Deep-Brain Stimulation for Aggressive and Disruptive Behavior

AQ: au *Angelo Franzini, Giovanni Broggi, Roberto Cordella, Ivano Dones, Giuseppe Messina*

Key words
- Aggressive behavior
- Deep brain stimulation
- Posterior hypothalamus

Abbreviations and Acronyms
CT: Computed tomography
DBS: Deep-brain stimulation
MRI: Magnetic resonance Imaging
pHyp: Posterior hypothalamus

Department of Neurosurgery, Fondazione IRCCS Istituto Nazionale Neurologico Carlo Besta, Milan, Italy

To whom correspondence should be addressed: Giuseppe Messina, M.D. [E-mail: giusmes@gmail.com]

Citation: World Neurosurg. (2012). http://dx.doi.org/10.1016/j.wneu.2012.06.038

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***

■ OBJECTIVE: **To describe our institutional experience with deep-brain stimulation (DBS) used in the treatment of aggressive and disruptive behavior refractory to conservative treatment.**

■ METHODS: **With stereotactic methodology and under general anesthesia, seven patients (from 2002 to 2010) were given DBS in the posterior hypothalamic region, bilaterally, and with the aid of intraoperative microrecording.**

■ RESULTS: **Six of seven patients presented a clear reduction in the aggression and disruptive bouts, with subsequent simplification of familiar management.**

■ CONCLUSIONS: **DBS of the posterior hypothalamic region could be an effective treatment for patients affected by mental retardation in whom disruptive and drug-refractory aggressive behavior coexists. Although several experimental data are available on this target, further studies are necessary to confirm the long-term efficacy and safety of this procedure.**

INTRODUCTION

Deep-brain stimulation of the posterior hypothalamus originally was introduced to treat trigeminal autonomic cephalalgias resulting from activation of the hypothalamus during bouts of pain (4, 10). Patients who experience chronic cluster headaches often present with aggressive bouts during the pain attacks (19). In the past, the posterior hypothalamic region (pHyp) was used as the target for lesioning in patients with aggressive behavior, epilepsy and, mental retardation (1, 2, 12-17). AQ: 1 Then, disruptive behavior was found to be induced by acute electrical stimulation within the so-called "triangle of Sano" in a Parkinsonian patient (2). The existing connections between the pHyp, the amygdala, and the Papez circuit (18) may explain the role of the pHyp in the development of disruptive behavior. The rationale for using pHyp as the target for the treatment of this pathologic condition is determined by the crucial role of this structure within the limbic loop, which appears to be dysregulated according to the results from several clinic and experimental data (5, 9, 13-16). We offered pHyp DBS to severely impaired patients affected by refractory aggressive behavior and mental retardation. The first surgery was performed in 2002 (5). The aim of this report is to describe our technique and long-term follow-up in seven patients.

METHODS

Since 2002, we have administered DBS of the pHyp region to seven patients (ages 20–68 years; one female) affected by refractory aggressive behavior. The lack of cooperation from all patients, which was attributable to the severity of both the disruptive behavior and of the most prominent comorbid condition (mental retardation) prevented us from performing specific neuropsychologic assessments; the only evaluation scales we used were IQ and the Overt Aggression Scale. These scores are summarized in **Table 1**. All patients were of below-average IQ. Two patients had refractory generalized multifocal epilepsy. The pathologic conditions associated with their disruptive behavior were: (1) posttraumatic bilateral damage of the temporomesial structures in one case; (2) congenital (unknown origin) in four cases; (3) congenital toxoplasmosis (the findings of magnetic resonance imaging [MRI] of the brain were normal in these patients); and (4) brain ischemia attributable to cardiac arrest in one case (findings from MRI demonstrated only diffuse damage of frontal cortex). AQ: 3

The Ethical Committee of our institution approved the surgical procedure in all of the patients, taking into account the chronicity and severity of the condition, the related burden to families, and the refractoriness to conservative treatments. AQ: 2 The relatives of all of the patients provided their written consent after a detailed explanation of its hypothetical rationale and of the surgical risks was given.

The stereotactic implantation was performed with the Leksell frame (Eleckta, Stockholm, Sweden) under general anesthesia in all patients. Preoperative antibiotics were administrated to all patients. A preoperative MRI (brain axial volumetric fast spin echo inversion recovery and T2 images) was used to obtain high-definition T1 images for the precise determination of both anterior and posterior commissures and midbrain structures below the commissural plane, such as the mammillary bodies and the red nucleus. MRIs were fused with 2-mm thick computed tomography (CT)

Table 1. General Patient Data, with a Comparison Between Preoperative and Postoperative OAS Scores

Patient	1	2	3	4	5	6	7
Age at surgery, years	26	34	21	64	37	20	43
Supposed cause of disruptive behavior	Idiopathic	Perinatal toxoplasmosis	Idiopathic	Post-anoxia	Post-traumatic	Idiopathic	Idiopathic
Previous treatments	Chlorpromazine Thioridazine Clotiapine Carbamazepine Clonazepam Valproate	Chlorpromazine Quetiapine	Chlorpromazine Clotiapine Bromazepam Haloperidol	Promazine Clonazepam	Clonazepam Diazepam Promazine Haloperidol	Promazine Chlorpromazine Clonazepam	Promazine Lorazepam Haloperidol
Brain MRI	Normal	Normal	Normal	Bilateral frontal cortical atrophy	Bilateral temporal porencephaly	Normal	Normal
IQ	<20	<20	40	30	<20	30	<20
Pre-op OAS	10	8	10	9	8	10	10
Post-op OAS	1	3	3	9	3	0	4
Follow-up, years	9	8	5	4	4	3	1

The related scores refer to the most severe violent attack reported by relatives and caregivers both in the overall preoperative and postoperative periods.
MRI, magnetic resonance imaging; OAS, Overt Aggression Scale.

slices that were obtained under stereotactic conditions by the use of an automated technique that is based on a mutual-information algorithm (Frame-link 4.0, Sofamor Danek Steathstation; Medtronic, Minneapolis, Minnesota, USA).

The workstation also provided stereotactic coordinates of the target: 3 mm behind the midcommissural point, 5 mm below this point, and 2 mm lateral from the midline. A possible error in this intervention could be attributable to the anatomical individual variability of the angle between the brainstem and the commissural plane. To correct this possible error, we introduced a third anatomical landmark, which allowed final target registration. We called this landmark the "interpeduncular nucleus" or "interpeduncular point," and it is placed in the apex of the interpeduncular cistern 8 mm below the commissural plane at the level of the maximum diameter of the mammillary bodies (6). The Y value of the definitive target (anteroposterior coordinate to the midcommissural point in the classical mid commissural reference system) was corrected in our patients, and the definitive target coordinate was chosen 2 mm posterior to the interpeduncular point instead of 3 mm posterior to the mid-commissural point. A dedicated program and atlas has been developed and is freely available on the internet to get the proper coordinates of the target (www.angelofranzini.com/BRAIN.htm).

During the surgical session, all patients received general anesthesia. Target control infusion was used. This method of intravenous infusion of anesthetic drugs has been studied for its ability to achieve targeted blood or effect-site concentration for selected drugs. Maintaining a constant plasma or effect compartment concentration of an intravenous anesthetic requires continuous adjustment of the infusion rate according to the pharmacokinetic properties of the drugs, which can be achieved by commercially available target controlled infusion pumps (in our study, we used Injectomat Agilia, Fresenius Kabi, France).

A rigid cannula was inserted through a 3-mm, coronal, paramedian twist-drill hole and placed up to 10 mm from the target. This cannula was used as both a guide for microrecording and for the placement of the definitive electrode (Quad 3389; Medtronic).

As far as microrecording is concerned, in two patients spontaneous neuronal activity was recorded along four trajectories (two in each patient). Along the trajectories, it was possible to identify several types of firing discharge rates and patterns. Of the several recorded neurons, a total of 14 cells located within the posterior hypothalamus were further analyzed. None showed either activation or inhibition after tactile and pin-prick stimulation. The average firing rate for these cells was 13 Hz (**Table 2**), although nine cells (64%) showed a low-frequency discharge at around 5 Hz, and the remaining five cells (36%) discharged at greater frequencies (26 Hz). Several firing patterns have been noticed: four cells exhibited tonic regular discharge, four cells exhibited tonic irregular discharge, four exhibited a bursting discharge, and two

Table 2. Electrophysiologic Characteristics of Explored Cells in Two Patients

Diagnosis	Number of Cells	Mean Firing Rate, Hz	SD, Hz	Minimum\Maximum, Hz	Firing Pattern	Rhythmicity
Aggressive behavior and epilepsy	4	19	13	6\33	Phasic	7–8 Hz
Aggressive behavior and head injury	10	10	10	2\32	Regular\irregular	Random
Total	14	13	12	2\33		

SD, standard deviation.

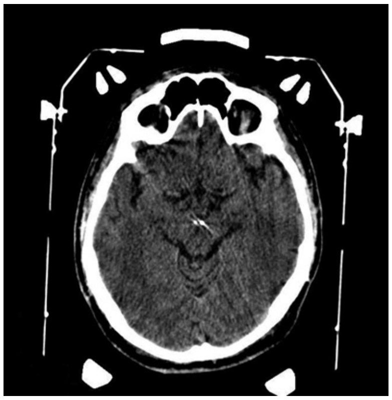

Figure 1. Postoperative computed tomography scan showing the electrode tips at the level of the posterior hypothalamic region, bilaterally.

had a sporadic firing. Periodicity was described in five units (four bursting and one regular), but the remaining one randomly fired (3). Microrecordings within the pHyp were performed within 2 mm of the stereotactic coordinates (specifically, as stated previously, 2 mm lateral to the commissural line, 3 mm posterior to the MCP, and 5 mm below the commissural line).

It is important to note that there is no clear evidence of the neurophysiologic characteristics of either the superior or inferior borders of the nucleus. However, the presence of greater firing rates more than 5 mm from the target may suggest that the microelectrode is passing through the thalamus, whereas the lack of neuronal activity at the target site and beyond may indicate that the microelectrode is not in the pHyp but in adjacent structures (that is, the interpeduncular cistern at the inferior border).

No vegetative responses or cardiovascular effects were elicited by intraoperative macrostimulation at therapeutic parameters (185 Hz, 80 microseconds, from 1 to 3 volts). At increasing charge density above this level, internal gaze deviation was observed in all cases. When side effects were ruled out at the standard parameters of stimulation, the guiding cannula was removed and the electrode secured to the skull with microplates.

Postoperative stereotactic CT was performed to assess the positioning of the electrode and rule out complications (**Figure 1**). A bilateral implantable pulse generator (IPG; Soletra; Medtronic.) was placed in the subclavicular pocket and connected to the brain electrode for chronic electrical stimulation. The parameters of chronically delivered electrical currents were 185 Hz, 60 to 90 microseconds, and 1 to 3 volts in unipolar configuration with case positive. The current amplitude was progressively increased until the impairment of ocular movement, a side effect, was reached in all cases.

RESULTS

Follow-up cases ranged from 1 to 9 years of age. Case 1's self-aggression promptly stopped, and bursts of uncontrolled violence became less frequent, disappearing completely within 3 weeks. The patient returned to family and began to attend a therapeutic community for mentally impaired patients. Generalized epileptic seizures disappeared, and partial seizures and absences were reduced 50%. Antiepileptic drug therapy was continually checked and was reduced to 30%.

Case 2 had an immediate disappearance of violence bursts and was discharged from the institution where he had been hospitalized for a long time. Major bed contention was withdrawn, and he was charged to a therapeutic community for mentally disabled patients. Three years later, after the IPG was temporary turned off for knee surgery, the patient's violent behavior relapsed, and when the chronic stimulation was restored, the therapeutic effect resulted considerably reduced despite the increase in current amplitude, which could not be set greater than 2 volts because of the appearance of side effects. The psychiatrists who had the patient in their charge suggested a possible evolution of the original disease to explain the loss of the therapeutic effect. With the IPG turned on, the burst of violence are still less frequent and less intense than in the absence of stimulation.

Case 3 had a marked reduction of the rate and duration of the violence attacks only when the amplitude of stimulation was set to 1.8 volts few months after surgery. This patient is still quiet, and her social activities have improved consistently. Now she is able to attend dedicated community and her family integration is good. Violence bursts may appear only if the patient is provoked by adverse events.

Case 4 had only an improvement in sleep habits (before surgery, he slept only 2 hours per night, and after surgery he sleep more than 6 hours per night). His behavior was not affected by the stimulation despite the electrical current increased to 2 volts' amplitude. Two years after surgery, the stimulator was turned off but the improvement of sleep was not reverted to the preoperative condition, and at 3 years follow-up, the patient still sleeps more than 6 hours per night. The same patient had a stable decrease of arterial pressure, and all antihypertensive drugs could be withdrawn; this effect is still persists despite the IPG being turned off.

Case 5 had a prompt, marked improvement of aggressive behavior, and care by the family became consistently easier. The therapeutic effect persisted at 1-year follow-up, but when both IPGs were turned off, the violent behavior reappeared within a few hours. The left IPG had been removed because of skin erosion (but has been subsequently reimplanted) and the therapeutic effects seemed to be sustained only by the right-side stimulation of the pHyp; the reimplantation of the left IPG anyway led to further reduction of the frequency of violent outbursts.

At 1-year follow-up, in case 6 the rate of epileptic seizures decreased to 50% of the preoperative condition just during the early postoperative weeks. In this patient the insertion of the second electrode at the target was immediately followed by the disappearance of interictal epileptic activity from the scalp electroencephalogram (EEG). During this intervention, infusion of a constant concentration of propofol was maintained, thus excluding the role of intraoperative anesthetics in the change in EEG activity. Anyway, no postoperative EEG was performed for this patient. The aggressive behavior has completely disappeared.

Case 7 had prompt disappearance of overall disruptive behavior; aggressive bouts now occur only episodically (about once every 2 months), but their duration and intensity is remarkably reduced (from about 9–10 episodes per day to 2–3 episodes per month). This improvement is present at the last follow-up, conducted 1 year after the intervention.

DISCUSSION

This series shows that patients affected by mental retardation in whom violent and aggressive behavior is associated could consistently benefit from high-frequency stimulation of the pHyp. No patient worsened after surgery, and no patient developed new neurologic symptoms in our series. The patients affected by drug-refractory epileptic syndromes also showed a marked decrease of frequency of epileptic episodes, and in both cases the pharmacologic therapy was consistently reduced. This observation was reported also by Espinosa et al., who used high-frequency stimulation to the pHyp to treat a patient with aggressive behavior and epileptic seizures (personal communication and poster presentation at the meeting of the AASFN held in Boston, June 2006). Experimental data are also available on this topic (11).

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Besides our series, two other cases treated with posterior hypothalamic DBS have been reported in the literature; Hernando et al. (8) reported the case of a 22-year-old patient with drug-resistant aggression and comorbid mental retardation who presented a significant improvement at a 18 months' follow-up; low-frequency stimulation was used in this case. Kuhn et al. (9) reported the case of a 22-year-old woman with self-mutilating behavior after severe traumatic brain injury. This patient experienced a resolution of symptoms 4months after beginning DBS.

CONCLUSION

In conclusion, the reversibility and the positive effects of pHyp chronic stimulation make this procedure ethically acceptable in mentally retarded patients with violent aggressive behavior. Our knowledge about the mechanisms that underlie pathologic aggressive and impulsive behavior is still incomplete; nonetheless, it has become clear from previous experimental studies that some specific structures play a role in the pathogenetic mechanism. Our group in the first article published on this topic (5) pointed out the role played by structures connected to the posterior hypothalamus (amygdala, dorsomedial thalamus, and orbito-frontal cortex) through loops reverberating within the limbic circuit; in 1988 Sano and Mayanagi (14) hypothesized the causative role of an imbalance between the "ergotropic" and the "trophotropic" circuits in favor of the former, thus justifying the use of a lesion in the "ergotropic" posterior hypothalamus to treat these patients. Kuhn et al. (9) also considered the role of zona incerta cells and their connections with the thalamus, superior colliculus, and pontomesencephalic tegmentum in the regulation of mood and circadian rhythms, given the proximity of this structure to the posterior hypothalamic area.

The possible adjunctive benefits of stimulation may include the control of refractory epilepsy, which sometimes is associated with these complex syndromes. At any rate, the reported methodology is the only neuromodulation procedure available to treat disruptive and aggressive behavior, and it is still the only alternative to classical lesional surgery; furthermore, it should be emphasized that DBS is a reversible treatment that may help patients chronically isolated in mental institutions to be integrate into society.

UNCITED REFERENCES

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 30 January 2012; accepted 21 June 2012

Citation: World Neurosurg. (2012). http://dx.doi.org/10.1016/j.wneu.2012.06.038

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