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Deep brain stimulation as a functional scalpel

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Summary

Since 1995, at the Istituto Nazionale Neurologico "Carlo Besta" in Milan (INNCB,) 401 deep brain electrodes were implanted to treat several drug-resistant neurological syndromes (Fig. 1). More than 200 patients are still available for follow-up and therapeutical considerations. In this paper our experience is reviewed and pioneered fields are highlighted.

The reported series of patients extends the use of deep brain stimulation beyond the field of Parkinson's disease to new fields such as cluster headache, disruptive behaviour, SUNCt, epilepsy and tardive dystonia.

The low complication rate, the reversibility of the procedure and the available image guided surgery tools will further increase the therapeutic applications of DBS. New therapeutical applications are expected for this functional scalpel.

Keywords: Deep brain stimulation; movement disorder; chronic pain; dystonia; Parkinson's disease.

Introduction

At the beginning of the century stereotactic neurosurgery was used on animals for experimental purpose with the aim of mapping the brain's electrical activity and functional responses. The mapping process was followed by the development of surgery that was capable of changing function of brain, through small lesions in a "key" area. In the nineties, deep brain stimulation (DBS), after its optimization by Benabid [2–5], for the control of parkinsonian tremor gained worldwide the role of a promising therapeutical tool. The administration of high frequency and low amplitude electric stimulation, allows the modulation of neuronal activity in a reversible way: the parameter of stimulation can be adapted according to the clinical response. Nevertheless the way DBS works is still unclear. More experimental data are required to understand whether the interaction with the neurological functions is obtained through the inhibition or the activation of cellular activity which modulates the output of specific neural networks. There is interest, moreover, to investigate new targets in order to find new therapeutical applications to approach otherwise untreatable diseases. The development of computer-based workstations allows the use of multimodality image sets for the surgical planning, while neuroimaging provides a functional scalpel and a powerful research tool in the hand of the neurosurgeon. Since 1995 at Istituto Nazionale Neurologico "Carlo Besta" in Milan (INNCB), 401 deep brain electrodes were implanted to treat several drug-resistant neurological syndromes (Fig. 1). More than 200 patients are still available for follow-up and therapeutical considerations. In this paper our experience is reviewed and pioneered fields are highlighted.

Patients and methods

Movement disorders

Parkinson's disease: The long term results of 85 parkinsonian patients submitted to bilateral stereotactically guided implant of electrodes into the subthalamic nucleus (STN) are available. Mean age 55.7 ± 7.7 yrs, duration of the disease 11.9 ± 4.2 yrs, follow-up 25.4 ± 16.7 yrs. UPDRS motor score were of 55.1 ± 14.8 in off-drug and 19.0 ± 11.0 in on-drug.

The present series extends to the long-term observation (FU > 12 months) of our previous follow-up [6, 7]. Eight more patients affected by dopa-related diskinesias underwent Gpi neurostimulation.

Tremor: twelve patients underwent Voa-Vop-Zi high frequency stimulation (HFS). Four patients were affected by multiple sclerosis (MS), three patients by posttraumatic tremor, and five patients Parkinsonian tremor. Four patients affected by essential familial tremor, underwent Vim (HFS).

Dystonia: twenty-eight dystonic patients underwent Gpi HFS. This series include patients affected by primary dystonia DYT 1−, DYT 1+ (only one patient) and symptomatic dystonia (including three cases of drug induced tardive dystonia). Onset of symptoms ranged between

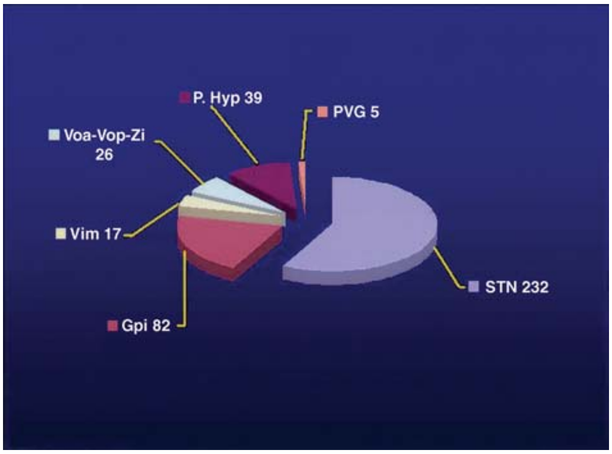

Fig. 1. Graphic representation of the whole series of deep brain electrodes implanted since 1995 at the neurological institute "C. Besta", Milan (*stn* subthalamic nucleus, *GPi* globus pallio pars interna, *Vim* ventralis intermediate nucleus, *Voa-Vop-Zi* ventral oralis ventral posterior and zona incerta, *P. Hyp* posterior hypothalamus, *PVG* periventricular grey)

2 and 50 years of age. Duration of the disease at the time of surgery ranged between 4 and 30 years. Preoperative and postoperative evaluation included video recording and assessment of dystonia with Burke-Fahn-Marsden Dystonia Rating Scales (BMFDRS).

Chronic pain

Posterior medial hypothalamic stimulation has been performed in 16 patients with chronic Cluster Headache (CH), one patient with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and three patients with neurogenic facial pain.

Disruptive behaviour

Posterior medial hypothalamic stimulation has been performed in two patients with major psychorganic diseases and disruptive behaviors, all patients were institutionalized and required continuous sedation.

Epilepsy

Chronic stimulation of the posteromedial portion of the substantia nigra has been performed in one young female (age 26) suffering from disabling posttraumatic drug resistant partial motor seizures (more than 100 seizures per month).

Surgical technique

Today different imaging modalities are available to calculate the target position coordinates by direct visualization of anatomical structures and by indirect calculations based on the commissural reference system. Even if the approach to planned target is more accurate than several years ago, many factors may lead to an error in the final position of the electrode (e.g. MRI distortion and individual variability). So microrecording of neuronal activity and micro-macrostimulation is still helpful. The introduction of this peroperative neurophysiological investigation has improved the safety and accuracy of functional neurosurgical procedures.

The day before surgery we perform accurate planning by imaging. MRI (T1 and fast spin echo inversion recovery sequences with double dose of contrast-agent) is used to obtain high definition anatomical images of the intercommissural plane, allowing the calculation of the midcommissural point coordinates. MR images are merged with computed tomography (CT) images obtained stereotactically (CRW or Leksell frame) through a dedicated workstation (Stealth Station Treon SofamorDanek, Medtronic Inc. Minneapolis/US). The stereotactic coordinates of the chosen target are obtained within the virtually built 3D space enriched by vessels enhancement. The planning of the target is refined comparing the results obtained by the workstation with a dedicated software developed at our Institute (Virtualventriculography, Solaris), which is a self learning atlas based on the statistical analysis of previous implants. In this way the targeting procedures may take advantages from a probabilistic functional stereotactic atlas (Fig. 3).

a

GPi	x	±19
	y	2
	z	-6

b

STN	x	±12
	y	-4
	z	-4

c

Zi	x	±15
	y	-7
	z	-4

d

SN	x	±10
	y	-7
	z	-6

e

Hypothalamus	x	2
	y	-3
	z	-5

Fig. 2. Target coordinates registered to the AC-PC midpoint: (a) Dystonia; (b) Parkinson's disease; (c) tremor; (d) epilepsy; (e) cluster headache and aggressive behaviour

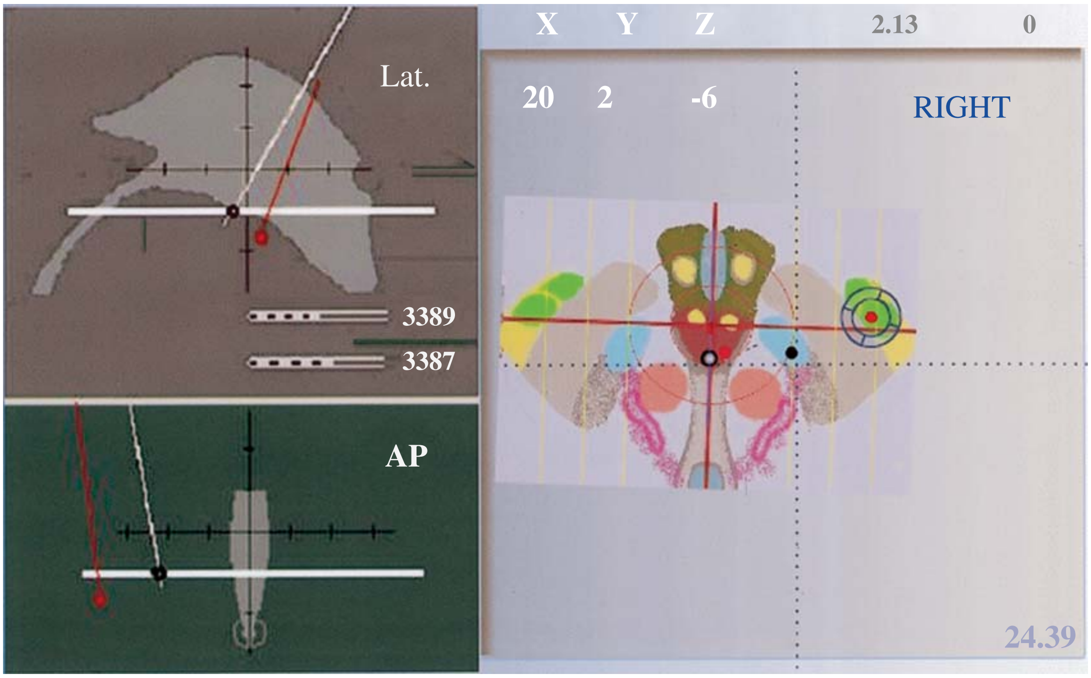

Fig. 3. Snapshot of the virtual ventriculography program (Wandor software, Dolgo, PC, Italy) showing the plate 6 mm below the commissural plane. The trajectories to the GPi (red) and STN (black) nuclei are represented on the ventricles AP and lateral profile. Targets are represented on the corresponding axial section (green: GPi, yellow: optic tract, cyan: STN, dark dotted grey: substantia nigra, pale grey: internal capsula, pink red nucleus, dotted violet: sensory lemniscal fibres)

Most of the procedures have been performed through a 7 mm precoronaric paramedian burr hole. Microrecording is used for the neurophysiological confirmation of the target in Parkinson's disease. Micro and/or macrostimulation has been performed in all procedures to rule out the adverse effects induced by electrical current delivered at therapeutical levels.

All the procedures were conducted in local anaesthesia except for generalized dystonia where general anaesthesia without curarization was preferred. Patients in general anaesthesia underwent only macrostimulation to establish the motor threshold avoiding implants too close to the internal capsule.

The individual variability of the target along the anteroposterior axis due to the high individual variability of the midbrain angle is considered and corrected in all the procedures below the commissural plane. In these cases a third point 8 mm below the commissural plane is considered to correct the AC-PC registered system. To verify the position of the electrode, CT was always performed after stereotactic surgery but before the pulse

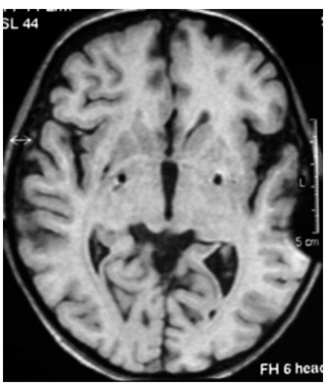

Fig. 4. Postoperative MRI merged with the preoperative MRI planning showing electrode position (T1 weighted images)

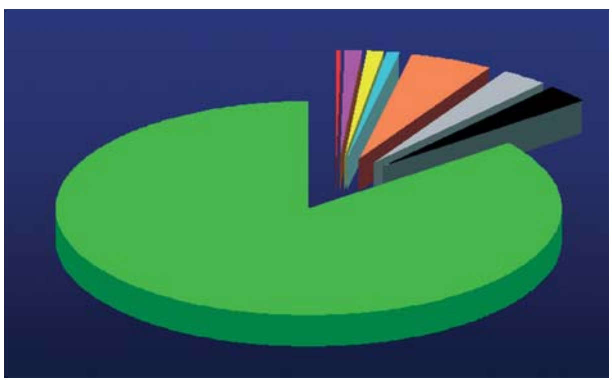

Fig. 5. Graphic representation of the complications (red: hemorrhage; violet: permanent neurological deficits, yellow: transient neurological deficits, cyan: postoperative seizures, brown: hardware removal, grey: hardware failure, black: electrodes migration, green: no complications)

generator was placed. This examem is merged with the preoperative planning in order to verify the electrode position [11] (Fig. 4).

Results

Movement disorders

Parkinson's disease: At a follow-up of 25.4 ± 16.7 months UPDRS in off-drug with stimulation is 26.4 ± 11.7, while in on-drug with stimulation is 15.4 ± 9.1. The variation off/off+ stimulation is -52.1% and variation on/on + stimulation is -19.1%.

Dystonia: All patients showed a clinical improvement, as evaluated by the BMFDRS scales, that ranged between 27 and 88%. The improvement was progressive over a period of 3–6 months after surgery, and persisted during the follow-up (4–48 months). Our results demonstrate that DBS is an effective treatment for dystonia, with no remarkable side effects, even in childhood. In tardive dystonia the results are higher than 90% with immediate effects.

Tremor: All patients regained autonomous self feeding and personal care at 12–36 months follow-up with continuous high frequency stimulation. All Vim, Voa-Vop-Zi targets showed efficacious results but the latter allowed a better control of the ataxic component.

Chronic pain

Cluster headache: At four years follow-up the percentage of the total number of days free from pain attacks improved from up to 78% and 10 patients of this series had a complete and persistent pain-free state.

SUNCT: At 18 months follow-up the patient had complete pain relief.

Neurogenic facial pain: Neurostimulation procedure was absolutely unsuccessful.

Disruptive behaviour

Stable improvement with a 12 months follow-up was obtained and a marked reduction in sedative drugs was achieved allowing us to stop the contentive hospital procedures.

Epilepsy

At 15 months follow-up the only operated patient reported a 60% dramatic reduction of seizures.

Complications

Massive brain haemorrhage occurred in one case of STN implant (0.4%); permanent neurological deficits due to deep haemorrhage occurred in four patients of which one was a Vim implant and the other STN implants (1%). Transient neurological deficits due to deep haemorrhage occurred in five patients (1.2%); postoperative seizures occurred in three patients (0.7%); hardware removal due to infection occurred in twenty-two cases (5.4%) one of which had cerebral abscess at the origin of the stereotactic trajectory; hardware failure occurred in twelve patients (2.9%); late electrode migration occurred in twelve patients (2.9%) of which eight were under fourteen years old.

Risk rate is referred to single electrode implant surgery, patients who need more than one electrode implant may expect a higher risk rate.

Discussion

Movement disorders

Parkinson's disease: As far as the field of movement disorders is concerned, advanced Parkinson's disease remains the main indication for DBS. Drug treatment of parkinsonian symptoms unfortunately cannot avoid disability in an advanced course of disease since long-term levodopa therapy often results in invalidating motor fluctuations and dyskinesias. In the 1980s, the side effects and limits of chronic L-dopa therapy became obvious and led to reintroduction of the surgical treatment of motor symptoms in Parkinson's disease (PD). Advances in stereotactic surgery, neuroimaging [15, 16], electrophysiologic recordings and the possibility to obtain therapeutic responses by high-frequency deep brain stimulation (DBS) have renewed interest in the surgical treatment of PD. During the last 10 years, several groups have demonstrated that chronic DBS of the VIM, subthalamic nucleus (STN), or globus pallidus internus is an effective treatment for disabling pharmacotherapy-resistant motor symptoms (tremor, rigidity, bradykinesia) in PD. Increasingly evidence in favour of the subthalamic nucleus (STN) as the target of choice has been collected [4–6]. The experimental data in MPTP monkeys along with clinical results in human PD patients after both STN lesion or high frequency stimulation, point toward a major role of STN hyperactivity in the pathophysiology of PD. Deep brain stimulation seems to produce a functional inhibition of the neurons in the targeted structure that mimics the result of lesioning. The main advantage of this procedure versus lesioning is related to the reversibility and adjustability of its effects without any cerebral permanent damage. The parameters of stimulation can be changed to increase efficacy or to reduce side effects. In the future a more oriented choice between the available targets (Vim-Zi-STN-Gpi-CM) will further improve clinical outcome.

Dystonia: Dystonia is a neurological syndrome characterized by abnormal postures and involuntary movements.

The physiopathologic basis of dystonia has not yet been completely clarified, however, the cortical-subcortical network and the globus pallidus internus (Gpi) are the structures primarily involved. Pharmacological treatment of dystonia is sometimes disappointing.

The practice of lesioning in dystonic patients was very common in the 1950s and 1960s, since at that time it was essentially the only available treatment for severe cases. These procedures, performed 50 years ago, were reported to have results not always satisfying, sometimes with severe side effects. By the 1980s, brain surgery for dystonia was abandoned. However, the increased understanding of the pathophysiology of movement disorders and the availability of DBS technology led to a resurgence of interest in the surgical treatment of dystonia; with globus pallidus internus (GPi) still the favourite target [9, 13, 21]. The timing of clinical improvement observed in dystonia is different from that observed in Parkinson's disease. In fact, days, weeks and most often months are required and, moreover, the improvement continues for years, suggesting a phenomenon of neuronal plasticity rather than a simple transitory functional inhibition of a pool of neurons.

Tardive dystonia (TDt) affects about 15% of patients treated by long term neuroleptics therapy and has the potential of becoming irreversible and untreatable in 1–4% of these patients. According to results from literature, when drug therapy is ineffective, thalamotomy can be applied with good but sometimes transient results. Side effects such as dysarthria, dysphonia, and motor disturbances have been described, particularly when thalamotomy is bilateral. The three patients we selected for surgical treatment presented with the typical features of drug resistant TDt: they were young males, TDt onset was observed after a long period of neuroleptics treatment, dystonia persisted after withdrawal of the causative drug with resistance to any medical treatment. Tottemberg [20] was the first surgeon to use DBS for TDt: he investigated the effect of two different targets, VIM and GPi, on the same patient. While VIM did not result in any improvement of movement control, GPi did. Therefore, we treated our patients with bilateral GPi high frequency stimulation. Stimulation started the first day after surgery and immediate improvement could be obtained, differently from what can be generally observed in dystonia of different origin. In our TDt patients neuroleptic drug administration was not discontinued: GPi neurostimulation was found to act as a sort of protection against this particular drug related side effect. High frequency chronic GPi stimulation was found to be safe, highly and promptly effective in these patients, and GPi stimulation has the potential to become the elective treatment of TDt, however these results has to be validated by larger series.

Tremor: The impressive reduction of tremor obtained either immediately during the surgical procedure or at long term follow-up in Parkinson's disease, lead to propose neurostimulation as a suitable treatment of symptomatic tremor in multiple sclerosis patients. The first reported cases of midbrain electrical stimulation on multiple sclerosis patients (MS) with ataxic tremor were reported by Brice and Mc Lellan in 1980. The four patients of our preliminary series were selected on the basis of major impairment provoked by intentional and at rest upper limb tremor. These findings raise the possibility that ataxic tremor could benefit from chronic high frequency Voa-Vop-Zi electrical stimulation.

Pain

Pain represents one of the most challenging issues for neurosurgeons. DBS and other neuromodulation procedures may offer a valid alternative to ablative procedures, which always produce a permanent damage that sometimes can give rise to neuropathic pain. Cluster headache (CH) in particular has been the first indication in the field of chronic pain: it was recognized starting from metabolic and functional neuroimaging which pointed to the postero medial hypothalamus. CH is a painful syndrome of the face often characterized also by symptoms of more general hypothalamic involvement such as psychomotor agitation. Recent imaging studies (PET and fMRI) demonstrated hypothalamic asymmetry and activation during pain attacks [13, 14, 19]. In line with these studies, suggesting the hypothalamus as the origin of pain attacks, we tried to interfere with the supposed hypothalamic hyperactivity through DBS.

Disruptive behaviour

Aggressive behaviour may be associated with different psychotic diseases and/or severe oligophrenic conditions. Control of aggressiveness in most cases may be obtained by drugs including phenothiazines and neuroleptics. Nevertheless, in selected cases, control of aggressive behaviour may be problematic due to the need of high dosages of drugs producing major side effects and sedation, which made caring for these patients even more distressing. In the sixties several neurosurgical procedures have been proposed and performed to treat the aggressiveness in psychotic patients, but the danger of irreversible lesions to CNS structures involved in the control of cognitive functions and mood put such surgery in conflict with ethics. Also, electroconvulsive therapy (ECT) was progressively decried in the seventies due to evidence of irreversible brain damage inflicted by repeated procedures. On the other hand, the last three decades have provided a huge amount of data and knowledge about the neurophysiological mechanisms of aggressive behaviour since the first experience of Delgado on animals with neurostimulators implanted in the limbic system. Since the last decade the Delgado experience and similar experimental studies have inspired more science fiction writers than neurosurgeons.

Bilateral stereotactic lesion of the posteromedial hypothalamus was first reported by Sano in the sixties. This kind of surgery, also known as sedative neurosurgery, found little diffusion for fear of irreversible effects. Our recent experience of chronic hypothalamic stimulation for the treatment of intractable cluster headache demonstrated the feasibility and safety of this procedure and renewed our interest in this target. Deep brain stimulation (DBS) of the posterior hypothalamus was then performed in two patients [13]. DBS of the posterior hypothalamus could lead to a resurgence of interest in the treatment of severe behavioural disorders.

Epilepsy

Although surgical resection of the seizure focus is the treatment of choice of refractory epilepsy, DBS may be an alternative procedure when the focus involves eloquent, unresectable areas. Stimulation of different brain structures such as the cerebellum (Cooper *et al.* 1973), the locus coeruleus (Faber and Vladyka, 1983), the thalamic centromedian nucleus (Velasco *et al.* 2000) and the STN-SN (Benabid *et al.*) has been effective in reducing seizure rate in humans [1, 9, 11, 17]. Several experimental data strongly suggested that basal ganglia and striatal pathways are involved in epileptic seizures threshold and diffusion.

Our results obtained in a young patient (26 yrs) submitted to DBS procedure of the SN-pars posteromedialis. Confirm the literature data and support application of DBS for the treatment of rolandic post-traumatic seizures.

Conclusions

The reported series of patients extend the use of DBS beyond the field of PD to new fields such as cluster headache, distruptive behaviour, SUNCT, epilepsy and tardive dystonia.

The low complication rate, the reversibility of the procedure and the available image guided surgery tools will further increase the therapeutic applications of DBS. New therapeutical applications are expected for this functional scalpel.

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