Deep brain stimulation of the subgenual cortex for treatment of refractory bipolar disorder: case report and literature review

Stimolazione cerebrale profonda della corteccia subgenuale per il trattamento del disturbo bipolare farmaco-resistente: case report e revisione della letteratura

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Summary

Introduction

Deep brain stimulation (DBS) has been proposed for the treatment of severe and refractory major depressive disorder, including DBS of Broadman's area 25 (BA 25 subgenual cortex).

Report

We report DBS of this cerebral region in a patient affected by long-lasting disabling and drug-resistant bipolar disorder previously submitted to electroconvulsive therapy (ECT) and vagal nerve stimulation (VNS).

Results

After the procedure and at 2.5 years follow-up the patient presented substantial improvement of depressive symptoms and maintained a stable drug therapy regimen

Discussion

Our results suggest a possible therapeutic role for BA 25 DBS even in patients affected by bipolar disorder previously treated by ECT and VNS.

Key words

Major depression • Bipolar disorder • Deep brain stimulation

Introduction

Major depression is the most common psychiatric disorder and the fourth most common disabling condition worldwide [1]; it is nowadays seen as a system-level pathological condition affecting several cerebral functional subcircuits, such as cortical, limbic, and subcortical circuits, and the system of related molecular and neurotransmitter mediators [2 3]. Pathogenesis of this disorder is multifactorial, involving genetic, mala-adaptive, and environmental factors; the treatment of the disease must thus take into account these complex physiopathological features, the heterogeneity of depression and its possible clinical evolution and worsening with time. Neuromodulation procedures have been proposed for patients who do not receive substantial benefit from conservative treatments, including drug therapy and psychotherapy; in particular, several and recent lines of evidence point to the role of subgenual cortex (Broadman area 25) as target of deep brain stimulation (DBS) in this disease and the theoretical feasibility of such modality even for bipolar patients [4 5].

We report the clinical case of a patient with refractory bipolar disorder who underwent area 25 DBS after being previously submitted to vagal nerve stimulation (VNS) without clinical benefit. Both procedures were performed at our Institute.

Case report

A 46-year-old male patient suffered from depression for 20 years before the first admittance at our Institute. Depressive symptoms developed when he was 22 after a disappointment in love. He started developing decrease of self-esteem, sadness and loss of interest in his daily activities which became progressively pervasive and led the patient into a complete anhedonic state. He lost his feelings for his parents, son and friends. He tried pharmacological treatment with several classes of antidepressant medications (selective serotonin reuptake inhibitors, noradrenalin reuptake inhibitors, tricyclic antidepressants, sodium valproate, promazine, aripiprazole, benzodiazepines) and in different combinations without clinical benefit. Depressive symptoms progressively worsened over time, and the patient started to refer suicidal intentions. Maniacal episodes (lasting about one month) were also present and intermingled with depressive episodes, with decreased need

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for sleep, increased sexual activity, ideas of grandiosity and unrestrained expenses with economical ruin).
Psychotherapy in combination with drug therapy was equally ineffective. Electroconvulsive therapy (ECT) administered on 6 sessions concomitantly with the most acute stages of the disease relieved symptoms for only few hours.
He was admitted to our Institute in 2006 with Hamilton Rating Scale for Depression (HRSD 21 items) score of 32 (severe depression). Drug therapy at that time consisted of carbamazepine 600 mg/day, venlafaxine 150 mg/day and mirtazapine 15 mg/day. The last maniac episode occurred 1 year before admittance.
After complete review of clinical history, extensive psychiatric evaluation and informed consent he was submitted to surgical intervention of positioning of VNS system. VNS was effective for a limited period (4 months), after which he progressively worsened and was unable to perform daily activities, including going out for a walk or gardening. Ingravescence of symptoms persisted even after gradual increase of the intensity of stimulation of the VNS system to 3.0 mA, and suicidal thoughts became increasingly frequent.
We then decided to propose surgical intervention of DBS of Broadman area 25.
After informed written consent, surgery was performed in January 2008.
DBS was carried on in stereotactic conditions with the Leksell headframe (Elekta Inc., Atlanta GA, USA). Computerized tomography (CT) was used to recognize the anterior and posterior commissures in the stereotactic space, after positioning of the head frame. The stereotactic CT images were then merged with the preoperative magnetic resonance images (MR; T1 and fast spin echo inversion recovery sequences with double dose of contrast-agent) and calculation of the target coordinates was performed with the neuronavigation system (Stealth Station Treon SofamorDanek, Medtronic Inc. Minneapolis, MN, USA). The definitive coordinates of the target (inferior bank of subgenual cortex, bilaterally), along with the planned trajectory, were established.
In the operating room, a rigid cannula was inserted trough a small hand drilled burr hole (5 mm diameter) and through the opened dura mater, bilaterally; the cannula was then indwelled till 10 mm above the estimated target. A high impedance microelectrode (250 µm tip, and impedance 1-1.5 MΩ; FHC Inc., Bowdoinham ME, USA) was introduced within the cannula and advanced progressively into the cortex and subcortical white matter. Microrecording tracks were performed with 0.5 mm steps until reaching the estimated target, and at this site rich multi-unit neuronal activity was confirmed, consistent with penetration of the electrode within a cortical structure (area 25 of Broadman) (Fig. 1).

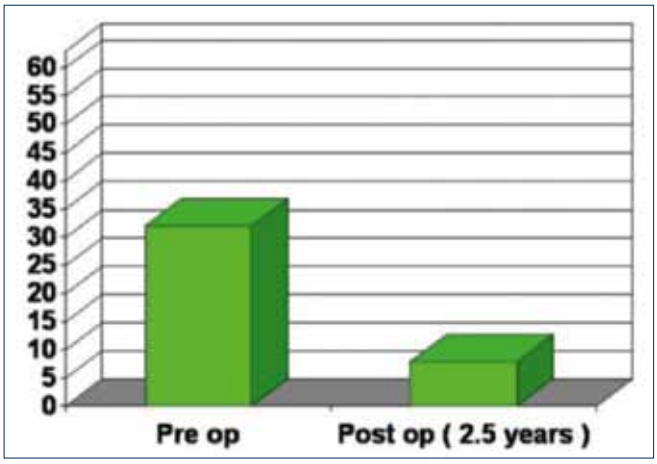

FIGURE 1.
Decrease of the score in the Hamilton Rating Scale for Depression in our patient. Functionality in the different spheres of his life gradually improved, and the patient now spends much more time in working and often goes out for a walk. Drug therapy has remained stable until the last follow-up. *Diminuzione del punteggio della Scala di Hamilton per la depressione nel nostro paziente. La funzionalità delle diverse sfere delle attività della vita quotidiana sono gradualmente migliorate; adesso il paziente trascorre molto più tempo nell'attività lavorativa e nel tempo libero. La terapia farmacologica è rimasta stabile all'ultimo follow-up.*

Intraoperative macrostimulation was then performed using several configurations among the four contacts of the DBS electrode (St Jude Medical, Inc., St Paul, MA, USA) in bipolar mode and in unipolar mode. It did not lead to any acute affective, cognitive or behavioural changes. At the end of the procedure a CT scan, again merged with pre-operative MRI images, confirmed the positioning of the electrode within the white matter of subgenual cortex, bilaterally, and excluded surgical complications. The patient was again led to the operating room and underwent positioning of the internal pulse generators (IPGs) under general anaesthesia.
After 6 months of chronic stimulation the patient gradually started to improve, although the search for stimulation parameters considered to be optimal for the clinical result were found only after 5 months of trial and error attempts (bilaterally: 2.5 mA, 91 microsec as pulse width, 130 Hz as frequency, unipolar stimulation with the most distal contact as cathode).
At 2.5 years-follow-up, the HRSD has decreased from 32 to 8 (mild depression) (Fig. 2).

Discussion

Up to 20% of patients with major depression are resistant to conservative therapeutic modalities, which include

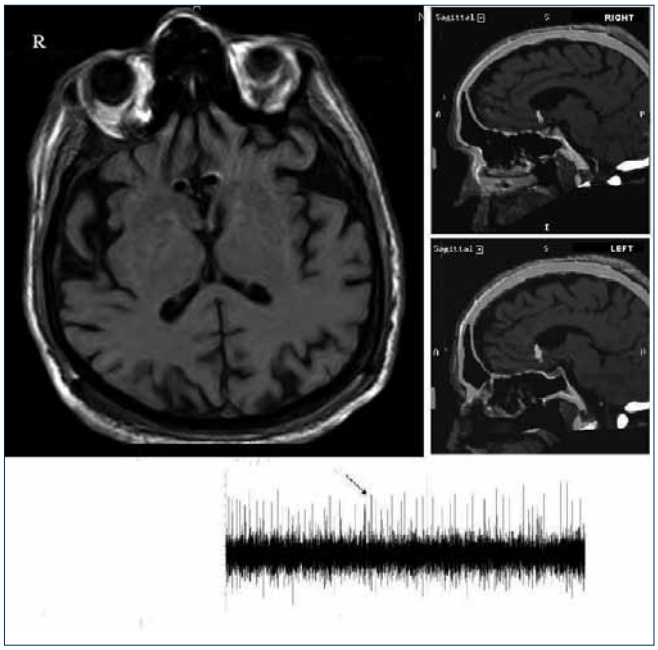

FIGURE 2.
Upper left: post operative magnetic resonance of the patient; the artefacts due to the presence of the electrodes are visible. *Upper right*: two sagittal slices of the postoperative CT scan merged with the preoperative MRI, showing the location of the electrodes. *Lower*: multi-unit neuronal activity recorded at the target (cortex of the subgenual gyrus). Sinistra, in alto: *Risonanza Magnetica encefalica post-operatoria del paziente; sono visibili gli artefatti dovuti alla presenza degli elettrodi.* Destra, in alto: *due sezioni sagittali dell'esame TAC encefalo post-operatorio fuse con l'esame RM encefalo pre-operatorio, che evidenzia la posizione degli elettrodi.* In basso: *Attività neuronale "Multi-unit" registrata al target (corteccia subgenuale).*

pharmacological treatment (often multimodal, with trial and error drug combinations), psychotherapy and electroconvulsive therapy. Given that functional neuroimaging is gaining wider acceptance as an important tool to understand some aspects of several neurological and neuropsychiatric conditions [6], correlating phenomenology to dysfunction, it is not surprising that it has recently played such a role for major depression.

In fact, Mayberg in 1999 and Seminowicz in 2004 [7 8] pointed out the increased metabolic activity of the subgenual cortex with regard to negative affective states and its relation to the efficacy of the different treatment modalities; metabolic activity of this region correlates with responsiveness to serotoninergic, ECT, ablative surgery and transcranial magnetic stimulation therapies [9-11].

Similar focal rise of metabolic activity had been previously detected within the posterior hypothalamus in patients with chronic cluster headache. In these patients, the high frequency chronic stimulation of the hypermetabolic area allowed control of headache attacks.

Therefore, it was possible to speculate about the efficacy of high frequency chronic stimulation of the CG 25 area to treat major depression through inhibition of hyperactive neuronal pools.

The first study to report the results of DBS of BA 25 was that of Mayberg in 2005 [12] in six patients. Selection criteria for surgery were clinical history of major depressive disorder (MDD) for at least one-year duration as diagnosed according to the DSM-IV, a minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HDRS), failure to a minimum of 4 treatment modalities (comprising medications, psychotherapy and ECT). Exclusion criteria were: comorbid Axis I disorders, cluster B Axis II disorders, suicidal behaviour within the past year and concomitant medical condition potentially interfering with surgery.

Response criteria was defined as a decrease of the HDRS score of 50% or more, remission criterion was a score in the HDRS of 7 or less; at six months follow-up the beneficial effect was maintained in four out of six patients; one responder patient underwent blinded discontinuation of the stimulation, with progressive loss of improvement after 3 weeks from turnoff.

Three years later the same group reported the results of BA 25 DBS in 14 additional patients, thus resulting into a series of 20 patients [4]. At 12 months follow-up, 55% of patients were responders and 35% were remitters; the maximal improvement of mood was achieved within 3 months, whereas improvement in the other aspects of the depressive disorder (such as anxiety and somatic symptoms) required longer times. Interestingly, PET scan performed in 8 patients who benefited from stimulation revealed a decrease in metabolism in the volumes adjacent to the electrodes, whereas significant changes in metabolism were observed in brain areas known to be functionally related to BA 25 (for instance, decrease in orbito-frontal cortex and medial prefrontal cortex and increase in the lateral prefrontal cortex and in the anterior and posterior cingulated gyrus).

Other targets for DBS in the treatment of major depression have been proposed, including the inferior thalamic peduncle (ITP), rostral cingulated cortex, nucleus accumbens/ventral striatum (Nacc) and lateral habenula; all these potential targets share substantial connections with several other cortical and subcortical structures of the limbic circuits thought to play a major role in the pathogenesis of this disorder based on metabolic and morphologic neuroimaging studies related to clinical observations [13]. Only three of the proposed targets have been used so far (ITP, Nacc and BA 25), with variable results.

In the present case, the patient was highly resistant to all conservative treatments attempted and to vagal nerve

stimulation, which has been reported to be effective in a substantial portion of patients in several studies [14-16]. The relative safety and efficacy of DBS of BA 25 as reported in the most recent studies convinced us to try such a modality for alleviating depressive symptoms in our patient, even though the diagnosis was bipolar disorder and not unipolar depressive disorder, the latter being the most frequent reported indication for DBS to date; our results seem encouraging enough to continue exploring the possibilities of DBS as adjunctive therapy in carefully selected patients in the future.

Future studies correlating neuroimaging and clinical data and involving larger groups of carefully selected patients are necessary to refine this procedure, from more accurate selection of patients to more precise assessment of predictive data. A multidisciplinary approach and regular cooperation with psychiatrists is mandatory.

Conclusion

Our positive results with the use of BA 25 DBS suggest a possible role for BA 25 DBS even in patients previously affected by maniac episodes within the context of a severe depressive syndrome; Finally, this case report suggests that the mechanisms of action of BA 25 chronic high frequency stimulation may be different from those of ECT and VNS.

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