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ORIGINAL ARTICLE - FUNCTIONAL

Delayed complications of deep brain stimulation: 16-year experience in 249 patients

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Abstract
Background Over the years, most of the deep brain stimulation (DBS) complications described have been mainly related to the surgery itself or the stimulation. Only a few authors have dealt with chronic complications or complications due to implanted material.
Methods We retrospectively analyzed complications beyond the 1st month after surgery in 249 patients undergoing DBS at our site for 16 years, with 321 interventions overall.
Results Our results show that infection is the most frequent delayed complication (12.5%), the pulse generator being the most common location. Lead breaks (9.3%) are the second most frequent complication. Symptomatic peri-lead edema and cyst formation were exceptional.
Conclusions The best knowledge about DBS complications allows for better solutions. In case of infection, conservative treatment or partial removal of the DBS system appears to be safe and reasonable. Intracranial complications related to DBS material such as peri-lead edema and cyst formation have a good prognosis. They may appear long after DBS implantation.

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Keywords Parkinson's disease · Deep brain stimulation · Delayed complications · Hardware complications

Introduction

Since the early 1990s, deep brain stimulation (DBS) has been widely used to treat movement disorders. Many studies have supported its effectiveness in Parkinson's disease [1], tremor, dystonia or chorea [11] when medical therapy is not enough. As experience in this field becomes larger, new complications related to DBS arise. Nevertheless, large series have so far focused on either acute complications, such as hemorrhage or infection, or follow-up complications, such as verbal fluency or gait abnormalities. Here we report our experience in 249 patients. We discuss, based on our knowledge and the literature, delayed *hardware* DBS complications and propose solutions.

Materials and methods

We reviewed 249 DBS patients between January 2000 and December 2016, all with two DBS electrodes, except two patients (symptomatic tremor). We operated on and followed up all patients in our Movement Disorders Unit. Mean follow-up was 67.8 months. Parkinson's disease (PD) was the most prevalent condition (229 patients), followed by essential tremor (7), idiopathic generalized dystonia (4), myoclonus-dystonia syndrome (3), symptomatic tremor (3), tardive dystonia, Meige syndrome and chorea-acanthocytosis (1 each). The subthalamic nucleus was the most used target (225 patients; all of them in PD patients), followed by the internal

globus pallidus (14) and ventral intermediate nucleus of the thalamus (10). The total number of interventions was 321; 54 patients (21.7%) needed at least one extra intervention. Frequencies of the main disturbing complications are shown in Tables 1 (acute complications within the first 4 weeks after the surgery) and 2 (delayed complications). Complications discussed in this article began after the 1st month of DBS implantation.

Results

Skin complications

Bowstringing

Bowstringing is an abnormal tethering of lead extensions between pulse generators (IPG) and stimulating electrodes, associated with pain and contracture of the neck over the extension cable. Risk factors are IPG caudal migration and weight gain in patients after DBS implantation. Sometimes surgery is required [12]. In our series, only one patient needed a cervical incision to excise scar tissue [3].

Granuloma

Granuloma is the result of chronic inflammation around a strange body. The most frequent localizations are around the IPG and retroauricular areas, where surgical incisions are made. Four cases (1.2%) required minor surgery to remove the tissue, in one patient three times.

Infection

IPG

Infection is the most frequent complication during the first 24 months after DBS [8]. The surgical IPG wound appears to be the most susceptible location. The risk of infection is aggravated by periodic replacements of non-rechargeable IPGs. The frequency of IPG infection varies among authors (ranging from 0 to 15% per patient), mainly because of the different criteria applied [7]. Infection rates tend to be lower in more recent series (less than 8%) [5]. In addition, management of infection also differs among centers.

Following our local protocol, if we observe local signs of superficial infection or mild cellulitis, we provide oral therapy with amoxicillin (1 g tid) for 7 days. If infection affects the underlying IPG, we carry out surgical cleaning and debridement. We complete the treatment with intravenous wide-spectrum cephalosporin (cefazolin 1 g tid) for 3 days followed by oral amoxicillin for 2 weeks. We grow cultures for bacteria with antibiograms in all cases. If the infection persists, we remove the IPG. IPG outsourcing rarely occurs. This is a dramatic situation, leading to the removal of IPG in all cases (Fig. 1). We try to keep the lead connections and extensions for a future IPG reimplantation. After 3 to 6 months without local and systemic signs of infection, we implant a new IPG whenever the inclusion criteria are still met.

In our series, we recorded delayed IPG infection in 24 dB cases (7.5%), most of them shortly after non-rechargeable IPG replacements. In 16, infection was resistant to conservative treatment. Six cases (1.9%) were successfully treated with IPG removal, keeping the rest of the device, and replacement. Ten cases (3.1%) needed total DBS removal. In four (1.2%), we implanted a new DBS. In the remaining patients, we did

Table 1 Acute DBS complication rates

	28 days after DBS (n = 321)
Infection	5 (1.6%)
DBS removal	1 (0.3%)
Cerebral hemorrhage	10 (3,1%)
Symptomatic CH	5 (1.6%)
Convulsion	6 (1.9%)*
Meningitis	2 (0.6%)
Stroke	1 (0.3%)**
Deep vein thrombosis	1 (0.3%)**
Cerebrospinal fluid leak	1 (0.3%)
Lead break	1 (0.3%)
Lead misplacement	2 (0.6%)

*Two were symptomatic after a cerebral hemorrhage

**The same patient suffered a paroxysmal embolism (patent foramen ovale)

Table 2 Delayed complication rates, excluding the first 4 weeks after DBS

	All DBS interventions (n = 321)
IPG infection	24 (7.5%)
Conservative	8 (2.5%)
IPG removal + replacement	6 (1.9%)
DBS removal + replacement	4 (1.2%)
Definitive DBS removal	6 (1.9%)
Lead infection	16 (5.0%)
Conservative	4 (1.2%)
One lead removal + replacement	5 (1.6%)
DBS removal + replacement	3 (0.9%)
Definitive DBS removal	4 (1.2%)
Lead break	30 (9.3%)
Lead migration	18 (5.6%)
Granuloma	4 (1.2%)
Edema	3 (0.9%)
Cyst formation	2 (0.6%)

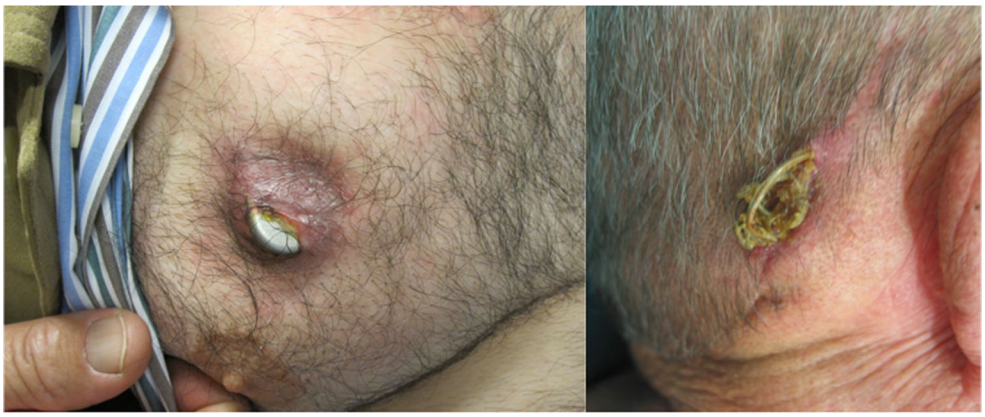

Fig. 1 IPG (left) and lead extension (right) outsourcing

not perform a new intervention because of advanced age and precarious disease conditions.

Cranial

Outsourcing and infection of the lead extension (Fig. 1) are more likely within the 1st months after DBS implantation, and later their frequency decreases significantly. Few reports differentiate infection according to its origin, either IPG or cranial, treating both as a whole.

In case of lead outsourcing, initially we perform surgical cleaning, debridement and retunneling by a neurosurgeon; then, we apply the same antibiotic schedule presented above. If infection is resistant, we remove the lead extensions. When possible, we attempt to keep at least one electrode to prolong the beneficial DBS effect and to avoid risks of a potential new electrode trajectory. Six months after removal, we reimplant the device, following new presurgical planning.

In our study, we had 16 cases (5.0%) of infection of cranial origin. In 12 cases, infection was resistant to conservative treatment. Five cases (1.6%) needed only one lead extension removal. Eventually, we reimplanted the extracted material in all five. Total DBS removal was done in seven cases (2.2%). We replaced the whole system in three of them (0.9%). As for the remaining four cases, two patients declined a new surgery and two had conditions too advanced for surgery. We observed that the complete DBS removal rate is higher in infection of cranial origin compared to IPG origin, as suggested in other series [7]. To date, we have not documented any cases of brain abscess or delayed meningitis, also very rare in the literature [14]. In our experience, the retroauricular area is the most frequent place for lead extension infection origins.

Complications related to DBS material

Twiddler and IPG migration

Twiddler's syndrome consists of rotating the IPG in the axial plane. This may give rise to DBS dysfunction due to a lead break or cause discomfort [9]. We only documented one case (Fig. 2) in which the IPG was placed in the right inferior abdominal area and was surgically solved. Since 2007, we

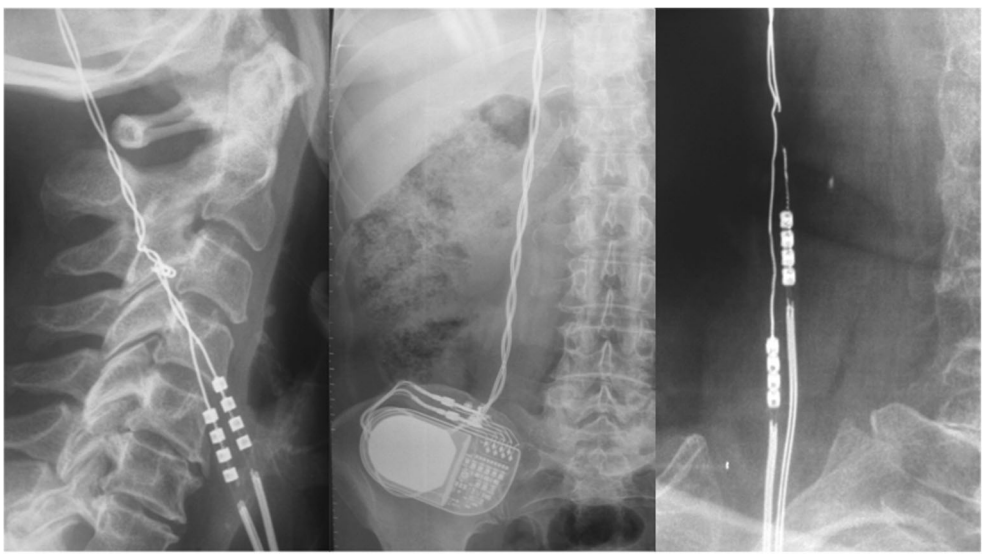

Fig. 2 Twiddler's syndrome and cervical lead extension rupture

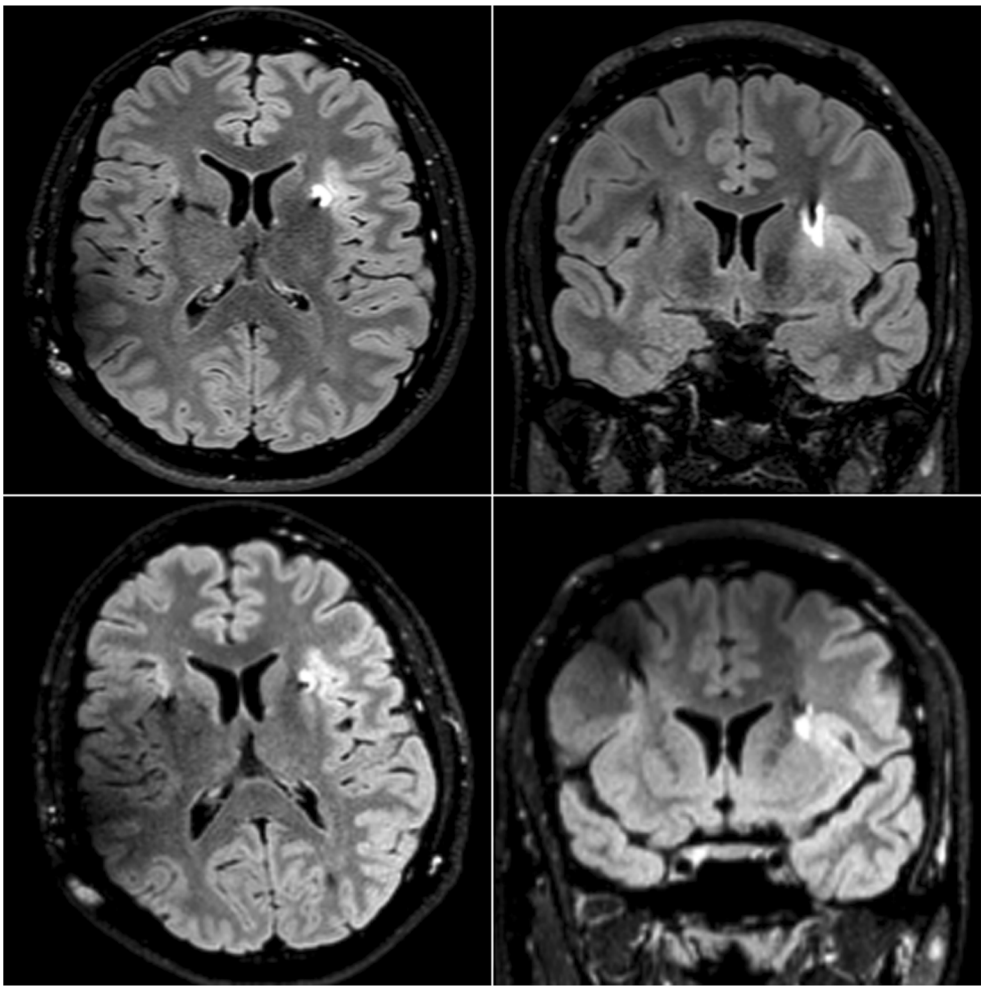

Fig. 3 Left peri-lead edema. Top: fluid attenuation inversion recovery (FLAIR) images in axial (left) and coronal (right) sections. Bottom: same sections 3 months later

placed IPGs in the infraclavicular area, so this phenomenon has become extremely rare.

Lead extension break

Lead extension break is a common complication that increases over time. We suspect this problem when the patient's condition suddenly worsens and there is a significant increase in the impedance factor. Previous works reported a mean lead break rate of 5% per patient [2].

We found 30 cases (9.3%), a number significantly higher than those reported in previous publications. An explanation for this high number is that we considered both cases of spontaneous break (Fig. 2) and cases of lead deterioration over time (around 2 of 3 cases). Replacement is required in two situations.

Contact lead migration

Minimal displacement of contact leads may cause a sudden worsening in a patient or give rise to undesirable effects. Minimal displacement may not be confirmed by a cranial x-ray or MRI. A new surgical approach is required in all cases if there is no contraindication. The frequency of lead migration in previous similar works was around 5% per electrode [2], but the results were variable.

In our study, 18 patients (5.6%) required relocation of DBS leads, 2 of them bilaterally.

Peri-lead brain edema

Abnormal T2-weighted signal hyperintensity surrounding DBS leads on MRI is an uncommon but well-recognized complication following DBS implantation. Most are asymptomatic or transiently symptomatic [4]. Retrospective analyses of postoperative MRI scans showed an incidence of 6.3% of all implants [6], but its true prevalence is unknown since no control MRIs are routinely performed after DBS surgery, as happens in our site. The signal characteristics are most consistent with vasogenic edema probably related to the inflammatory response to DBS material. In symptomatic cases, steroid treatment is helpful. Usually, DBS lead removal is not necessary.

We identified three cases of delayed peri-lead edema (0.9%) (Fig. 3), two of them after a rapid worsening of

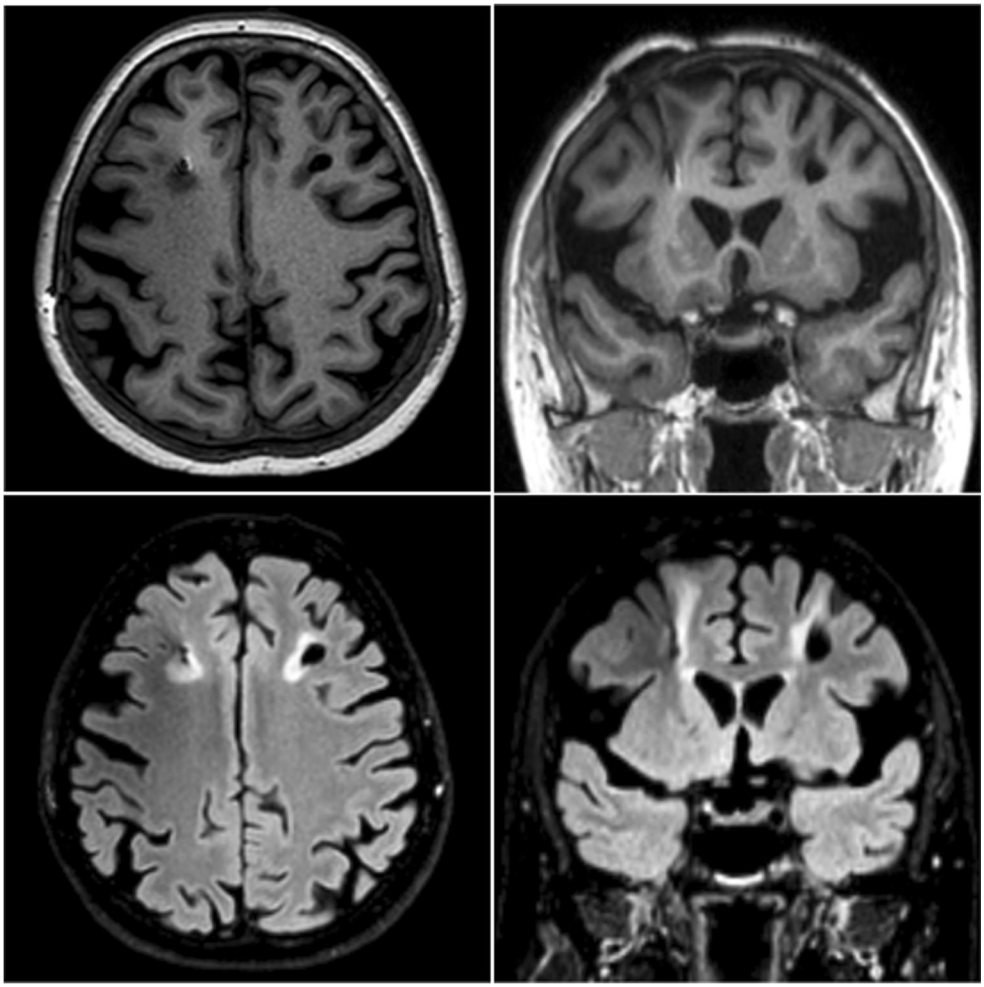

Fig. 4 Left intraparenchymal cyst and right peri-lead edema. Top: T1 images in axial (left) and coronal (right) sections. Bottom: same sections on FLAIR images

previous symptoms. We administered intravenous dexamethasone (4 mg qid) followed by a gradual reduction for 2 months. Normal functioning of DBS stimulation and patient improvement had been gradually achieved since the 2nd week of treatment. The third case was observed in an MRI scan done for a cystic cavitation follow-up (Fig. 4). It was asymptomatic, and non-steroidal therapy was needed (see below, Discussion section). Removal of the lead extension was not required in any of the cases.

Cyst formation

The formation of intraparenchymal cysts seems to be the progression of peri-lead edema, being part of the same spectrum of reactions as the DBS material [4, 6, 10]. Development of intraparenchymal cysts usually tends to go along with worsening of disease symptoms. Although MRI images usually are unequivocal, an infectious etiology should be excluded. Steroid therapy is widely accepted, but there is no consensus about whether or not to remove the DBS system.

We identified two PD cases of cyst formation in our study (0.8%). Peri-lead edema, the previous phase, was considered asymptomatic in these patients. MRI showed the typical findings described. We removed the affected DBS lead in both cases. Patients did not show signs of infection at any time, and blood tests were normal. Intraoperative biochemical analysis of cerebral cyst fluid revealed normal CSF characteristics. No steroid therapy was indicated in any of them. Six- and 12-month MRI showed a progressive reduction of the cystic lesion (Fig. 5). We successfully replaced DBS leads around 12 months after removal.

Discussion

Despite complications of invasive techniques such as DBS, this therapy provides a great benefit when the medication fails. Over time, experience has been gained and complications have become less frequent, although new ones arise. We focused on delayed complications, which have been less well characterized.

In general terms, we found our dates are similar to those of other studies. However, a direct comparison between them is not entirely valid given the different criteria applied to define

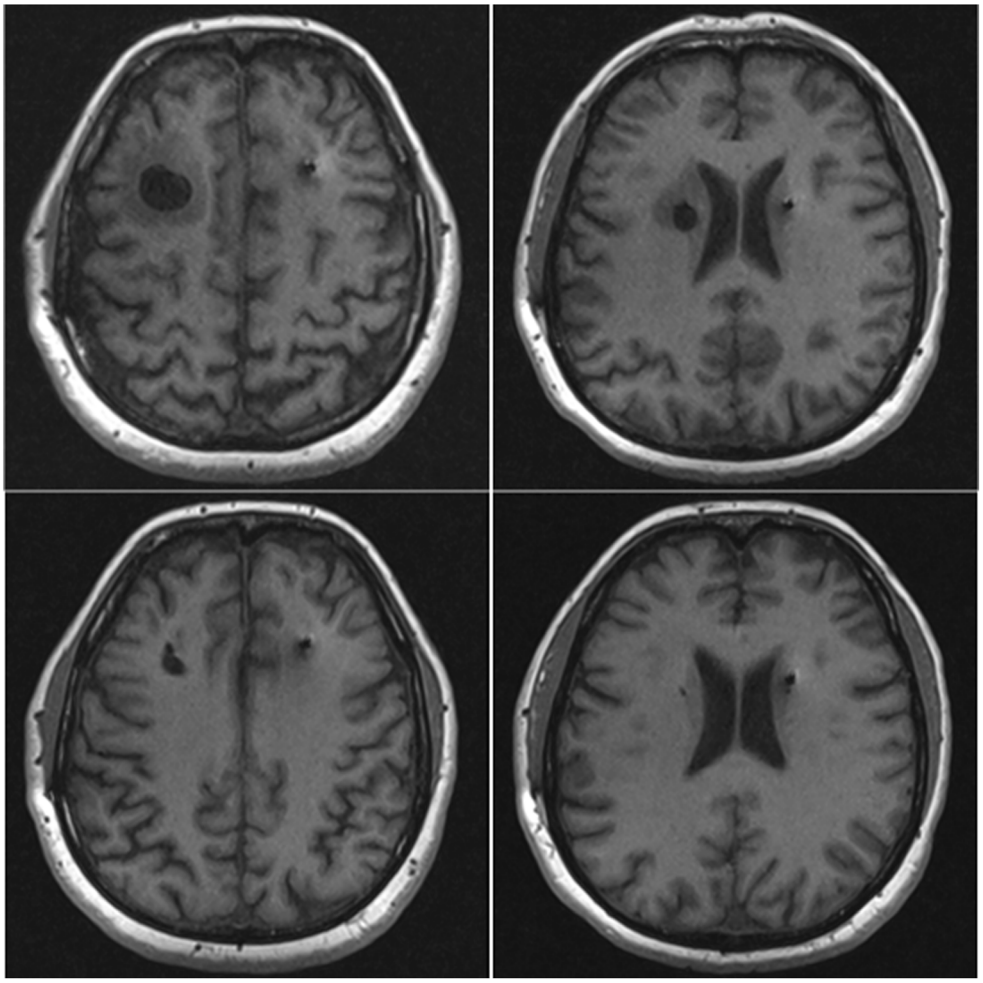

Fig. 5 Left intraparenchymal cyst. Top: T1 images in axial (left) and coronal (right) sections. Bottom: same sections 12 months later

most complications. Without going further, in some of them DBS infection is restricted to positive cultures; in others superficial infections are not considered [2]. As we described, there are important differences in the therapies used. Currently, there are no consensus protocols, and each specialized center acts differently.

It is not our purpose to analyze these differences. However, we will highlight one concerning point. When DBS therapy provides a significant clinical benefit, we should first attempt conservative treatment consisting of antibiotic treatment and surgical debridement. When the response to this is not enough, we partially remove the DBS material. Then, if infection continues to be resistant, we completely remove the DBS. We had 40 cases of infection. In 12, the problem was solved conservatively; in 11, dB removal was only partial (IPG or one lead). It means that over half of the infection cases benefited from a more cautious strategy.

In terms of intracranial complications potentially related to DBS material, to date peri-lead edema has appeared as an acute complication [4, 6]. Currently, its recognition is biased mainly because it is mostly asymptomatic and also because of the lack of routine MRI scans in DBS patients. Our two symptomatic cases differ in time because of DBS implantation and the appearance of symptoms. In the first, a PD case, symptoms were identified 3 months after the replacement of a broken electrode. In the second, a young myoclonus-dystonia case, the patient developed the symptoms about 5 years after surgery. Of note, the patient had suffered a contralateral spontaneous electrode break 14 months earlier, which was replaced. Based on this, the peri-lead edema should no longer be considered solely as an early or transient complication, with big differences between cases identified postoperatively and these. In both cases, steroid treatment was effective with early resolution of the symptoms and more delay of the alterations on the MRI. Anyway, it is important to highlight the relatively safe nature of the peri-lead edema, making explanting the DBS electrodes unnecessary.

The peri-lead edema is considered the pre-development phase of cystic formation. Cases reported to date reach 4 [10], 3 and 8 months [13] after DBS implantation. In our first case, cyst formation was identified in MRI scans performed 4 months after DBS implantation. In the second case, cyst formation was identified 59 months after DBS implantation. In case of the development of cystic cavitation, the convenience

of explanting the electrodes remains unclear [10]. It partially depends on whether these cystic formations are symptomatic or not. In our two cases, the electrode involved was removed. Reimplantation was done 12 months later after checking the favorable evolution of the cysts.

We find this last case exemplary. First, the long period between DBS implantation and cyst formation is significantly higher with respect to the other cases reported. Second, we observed an incidental peri-lead edema in the MRI scans performed at 6 and 12 months that had not been noticed in the first MRI after the patient's worsening. No more considerations were given after presuming this finding was asymptomatic. Reimplantation of the left electrode was done given the successful evolution of cyst formation. This occurring in the same patient indicates that both phenomena are part of the same spectrum and that they may appear in a very late and insidious way in DBS patients.

Compliance with ethical standards

Funding No funding was received for this research.

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical aproval and informed consent For this type of study, formal or informed consent is not required.

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