

Nucleus Accumbens Deep Brain Stimulation In Patients With Treatment-Resistant Depression: Report Of Four Cases

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Introduction: Deep brain stimulation (DBS) has been proposed as a therapeutic alternative for treating treatment-resistant depression (DRT). However, there are various goals for neurostimulation and the optimal neuroanatomic landmark is not known for this pathology. As part of the reward circuit, the nucleus accumbens has been studied in models of depression and anhedonia. The objective of this Article is to describe clinical experience of implanting deep brain stimulation bilateral electrodes in nucleus accumbens. **Cases report:** The experience of four women between 17 to 41 years old with treatment-resistant depression (DRT) is described. These cases had a background of multiple hospitalizations and severe suicide attempts, despite they were previously treated with pharmacological therapy, psychotherapy and electroconvulsive therapy (TECAR) with anaesthesia and relaxation. Six months after starting Deep brain stimulation (DBS), improved depression symptoms were observed in the Hamilton Scale and an increase in the global functionality scale. Anhedonia and abulia persisted after surgery, although with a lower intensity. **Conclusion:** DBS of the NAc may be an effective strategy for treating DRT patients, impacting on functionality and reduced suicidal risk.

Key words: Deep Brain Stimulation, nucleus accumbens, treatment-resistant depression, suicidal ideas:

INTRODUCTION

Major depression is the most prevalent neuropsychiatric disorder in South America and the Caribbean Area, affecting 13.2% of the population.¹ It is featured by sad affect, abulia, anhedonia, somatic symptoms and/or cognitive changes impacting

on functionality.² Strategies for treatment include pharmacotherapy, psychotherapy and electroconvulsive therapy with anaesthesia and relaxation (TECAR). However, between 10% to 30% of patients who have major depressive disorders do not properly respond to treatment.^{3,4}

Treatment-resistant depression (DRT) is defined as therapeutic failure of, at least,

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two anti depression medications with various pharmacologic features, during enough time and with a proper therapeutic dosage. Those patients who do not respond to optimum treatment shall chronically suffer weakening symptoms that may threat their lives. Suicidal attempts incidence in this population is estimated to be 4.66 out of 100 people-year, therefore DRT is a challenge for psychiatry. That is why some effective therapeutic alternatives must be investigated.⁵

Because of the impact DRT has on Public Health and the limited effect of antidepressants, other treatment options, such as invasive procedures have been included within management of the patients. 3 Mechanisms altering affective stimuli processing in major depression are not well known yet.⁶ However, recent studies describe malfunction in pore encephalic networks within which reward circuit is included.

Deep brain stimulation (DBS) is a surgical procedure consisting of estereotactic implantation of electrodes to modulate specific neuroanatomical targets. DBS effect has been assessed in DRT patients, stimulating various cerebral regions, such as the gyrus of the cingulum, the corpus striatum, the subthalamic nucleus, posterior hypothalamus, the nucleus accumbens (NAc) and the forebrain pack.^{4,7} General neurobiological theories describe NAc as the entry to the reward and pleasure circuit, so when it is malfunctioning that is directly correlated with with two main symptoms of depressive disorder: i.e. anhedonia and abulia.⁸

Previous Reports of DRTpatients subject to DBS in NAc have described mood improvements and even favorable change sin social life.⁹⁻¹¹ However, the amount of analyzed cases is still low as to prove DBS effectiveness in this surgical target. The objective of this Article is to describe clinical experience of implantation of bilateral DBS electrodes in the NAc in four women between 17 to 41 years old who suffer DRT.

INTRODUCTION OF THE CASES

The history of four women between 17 to 41 years old who had a DRT diagnosis subject to DBS of the NAc was retrospectively reviewed.

According to the Institutional Protocol, prior to intervening assessment on psychiatry, social work, neuropsychology, psychology and neurosurgery are made. Psychiatry assessment included a semi structured interview and application of Hamilton Depression Rating Scale (HDRS), the Global Assessment of Functioning. Scale (GAF) measuring the degree of functionality and the Clinical Global Impressions Scale (CGI) which allows to assess the severity of the case and its improvement in time.¹²⁻¹⁴ The cases were reviewed in the Interdisciplinary Board to be later presented before the Medical Ethics Committee of the Institution. After the surgical intervention, the follow up was documented with scales, six months after the surgery.

Surgical description of the DBS implant in the NAc

Under sedation and with local anesthesia, a Leksell Stereotactic Frame was attached (Elekta, Stocolm, Sweden). A 3D Magnetic resonance imaging of the brain was obtained with 3D reconstruction. It was used for planning the targets and arrangement of the electrodes using Brainlab I-Plan (Brainlab AG, Múnich, Germany). For NAc attachment, anatomical references were used (limits of the III ventriculus) and location of the core with respect to the line AC-PC. (**Figure 1**). The patient was taken to the surgical room where the procedure was continued. Under sedation, in a supine position, implantation was performed, led by microrecord assisted stereotaxy, with an FHC equipment guideline 4000 LP+ (Bowdoin, USA) a Vercise Boston Scientific System (Boston Scientific, Marlborough, USA). The three lower contacts for each electrode were energized, using the following stimulation parameters: power, 5 miliamperes, , frequency 180 Hertz and pulse width 220 microseconds.

During surgery, parameters were adjusted by using an external stimulator; the patient was alert, predominant symptomatology was assessed by means of a semi structured interview. The implanted equipment is made up of electrodes containing platinum, iridium, urethane; flexible extensions made of platinum, iridium, urethane polycarbonate and silicone elastomers going from the electrodes to an

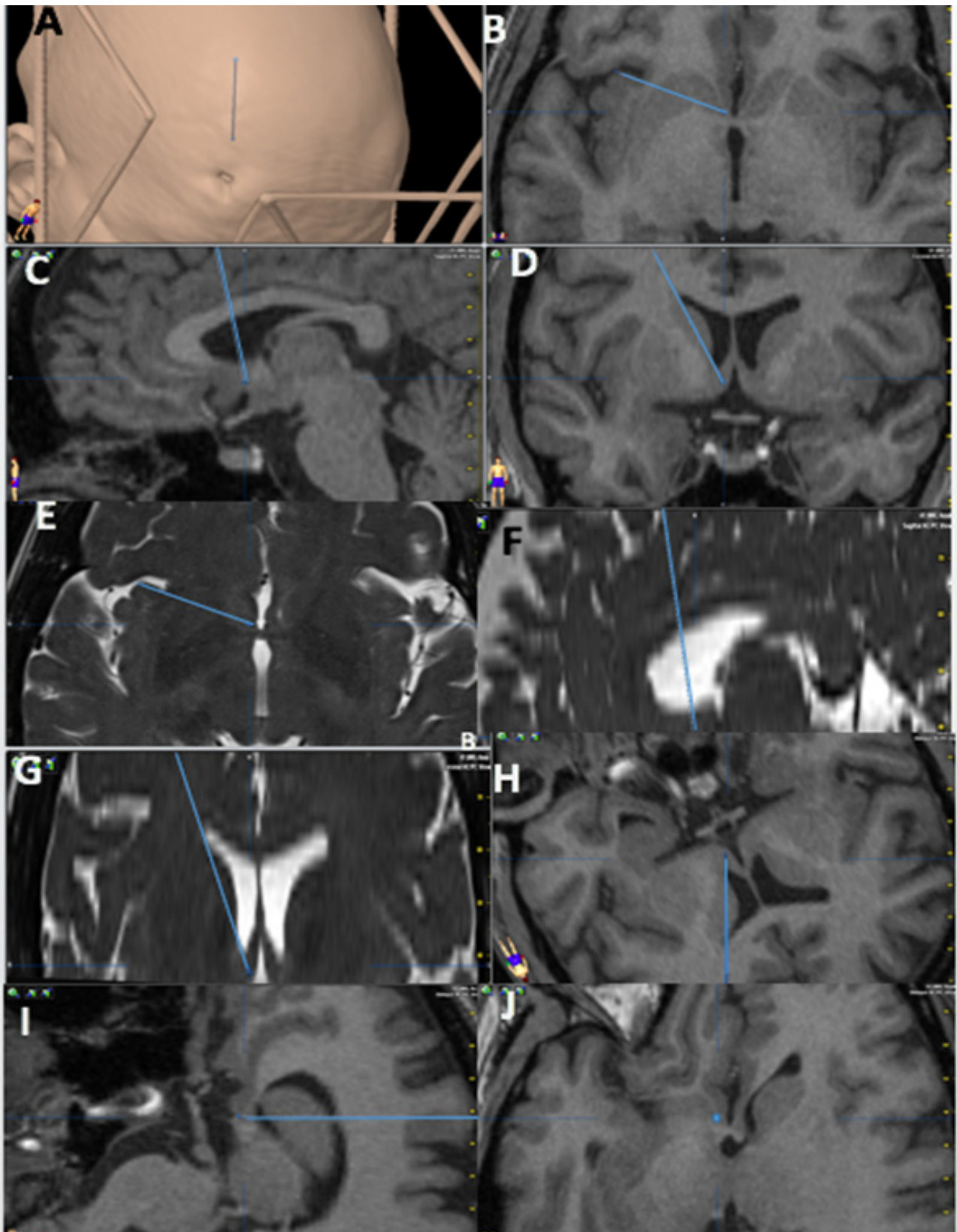


Figure 1. Anatomic location of the nucleus accumbens with brain magnetic resonance taken during pre surgery planning, the end of the blue line shows the surgical target: A: External view of the patient and stereotactic framework B: T1 Sequence, axial cut. C: T1 Sequence, sagittal cut. D: T1 Sequence, coronal cut. E: B :T1 Sequence, axial cut. F: B :T1 Sequence, sagittal cut. G: T2 Sequence, coronal cut. H: Sequence T1, axial cut, the blue line shows the direction of the electrode to the nucleus accumbens. I: T1 Sequence, sagittal cut, the blue line shows the direction of the electrode and at the end it is attached to the nucleus accumbens. J: T1 Sequence T1, coronal cut, the blue point finds the surgical target.

implantable pulse generator located in the anterior area of the thorax, right below the clavicle. All devices had an external control to adjust stimulation parameters, apart from a wireless charger. Patients were hospitalized during 24 hours in order to have a follow up after post operative time.

Pre surgical description of the cases

Case 1:

At the time of the electrodes implantation for DBS in 2014, the patient was 21 years old and since 15 had a case with depression symptoms, aggressive behavior, persistent suicidal ideas, in some cases with delirious ideas, the symptomatology caused functional compromise. The patient had a history of 7 hospitalizations, 4 suicidal attempts, one of them need ICU assistance. He was managed with various antidepressants, antipsychotics, mood stabilizers with partial response. TECAR was used twice, with partial response. The patient had therapy twice a week during more than 3 years, with no response.

Case 2:

43-year-old patient at the time of the electrodes implantation for DBS in 2015. With psychiatric diagnosis/treatment since 1999 due to depressive disorder, obsessive-compulsive disorder and anorexia; the patient additionally had a diagnosis of migraine, fibromyalgia and irritable bowel syndrome. The patient had severe depression symptoms, death ideation and recurrent suicidal thoughts, with no psychotic symptoms. The patient had a pension because of her mental illness. The patient had been hospitalized 8 times, had 3 suicidal attempts, one of them needed ICU assistance. She was managed with various antidepressants, antipsychotics, mood stabilizers TECAR and had psychotherapy for more than 5 years, with no response.

Case 3:

17-year-old patient at the time of the electrodes implantation for DBS in the NAc, 2015. Since 9 having a case of depression/obsessive-compulsive symptoms. The patient had severe depression symptoms and persistent suicidal ideas, hyporexia with weight loss

and sometimes psychotic symptoms. The patient had functional/social/family/academic compromise. The patient had been hospitalized several times, had suicidal attempts, one of them needed ICU assistance. Management with various antidepressants, affective modulators and antipsychotics with a poor response. The patient was managed with TECAR and had psychotherapy for more than 4 years.

Case 4:

23-year-old patient at the time of the implantation, in 2016. The patient had a history of depression symptoms since 18, and with persistent suicidal ideas, no psychotic symptoms. The patient had attention/concentration disorders; functional/social/family/academic compromise. The patient had been hospitalized several times, had 4 suicidal attempts, one of them needed ICU assistance. The patient had a treatment with various antidepressants, antipsychotics and mood stabilizers. The patient was managed with TECAR, with a poor response and had psychotherapy for two years.

Follow up of the Cases

Table 1 depicts valuations made before and after six months of evolution. In all four cases depression symptoms improvement was observed with 21 or less points in the HDRS value. A reduction from 1 to 3 points in CGI and an increase from 20 to 40 points in EEAG. Patients had a continuous follow up. The latest valuation was made in 2018, identifying the current condition of the cases:

Case 1: No depression symptoms or suicidal ideas during the last year, with no suicide attempts since the implantation, adherence to pharmacological management.

Case 2: No suicide attempts, lingering symptoms, such as abulia and emotional isolation.

Case 3: Episodes of lipothymia and syncope were reported, which are currently under study, thus limiting functionality and a wheel chair had to be used in order to avoid falls. Persistent/periodical depression symptoms, although less severe against pre surgical period. The patient's

care takers decided to cease use of DBS for a week. The patient had another suicide attempt. The device was resumed later.

Case 4: No suicide attempts since implantation, regular attendance to control, intermittent depression symptoms were reported.

DISCUSSION

Treatment of patients with DRT is still a challenge for psychiatrists. Despite the progress made with psychopharmaceuticals, up to 30% of patients with a diagnosed major depression do not respond to conventional therapies, including TECAR.^{3,4} This has caused research on alternative therapeutic modalities. Although these are more invasive for managing these patients. Historically some ablative procedures have been performed, such as cingulotomy, subcaudate tractotomy and limbic leukotomy for treating DRT patients in whom other interventions have failed.¹⁵ However, these surgical procedures are irreversible and although have proved to be effective in some cohorts, they are not free from complications.^{16,17}

DBS was first used as an alternative for treating abnormal movements. Since then its use has been extended to various areas, including psychiatric illnesses.¹⁸ Even though DBS is still an emerging treatment, some promissory results have been found with excellent safety profile in DRT pa, which has led to do research on various targets for stimulation. Clinical studies have valued DBS effects, mainly in Brodmann area 25 (BA25) or cingulum subcallosal gyrus, NAc, ventral capsule/ventral striatum (VC/VS), ventral portion of the anterior limb of the internal capsule (vALIC), among others. However, the target and the ideal parameters to get top effects in DRT patients are still not clear.¹¹

NAc is part of the reward circuit and has been recognized as a significant structure in depression physiopathology. It has been even reported that stress and substances associated to depression alter dopaminergic activity of the NAc and malfunction thereof.¹⁹ Considering clinical depression is marked by anhedonia (decreasing interest in pleasure). Malfunction of reward circuit contribute to depression

symptoms; therefore, this target has been studied for stimulation in DRT patients.

Although DBS literature in NAc is still limited, Mayberg et al., proved effectiveness of stimulation when managing DRT in tests targeted to areas, such as the ventral capsule, ventral striatum and NAc.¹⁴ The biggest series fund in literature is Bewernick et al. where 5 out of 11 patients (45%) with DBS in the NAc had significant improvements, reducing 50% DRS values two months after surgery.⁶ Follow up of these patients 48 months later found persistent improvement of depression symptoms 48 months.⁹

Our experience with bilateral DBS of the NAc when handling DRT patients is encouraging; observing positive results, similar to those found in literature even with quick response experiences during surgery. Even though our cohort is small (4 patients), 100% of them had improved depression symptoms with a decrease lower than 50% in HDRS after six months. Likewise, the variation found in CGI Scale was considerable and proves a lower severity of pathology, after the implant. Literature review did not find other studies including this Scale. Patients improved their global functionality, expressed by a increasing EEAG values, similar to those reported by Raymaekers et al.⁴

It is important to highlight that at the time of the DBS implantation, patients had active suicidal ideas and highly lethal prior suicidal attempts, even requiring use of ICU. Additionally, patients had received two or more treatments with antidepressants having various pharmacologic features during more than two years, apart from psychotherapy and TECAR, with no further symptoms improvement. Because of the high risk of short-term self aggression and suicide, DBS neuromodulation was deemed as the best available therapeutic option.

DBS compared with proposed ablative surgical propositions has less morbidity and it is a reversible procedure. So far none of the patients has had conditions correlated with intervention and suicidal ideas has been satisfactorily controlled. Although some prospective studies and bigger cohorts are necessary, our experience proves that NAc may be a significant target to be considered with high

suicidal risk patients. DBS could be considered as a therapeutic measure aimed to mitigate suicidal risk. In this way, possibly to reduce mortality in the group of DRT patients. It is important to highlight that, given the limitation on sample size, data and conclusions herein described must be considered as preliminary, so, it is necessary to keep research lines.

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