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Deep brain stimulation in critical care conditions

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Abstract Some neurological conditions require admission to an intensive care unit (ICU) where deep sedation and mechanical ventilation are administered to improve the patient's condition. Nevertheless, these treatments are not always helpful in disease control. At this stage, deep brain stimulation (DBS) could become a viable alternative in the treatment of critical neurological conditions with long-lasting clinical benefit. The value of deep brain stimulation has been investigated in the treatment of patients who had undergone surgical electrode implants as an emergency procedure to treat acute life-threatening conditions requiring admission to neurological ICU (NICU). A before-and-after perspective study was examined of seven patients who were treated with DBS for status dystonicus (SD) and post-stroke severe hemiballismus. Bilateral globus pallidus internus (GPi) DBS was performed in five SD patients and unilateral ventralis oralis anterior and posterior (Voa/Vop) nucleus of the thalamus DBS in two post-stroke hemiballismus patients. Bilateral GPi-DBS allowed SD resolution in a time lapse varying from 1 week to 3 months. No clear improvements compared to the baseline clinical condition were observed. Unilateral Voa/Vop-DBS intervention controlled hemiballismus after 10 h, and the patient was discharged in 2 days. The other patient was transferred from the NICU to the neurosurgery ward after 13 days. No surgical complications were observed in any of the above procedures. Neurostimulation procedures could represent a valuable choice in critical care conditions, when involuntary movements are continuous, life-threatening and refractory to intensive care procedures. DBS is feasible, safe and effective in selected cases.

Keywords Deep brain stimulation · Emergency neurosurgery · Globus pallidus · Hemiballismus · Status dystonicus

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Introduction

Deep brain stimulation (DBS) is well documented as a legitimate treatment of chronic neurological diseases such as Parkinson disease (Benabid et al. 1987, 1994; Moro et al. 2010), primary dystonia (Coubes et al. 2000; Krauss et al. 1999; Mueller et al. 2008) and essential tremor (Benabid et al. 1989; Koller et al. 1997, 2001; Rehncrona et al. 2003). Emerging indications include refractory epilepsy (Fisher et al. 2010; Franzini et al. 2008; Velasco et al. 2007), chronic cluster headaches (Franzini et al. 2010; Leone et al. 2004), major depression (Mayberg et al. 2005), obsessive–compulsive disorder (Nuttin et al. 1999), disruptive behavior (Franzini et al. 2005b) and Gilles de la Tourette syndrome (Porta et al. 2009; Visser-Vandewalle et al. 2006). DBS may

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also be an option in treating acute or sudden dramatic worsening of pre-existing diseases such as hyperkinetic movement disorders (Robottom et al. 2011) and status epilepticus (Shorvon and Ferlisi 2011). Nevertheless, the number of reported cases treated with DBS is very small, and schematic and efficacious interventions are at the moment just proposals. Among hyperkinetic disorders, DBS has shown good results in the treatment of status dystonicus (Fasano et al. 2012) and hemiballismus (Hasegawa et al. 2009). Status dystonicus (SD) is a rare, although life-threatening, disorder which develops in patients with primary and secondary dystonia (Manji et al. 1998). Recently, clinical observations have been described and a treatment flowchart has been proposed to manage SD-affected patients (Fasano et al. 2012). Hemichorea–hemiballismus is generally a consequence of cerebrovascular disease in elderly patients, causing unilateral cerebral damage at the level of the basal ganglia. This rare condition can resolve spontaneously, but oral drug medications such as dopamine receptor antagonists (such as tetrabenazine), neuroleptic (mostly haloperidol) and gabaergic drugs can be considered, with conflicting results. For this reason, there is no consensus in the medical treatment of the disorder (Dewey and Jankovic 1989; Lai et al. 2008; Vidaković et al. 1994).

However, despite significant differences in etiopathogenesis, symptoms and cures, the above-mentioned phenomena might be refractory to conservative treatments and consequently require admission to a NICU. A few cases of both these disorders can be refractory to medical treatment and neurosurgical procedures are proposed (Francisco 2006; Krauss and Mundinger 1996).

The advantage of DBS has been investigated in the treatment of seven patients admitted to NICU, who underwent surgical electrode implants as an emergency procedure to treat acute life-threatening conditions. Five patients suffered from status dystonicus and two had post-ischemic acute hemichorea/hemiballismus. Patients and surgical methodology are described. In addition, the indications/implications are discussed in view of an increased request for DBS in patients affected by the reported life-threatening conditions.

Patients and methods

Status dystonicus

Five patients affected by childhood onset dystonia developed status dystonicus during the course of the disease. SD has been defined as "increasingly frequent and relentless episodes of devastating generalized dystonia which may be refractory/resistant to standard drug therapy". All cases required admission to an ICU. Patients' characteristics are reported in Table 1. Median age of dystonia onset was 1.5 years (6 months–12 years), while SD onset ranged from between one and thirteen-and-half years after the beginning of the disease (median value 7 years). Two patients had primary DYT1-negative dystonia (patients 1 and 3); one had an inherited degenerative dystonia of unknown origin (patient 2); one had symptomatic dystonia due to kernicterus (patient 4) and one suffered from neurodegeneration with brain iron buildup due to PANK-2 gene deficit (patient 5). In three patients, SD onset was acute, following a concomitant infection of the upper respiratory tract (patient 2), mononucleosis (patient 4) and a fever of unknown origin (patient 5). In patients 1 and 3, the cause of SD was unknown and developed progressively over a period of months. Symptomatology of patient 1 included generalized florid and prolonged painful dystonic spasms; patients 2 and 3 suffered from continuous generalized dystonic movements, also involving cranial muscles, and were associated with more rapid, irregular hyperkinesias of unpredictable amplitude. In patient 4, both mobile and fixed components (along with opisthotonus) were associated; patient 5 suffered from continuous dystonic movements. In 4 out of 5 patients, a pre- and post-op Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) evaluation was feasible (Table 2); one patient, before SD, was followed in another neurological center, where BFMDRS was not available.

Pharmacological treatment administered consisted of trihexyphenidyl and oral baclofen, as well as clozapine, carbamazepine, tetrabenazine, pimozide and haloperidol (Table 1). However, these treatments failed to reverse SD. As a result, all patients had to be admitted to an intensive care unit where mechanical ventilation and continuous sedation through midazolam (up to 170 mg\die) were the options chosen to improve the symptoms. This approach failed and the next step was to introduce propofol sedation (up to 20 ml\h). Tracheostomy was required in only one patient (patient 4). Rhabdomyolysis and renal failure occurred in patient 2. When propofol sedation failed, a neuromodulation procedure, bilateral GPi-DBS, was proposed to the caregivers.

Hemiballismus

Case 1

This is a 77-year-old male patient whose clinical history started in August 2008 with a traumatic head injury. CT scans revealed a subcortical injury to the left temporal lobe, bleeding at the left capsule–thalamic junction and subarachnoid hemorrhage (SAH) in the left parietal lobe. Subsequently, highly disabling post-traumatic hemiballismus emerged to the right hemisoma with involuntary

Table 1 SD Patients pre-op characteristics

Pt No	Diagnosis	Age at onset of dystonia (years)	Dystonia features	SD onset after disease onset (years)	SD way of presentation/ precipitating factor	Age at surgery (years) and type of surgery	Duration of SD (weeks, months)	Ventilation (yes/no, months)	Complications of SD	Medical therapy at surgery
1	Primary generalized DYT1-	1.5	Prolonged generalized dystonic spasms	6.5	Acute/unknown	8.2 GPi-DBS	4 months	Yes, 4	Recurrent pneumonia and TVP	THP 16 mg, BLF 50 mg, CNP 3 mg, sedation with PPF and MDZ
2	Encephalopathy of unknown origin	0.5	Dystonic movements and more rapid hyperkinesias	13.5	Progressive/ infection upper resp. tract	14.2 and 17 GPi-DBS	2 months	Yes, 2	Rhabdomyolysis, renal failure, partial epilepsy	PHB 150 mg, PHT 700 mg, sedation with PPF and CLOZ
3	Primary generalized DYT1-	3	Dystonic movements and more rapid hyperkinesias, pain, and right leg fixed postures	7	Progressive/ unknown	10.5 GPi-DBS	6 months	No	No	THP 28 mg, BLF 45 mg, TBN 25 mg, sedation with CNP and DZP
4	Kernicterus	0.5	Prolonged painful dystonic movements and spasms	10	Progressive/ mononucleosis	10 GPi-DBS	1 week	Yes, 1 month	Respiratory distress	TBN, THP, sedation with MDZ, RMF, PPF, TPS,
5	PKAN	12	Prolonged dystonic movements	1	Progressive/ fever	12 GPi-DBS	2 weeks	Yes, 0.3 month	Rhabdomyolysis	THP, CNP, sedation with MDZ 10 mg/h, TPS boli

BLF baclofen, *CLOZ* clozapine, *CNP* clonazepam, *DZP* diazepam, *MDZ* midazolam, *PHB* phenobarbital, *PHT* phenytoin, *PMZ* pimozide, *PPF* propofol, *TBN* tetrabenazine, *THP* trihexyphenidyl, *TPS* sodium thiopental

self-mutilation episodes. Hemiballismus refers to large-amplitude, flinging movements of one side of the body that can be violent. When secondary to stroke, the movements typically subside over a period of months. The patient also developed jactitation that along with all the other symptoms became refractory/resistant to conservative therapy (including clonazepam, up to 8 mg\day; tetrabenazine, up to 75 mg\day, gabapentin, up to 100 mg\day and zolpidem tartrate, up to 10 mg\day). As a consequence, the patient was admitted to the NICU for deep sedation and underwent orotracheal intubation. This was achieved by the administration of propofol (20 mg\h) and remifentanil (2 mg\h). Subsequently, a continuous infusion of propofol, up to 80 mg/h, obtained a remission of the symptomatology. Propofol was reduced to 20 mg/h in the next days, but the involuntary movements reappeared. Therefore, it was increased to 150 mg/h, achieving the objective of halting the symptomatology. Left Voa\Vop (ventral oral anterior\ventral oral posterior) DBS was proposed with the aim of reversing the symptoms.

Case 2

The case of an 82-year-old woman who started to suffer from left hemiballismus in July 2012 as a result of a thalamic ischemic stroke is presented. The patient was unsuccessfully treated in another hospital with conservative medication (including tetrabenazine, up to 75 mg\day; clonazepam, up to 8 mg\day). Then she was transferred to the NICU of our hospital and submitted to orotracheal intubation and deep sedation with propofol (up to 150 mg/h in 4 days) and remifentanil (up to 0.15 mcg/kg/min). Preoperative biochemical assessment revealed prolonged bleeding time which signaled a contraindication for the surgical procedure. The patient had progressive hypermyoglobinemia after 2 days in the NICU; thus propofol was replaced with midazolam (up to 8 mg/h). However, this intervention partially failed, though beneficial effects were observed with the administration of rocuronium (up to 18 mg/h). After 5 days in ICU, bleeding time normalized and a right Voa/Vop-DBS was proposed to the caregivers.

Surgical methodology

The study was approved by the institutional review board, while the caregivers of the patients gave written informed consent prior to the surgery. All procedures were performed under propofol general anesthesia. Antibiotic treatment was administered during the perioperative period (first/second generation cephalosporin, 2 g, 30 min before intervention). The level of sedation was continuously

Table 2 SD post-op clinical outcome

Pt	DBS parameters which brought SD resolution	Surgery outcome	Follow-up after surgery (months, years)	Pre-op BFMDRS[a] (DIS-SEV/total score)	Post-op BFMDRS[b] (DIS-SEV/total score)	Medical treatment at last follow-up	Surgery complications	DBS parameters at last follow-up
1	4.3 V, 150 μs, 185 Hz	SD resolution 3 months after surgery	8 years	20-91/111	20-91/111	THP 8 mg, BLF 50 mg	Connection cable breakage: second intervention	4.2 V, 120 μs, 185 Hz
2	N/A	SD resolution 1 week in both episodes	6 years	19-79,5/98,5	10-63/73[c]	PHB 150 mg CLOZ 37 mg	Connection cable fracture and electrode migration	died after a trauma not related to SD.
3	3.2 V, 90 μs, 185 Hz (right side) 3.9 V, 90 μs, 185 Hz (left side)	SD resolution 1 month after surgery	8 years	26-107/133	23-88/111	DZP 5 mg	2 software complications (accidental switching off)	Not changed
4	2.5 V, 90 μs, 185 Hz	SD resolution 1 month after surgery	1 year	6-10/16	10-16/26	PHB 150 mg/day, TBN 75 mg/day, THP 6 mg/day	None	3 V, 90 μs, 130 Hz
5	3.7 V, 90 μs, 185 Hz	SD resolution 2 weeks after surgery	1 year	Never performed	15-45/60	None	None	2.5 V, 90 μs, 185 Hz

DIS disability score, *SEV* severity score, *BLF* baclofen, *CLOZ* clozapine, *DZP* diazepam, *PHB* phenobarbital, *TBN* tetrabenazine, *THP* trihexyphenidyl

[a] Pre-SD scores

[b] At last follow-up

[c] This patient died from sequelae of SD recurrence

monitored through the bispectral index (BIS, Aspect Medical Systems, Newton, MA, USA). CT scans were achieved in stereotactic conditions through the Leksell frame (Stockholm, Sweden) using a volumetric technique with a slice thickness of 1.5 mm and a gantry angle of 0. The stereotactic coordinates of the anterior and posterior commissures were calculated from the stereotactic CT scans and passed as inputs to the stereotactic computerized atlas software (www.angelofranzini.com/BRAIN.htm) that provided the target stereotactic coordinates. The atlas coordinates related to the AC–PC midpoint were: globus pallidus internus (GPi) = lateral 20 mm, antero-posterior 2 mm, and vertical 6 mm below the commissural plane; nucleus ventralis oralis posterior of the thalamus (Vop) = lateral 13 mm, anteroposterior 1 mm, vertical 1 mm above the commissural plane. A rigid cannula was inserted through the precoronal paramedian burr hole up to 10 mm from the target. A quadripolar DBS electrode (DBS-3389; Medtronic, Inc., Minneapolis, MN) was then inserted at the estimated target and secured in the burr hole by means of a flange (Ethicon Bioplate Co., J&J, Raynham, MA). DBS leads were connected to an internal pulse generator (IPG; Soletra; Medtronic, Inc.) and placed in a sub-clavicular subcutaneous pocket using a tunnelized latero-cervical subcutaneous guide. For all the patients, stimulation was turned on the day following the surgery.

Results

Status dystonicus

The mean age at surgery was 11 years (range 8.2–14.2 years) and electrode implantation (Fig. 1) was performed at a mean of 3 months (range 1 week–6 months) after SD onset. Median follow-up after surgery was 6 years (range 1–8 years) (Table 2). Once DBS was turned on, a progressive decrease of intensity and frequency of involuntary movements was observed in every patient. In one patient, the pathological conditions were completely resolved within a week; in three out of five patients the time frame was after 1 month. In one patient improvement was noticed after a few weeks; thus sedation was progressively reduced until it was totally withdrawn within 3 months (Table 2). Sedation and ventilation were halted in all cases. All patients were discharged from the intensive care unit and underwent intensive motor and respiratory rehabilitation. In one patient, all treatments were withdrawn a year after electrode implantation. DBS was maintained preventing SD recurrences. The stimulation parameters ranged between 2 and 5 V, 130 and 185 Hz, and 90 and 200 ms (monopolar). In one patient, SD re-developed due to electrode fracture, but following re-implantation, symptomatology resolved; one patient died a few years later due to causes (ab ingestis) unrelated to DBS implant. In two patients a significant improvement of dystonic condition, matching pre- and post-SD periods, was recorded. In one patient, dystonia was unchanged. In another one, worsening was observed (Table 2).

Hemiballismus

In patient 1, the hemiballistic movements were controlled 10 h after the DBS (Fig. 2) was turned on. Consequently, he was discharged from the NICU 2 days after surgery. Stimulation parameters were: 3.5 V, 185 Hz, 210 ms (monopolar 0, −/1, −/2, −/3, −/case, +). This arrangement was optimal in controlling the movement disorder. A few attempts at reducing the stimulation voltage caused the aggravation of the symptoms. At present, at 18 months of follow-up, DBS is still turned on with no relapse of the disease and no daily life consequences.

Patient 2 progressively awoke from general anesthesia, with complete awakening in 3 days. Once DBS was turned on, the symptomatology mildly improved and she was discharged from the NICU 13 days after surgery. At this time, all the sedation drugs were gradually weaned off although low-amplitude hemiballistic movements and jactitation with lower limb self-lesioning were still observed. Stimulation parameters were modified to control the symptomatology, which was under control with the following parameters: 3.4 V, 180 Hz, 90 μs (monopolar −1, −2, −3; case +). Any attempts to reduce the stimulation amplitude resulted in the worsening of the symptoms. At present, at 12 months of follow-up, DBS is still turned on and the disorder is completely under control.

Discussion and conclusion

This report describes the value of DBS as an emergency procedure to treat acute life-threatening conditions requiring admission to the NICU in five patients affected by status dystonicus and two by hemiballismus. All symptoms were refractory/resistant to conservative medications. Following DBS implants, recovery from the acute condition was observed in all patients, allowing for the weaning off of mechanical ventilation and subsequent discharge from the intensive care unit after surgery. None of the patients experienced any recurrence of the acute condition. The number of neuromodulation procedures performed to treat CNS diseases is growing (Awan et al. 2009; Krack et al. 2010; Ponce and Lozano 2010). Nevertheless, clear-cut indications for DBS are still lacking and clinical trials are often hampered by economic restraints, which orientate the companies' financial investments toward diseases that

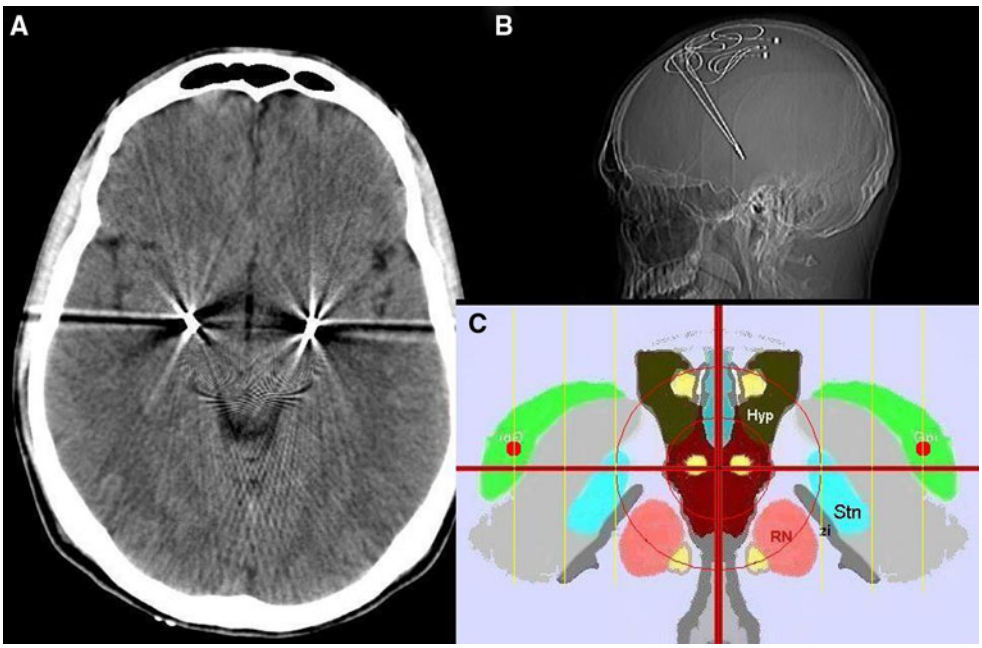

Fig. 1 **a** CT scan, axial: bilateral correct placement of DBS electrodes in the GPi; **b** skull Rx: DBS electrodes after implantation and before IPGs positioning in the subclavian regions; **c** images from the computerized atlas software (www.angelofranzini.com/BRAIN.htm), used for GPi targeting

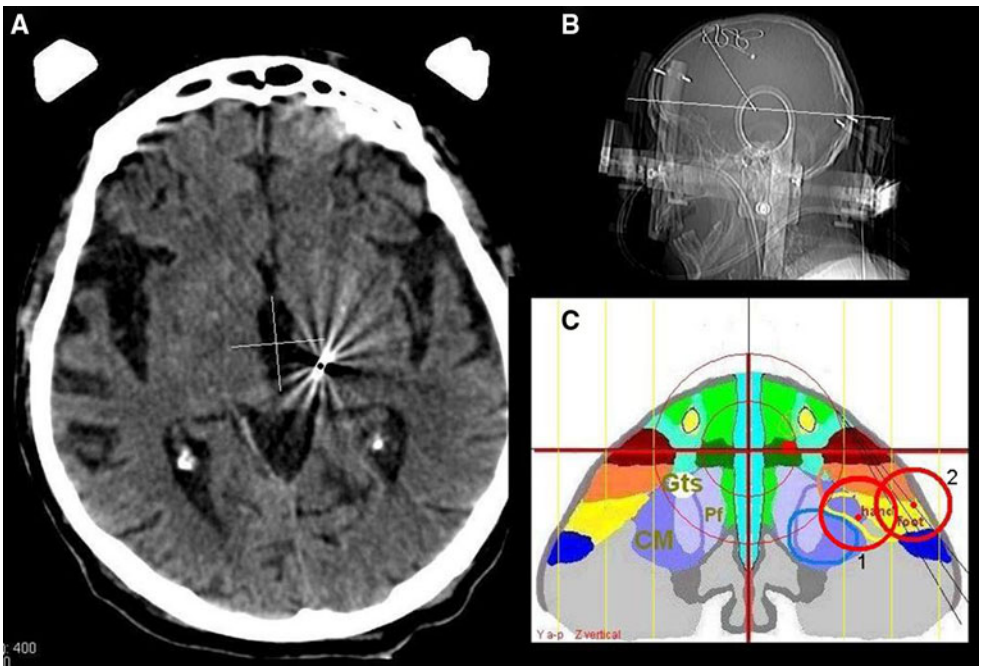

Fig. 2 **a** CT scan, axial: left correct placement of DBS electrodes in the Voa/Vop thalamic complex; **b** skull Rx: DBS electrode after implantation and before IPGs positioning in the subclavian regions. **c** Images from the computerized atlas software (www.angelofranzini.com/BRAIN.htm), used for Voa/Vop targeting. *Circles* represent the VOA/VOP hand (*1*) and leg's topographic representation (*2*)

involve a larger number of potential users of neuromodulation devices. A few studies and case reports have dealt with the rare, but severe conditions reported in this paper. Sporadic cases and a short series of patients affected by status dystonicus treated with DBS are reported in the literature (Apetauerova et al. 2010; Fasano et al. 2012; Jech et al. 2009; Kiss et al. 2007; Teive et al. 2005; Zorzi et al. 2005), as well as studies on patients with secondary hemiballismus (Koller et al. 2001; Rehncrona et al. 2003; Torres et al. 2010). However, neither guidelines nor

homogeneous experiences are available for their management. Regarding this point, a useful flowchart has been proposed to revert status dystonicus (Mariotti et al. 2007). It is important to highlight that pharmacological strategies regress SD in only a few patients (Fasano et al. 2012). Indeed, the probability of admitting these patients to NICU is very high and several lines of actions might be employed. In our series all patients were admitted to the NICU as a consequence of the failure of conservative pharmacological therapies. Neuromodulation procedures were performed after iv benzodiazepines or propofol therapy failed. Intrathecal baclofen (ITB) pumps have never been placed. It is worth mentioning that ITB is not definitive and complications such as catheter-site leakage or pump infection limit its use over a long period (Fasano et al. 2012). In our series, bilateral GPi-DBS reversed SD in all patients in a period of time ranging between 1 week and 3 months, and none had SD recurrence. Nevertheless, the long-term follow-up showed worsening of dystonia, compared to pre-SD BFMDRS score, in one patient, and in another case no changes in dystonic symptoms were observed. Interestingly, a recent literature review reported that surgery reversed SD in 30 % of the treated cases, and that all treatment strategies (conservative and surgical) failed to improve symptoms, compared to pre-SD, in 37 % of the patients (Fasano et al. 2012). It is worth mentioning that the patient, who presented disease worsening, was described as having a kernicterus, which, in our experience, is not considered an effective target for neuromodulation (Franzini et al. 2011). This might represent a limit of the surgical procedure, although all of them experienced SD relapse. Interestingly, patient 1 had a new episode of SD, following electrode fracture, which reversed after electrode re-implantation. Bilateral DBS of the globus pallidus internus (GPi) has been used to treat dystonia with encouraging results in adults (Krauss et al. 1999; Tronnier and Fogel 2000) and children (Angelini et al. 2000; Zorzi et al. 2005). It must be pointed out that in some cases DBS alone cannot revert status dystonicus, and lesional procedures might be needed. Thalamotomy and pallidotomy have shown promising results (Fasano et al. 2012; Ford 2004). Both might be performed at the DBS target utilizing the previously inserted DBS electrode (Marras et al. 2009) or targeting other structures of the hypothesized network loop.

To our knowledge, it is the first time that persistent post-ischemic hemiballismus was so severe that admission to the ICU and treatment with unilateral stimulation of the ventral lateral portion of the thalamus (VOA\VOP nuclei) were necessary. Both patients were discharged from NICU in the first 2 weeks following surgery. At follow-up, the patients did not present with hemiballismus. We did not turn off the stimulator after NICU discharge, investigating DBS efficacy. In both patients, modification of stimulation parameters (voltage augmentation) was necessary to improve symptoms until the actual parameters were effective. Any attempt to diminish the voltage of stimulation resulted in worsening of symptoms. The age of the patients raised questions about the opportunity of a DBS treatment; it was finally performed because patients presented in good clinical condition before the ictal event.

The fact that symptom improvement was observed in all patients the day following the surgery after DBS was turned on led us to speculate that DBS might modulate the neuronal network loops in charge of self-maintaining abnormal neuronal discharge pattern. The mechanisms by which DBS functions are not yet fully known. The most reliable hypotheses (McIntyre and Hahn 2010) suggest that they influence the inhibition of a limited pool of neurons in the electrical field, induced and maintained by means of chronic electrical current delivered by the active contacts of lead. According to the current knowledge, DBS should introduce a high-frequency noise (up to 185 Hz stimulation) into the hypothesized reverberating circuits and eventually halt the loops responsible for both of the repetitive movement disorders. Similarly, in SD both GPi and the thalamus were the targets for placing DBS leads or to perform radiofrequency lesions. In spite of scarce data regarding DBS's neurophysiological mechanisms of action, clinical data suggest that this procedure should be considered as a first-choice invasive procedure in critical care conditions, when involuntary movements become continuous and life threatening and all conservative therapies fail. All of the patients responded to neurostimulation and recovered spontaneously from ventilation after deep sedation withdrawal and were consequently discharged from NICU. In conclusion, DBS is feasible, safe, reversible and effective in selected cases. It limits the use of lesional procedures in patients refractory to DBS (about 30 % of patients affected by status dystonicus). Finally, an additional scope of this report is to advocate the early use of DBS for the described diseases to avoid complications due to prolonged sedation and mechanical ventilation.

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