Deep brain stimulation: Subthalamic nucleus electrophysiological activity in awake and anesthetized patients

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HIGHLIGHTS

This paper analyses the subthalamic nucleus neuronal activity in parkinsonian patients undergone DBS surgery.

In our patients general anesthesia did not alter any neuronal activity when compared to local anesthesia, keeping the feasibility of microelectrode recording, an important feature to identify the subthalamic nucleus area.

Ketamine can be proposed as an alternative anesthetic drug during DBS surgery for those patients who do not accept an awake technique.

Objective: The purpose of this study was to evaluate changes in subthalamic nucleus (STN) neuronal activity in Parkinson’s disease (PD) patients during deep brain stimulation (DBS) surgery under general anesthesia, and to compare these data with those recorded in the same subjects during previous surgery under local anesthesia.

Methods: Five patients with advanced PD, who had previously undergone bilateral STN-DBS under local anesthesia, underwent re-implantation under general anesthesia (with an anesthetic protocol based on the intravenous infusion of remifentanil and ketamine) owing to surgical device complications. The microelectrode recording (MER) data obtained were analyzed by an off-line spike-sorting software. Neurophysiological data (number of spikes detected, mean firing rate, pause index and burst index) obtained under local and general anesthesia were then evaluated and compared by means of statistical analysis.

Results: We found no statistically significant difference between the first and second surgical procedures in any of the neurophysiological parameters analyzed.

Conclusions: Bilateral STN-DBS for advanced PD with MER guidance is possible and reliable under a ketamine-based anesthetic protocol.

Significance: General anesthesia can be proposed for those patients who do not accept an “awake surgery” for clinical reasons, such as excessive fear, poor cooperation or severe “off”-medication effects.

1. Introduction

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is one of the most effective treatments for advanced idiopathic Parkinson’s disease (PD) (Limousin et al., 1998; Limousin and Martinez-Torres, 2008; Benabd et al., 2009). The postoperative
clinical outcome depends on the quality of the inclusion clinical criteria and of lead targeting, which is based on neuroimaging techniques and intraoperative electrophysiology (microwire recordings – MER – and macro- or micro-stimulation) (Hutchison et al., 1998; Rodriguez-Oroz et al., 2001; Welter et al., 2002).

Surgery is usually performed while the patient is awake, off drug therapy and under local anesthesia, as this condition enables to obtain reliable MER and allows the evaluation of the intraoperative stimulation-induced improvement in parkinsonian signs and dyskinesias, as well as possible adverse effects caused by the diffusion of current to adjacent structures such as the internal capsule or medial lemniscus (Houeto et al., 2003). However, general anesthesia may be needed for specific groups of PD patients who are afraid to undergo surgery while awake or suffer from chronic pain syndromes, severe “off-medication” movements and severe dystonia.

In such cases, general anesthesia may improve patient acceptance of DBS, thereby increasing the number of patients who can be treated. Nevertheless, it can interfere with MER by lowering or eliminating spontaneous neuronal firing (Ruskin et al., 1999; Hutchison and Lozano, 2000) and hinder the evaluation of the clinical benefits of intraoperative stimulation by suppressing motor signs such as tremors and rigidity (Anderson et al., 1994; Bohmdorfer et al., 2003). Moreover, the patient cannot report subjective adverse effects, such as paresthesia or abnormal motor activity due to stimulation of adjacent structures.

To what extent different anesthetic drugs may influence MER is not yet completely known, as they exert inhomogeneous effects on different regions of the brain. Few reports are available in the literature and no prospective, randomized, blind studies comparing the clinical outcome of surgery performed under general anesthesia with that of an awake technique have been performed (Velly et al., 2007).

When sedation or general anesthesia is required during microelectrode insertion, propofol is the most frequently used anesthetic drug. However, when propofol is used, differences in the pattern of neuronal activity among individual target sites and within the same target site have been reported in different diseases, such as dystonia or PD (Hutchison et al., 2003; Maltete et al., 2004). Moreover, owing to the sensitivity of subcortical areas of the brain to GABA receptor-mediated medications, propofol can make MER impossible (Ruskin et al., 1999; Hutchison and Lozano, 2000) and may cause dyskinetic effects (Krauss et al., 1996; Deogaonkar et al., 2006) or suppress tremor (Bohmdorfer et al., 2003). Consequently, there are a number of reports on the successful use of this drug during functional surgery, both alone (Bekker et al., 2001; Mack et al., 2004; Rozet, 2008) and in combination with intermittent propofol.

Ketamine is frequently described as a “unique drug” because it exerts hypnotic, analgesic and amnesic effects. It acts basically as an antagonist of the glutamate receptors NMDA and produces an anesthetic state which has been called “dissociative anesthesia”, characterized by analgesia and changes in vigilance and perception; the patient rapidly goes into a trance-like state, with wide-open eyes and nystagmus. The patient is unconscious, amnesic and deeply analgesic. This state is a result of reduced activation in the thalamic-cortical structures and increased activity in the limbic system and hippocampus (Sinner and Graf, 2008). In animal models, but not yet in humans, it has been shown that ketamine does not alter either the number of active basal ganglia neurons or their spontaneous firing rate (Kelland et al., 1991).

The objective of this study was to investigate the effect of a ketamine-based anesthetic protocol on spontaneous STN neuronal activity in a population of PD patients who underwent bilateral STN-DBS surgery under general anesthesia, and to compare the neurophysiological results with those obtained in the same patients who had previously undergone the same surgical procedure under local anesthesia.

2. Patients and methods

2.1. Patients

A total of 5 patients (3 women and 2 men) affected by advanced idiopathic Parkinson's disease, diagnosed according to Brain Bank Criteria, underwent bilateral STN-DBS: their clinical features are summarized in Table 1.

With regard to their motor deficit, they fulfilled the criteria of the Core Assessment Program for Surgical Interventional Therapies in PD (Defer et al., 1999). The patients were assessed by means of current clinical rating scales: the Unified Parkinson's Disease Rating scale (UPDRS), modified Schwab and England score, and the Hoehn and Yahr scale.

Table 1
Clinical features of the parkinsonian patients who underwent bilateral STN-DBS.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Clinical pattern</th>
<th>Age</th>
<th>Time between the 1st and 2nd surgery (days)</th>
<th>Baseline UPDRS-III at 1st surgery off-medication</th>
<th>Baseline UPDRS-III at 2nd surgery off-medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.L.</td>
<td>F</td>
<td>Tremor-dominant</td>
<td>54</td>
<td>187</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Z.M.R.</td>
<td>F</td>
<td>Akinetic-rigid</td>
<td>51</td>
<td>267</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>B.M.</td>
<td>M</td>
<td>All cardinal motor signs (akinesia, rigidity, rest tremor)</td>
<td>69</td>
<td>347</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>S.A.</td>
<td>M</td>
<td>Akinetic-rigid</td>
<td>59</td>
<td>221</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>B.M.</td>
<td>F</td>
<td>Akinetic-rigid</td>
<td>56</td>
<td>316</td>
<td>30</td>
<td>31</td>
</tr>
</tbody>
</table>
These 5 patients underwent bilateral STN-DBS twice because of surgical complications after the first surgery. In the past decade our group has performed bilateral STN-DBS in 200 parkinsonian patients (400 leads implantation) with hardware failure only in these 5 patients with an incidence of 2.5%, similarly to data shown in the literature (Kleiner-Fisman et al., 2006). In two of them bilateral fracture of the leads occurred as consequence of traumatic skull injuries; in one patient bilateral migration of the leads occurred because the leads had not been fixed to the cranium adequately; finally, in the last two patients, because of the migration of intra-thoracic pulse generator, a solution of continuity occurred in both leads with subsequent hardware malfunctioning as shown by electrode impedance test (current <15 \mu A; impedance >4000 \Omega).

In our series, other two subjects (1%) presented bleeding after surgery; one patient without any significant neurological deficit, the other one with mild neurological deficit (left hemiparesis). No other surgical complications occurred.

2.2. Methods

Preoperative, non-stereotactic MRI scans (T1 with gadolinium and T2; slice thickness: 1.5 mm; without gap or overlap) were performed some days before the operation.

On the day of surgery, the patients underwent a stereotactic computed tomographic (CT) scan with 2-mm thick slices. Within 48 h after surgery, all patients also underwent a non-stereotactic CT scan with the same imaging parameters as those used preoperatively. Those data were also matched with the preoperative planning data for quality control of the lead placement.

The stereotactic frame (Leksell) was placed parallel to the intercommisural line and a stereotactic CT scan was obtained, as described above. The MRI datasets were matched with the CT data at the Medtronic Stealth Station (Framelink©; Medtronic, Minneapolis, MN). The target point was calculated indirectly by determining the midcommissural point on the T1-weighted MRI scan, and was adjusted according to the T2-weighted MRI scan.

All dopamine-agonist drugs were stopped 7 days before surgery and L-Dopa at least 12 h before surgery.

MER was performed by means of the Leadpoint system (Medtronic®, Minneapolis, MN) and Medtronic microelectrodes (electrode impedance = 1 MΩ). Recording started 10 mm above the calculated target and was performed on three tracks on each side (anterior, central and posterior, as in the “Bengun” microdrive) in 1 mm steps until no typical STN pattern was seen (maximum 3 mm below the calculated target point). On average, MER was performed at 13 different level per each track, so we collected 390 different MERs for DBS surgery in local anesthesia and other 390 different MERs for DBS surgery under general anesthesia (total: 780 MER).

As typical STN patterns, we looked for bursting cells and a widening of the background noise. Intraoperative test stimulation was performed at the beginning, at the end and in the middle of the typical STN signals (maximum length of STN signals) in the track that displayed the richest cellularity during MER. The permanent electrode (Medtronic mod. 3389-40®) was also implanted in this track, unless test stimulation showed capsular responses at lower current intensities. The test stimulation (macro-stimulation) was performed with the Medtronic electrodes with the following parameters: 60 \mu s, 130 Hz, up to 5 mA. In our patients, an exact correspondence between “anatomical target” (central track on the “Bengun” microdrive), calculated by means of preoperative brain MRI–CT scan fusion, and “functional target”, obtained during MER, was found only in 12 of 20 implantation (60%) procedures.

All permanent leads were fixed to the cranium with the Medtronic burrhole cap. Several days later, all patients underwent a second surgical procedure, in which an implantable pulse generator (Activa PC®; Medtronic) was inserted under general anesthesia. The patients received a perioperative prophylaxis with cephalosporins in both surgical procedures.

In each subject we performed a post-operative CT-scan in order to verify the final lead position: by means of the Medtronic Stealth Station software (Framelink©, Medtronic, Minneapolis, MN), postoperative data were matched with the preoperative CT data; we also compared post-operative CT data between the first and second surgery as shown in the Fig. 1. We found a difference in all the anatomical coordinates (x, y and z) less than 1 mm (0.45 ± 0.1 mm: mean ± SD) between the first and second surgery (M. Mondani, unpublished data, November 2011 at SITHA Conference, Udine, Italy).

The first surgical procedure was performed under local anesthesia in all cases; subsequently, because of the surgical complications described before, the same surgical procedure was repeated. This time, however, it was performed under general anesthesia in order to achieve better compliance. The time between the two procedures was: 267.6 ± 65.8 days (mean ± SD). The range was 187–347 days. In the second surgical procedure, all the patients were mechanically ventilated; we did not use propofol neither during induction or maintenance of anesthesia but only ketamine plus remifentanyl as follows: induction with 4 \mu g/kg remifentanyl (Ultiva®) plus 0.5–1 mg/kg S(+) ketamine (Ketanest®) followed by continuous infusion of 0.25–1 \mu g/kg/min remifentanyl and 0.5–3 mg/kg/h S(+) ketamine.

3. Data analysis

Neurophysiological data were analyzed off-line by means of a spike-sorting software (Fuzzy Spike Sorting – FSPS, Section of Human Physiology, University of Ferrara, Italy; A. Oliynyk, unpublished data, April 2006 at CogSysII conference, The Netherlands) for the discrimination of single populations of action potentials.

The statistical analysis was performed only for the tracks used for definitive lead insertion.

So we analyzed a total of 260 MERs (130 MERs under local anesthesia and 130 MERs under general anesthesia). Neuronal data were included in this study only if action potentials could be discriminated with an high degree of certainty, if the number of action potentials recorded was >800, and if the spontaneous activity of the neuron was recorded for >15 s. For each spike found, we evaluated the mean firing rate, “burst index” and “pause index”, as indicators of irregular activity. In accordance with Favre et al. (1999) the burst index was calculated as the number of interspike intervals <10 ms divided by the number of interspike intervals >10 ms, while the pause index was calculated as the number of interspike intervals >50 ms divided by the number of interspike intervals <50 ms.

An example of our off-line neurophysiological analysis is reported in Fig. 2.

4. Statistical analysis

Mann–Whitney non-parametric test and t-test were used to compare MER data obtained during local anesthesia with those obtained during general anesthesia in all the patients considered as a group (i.e. local anesthesia versus general anesthesia), values of P < .05 were considered statistically significant.

5. Results

MER enabled good STN activity to be identified in all cases studied, during both local and general anesthesia.
In all patients we were able to register typical STN bursting cells: during surgery under local anesthesia, we found a frequency of 29.5 ± 8.8 Hz (mean ± SD), while during surgery under general anesthesia we found a frequency of 24.0 ± 10.4 Hz (mean ± SD). However, a significant widening of the baseline background noise could not be identified in the STN under general anesthesia with a subsequent better "signal/noise" ratio.

Detailed neurophysiological results are summarized in Table 2. In none of the neurophysiological parameters analyzed (mean frequency, burst index, pause index and number of spikes detected) we found any statistical significant difference between the first and second surgical procedure. Considering the time interval between the two surgical procedures, it is reasonable that a deterioration in the disease affecting the firing pattern of the STN can be occurred; therefore, as shown in a recent paper by Harries et al. (2011), this deterioration, expressed by means of UPDRS-III, is only minimal over time, up to 7 years following the operation. Moreover, in all patients we did not observe any significant difference in the UPDRS-III values, in off-drug condition, registered before the two surgical procedures (see Table 1).

At the end of the surgery under general anesthesia, no adverse neuro-psychiatric effects were detected. At now, we are not able to compare any data regarding the clinical outcome between the first and the second surgery both because of the short-term clinical follow-up after the second procedure and because of the short time interval between the two surgeries. However the aim of the present study was only to compare the neurophysiological data between the two lead implantation procedures.

6. Discussion

The success of the post-operative clinical outcome of STN-DBS surgery depends principally on the accurate selection of patients.
and on optimal targeting, which is based on neuroimaging techniques and intraoperative electrophysiology. Surgery is usually performed while the patient is awake, as MER is not altered by local anesthesia and clinical intraoperative assessment can be carried out by evaluating possible adverse effects and improvement in parkinsonian signs during intraoperative macro-stimulation (Hutchison et al., 1998; Rodriguez-Oroz et al., 2001; Welter et al., 2002). Despite widespread use of MER to delineate the boundaries of the STN prior to stimulator implantation, it remains unclear to what extent MER improves the clinical efficacy of this procedure. Recently, some papers conclude that image-guided STN-DBS without microelectrode recording can lead to substantial improvements in motor disability of well-selected PD patients with accompanying improvements in quality of life and most importantly, with very low morbidity (Starr et al., 2010; Foltynie et al., 2011; Nakajima et al., 2011).

Therefore, little is known about the correlation between the position of the STN as seen on MRI and the one determined by MER mapping: some recent papers state the importance of microelectrode recording during DBS procedures in consideration of the discrepancies between the electrophysiologically and MRI-defined subthalamic nucleus targeting (Hamani et al., 2005; Senatus et al., 2006; Shin et al., 2007; Bour et al., 2010; Chen et al., 2011; Schlaier et al., 2011).

Table 2
Comparison of the neurophysiological data obtained from the subthalamic nucleus (STN) of our 5 patients after the first surgical procedure (under local anesthesia) with those obtained from the same patients after the second procedure (under general anesthesia).

<table>
<thead>
<tr>
<th>Subthalamic nucleus (STN) activity</th>
<th>1st surgical procedure (local anesthesia), mean ± SD (range)</th>
<th>2nd surgical procedure (general anesthesia), mean ± SD (range)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spikes found</td>
<td>2826.9 ± 899.5 (1822–4635)</td>
<td>3674.7 ± 1603.2 (1914–6180)</td>
<td>0.253²</td>
</tr>
<tr>
<td>Burst index</td>
<td>0.8 ± 0.6 (0.5–2.4)</td>
<td>0.7 ± 0.4 (0.2–1.4)</td>
<td>0.967²</td>
</tr>
<tr>
<td>Pause index</td>
<td>0.3 ± 0.3 (0.1–1.0)</td>
<td>0.4 ± 0.2 (0.1–0.8)</td>
<td>0.307²</td>
</tr>
<tr>
<td>Mean firing rate (Hz)</td>
<td>29.5 ± 8.8 (18.4–46.0)</td>
<td>24.0 ± 10.4 (10.0–41.0)</td>
<td>0.227²</td>
</tr>
</tbody>
</table>

² Mann–Whitney test.
² t-Test.
Moreover, Lefaucheur et al. (2008) showed that, among the various pre- and intra-operative data, the most important predictive factor for the clinical efficacy of STN stimulation was the length of hyperactivity along the best track observed in intra-operative multi-unit recordings.

So, at now, the optimal method for targeting the STN before implanting the definitive DBS electrode is still a matter of debates.

General anesthesia is generally contraindicated during MER, as it depresses neural activity. Moreover, as it suppresses clinical symptoms such as tremors and rigidity, it interferes with the evaluation of the clinical benefits of DBS. Nevertheless, it may be the only alternative for specific groups of patients who are unable to tolerate an “awake” surgical procedure because of excessive fear, severe “off-medication” states or chronic pain syndromes.

To our knowledge, this is the first study to compare MER data in the same subjects in two different neurosurgical settings, in the awake state and during application of a ketamine-based anesthesia protocol, using the same neurofunctional surgery technique in a homogeneous group of parkinsonian patients.

Ketamine is frequently described as a “unique drug” because it exerts hypnotic, analgesic and amnestic effects. It produces an anesthetic state which has been called “disassociative anesthesia”, characterized by analgesia and changes in vigilance and perception.

Ketamine is characterized by a chiral structure consisting of two pure optical isomers having identical chemical and physical properties except that one isomer turns polarized light left (−) and the other turns it right (+). It acts principally as an antagonist of glutamate N-methyl-D-aspartate (NMDA) receptor (Irfune et al., 1992).

The NMDA receptor is a trans-membrane protein and forms an ion channel for Na+, K+ and Ca2+. Thereby it spans the electric field generated by the membrane potential. Depending on agonist binding, the channel has different conducting states. Ketamine blocks the open channel and reduces channel mean open time and it also decreases the frequency of channel opening by allosteric mechanisms. Both ketamine stereoisomers act via the same binding sites but with different affinities and potencies. The S(+)-isomer has a 3–4 times higher affinity than the R-enantiomer (Zeilhofer et al., 1992). In animal experiments, ketamine also acts on all opioid receptors (Sarton et al., 2001) with different affinities (μ > k > δ) (Smith and Bouchal, 1987; Sarton et al., 2001). S(+)-ketamine is about 2–4 times more potent on μ- and κ-receptors than the R-isomer whereas there is no stereoselective difference on the δ-receptor (Hustvet et al., 1995). The angesic effects of ketamine are only partly reversible with high doses of naloxone, indicating an effect on the κ rather than on the μ-receptors. Other mechanisms of action of ketamine include antagonism on nicotinic and muscarinic ACh receptor (Fisher and Durieux, 1996; Yamakura et al., 2000).

Ketamine can be used safely in neurologically impaired patients under conditions of controlled ventilation, and co-administration of a GABA A receptor agonist (such as benzodiazepines) or opioids. Ketamine can increase intracranial pressure (ICP) especially when the ICP is already increased and when the dose exceeds 1 mg/kg i.v. Two causes seem to be responsible: increased cerebral perfusion, as a result of accelerated arterial pressure, and increased PaCO2 due to hypoventilation and concomitantly increased cerebral volume. Independent of pre-existing ICP, ketamine does not increase ICP when normocapnia is maintained by controlled ventilation (Bourgon et al., 2003). A mild increase in ICP during controlled ventilation can be attenuated by hyperventilation or the co-administration of benzodiazepines or propofol (Albanèse et al., 1997).

Potential adverse effects of ketamine administration include hypersalivation, hyperreflexia, muscle hypertonicity, transient clonus, increased intraocular pressure, emesis, transient rash and agitation. Hypertension, tachycardia, increase pulmonary pressures and even pulmonary edema can also be seen as an effect of sympathomimetic stimulation by ketamine. In combination with halothane, cefotaxim or thyroid hormones, hypertension and arrhythmias can be aggravated.

Although the maintenance of spontaneous breathing is a positive effect of ketamine, in higher concentrations respiratory depression is seen and artificial ventilation is necessary. Laryngospasm is frequently cited as an adverse effect of ketamine, but it is rarely observed. Especially in children (who are more susceptible), it is usually caused by stimulation of the vocal cords by instrumentation or secretions. Based on pooled data, the previous literature shows the risk of laryngospasm that required intubation during ketamine anesthesia at 1 per 5000 individuals (0.02%), which is nearly 100 times lower compared to other anesthetic agents (Green and Krauss, 2004).

Psychotomimetic reactions include anxiety, chest pain, palpitations, agitation, flashbacks, delirium, dystonia, psychosis, schizophrenic-like symptoms, dizziness, seizures, and paranoia (Sinner and Graf, 2008).

In our series, at the end of surgery under general anesthesia, no adverse neuro-psychiatric or hemodynamic effects were detected. Probably this was due to the co-administration of remifentanil which allowed us to administer ketamine at lower dosages.

In agreement with data obtained in animal models, (Kelland et al., 1991) our results confirm that this anesthesia protocol does not significantly influence the number of active cells, the mean firing rate or the firing pattern of subthalamic neurons or the quality of neuronal discharge (“pause index” and “burst index” parameters) and therefore does not impair the reliability of MER.

Starr et al. reported the use of ketamine plus remifentanil during CPG-DBS in some dystonic patients with good clinical results (Starr et al., 2006).

There are some reports in the literature on the use of general anesthetic drugs for DBS lead insertion; the anesthetic techniques used varied from conscious sedation with propofol and dexmedetomidine, with no airway manipulation, to general anesthesia by means of either intravenous or inhalation techniques, with endotracheal intubation (Fabregas et al., 2002; Maltette et al., 2004; Rozet et al., 2006; Hertel et al., 2006; Yamada et al., 2007; Elías et al., 2008; Lefaucheur et al., 2008; Rozet, 2008; Lin et al., 2008; Chen et al., 2011; Nakajima et al., 2011; Harries et al., 2012). To date, however, no prospective, randomized, blind studies have compared the clinical outcome with that of an “awake” technique.

Yamada et al. (2007) found that general anesthesia with anesthetic gas and intravenous agents (i.e. propofol and remifentanil) in 15 patients with Parkinson’s disease did not adversely affect postoperative improvements in motor and daily activity scores, except for “off-medication” bradykinesia, when compared with 10 patients who had undergone local anesthesia. Similarly, Hertel et al. (2006) showed that, in 9 PD patients undergoing STN-DBS surgery under general anesthesia with intravenous propofol and remifentanil, the STN could be adequately identified intraoperatively, and that their clinical outcome was comparable to that reported in the literature. In another study, involving 10 patients, Lin et al. (2008) found that MER during desflurane anesthesia allowed successful DBS device insertion.

Lefaucheur et al. found no significant differences in clinical outcome in their retrospective analysis of bilateral STN DBS in 24 patients operated under local anesthesia and 30 patients operated under general anesthesia (Lefaucheur et al., 2008).

Chen et al. compared the outcome of 33 parkinsonian patients who underwent STN DBS under general anesthesia (with desflurane) with that of 19 patients who were operated under local anesthesia. Postoperatively, there was no significant difference on the UPDRS scores in either groups, even if a significant deterioration in cognitive function in the general anesthesia group was observed.
The average tracks for the MER and STN depth were comparable in both groups (Chen et al., 2011). Nakajima et al. found that MRI-guided STN DBS under general anesthesia (induction with midazolam, fentanyl and propofol, maintenance with sevoflurane at 1.0 MAC and remifentanyl) did not have a negative effect on efficacy or safety (Nakajima et al., 2011).

Harries et al. analyzed long-term outcome in 82 patients undergone bilateral placement of DBS electrodes under general anesthesia (induction with propofol and remifentanyl, maintenance with nitrous oxide and isoflurane): following surgery, there was an improvement in the total UPDRS score up to 7 years postoperatively. Moreover, excellent quality of MER of the STN was obtained under general anesthesia. This paper confirms that performing STN DBS under general anesthesia it’s both safe and effective (Harries et al., 2012).

In all of these reports, however, neurophysiological data obtained from patients undergoing surgery under general anesthesia were compared with those obtained from different patients undergoing surgery under local anesthesia. By contrast, in our study, both surgical procedures were performed in the same patients; thus, each patient served as his/her own control. For this reason, in spite of the small number of patients involved, our results are particularly meaningful. Moreover, the correct localization of the definitive lead in the STN was confirmed in each patient by the comparison of the post-operative CT scan between the first and the second surgery as shown in Fig. 1. We found a difference in all the anatomical coordinates (x, y and z) less than 1 mm (0.45 ± 0.1 mm: mean ± SD) between the first and the second surgery (M. Mondani, unpublished data, November 2011 at SITHA Conference, Udine, Italy). This suggests a good correlation between MER and neuroradiological data in both surgery procedures.

As shown, ketamine can be considered a safe and effective alternative to other drugs used to induce general anesthesia for DBS surgery, since it preserves the feasibility of MER. Moreover, in our personal experience (C. Lettieri, unpublished data, June 2011 at ECCN conference, Italy), the problem of evaluating possible side effects (i.e. internal capsule activation) during micro- or macro-stimulation under general anesthesia could be overcome by recording the free-running electromyogram (EMG) of several facial and limb muscles. This electrophysiological technique can easily detect a subtle cMAP (compound muscle action potential) during stimulation, indicating a serious capsular effect.

7. Conclusions

In patients unable to tolerate an “awake” procedure, DBS device insertion with the aid of electrophysiological mapping can be performed under general anesthesia induced through careful titration of ketamine and remifentanly. However, in order to compare the long-term clinical outcome with that obtained in patients who underwent surgery under local anesthesia, further randomized controlled studies in larger populations are needed.

Conflicts of interest

All authors state that they do not have any personal or institutional financial interest in drugs, materials or devices described in the present submission.

References
