi, while low-frequency (40–50 Hz) stimulation actually worsened trunk spasm (Table 2). Wihl et al. [8] found no improvement with either low- or with high-frequency DBS stimulation of the GPi. The longest follow-up duration in these published cases was 2 years.

High-frequency DBS has been reported to benefit patients with other forms of chorea, including Huntington's disease [9], senile chorea [10] and cerebral palsy [11]. The reasons for this discrepancy remain poorly understood because only a small number of choreo-acanthocytosis patients have been documented. Confounding factors like the duration and severity of the disease atrophy at the DBS electrode implantation site, overall atrophy of the basal ganglia, and the pre-operative severity of chorea and dystonia should be considered when selecting suitable candidates for DBS treatment. Symptomatic treatment with DBS should also be reserved for selected patients who have shown resistance to traditional drug treatment. We could not observe changes in basal ganglia metabolic rate in the two choreo-acanthocytosis patients treated with DBS during short- time follow-up. Long-term study and larger patient cohorts may be helpful to clarify it. Overall, the result of our case studies suggests that DBS can be useful for symptomatic improvement in cases of choreo-acanthocytosis that are resistant to medical treatment. Chorea in particular was improved in our patients by low-frequency DBS.

Conflict of interest There is no actual or potential financial and other conflict of interest related to the submitted manuscript.

References

1. Walker RH, Danek A, Dobson-Stone C, Guerrini R, Jung HH, Lafontaine AL, Rampoldi L, Tison F, Andermann E (2006) Developments in neuroacanthocytosis: expanding the spectrum of choreatic syndromes. Mov Disord 21(11):1794–1805
2. Ueno S, Maruki Y, Nakamura M, Tomemori Y, Kamae K, Tanabe H, Yamashita Y, Matsuda S, Kaneko S, Sano A (2001) The gene encoding a newly discovered protein, chorein, is mutated in chorea-acanthocytosis. Nat Genet 28(2):121–122
3. Loher TJ, Burgunder JM, Pohle T, Weber S, Sommerhalder R, Krauss JK (2002) Long-term pallidal deep brain stimulation in patients with advanced Parkinson disease: 1-year follow-up study. J Neurosurg 96(5):844–853
4. Krauss JK, Loher TJ, Weigel R, Capelle HH, Weber S, Burgunder JM (2003) Chronic stimulation of the globus pallidus internus for treatment of non-dYT1 generalized dystonia and choreoathetosis: 2-year follow-up. J Neurosurg 98(4):785–792
5. Burbaud P, Rougier A, Ferrer X, Guehl D, Cuny E, Arne P, Gross C, Bioulac B (2002) Improvement of severe trunk spasms by bilateral high-frequency stimulation of the motor thalamus in a patient with chorea-acanthocytosis. Mov Disord 17(1):204–207
6. Ruiz PJ, Ayerbe J, Bader B, Danek A, Sainz MJ, Cabo I, Frech FA (2009) Deep brain stimulation in chorea acanthocytosis. Mov Disord 24(10):1546–1547
7. Guehl D, Cuny E, Tison F, Benazzouz A, Bardinet E, Sibon Y, Ghorayeb I, Yelnick J, Rougier A, Bioulac B, Burbaud P (2007) Deep brain pallidal stimulation for movement disorders in neuroacanthocytosis. Neurology 68(2):160–161
8. Wihl G, Volkmann J, Allert N, Lehrke R, Sturm V, Freund HJ (2001) Deep brain stimulation of the internal pallidum did not improve chorea in a patient with neuro-acanthocytosis. Mov Disord 16(3):572–575
9. Biolsi B, Cif L, Fertit HE, Robles SG, Coubes P (2008) Long-term follow-up of Huntington disease treated by bilateral deep brain stimulation of the internal globus pallidus. J Neurosurg 109(1):130–132
10. Yianni J, Nandi D, Bradley K, Soper N, Gregory R, Joint C, Stein J, Scott R, Aziz T (2004) Senile chorea treated by deep brain stimulation: a clinical, neurophysiological and functional imaging study. Mov Disord 19(5):597–602
11. Berweck S (2009) BP-DBS for dystonia-choreoathetosis cerebral palsy. Lancet Neurol 8(8):692–693