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How to cite

ANHEIM, Mathieu et al. Lifetime of Itrel II pulse generators for subthalamic nucleus stimulation in Parkinson's disease. In: Movement disorders, 2007, vol. 22, n° 16, p. 2436–2439. doi: 10.1002/mds.21726

This publication URL: https://archive-ouverte.unige.ch//unige:95907

Publication DOI: 10.1002/mds.21726

Movement Disorders
Vol. 22, No. 16, 2007, pp. 2436–2449

Brief Reports

Lifetime of Itrel II Pulse Generators for Subthalamic Nucleus Stimulation in Parkinson's Disease

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Abstract: **The efficacy of bilateral subthalamic nucleus (STN) stimulation in Parkinson's disease (PD) is well-established but little is known about the lifetime of implanted pulse generators (IPG). To investigate the lifetime of the bilaterally implanted Itrel II® (Medtronic, Minneapolis) pulse generator, the first 49 consecutive patients with PD having been operated on at our center for bilateral STN chronic stimulation were reviewed with noting of the stimulation parameters in use prior to IPG replacement. The mean electrical voltage was 3.2 ± 0.3 V, mean pulse width was 65 ± 10 μs, and mean frequency was 145 ± 16 Hz. Replacement of an IPG was anticipated in 25% due to unilateral low-battery signaling, or end of life. In either case, replacement of the contralateral IPG was undertaken simultaneously. The mean IPG lifetime was 83 ± 14 [40–113] months. The IPG lifetime correlated with the total electrical energy delivered ($P = 0.002$, $r = -0.496$). Unilateral IPG end-of-life generally led to subacute worsening of contralateral parkinsonism. In 25% of patients, there was also a worsening of axial symptoms leading to potential medical emergencies such as falls (10%), aspiration pneumonia (10%), or psychosis (5%). A close monitoring of patients and an anticipation of IPG replacement in the case of a low-battery signal are recommended.** © 2007 Movement Disorder Society

Key words: Parkinson's disease; subthalamic nucleus stimulation; implanted pulse generator.

Bilateral subthalamic nucleus (STN) stimulation acts by mimicking the effect of levodopa on parkinsonian motor symptoms thereby enabling a reduction in the equivalent daily-dose of levodopa (LEDD) and by consequence, dyskinesias, in patients with severe levodopa-induced motor complications.[1,2] Such a benefit depends upon an adjustment of the electrical stimulation settings (ESS) selected to maximize clinical advantage while minimizing potential side effects. Other associated variables include an appropriate selection of patients and the precise placement of the electrodes in the STN.

We report here a study of the life expectancy of implanted pulse generators (IPG) for the first 49 consecutive patients operated on at our center and undertaking regular long-term follow-up. The outcome for these patients during the 5 years subsequent to their operation has been the subject of a previous report.[2] Little is known in detail of the lifetime of IPGs in use as STN chronic stimulators in Parkinson's disease (PD),[3] and yet this issue remains an important one since an increasing number of patients with PD are being operated on for either STN stimulation or IPG replacement since the adoption of this neurosurgical procedure in 1993.[4] The cost to public health resources of IPGs and the number of adverse events related to IPG end-of-life or to repeated IPG replacements depends significantly upon the IPG lifetime. An improvement in the knowledge of the acute clinical consequences of IPG end-of-life must be effected in order to better manage these patients and avoid possible complications.

METHODS

During February 2006, a retrospective review was undertaken of the first 49 consecutive patients treated with bilateral STN chronic stimulation in our institution between February 1993 and February 1997 to investigate the battery lifetime of their IPG, the ESS used for chronic stimulation, and the clinical consequences of IPG end-of-life. The baseline characteristics and long-term outcome of the patients have been given in a previous report.[2] For all patients, two IPG (Itrel II®, Medtronic) were subcutaneously implanted in the right and left subclavicular areas. The time in months between the beginning of stimulation and the end-of-life of at least one IPG, or its replacement anticipated due to a low-battery signal, was noted. Both IPGs were replaced in a single operation even if one of them was still functional. To optimize the clinical effects, the ESS remain adjustable and frequent modifications are made during the initial postoperative months though later a constant parameter

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Received 7 March 2007; Revised 8 August 2007; Accepted 10 August 2007

Published online 25 October 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21726

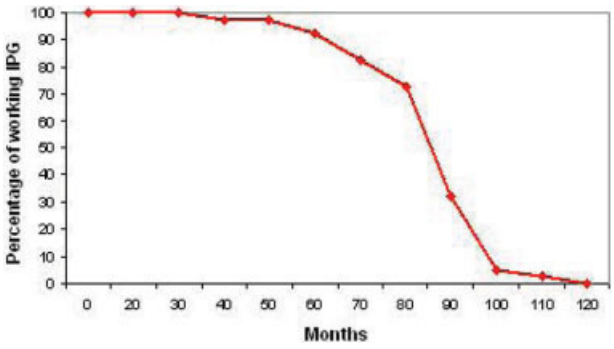

FIG. 1. Percentage of IPG still effective up to 120 months following the intiation of stimulation.

level is reached and subsequently maintained.[5] For this reason the ESS employed during the year prior to replacement became a parameter for comparison. The used capacity of the pulse generator can be assessed during routine IPG checking. A low-battery signal appears if more than 85% of the capacity has been exhausted while spontaneous extinction may occur if more than 95% has been used. In the latter case, the "Power On Reset" state may occur. This is a safety function of the IPG which self-initiates at the onset of end of life preventing an intermittent stimulation. An evaluation of the total electrical energy delivered (TEED) by the IPG was performed using an equation previously proposed: TEED = (voltage^2 $\times$ pulse width $\times$ frequency)/impedance.[6] Unfortunately, the impedance measurement through the Medtronic Itrel II®, designed to inform about short ($<$50 Ω) or open circuits ($>$2,000 Ω), lacks precision under normal functioning conditions and provides an impedance which is generally around 1,000 Ω.[7] This impedance of 1,000 Ω was adopted arbitrarily to calculate TEED. The acute clinical consequences of IPG end-of-life were duly noted and the Spearman correlation test was performed for a statistical evaluation of correlation between IPG lifetime and TEED.

RESULTS

During the 13-year follow-up, from among the 49 patients, 5 were lost from the follow-up and 4 others died though their IPGs were working correctly. The mean IPG lifetime of the 40 remaining patients was 83 $\pm$ 14 (range 40–113) months, a figure approaching 7 years. The mean voltage was 3.2 $\pm$ 0.3 (2.3–3.6) V, the pulse width 60 μs in 34 patients and 90 μs in the remaining 6 patients and a mean frequency of 145 $\pm$ 16.3 (130–185) Hz. After 36 months no IPG had been replaced, and after 80 months 72.5% (58/80) of IPGs were still working (see Fig. 1). In 50% of patients (20/40), IPG replacement occurred between 84 and 96 months (7–8 years) following the initiation of stimulation (see Fig. 1). Two patients still had the same IPGs after 100 months (see Fig. 1), while for a single patient IPG lifetime was 113 months, the longest recorded, having mean electrical parameters for the two IPGs of 2.95 V/60 μs/137.5 Hz. The shortest recorded IPG lifetime (40 months) belonged to a patient living overseas whose parameter settings, which were unusually high, had been adjusted at another center. The overall mean TEED was 111 $\pm$ 45 (49–216). The IPG life-time of each patient was correlated with the TEED (P = 0.002, r = $-$0.496) (see Fig. 2). Of the 80 electrodes, stimulation was monopolar in 92% and double monopolar in 8%, with zero bipolar. The mean IPG lifetime associated with the double monopolar stimulation was only 67 (57–82) months. The contacts used for chronic stimulation were 0$-$ in 10%, 1$-$ in 8%, 2$-$ in 47%, 3$-$ in 27%, and were 2$-$ to 3$-$ in 8%. Unilateral end of battery life generally resulted in subacute worsening of contralateral parkinsonism with tendencies toward a worsening of axial symptoms including gait, speech, and swallowing difficulties. Unilateral IPG end-of-life led to sudden and severe aggravation of parkinsonian symptoms in 10 patients, falls in 4 patients, aspiration pneumonia or respiratory failure in 4 patients and psychosis, including delirium, hallucinations and agitation in 2 patients. Among the total group of patients 25% (10/40) had anticipated IPG replacements, either due to unilateral low-battery signaling (i.e. $>$ 85% of capacity used) discovered during routine IPG checking in patient(s) with known severe motor state in off-stimulation condition, or because of a progressive worsening of parkinsonian symptoms leading to a diagnosis of low-battery signaling. Of these 10 patients, during the period just prior to the definitive termination of IPG function, 3

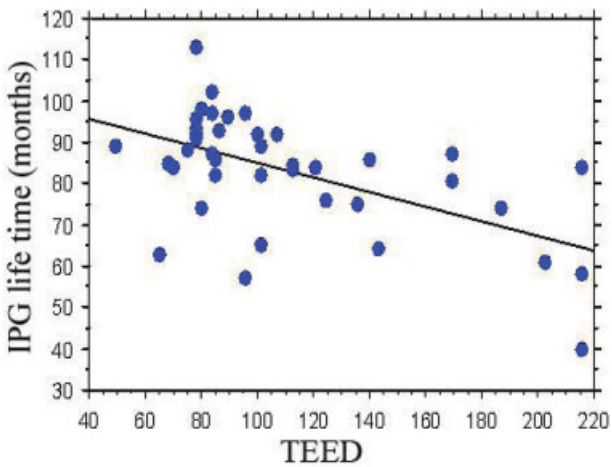

FIG. 2. Correlation between the IPG lifetime and the TEED of the 40 patients (P = 0.002, r = $-$0.496).

had transient, spontaneous "Power On Reset" states alternating with periods of normal functioning. These IPG failures were responsible for aggravation of parkinsonian motor symptoms and, in one case, unexpected spontaneous ESS changes. For a small number of patients, IPG status verification gave a normal battery signal yet the IPG end-of-life occurred days later. This was in contrast to the appearance of the end-of-life or low-battery signal which should have occurred once the used capacity had reached >85% (i.e. several months before the definitive IPG termination). In 1 patient, the IPG replacement was further complicated with peri-generator subcutaneous inflammation and seroma, though this eventually resolved itself.

DISCUSSION

The mean IPG lifetime was 83 months with electrical settings of 3.2 ± 0.3 V/65 ± 10 μs/145 ± 16 Hz. All of the data from this retrospective study were not available since 4 patients died and 5 were lost from the follow-up. Chronic stimulation was monopolar with contact 2 in 47% of electrodes while double monopolar stimulation was only used in 8%. The energy required for the same effect in a target of STN increases with the square of the distance between the delivering contact and the target.[8] Therefore, the more distant the contact from the target, the higher the TEED required and therefore the shorter the IPG lifetime. In this study, the battery lifetime is correlated with the ESS that depends, among other things, on precision electrode implantation in the STN. The correlation between battery longevity and TEED has been reported previously in a population of 11 patients suffering with PD and having a mean IPG longevity of 47 months, mean voltage of 3 V, mean pulse width of 90 μs, and mean frequency of 185 Hz.[3] In the study above, there were no significant differences in the ESS parameters, in the IPG lifetime and between the various brain targets (STN, globus pallidus internus, and nucleus ventralis intermediate of the thalamus). Goodman et al. reported their findings concerning 100 patients with advanced PD treated consecutively with microelectrode-guided STN chronic stimulation.[9] In blinded reviews of videotaped neurological examinations, the off-medication UPDRS III (motor) score improved by 29.5% following 1 year though this is, however, less than reported by our group (54% of improvement UPDRS III after 5 years). Of the 100 patients in the Goodman study, 10 had a battery failure within 2 years of IPG implantation. These reduced IPG lifetimes could be due to suboptimal electrode implantation requiring higher stimulation parameters or to differing strategies in the specific handling of stimulation parameters.[10]

In our review IPG end-of-life, even if unilateral, could lead to subacute worsening of parkinsonism symptoms with falls, psychosis, and respiratory distress due to aspiration pneumonia. These data confirm that IPG failure in STN chronic stimulated parkinsonian patients may be considered a medical emergency[11] that may require the resumption of the levodopa therapy. Almost 50% of IPG end-of-life events occur between 84 and 96 months assuming that the electrical parameters are not much higher than 3.0 V/60 μs/130 Hz and that a single contact is used as a monopolar electrode. Therefore, an IPG replacement should be considered before the completion of 7 years following surgery in patients with severe disability in off-stimulation and low-battery signal conditions. The recommendation must be for a close monitoring of patients and the replacement of the IPG when the battery indicates low capacity. Indeed, the off-stimulation motor disability of parkinsonian patients increases progressively over the long-term despite chronic stimulation. This could explain unexpected severe and acute worsening of parkinsonian symptoms subsequent to IPG end-of-life, even in the case of unilateral end-of-life. Surgery for PD has transformed this slowly progressing, chronic disease to the one that may be held in check by artificial in situ electrical stimulation of appropriate brain components, but that may require medical and surgical emergency care should the bilateral stimulation suddenly stop as a result of either battery depletion or malfunction. Regular checking of IPG for low-battery signaling is recommended though this is not always reliable. For IPG parameters, in the average range routine, checking should begin between 4 and 5 years following surgery. Our results hold true for the Itrel II® IPG (almost identical to the commercially available Soletra®, Medtronic) though cannot be extended to other IPGs or other targets. For the Kinetra®, the use of a single stimulator for bilateral stimulation will induce a greater risk as stimulator arrest will lead to a bilateral worsening of parkinsonism.

All of the patients in our study had implants in the STN which is nowadays considered the best target in the treatment of PD. The IPG energy consumption varies according to targets and disorders. Indeed, the pallidal target that is effective in treating dystonia[12] requires stimulation which employs higher electrical parameters leading by consequence to a shorter IPG lifetime than the STN target in patients with PD.

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The Prevalence of *LRRK2* Gly2385Arg Variant in Chinese Han Population with Parkinson's Disease

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Abstract: **We conducted a case–control study to determine the prevalence of the *LRRK2* Gly2385Arg variant in patients with Parkinson's disease in Han population in mainland China. Heterozygous *LRRK2* Gly2385Arg variant was identified in 14 of 235 patients with Parkinson's disease (5.69%), but not in 214 unrelated healthy controls. Multivariate analysis indicated the frequency of Gly2385Arg variant in the female patients with early age at onset is higher than their male counterparts. The founder haplotype analysis showed the variant carriers shared the same founder. Clinically, the *LRRK2* Gly2385Arg carriers presented with classical Parkinson's disease symptoms. Our study indicates that the *LRRK2* Gly2385Arg variant is a potential ethnic-specific genetic risk factor of Parkinson's disease within Chinese Han ethnicity.**

Key words: Parkinson's disease; *LRRK2*; Gly2385Arg; Han ethnicity; China.

Parkinson's disease (PD) is the second most common neurodegenerative diseases. It is characterized by resting tremor, rigidity, bradykinesia, and postural instability. The *LRRK2* gene is associated with autosomal dominant familial PD, while its mutations are also discovered in sporadic PD.[1,2] The *LRRK2* mutations vary among different ethnicities. Arg1441Gly, one of the first discovered mutations, is mainly associated with the patient population in the Basque

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Received 11 April 2007; Revised 4 September 2007; Accepted 7 September 2007

Published online 25 October 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21763