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DBS-withdrawal syndrome in PD: risk factors and pathophysiological hypotheses of a life-threatening emergency

Running title: DBS-withdrawal syndrome in PD, an emergency

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Abstract

Background and objectives: Subthalamic nucleus (STN) Deep Brain Stimulation (DBS) is the most common therapeutic surgical procedure for Parkinson's Disease (PD) patients with motor fluctuations, dyskinesia, or tremor. Routine follow-up of patients allows clinicians to anticipate replacement of the DBS battery reaching the end of its life. Patients who unfortunately experience a sudden stop of the DBS battery experience a rapid worsening of symptoms unresponsive to high dose of levodopa, in a life threatening phenomenon called "DBS-withdrawal syndrome". In the current context of the COVID pandemic, where many surgeries are being deprogrammed, it is of utmost importance to determine to what extent DBS battery replacement surgeries (BRS) should be considered as an emergency. Herein we attempt to identify risk factors of DBS-withdrawal syndrome and provide new insights about pathophysiological hypotheses. We then elaborate on the optimal approach to avoid and manage such a situation.

Methods: We conducted a systematic review of the literature on the subject and reported the cases of 20 patients (including 5 from our experience) with DBS-withdrawal syndrome comparing them to 15 undisturbed patients (including 3 from our experience) all having undergone neurostimulation discontinuation.

Results: A long disease duration at battery removal and many years of DBS therapy are the main potential identified risk factors ($p < 0.005$). Also, a trend for older age at the event and higher UPDRS motor score before initial DBS implantation (evaluated in OFF drug condition) was found ($p < 0.05$). We discuss several hypothesis that might explain this phenomenon, including discontinued functioning of the thalamic-basal ganglia loop because of DBS-stimulation cessation in a context where cortical-basal ganglia loop had lost its cortical input;

and possible onset of a severe bradykinesia through the simultaneously occurring of an alpha and high-beta synchronized state.

Conclusion: Patients' clinical condition may deteriorate rapidly, be unresponsive to high dose of levodopa and become life-threatening. Hospitalization is suggested for clinical monitoring. In the context of the current COVID pandemic, it is important to widely communicate the replacement of DBS batteries reaching the end of their life. More importantly, in cases where the battery has stopped, there should be no delay in performing replacement as an emergent surgery.

Keywords: Parkinson Disease, Deep Brain Stimulation, Emergencies, Risk Factors

DBS-withdrawal syndrome in PD: risk factors and pathophysiological hypotheses of a life-threatening emergency

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease related to the loss of dopaminergic neurons in the substantia nigra ¹. Subthalamic nucleus (STN) Deep Brain Stimulation (DBS) is currently the most common therapeutic surgical procedure for PD patients with severe and medication refractory ON–OFF motor fluctuations, dyskinesia, or tremor ².

The increase in life expectancy ³ in PD patients, associated with evidence (even if controversial) for operating in early-stage PD ⁴, raise questions of appropriate timing for battery replacement surgery. Therefore, rechargeable devices have been developed and have shown a better long-term cost-effectiveness ⁵.

In most cases, the routine follow-up of patients allows clinicians to anticipate the replacement of a battery that is approaching its end of life. Some patients unfortunately experience a sudden stop of the DBS battery which is followed by a rapid worsening of their symptoms, a rare phenomenon described as DBS-withdrawal syndrome which can be life-threatening ^{6 7 8 9 10 11 12 13}. In the current context of the COVID pandemic, where many surgeries are being deprogrammed, it is of utmost importance to determine to what extent DBS battery replacement surgeries (BRS), usually scheduled as elective surgeries, should be considered as an emergency ¹⁴. Herein we discuss this critical issue based on a systematic review of the literature and on 8 patients from our experience who have been through a neurostimulation acute discontinuation, including 5 patients who presented with a DBS-withdrawal syndrome. We then attempt to

identify risk factors and provide new insights about pathophysiological hypotheses. We also elaborate on the optimal approach to avoid and manage such situation.

2. Methods

To address our questions, we report the cases of 8 patients from our experience who have been through a neurostimulation acute discontinuation, including 5 patients who presented with a DBS-withdrawal syndrome during the period 2018 to 2022. All parkinsonian patients treated with DBS are included in a local register allowing us to follow their evolution over time. We collected various parameters to best describe the phenotype of these patients: age at which the event occurred, disease duration, comorbidities, DBS duration since first implantation, DBS parameters before and after battery replacement, Unified Parkinson Disease Rating Scale part III (UPDRS III) OFF and ON drug before the first DBS implantation, last UPDRS III and Hoehn & Yahr scores known when DBS was ON and when the patient was also ON dopaminergic treatment (UPDRS III or Hoehn & Yahr “before battery removal, ON drug”), but also when the DBS was removed with increased dopaminergic treatment in an attempt to fight against the parkinsonian syndrome (UPDRS III or Hoehn & Yahr “after battery removal, ON drug”), last known Levodopa Equivalent Dose (LED) before battery replacement (LED before battery removal) and after, taking into account increase in dopaminergic treatment dosages (LED after battery removal). Creatine Phospho-Kinase (CPK in UI/mL) dosage was also performed when the patients experienced the DBS-withdrawal syndrome and was compared to a new dosage within two weeks after the battery replacement surgery, when the patient had fully recovered.

We performed a systematic review of literature. The literature search was conducted via the PubMed database in April 2022 using the combination of the terms: “DBS-withdrawal

syndrome” and “Parkinson”. Forty-two matches were found. We reviewed titles, abstracts, and/or full texts and selected papers that accurately described cases of patients with DBS-withdrawal syndrome. We identified 8 relevant papers reporting on the cases of 15 patients. The excluded papers only referred to a general description of this syndrome and/or to the cases described in the princeps papers.

Pooling patients from the literature and from our experience, comparisons within and between groups were performed with a sample t-test. A two-sided p-value < 0.01 was considered statistically significant for within group comparisons and < 0.005 for between groups comparisons after Bonferroni corrections to take in account multiple comparisons. Statistical analyses were performed using JMP software JMP 9.0.1 (SAS Institute). Graphical plots were made with Prism 9.4.1 (GraphPad Software MacKiev).

3. Results

Eight patients from our hospital experienced a had to undergo a BRS (Table 1 and 2). Five of them presented to the emergency department or directly to our neurology department. For these 5 patients, parkinsonian symptoms were so severe that they were no longer able to walk on their own or even swallow. Despite a huge increase in levodopa intake (up to 3500mg/d), sometimes administered through a nasogastric tube (patients 2, 3 & 4) or even with levodopa/carbidopa intestinal gel (patient 4), there was no significant improvement of symptoms. However, their condition improved totally after BRS (they all clinically returned to their UPDRSIII and Hoehn & Yahr before battery removal, ON drug scores). More history on the 5 patients with the most severe symptoms is presented below and clinical/biological metrics are reported in Table 1.

Concerning the other 3 patients whose battery had to be removed for infection, no signs of severity were reported, and surgery could be performed after treatment of the infection (Table 2).

Cases list of patients requiring BRS with or without DBS-withdrawal syndrome and identified through the literature review are reported in Table 3.

We pooled our results with those of other cases reports (Table 4 and Figure 1). Although statistical tests should be interpreted with caution due to the small number of patients, it is interesting to note that some parameters seem to be discriminating between the two groups. The main differences between the two groups of patients concern disease duration (22 years \pm 5 vs 13 years \pm 6, $p < 0.001$) and DBS duration at the event 10 years \pm 4 vs 3 years \pm 2, $p < 0.001$). Differences in UPDRS III after battery removal, ON drug score (69 \pm 10 vs 14 \pm 10.02, $p < 0.001$), Hoehn & Yahr after battery removal, ON drug score (4 \pm 0 vs 2 \pm 0.58, $p = 0.019$) and increase in LED after battery removal (2217 mg/day \pm 1453 vs 1292 mg/day \pm 662, $p = 0.013$) account for the clinical severity in this DBS-withdrawal syndrome. A trend was found for age at the event (66 years \pm 8 vs 58 years \pm 9, $p = 0.007$), UPDRSIII OFF evaluated before initial DBS implantation (44 \pm 7 vs 30 \pm 6, $p = 0.022$) and CPK values (1555 UI/mL \pm 1348 vs 62 UI/mL \pm 3, $p = 0.006$).

Short history of our 5 patients experiencing DBS-withdrawal syndrome:

Patient 1. This 71-years-old male patient with atrial fibrillation and a 24-years of PD history, was admitted to the emergency department because of sudden onset of tremor of the right lower limb, rapidly followed in the next 24 hours by dysarthria and a resurgence of his parkinsonian syndrome. Despite administration of a significantly increased dose of dopamine (x4, up to 1200 mg/day), his motor condition was so severe that he was no longer able to walk on his own and

had to be hospitalized. Fortunately, food and medication could be maintained orally. No aspiration pneumonia occurred. His condition improved totally after replacement of the DBS battery.

Patient 2. This 68-years-old female patient with rheumatoid arthritis not requiring active treatment and a 20-years of PD history, was admitted to our department because she presented with abrupt resurgence of a severe parkinsonian syndrome with an important tremor. She was not able to move alone and to get out of her bed. A nasogastric tube was required to give her a higher dosage of levodopa that she usually took but this action did not lead to clinical improvement. No aspiration pneumonia occurred. She recovered totally after replacement of the DBS battery.

Patient 3. A 64-year-old female patient with orthostatic hypotension and a 26-years of PD history, was admitted to the emergency department after she woke up with a severe akinetic-rigid syndrome associated with polypnea, chest congestion and difficulty in coughing. She was diagnosed with aspiration pneumonia and required oxygen therapy. She was unable to move on her own from bed and had significant difficulty swallowing, necessitating nasogastric tube through which she was administered levodopa at a higher dose than she usually took. This action did not lead to clinical improvement. She recovered totally after replacement of the DBS battery and antibiotic treatment.

Patient 4. A 71-years-old male patient with past medical history of femur fracture from a ski accident, appendectomy during childhood, a stroke without sequelae, and a 25-year long diagnosis of PD, was hospitalized for the planned removal of the DBS battery because of local skin necrosis without patent infection. Indeed, due to significant weight loss, the friction of the

device led to pectoral skin necrosis which was visible. Within the next 24 hours following surgery, the patient could not move or talk. Neither a high dosage of levodopa administered via nasogastric tube nor subcutaneous apomorphine infusion could improve his motor condition. Because of the skin infection, placement of a new battery was not possible for 3 months. The decision was made to operate urgently to create a gastrojejunostomy in order to facilitate feeding and administer high dose of levodopa/carbidopa intestinal gel. Unfortunately, there was little improvement in the patient's symptoms who continued needing the assistance of two people to stand up and ambulate short distances. No aspiration pneumonia occurred. His condition improved completely following replacement of the DBS battery, but intensive rehabilitation for 3 months was necessary due to his prolonged confinement to bed.

Patient 5. This 54-years-old male patient with left shoulder dislocation in a car accident and a 24-years of PD history, was hospitalized for planned removal of the DBS battery reaching the end of its life. Two days prior to surgery, the patient presented with intense tremors and major rigidity of the limbs. While the patient was not usually taking dopaminergic treatment, he was administered a high dose orally in an unsuccessful attempt to reduce his symptoms. No aspiration pneumonia occurred. DBS battery replacement surgery resolved the patient's symptoms immediately. A sudden battery shutdown while at home could potentially turn into a life-threatening emergency for this patient. For this reason, his battery life has been since closely monitored in order to avoid an unexpected shutdown.

4. Discussion

4.1 Risk-factors for the DBS-withdrawal syndrome.

Few cases of DBS-withdrawal syndrome in PD have been reported in the literature^{6 7 8 9 10 11 12 13} (Table 3). Compiled with patients' clinical data from our experience, we were able to highlight several interesting common points:

1/ The rapid onset (sudden or < 72 hours) of a severe parkinsonian syndrome affecting autonomy⁸.

2/ The life-threatening risk related to fever, swallowing disorders (that may be responsible for aspiration pneumonia) and to rhabdomyolysis because of severe tremor and rigidity or prolonged immobility^{6 7 15}. However, in our case series, CPK elevation was not high enough to cause metabolic disorders such as renal failure or dyskalemia due to a rapid monitoring and intervention.

3/ The low efficacy of levodopa in these patients despite a significant increase in the administered dosage of dopamine. Of note, in all patients, the usual dopamine needs were quite low (from 0 to 900 mg/d, mean 489 mg/d \pm 267) when DBS was active.

4/ The mean age of the patients at the time of battery discontinuation was 66 \pm 8 years-old, most of them had more than 11 years of disease history, and more than 5 years of DBS history. Analysis of these patients' clinical records revealed that before DBS implantation, their parkinsonian syndrome in OFF-drug was already severe. Nevertheless, there was significant improvement in parkinsonian symptoms following the administration of dopamine at that time.

5/ The BRS enabled a marked improvement of the symptoms suggesting a specific effect of the DBS in stark contrast with the refractoriness to dopaminergic medication.

Then, the identified potential risk factors to experience a DBS-withdrawal syndrome seems to be:

1/ a long disease duration (mostly >11 years ; mean > 21 years) and,

2/ a long DBD therapy (mostly > 5 years ; mean > 10 years).

Additional risk factors may include later age at explantation and advanced symptoms at the time of initial surgery (evaluated by UPDRS-III before the first DBS implantation).

4.2 What might be the underlying pathophysiology?

In several studies investigating dopamine responsiveness in DBS patients, the percentage improvement of UPDRS-III scores after levodopa intake was approximately 68% at baseline, 60% at 1 year, 45% at 5 years and 37% at 9 years^{16 17}. This decrease may be attributed, at least in part, to decreased dopaminergic receptor sensitivity over the years related to chronic reduction in levodopa intake¹⁸ and to disease progression¹⁹.

When experiencing DBS-withdrawal syndrome, patients show severe symptoms with no responsiveness to levodopa contrasting with a return to their previous state after the BRS suggesting a specific effect of chronic DBS^{8 13}. It is known that DBS helps control motor condition in the long term but its independent effect from dopamine may be raised.

First, Castrioto et al. reported a significant improvement in UPDRS-III scores assessed by a rater who was blinded as to whether the DBS was ON or OFF in 18 patients who had received DBS for 10 years²⁰.

Then, as hypothesized by Reuter et al.¹³, because of the elimination of dopaminergic dendritic spines of the striatal projection neurons within the putamen²¹, the cortical-basal ganglia loop might lose its cortical input, and the flow is disturbed at the front door of the basal ganglia loop. STN-DBS may act on the thalamic-basal ganglia loop regardless as it interferes with

information flow downstream from the lesioned putamen. The observed low responsiveness to dopamine and preserved responsiveness to STN-DBS might thus be explained.

A complementary hypothesis might be the role of the reemergent beta oscillations but also a higher alpha-band activity after cessation of DBS stimulation. Indeed, it was reported that the degree of neuronal beta oscillatory activity (13–30 Hz) in STN was related to the magnitude of response of the basal ganglia to dopaminergic agents^{22 23}. DBS in STN disrupts this oscillatory activity leading to an immediate improvement of PD symptoms²⁴. After 3 and even 5 years of chronic DBS, there were no increases in STN beta-band dynamics evaluated 1 hour after turning OFF DBS activity but there were increases in alpha-band (8-12 Hz) dynamics²⁵.

Unlike beta band activity, the role of alpha band activity within the STN and its relation to the cortex is not well characterized. Nevertheless, several studies have shown correlations between STN activities in a combined alpha-beta band and motor impairment^{26 27} or axial symptoms²⁸. In one study it was demonstrated that stimulating the STN in PD patients at 10Hz, deteriorated motor symptoms. One might speculate whether stimulation of the STN at 10 Hz aggravates a pathological synchronization in the neuronal oscillatory network of motor areas leading to further dysfunction of the premotor cortex and medial wall motor areas. A dysfunction of these areas could lead to a stimulation-induced deterioration in motor symptoms²⁹.

Also, it has been shown that the alpha frequency band coherence between temporal cortical areas and the STN is reduced following movement onset and that the degree of suppression in alpha coherence is significantly greater ON than OFF dopaminergic medication. In contrast, alpha power was suppressed up to two seconds before movement and this was unaffected by dopaminergic medication³⁰. Then, on the contrary to beta oscillatory activity, intake of dopamine may only partially change alpha dynamics^{30 31}.

Therefore, we hypothesize that continuous STN stimulation may induce plastic neuronal changes that lead to decreased dopamine sensitivity and severe bradykinesia through the simultaneous occurrence of an alpha and high-beta synchronized state ²⁷. If the DBS is turned OFF after many years of constant stimulation, there may be a reemergence of beta oscillations but also a higher alpha-band activity, the latter of which is likely unresponsive to dopamine. This combined with decreased dopamine sensitivity caused by cell loss related to disease duration ¹⁹ and of chronic reduction in levodopa intake ¹⁸ conceivably contribute to the arousal of severe parkinsonian symptoms which can only be improved by neurostimulation.

The commercial availability of systems which can record beta band and alpha frequency in the STN ³² may contribute to validate this hypothesis once patients have had sufficient years of post-operative evolution.

4.3 What then could be the appropriate approach to avoid and manage such a situation?

Apart from an emergency where the DBS must be removed, for example due to a hardware infection, routine follow-up of patients allows clinicians to identify DBS batteries approaching the end of life and appropriately schedule their replacement as an elective surgery. However, attention must be paid to avoid any unexpected interruption of neurostimulation, for example due to a very sharp drop in the battery's capacity. It is thus necessary to systematically plan the BRS well before its alert threshold.

In patients with risk factors for DBS-withdrawal syndrome, Helmers et al.³³ discussed the possibility of removing an infected battery and cables with contralateral replacement in the same session to avoid a DBS-withdrawal syndrome. None of the 6 patients in this study experienced acute parkinsonism deterioration.

The current COVID pandemic situation, during which many surgeries have been canceled and then rescheduled, has revealed the need to reconsider the importance of certain surgeries that are usually considered elective. A sudden battery exhaustion event poses a life-threatening risk to the patient. The DBS battery must be replaced as soon as possible³⁴ and actually treated as a surgical emergency. An admission for clinical monitoring is recommended. Levodopa responsiveness must be carried out so as to not ignore residual benefit of increased dopaminergic treatment while awaiting the BRS.

Rechargeable batteries are of interest as they can reduce the number of surgeries performed. However, patients and their caretakers must exercise caution as to not forget equipment necessary to recharge the battery, for example while traveling.

Due to the high-cost of equipment and surgery, the replacement of a neurostimulation generator may not be done easily in many countries. Thus, it is important to consider that stereotactic lesions, such as pallidotomy, may be proposed to the patient. Indeed, pallidotomy for PD is considered as evidence based and efficient in advanced PD³⁵. Aside from being a relatively inexpensive procedure³⁶, it can be quite effective in breaking the vicious circle of sudden parkinsonian crisis as well as dystonic crisis, stemming from abrupt cessation of chronic DBS, or for any other reason^{37,38}.

Finally, concerning the case of an elderly patient, who is bedridden, wheelchair-bound and has cognitive impairment, one may wonder whether it is appropriate to replace the DBS battery which is reaching the end of its life. If possible, a hospitalization should be proposed to turn off the battery and evaluate the patients' dependence on DBS during the next 24-48 hours. Here also, or in case of infections that require total removal of the stimulation hardware without immediate re-implantation possibility, unilateral pallidotomy has been proposed as an emergent surgery to reduce severe dystonia with success³⁸.

5. Conclusion

Despite regular verification of DBS battery and careful planning of replacement, some patients may still experience a sudden stop of battery and suffer from a DBS-withdrawal syndrome. A long disease duration and several years of DBS therapy are identified as the main potential risk factors. These patients experience a rapid life threatening clinical deterioration refractory to treatment with high dose of levodopa. In the context of the current COVID pandemic, where many surgeries considered to be low priority (such as planned BRS) are rescheduled, it is important to widely communicate that replacement of DBS batteries approaching the end of life or more importantly those that have stopped, should be performed as an emergent surgery.

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Table 1. Patients' characteristics from our experience with DBS-withdrawal syndrome

	Patient 1 (M)	Patient 2 (F)	Patient 3 (F)	Patient 4 (M)	Patient 5 (M)	Mean	SD	p (comparison before and after battery removal)
Age at the event (years)	71	68	64	71	54	66	7	/
Disease duration at the event (years)	24	20	26	25	24	24	2	/
DBS duration at the event (years)	12	3	15	20	16	13	6	/
DBS parameters before battery removal	L. STN 7- / 2.6V / 60 μ s / 145 Hz	L. STN 11- / 2.9 V / 60 μ s / 180 Hz	L. STN 6- / 3.3 V / 60 μ s / 130 Hz	L. STN 10- / 2.8 V / 60 μ s / 130 Hz	L. STN alternating 6- & 7- / 4 V / 60 μ s / 150 Hz	/	/	/
	R. STN 3- / 2.6V / 60 μ s / 145 Hz	R. STN 3- / 3.0 V / 60 μ s / 180 Hz	R. STN 2- / 3.3 V / 60 μ s / 130 Hz	R. STN 2- / 2.8 V / 60 μ s / 130 Hz	R. STN 2- / 3.2 V / 60 μ s / 150 Hz	/	/	/
DBS parameters after replacement surgery	L. STN 7- / 2.4V / 60 μ s / 145 Hz	L. STN 11- / 2.6 V / 60 μ s / 180 Hz	L. STN 6- / 3.0 V / 60 μ s / 130 Hz	L. STN 10- / 2.7 V / 60 μ s / 130 Hz	L. STN alternating 6- & 7- / 3.6 V / 60 μ s / 150 Hz	/	/	/
	R. STN 3- / 2.4V / 60 μ s / 145 Hz	R. STN 3- / 2.9 V / 60 μ s / 180 Hz	R. STN 2- / 3.0 V / 60 μ s / 130 Hz	R. STN 2- / 2.7 V / 60 μ s / 130 Hz	R. STN 2- / 3.0 V / 60 μ s / 150 Hz	/	/	/
Duration (days) between battery exhaustion and replacement surgery	11	20	4	80	2	23	32	/
UPDRSIII before initial DBS implantation, OFF drug	38	52	41	43	36	42	6	/

UPDRSIII before initial DBS implantation, ON drug	14	24	18	18	4	16	7	/
UPDRS III after battery removal, ON drug	52	72	78	76	68	69	10	0,000*
UPDRS III before battery removal, ON drug	2	20	10	37	10	16	13	
% of aggravation after battery removal	2500	260	680	105	580	825	965	/
Hoehn & Yahr after battery removal, ON drug	4	4	4	4	4	4	0	0,000*
Hoehn & Yahr before battery removal, ON drug	1	2	1,5	2,5	1	1,6	0,7	
Levodopa Equivalent Dose (LED) after battery removal	1275	1000	1200	3500	800	1555	1103	0,045
Levodopa Equivalent Dose (LED) before battery removal	300	300	400	760	0	352	273	
% of increase in LED when battery was removed	325	233	200	361	80000	1622 4	3565 2	/
CPK (UI/mL) after battery removal	NK	989	115	346	NK	483	453	0,117
CPK (UI/mL) before battery removal	NK	90	13	24	131	65	56	
% of increase of CPK after battery removal	/	999	785	1342	/	1042	281	/

CPK: Creatine PhosphoKinase; DBS: Deep Brain Stimulation; NK: Not Known; UPDRS : Unified Parkinson Disease Rating Scale

*survive after multiple comparisons

Table 2. Patients' characteristics from our experience without DBS-withdrawal syndrome

	Patient 7 (M)	Patient 8 (F)	Patient 9 (M)	Mean	SD	p (comparison before and after battery removal)	p (comparison between the 5 most severe patients vs the 3 undisturbed patients)
Age at the event (years)	49	57	54	53	4	/	0.021
Disease duration at the event (years)	9	14	9	11	3	/	0.003*
DBS duration at the event (years)	3	5	1	3	2	/	0.020
DBS parameters before battery removal	L. STN 11- / 2.5 V / 60 μ s / 130 Hz	L. STN 10- / 2.0 V / 60 μ s / 130 Hz	L. STN 10- / 2.5 V / 60 μ s / 150 Hz	/	/	/	/
	R. STN 2- / 2.5 V / 60 μ s / 130 Hz	R. STN 3- / 2.0 V / 60 μ s / 130 Hz	R. STN 2- / 1.3 V / 60 μ s / 150 Hz	/	/	/	/
DBS parameters after replacement surgery	L. STN 11- / 2.3 V / 60 μ s / 130 Hz	/	L. STN 10- / 2.7 V / 60 μ s / 130 Hz	/	/	/	/
	R. STN 2- / 2.3 V / 60 μ s / 130 Hz	/	R. STN 2- / 2.7 V / 60 μ s / 130 Hz	/	/	/	/

Short clinical history	Medical history: high blood pressure. Prompt scheduling for removal of the DBS battery because of hardware infection. When the device was removed, parkinsonism worsened but the adaptation of the oral treatments improved the patient's discomfort. Re-implantation was delayed because of the initial patient refusal to be re-operated.	Medical history: wrist fracture. Prompt scheduling for removal of the DBS battery because of severe hardware infection. When the device was removed, parkinsonism worsened but the adaptation of the oral treatments improved the patient's discomfort. Nevertheless, onset of regular peak dose dyskinesias. After a long period of antibiotic treatment, the patient didn't want to be re-operated because oral treatments relieved her symptoms.	Medical history: high blood pressure. Prompt scheduling for removal of the DBS battery because of hardware infection. When the device was removed, parkinsonism worsened but the adaptation of the oral treatments improved the patient's discomfort.	/	/	/	/
Duration (days) between battery exhaustion and replacement surgery	1095	/	289	692	570	/	0.345
UPDRSIII before initial DBS implantation, OFF drug	35	23	33	30	6	/	0.063
UPDRSIII before initial DBS implantation, ON drug	6	1	1	3	3	/	0.094
UPDRS III after battery removal, ON drug	10	6	25	14	10	0,279	0.001*

UPDRS III before battery removal, ON drug	4	2	11	6	5		0,266
% of aggravation after battery removal	150	200	127	159	37	/	/
Hoehn & Yahr after battery removal, ON drug	2	1	2	2	1	0,101	0.019
Hoehn & Yahr before battery removal, ON drug	0	1	1	1	1		0.999
Levodopa Equivalent Dose (LED) after battery removal	800	660	1565	1008	487	0,082	0.374
Levodopa Equivalent Dose (LED) before battery removal	250	450	330	343	101		0.951
% of increase in LED when battery was removed	220	47	374	214	164	/	/
CPK (UI/mL) after battery removal	NK	60	64	62	3	0,440	0.248
CPK (UI/mL) before battery removal	NK	62	49	56	9		0.974
% of increase of CPK after battery removal	NK	-3	31	14	24	/	/

CPK: Creatine PhosphoKinase; DBS: Deep Brain Stimulation; NK: Not Known; UPDRS : Unified Parkinson Disease Rating Scale
 *survive after multiple comparisons

Table 3. Patients' characteristics from the literature with and without DBS-withdrawal syndrome

Author	Article title	age at the event (years)	gender	Disease duration at the event (years)	DBS duration at the event (years)	UPDRSIII before initial DBS implantation, OFF drug	LED before battery removal (mg/d)	LED after battery removal (mg/d)	CPK (UI/mL)	Other	cause of DBS failure	DBS restoration	Outcome
Patients with DBS-withdrawal syndrome													
Neuneier et al., 2013 ⁶	Malignant deep brain stimulation-withdrawal syndrome in a patient with Parkinson's disease	77	M	22	9	43	150	1000	?	/	battery depletion	Late IPG reimplantation	death
Rajan et al., 2016 ⁷	Malignant Subthalamic Nucleus-Deep Brain Stimulation Withdrawal Syndrome in Parkinson's Disease	51	M	11	7	35	310	2150	4380 μ /L	fever	battery depletion	Battery was replaced	recovery
		54	F	?	11	45	?	1800	606 μ /L	/	battery depletion	Battery was replaced	recovery
Reuter et al., 2015 ¹³	Uncoupling of dopaminergic and subthalamic stimulation: Life-threatening DBS withdrawal syndrome	75	M	19	9	38	550	4800	?	/	battery infection	battery was not reimplanted	death
		74	M	24	10	58	800	2188	?	/	battery infection	battery was not reimplanted	death

		52	M	20	8	41	250	976	?	/	battery infection	battery was reimplanted	recovery
Azar et al., 2019 ⁹	Malignant deep brain stimulator withdrawal syndrome	67	F	23	7	?	?	?	1615 U/L	fever	battery depletion	Battery was replaced	recovery
Joyce Liu et al., 2017 ¹⁰	Whether to Proceed With Deep Brain Stimulator Battery Change in a Patient With Signs of Potential Sepsis and Parkinson Hyperpyrexia Syndrome: A Case Report	69	M	16	9	?	800	1000	1250 IU/L	fever	battery depletion	Battery was replaced	recovery
Artusi et al., 2015 ¹¹	Parkinsonism-hyperpyrexia syndrome and deep brain stimulation	63	M	18	5	?	900	?	2820 U/L	fever	battery depletion	Battery was replaced	recovery
Kadowaki et al., 2011 ¹²	Case Report: Recurrent Parkinsonism-Hyperpyrexia Syndrome Following Discontinuation of Subthalamic Deep Brain Stimulation	60	M	17	8	54	?	?	1878 U/L	fever	tuned OFF because of manic symptoms	low voltage stimulation was applied	recovery

Reuter et al.,2018 ⁸	Life-threatening DBS withdrawal syndrome in Parkinson's disease can be treated with early reimplantation	77	M	19	4	?	532	5424	?	/	battery infection	Battery was replaced	recovery
		62	M	26	13	?	468	2880	?	/	battery infection	Battery was replaced	recovery
		71	M	37	15	?	823	4186	?	/	infection of the electrode lead at the level of the burr hole	Battery and electrodes were replaced	recovery
		68	M	23	10	?	666	1350	?	/	battery infection	Battery was replaced	recovery
		67	M	18	15	?	300	2161	?	/	battery infection	Battery was replaced	recovery
Patients without DBS-withdrawal syndrome													
Reuter et al.,2015 ¹³	Uncoupling of dopaminergic and subthalamic stimulation: Life-	48	F	12	1	?	300	175	/	/	battery infection	/	/
		51	M	15	4	?	300	1400	/	/	battery infection	/	/

threatening DBS withdrawal syndrome	66	M	9	0	?	700	1600	/	/	battery infection	/	/
	65	M	27	5	?	0	1660	/	/	battery infection	/	/
	53	M	8	0	?	650	1700	/	/	battery infection	/	/
	57	F	13	1	?	350	1800	/	/	battery infection	/	/
	43	F	6	1	?	225	675	/	/	battery infection	/	/
	69	M	26	4	?	300	1200	/	/	battery infection	/	/
	52	M	15	1	?	450	625	/	/	battery infection	/	/
	59	F	9	3	?	1000	2925	/	/	battery infection	/	/
	68	F	19	1	?	800	1325	/	/	battery infection	/	/
	77	M	8	8	?	850	1250	/	/	battery infection	/	/

CPK: Creatine PhosphoKinase; DBS: Deep Brain Stimulation; LED: Levodopa Equivalent Dose ; UPDRS : Unified Parkinson Disease Rating Scale

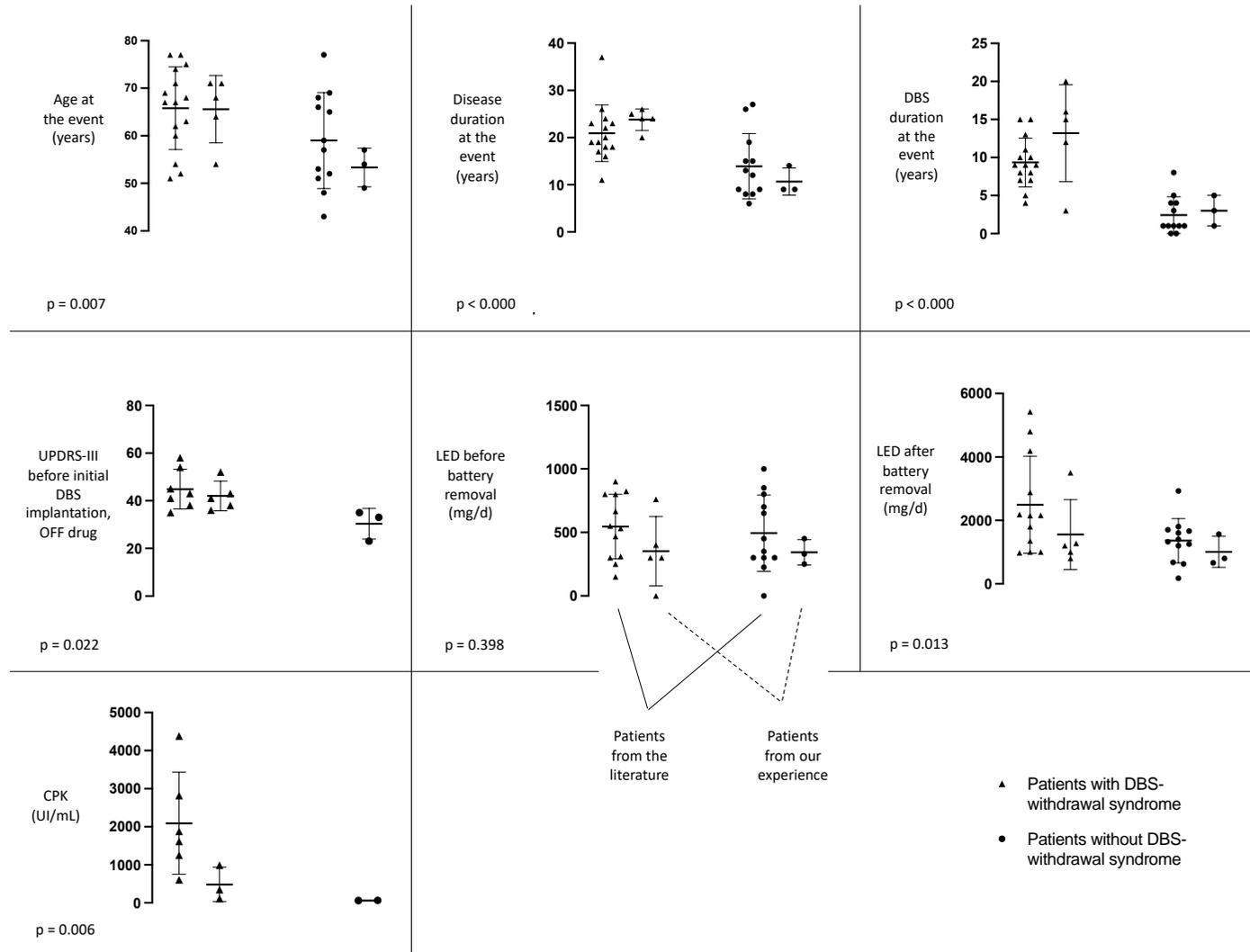
Table 4. Comparison of the characteristics concerning both patients from literature and from our experience with and without DBS-withdrawal syndrome

		age at the event (years)	Disease duration at the event (years)	DBS duration at the event (years)	UPDRSIII before initial DBS implantation, OFF drug	LED before battery removal (mg/d)	LED after battery removal (mg/d)	CPK (UI/mL)
Patients with DBS- withdrawal syndrome N = 20	mean	66	22	10	44	489	2217	1555
	SD	8	5	4	7	267	1453	1348
Patients without DBS- withdrawal syndrome N = 15	mean	58	13	3	30	464	1291	62
	SD	9	6	2	6	276	662	3
p		0,007	0,000*	0,000*	0,022	0,398	0,013	0,006

CPK: Creatine PhosphoKinase; DBS: Deep Brain Stimulation; LED: Levodopa Equivalent Dose ; UPDRS : Unified Parkinson Disease Rating Scale

*Survive after multiple comparisons

Figure 1. Distribution of patients with and without DBS-withdrawal syndrome depending on their clinical characteristics



CPK: Creatine PhosphoKinase; DBS: Deep Brain Stimulation; LED: Levodopa Equivalent Dose ; UPDRS : Unified Parkinson Disease Rating Scale