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Deep Brain Stimulation Withdrawal Syndrome, a Rare Life-Threatening Condition in Neurology and Neurosurgery

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Abstract

The article addresses an acute condition associated with an abrupt cessation of neurostimulation of deep brain structures, which is manifested by acute hypokinesia and rigidity with further development of akinesia, anarthria and dysphagia. This may result in the need for emergency hospitalization and admission to an intensive care unit. The article presents literature review and clinical case reports. We discuss causes and approaches to the prevention and management of acute decompensation in patients with Parkinson's disease associated with abrupt deep brain stimulation cessation.

Keywords: *neurostimulation of deep brain structures; Parkinson's disease; akinesia; parkinsonian hyperpyrexia syndrome; malignant neuroleptic syndrome; withdrawal syndrome; deep brain stimulation*

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Синдром отмены нейростимуляции у пациентов с болезнью Паркинсона – редкое неотложное состояние в неврологии и нейрохирургии

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Аннотация

Статья посвящена острому состоянию, связанному с внезапным прекращением стимуляции глубоких структур головного мозга, которое проявляется резким нарастанием гипокинезии и ригидности с развитием обездвиженности, анартрии и нарушений глотания, в результате чего пациенты могут быть экстренно госпитализированы, в том числе в отделение реанимации. Представлены обзор литературы и клинические наблюдения. Обсуждаются причины, пути профилактики и способы коррекции острой декомпенсации состояния у пациентов с болезнью Паркинсона, связанной с внезапным прекращением глубокой стимуляции мозга.

Ключевые слова: *нейростимуляция глубоких структур головного мозга; болезнь Паркинсона; акинетический криз; синдром паркинсонизма-гиперпирексии; злокачественный нейролептический синдром; синдром отмены; deep brain stimulation*

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Introduction

The deep brain stimulation (DBS) technique has a long history of success in treating complications of long-term dopamine replacement therapy (DRT) and tremor in patients with Parkinson's disease (PD) [1].

Patients with advanced PD may develop acute worsening of the condition with rapidly progressing hypokinesia and rigidity, immobility, anarthria, dysphagia (akinetic crisis, acute akinesia), in some cases accompanied by hyperthermia (akinetic-hyperthermic syndrome, parkinsonian hyperpyrexia syndrome). The main cause is errors in antiparkinsonian medication regimen. Dopamine receptor-blocking agents, gastrointestinal diseases, COVID-19, hospitalization due to exacerbation of concomitant diseases, traumas, surgery, especially accompanied by electrolyte disorders, can also cause decompensation in PD patients [2, 3].

Acute decompensation associated with withdrawal or excessively reduced doses of antiparkinsonian agents, perioperatively or during selection of the primary neurostimulation options, was described in patients who underwent DBS surgery [4–9]. At the same time, effective DBS without reducing high doses of antiparkinsonian agents can also be accompanied by decompensation triggered by abrupt tapering or stopping dopaminergic agents [10, 11].

However, with an increasing number of operated patients worldwide, the main challenge is acute DBS discontinuation, which can be potentially life-threatening [12]. The first two clinical case reports of unintentional unilateral DBS hardware turn-off resulted in severe parkinsonism syndrome close to akinesia were presented by M.I. Hariz et al. in 2001 [13]. Already with their first experience in DBS technique, the authors noticed that abrupt withdrawal of effective stimulation of subthalamic nucleus (STN-DBS) resulted in an emergency requiring immediate hospitalization of the patient. Subsequently, a number of clinical case reports on various causes of implantable pulse generator (IPG) failure have been published.

Discontinuation of effective DBS, as well as withdrawal of antiparkinsonian medication, will always cause an increase in the severity of motor impairment in PD patients, but it does not always cause severe DBS withdrawal syndrome (DBS-WDS).

DBS-WDS is regarded as a rare condition, although there is currently no data available regarding its actual incidence. S. Reuter et al. report the following data: 8 cases of DBS-WDS per 434 DBS implantations between 1999 and 2014 and 216 IPG changes between 2008 and 2015 [14]. M. Anheim et al. observed 10 clinical cases over the period of 13 years, in which patients exhibited severe worsening in PD symptoms following the IPG battery depletion [15]. K. Fakhar et al. reported symptom improvement in 38 patients from a cohort of 320 patients (including 131 patients with PD) who underwent IPG battery replacement between 2002 and 2012 [16]. A.K. Helmers et al. presented results for 6 patients with a high risk of DBS-WDS who were followed up over a period of 2017–2020 [17].

Some studies used stimulation OFF mode (STIM OFF) on purpose to evaluate the results of PD treatment in patients with DBS, but it did not lead to severe decompensation.[18] In one of the key studies, M. Fabbri et al. analyzed the effects of STN-DBS in patients with late-stage PD (Hoehn Yahr score $\geqslant 4$ and Schwab and England score $< 50\%$) [19]. The DBS was switched off with subsequent assessment of the motor impairment severity. Most of the patients did not experience serious adverse events, but the DBS response was significant in 80% of patients; 5% could not tolerate the DBS OFF mode for more than 10 min because of the pronounced discomfort and worsening of parkinsonism. In 4 (11%) patients, stimulation was switched

back on because of delayed worsening of their condition (up to 10 days). In total, 92% of patients show a meaningful response to STN-DBS and only 3 (8%) patients remained with STIM OFF with no symptoms of DBS-WDS [20].

We searched the PubMed database for "parkinsonism-hyperpyrexia syndrome after DBS", "neuroleptic malignant syndrome after DBS", and "deep brain stimulation withdrawal syndrome". We then selected articles that provided comprehensive clinical observations of severe decompensation following the abrupt cessation of neurostimulation, necessitating hospitalization and intensive care [11, 14, 21–32]. Fourteen articles describing 27 clinical cases are presented in Table 1.

In the majority of the described clinical cases, this condition was caused by IPG battery depletion, infection in the area

Table 1. Published cases of severe DBS withdrawal syndrome (WDS)

No.	Author, year	Age, years	PD duration/DBS duration, years	Reasons for stimulation discontinuation	Hyperthermia/ hyperpyrexia	Reimplantation	Outcome
1	K. Chou et al., 2004 [21]	63	17/4	Depletion of IPG on one side	No	Yes	Alive
		76	17/3		No	Yes	Alive
2	T. Kadowaki et al., 2011 [22]	60	11/2	Switch-off of the stimulator due to mental disorders	Yes	IPG was not removed, low-frequency mode	Alive
3	J. Neuneier et al., 2013 [23]	77	18/5	Depletion of IPG	Yes	Yes	Died
4	S. Hocker et al., 2013 [24]	74	–/4	Switch-off of the stimulator	Yes	No	Alive
5	C.A. Artusi et al., 2015 [25]	63	18/5	Depletion of IPG	Yes	Yes	Alive
6	S. Reuter et al., 2015 [26]	52	20/8	IPG removal due to infection	No	Yes	Alive
		74	24/10		No	Нет I No	Died
		75	19/9		Yes	Нет I No	Died
7	R. Rajan et al., 2016 [27]	51	18 /7	Depletion of IPG	Yes	Yes	Alive
		54	22 /11		No	Yes	Alive
8	C.J. Liu et al. 2017 [28]	69	12/3	Depletion of IPG	Yes	Yes	Alive
9	S. Reuter et al., 2018 [14]	77	19/4	IPG removal due to infection	No	Yes, in 23 days (range 3–45 days)	Alive
		62	26/13		No		Alive
		71	37/15		No		Alive
		68	23/10		No		Alive
		67	18/15		No		Alive
10	J. Azar et al., 2019 [29]	67	23/7	Depletion of IPG	Yes	Yes	Alive
11	W.A. Kamel et al., 2019 [30]	73	21/12	Depletion of IPG	No	Yes	Alive
12	V. Holla et al., 2020 [31]	67	17/4	Depletion of IPG	No	Yes	Alive
		60	17/4		No	Yes	Alive
13	J. Azar et al., 2022 [11]	76	14/9	Depletion of IPG	Yes	Yes	Alive
14	S. Grimaldi et al., 2023 [32]	71	24/12	Depletion of IPG	No	Yes	Alive
		68	20/3	Depletion of IPG	No	Yes	Alive
		64	26/15	Depletion of IPG	No	Yes	Alive
		71	25/20	IPG removal due to infection	No	Yes, in 80 days	Alive
		54	24/16	Depletion of IPG	No	Yes	Alive

Table 2. Characteristics of patients with severe DBS WDS (own data)

No.	Age, years; sex	Duration of PD/duration of DBS, years	DBS target	LED before DBS/ LED DBS, mg	Hyperthermia/ hyperpyrexia	Reimplantation	Outcome
1	56; male	19/8	STN	2450/1750	Yes	Yes	Died
2	60; male	22/3	GPi	1700/1050	No	Yes	Alive
3	63; male	19/7	(DBS in other center)	No data available	Yes	No	Died
4	65; female	13/5	STN	5450/950	Yes	No	Died
5	67; female	17/4,5	STN	850/850	Yes	No	Died
6	63; male	17/4	STN	1250/525	No data available	No	Died

Note. LED — levodopa equivalent dose.

of DBS hardware that required removal of its components, and accidental turn off of the neurostimulator. In all of the described clinical cases, the patients were treated with STN-DBS. With the advent of rechargeable neurostimulation systems, DBS-WDS can also be caused by untimely IPG battery charging or malfunction of the charger.

In this article, we report 6 clinical cases of PD patients with severe DBS-WDS accompanied by impaired vital functions with various outcomes. The general characteristics of the patients are presented in Table 2. In all of these cases, WDS was triggered by IPG battery depletion.

Outpatient cases of neurostimulation discontinuation with growing severity of parkinsonism syndrome without vital disorders were observed significantly more often. These cases were caused by accidental turn off of the neurostimulator by the patient or caregiver, depletion of IPG battery, malfunction of the charger causing IPG battery drain, or DBS hardware infection with subsequent removal of the neurostimulator. In most cases, short-term or long-term DBS discontinuation caused no vital disorders and was not included into this study.

Only two patients with acute DBS-WDS were treated in the Burdenko National Medical Research Center for Neurosurgery. They underwent urgent IPG replacement (clinical cases 1 and 2). One patient (clinical case 3) was followed up by the specialists of the Neurology Department at the Russian Medical Academy of Continuous Professional Education. The patient was admitted to the Botkin State Clinical Hospital, and the DBS hardware was implanted in another medical facility. These 3 clinical cases are described below.

Clinical case 1

Patient aged 56 years had been suffering from PD for 19 years. He had been receiving levodopa for 13 years. Eight years after the treatment initiation, at the peak of levodopa action, violent movements appeared, which were accompanied by a gradual decrease in the time of drug action. Further, during 2 years at the start of levodopa action, the patient had painful leg dystonia and trunk muscle pain in the OFF-period. Eleven years after the onset of motor disorders, a bilateral STN-DBS system was implanted at the Burdenko National Medical Research Center for Neurosurgery. With the start of neurostimulation, a significant decrease in the severity of parkinsonism syndrome was observed throughout the entire follow-up period. After 4.5 years, the first scheduled IPG replacement was performed.

The patient was admitted to the Burdenko National Medical Center of Neurosurgery on an emergency basis. As reported by the patient's wife, the patient's motor status, speech disorders (dysarthria), dysphagia, and consciousness decline occurred within two days of complete discharge and turning off the neurostimulator. Additionally, the patient exhibited hyperthermia. Due to dysphagia, the patient practically did not take any water, food or antiparkinsonian drugs.

With acute akinesia symptoms, the patient was admitted to an intensive care unit (ICU). Levodopa/carbidopa administration via nasogastric tube was initiated at a dosage of 250/50 mg every 4 hours (6 times per day). Due to an emergency, the subcutaneous pulse generator was replaced on the admission day. The DBS was set with the previous parameters. Further, despite infusion of antibacterial agents, inotropic support, and resumed DBS, the symptoms of consciousness decline and motor disorders persisted. Rhabdomyolysis with rhabdomyolysis-induced acute kidney injury, secondary somatic (bilateral pneumonia, urinary tract infection, sepsis) and neurological (hypoxic encephalopathy) complications were diagnosed. Brain MRI revealed multiple new ischemic foci in the deep parts of the cerebral hemispheres. Once the patient's condition had stabilized on day 44 of the treatment, he was referred for further therapy and rehabilitation to the hospital at the place of residence, where he died within a month.

Clinical case 2

Patient aged 60 years has been ill for 22 years. PD was diagnosed five years after the onset of motor disorders (tremor) and a treatment was prescribed. Five years after the PD diagnosis, levodopa was introduced as an additional treatment. The levodopa wearing-off was associated with the gradual progression of motor fluctuations and dyskinesia, and further

with patient's falls. 14 years after the diagnosis was established, bilateral implantation of DBS system in the internal segment of the globus pallidus (GPi) resulted in motor symptom improvement and a decrease in motor fluctuations and dyskinesia. Walking disorders with propulsive gait and rare falls remained.

After 3 years of effective GPi neurostimulation, an acute increase in the severity of parkinsonism syndrome, pronounced stiffness, immobility, speech and swallowing disorders were noted. The patient was admitted to a city hospital, then transferred to an ICU, where IPG battery depletion and cessation of stimulation were detected. Levodopa/carbidopa administration via nasogastric tube at a dosage of 250/50 mg every 3 hours was initiated.

The patient was transferred to the Burdenko National Medical Center of Neurosurgery on day 5 after cessation of neurostimulation. On the day of admission the subcutaneous IPG was replaced. As neurostimulation was resumed, the severity of bradykinesia decreased, motor activity and speech improved, independent swallowing/feeding restored. On the following day, the patient was placed in a vertical position. Two days later, his motor activity returned to normal, and antiparkinsonian medication was restarted at the previously administered doses. The patient was discharged on day 6 in satisfactory condition with full recovery of neurological status and daily activity.

Clinical case 3

Patient aged 63 years, duration of PD 19 years. Motor fluctuations and drug-induced dyskinesia gradually progressed. 11 years after the disease onset bilateral STN-DBS system was implanted with positive effect. Further, according to the relatives, the patient neither consulted neurologists, nor came for correction of neurostimulation parameters, nor controlled the IPG battery charge level. However, he constantly took antiparkinsonian agents (levodopa/carbidopa at the dose of 250/50 mg, 1/2 tablets 5 times a day).

The patient was admitted to the intensive care unit (ICU) of Botkin State Clinical Hospital three days after the stimulator was turned off. At the time of admission, the patient was in a severe condition, presenting with hyperthermia, immobility, and dysphagia. Despite the administration of therapeutic measures, the patient continued to experience hyperthermia. Additionally, the patient developed acute renal failure, and four days after admission, the patient died from multi-organ failure. Due to the extremely severe condition of the patient, IPG replacement was not considered.

Clinical cases 4–6

Three patients were treated at their place of residence, and their data were obtained from their relatives. Two of them died in the acute period of DBS-WDS (clinical cases 4 and 5).

In patient 5, rechargeable neurostimulator failure occurred 4.5 years after surgery. The cause of the malfunction remained unidentified. The patient died on day 3 after admission to the hospital at her place of residence.

Patient 6 was admitted to an ICU at his place of residence. He survived the acute period. After a long period of conservative treatment, the patient was discharged with severe motor and cognitive impairment. The relatives refused to replace the IPG. Much later, the patient died at the place of residence in a state of severe disability.

In case of acute parkinsonism in a patient with DBS, other predisposing factors and triggers must be ruled out!

Dopamine replacement therapy-induced acute parkinsonism

- **Termination/change of DBS**
- **Therapy tapering (dose reduction) or abrupt discontinuation:**
  - suboptimal treatment adherence;
  - mental disorders (mental confusion, hallucinations);
  - severe dyskinesia;
  - post-operative period
- **Malabsorption:**
  - gastrointestinal disorders (severe constipation, intestinal obstruction)
- **Additional therapy with dopamine blockers (haloperidol, pimozide, sulpiride, etc.)**

Not related to dopamine replacement therapy

- Aggravating factors;
- Infection;
- Trauma;
- Subdural haematoma (if the condition worsening is preceded by a fall);
- Stress;
- Dehydration;
- Excessively hot weather

Fig. 1. Factors leading to acute decompensation in Parkinson's disease patients receiving DBS.

Discussion

Despite the fact that DBS technique has a long history of use in PD patients, including in Russia, the conditions associated with abrupt DBS discontinuation remain poorly defined. Thus, DBS-WDS is an emergency condition arising from abrupt neurostimulation turn off and characterized by acute hypo/akinesia, rigidity and/or tremor, accompanied by levodopa wearing-off phenomenon. The main causes of DBS-WDS are IPG battery depletion or rechargeable battery drain, accidental turn off, hardware failure, or infection in the implantation area. They all require DBS system removal (Figure 1) [11].

Provisional scale of DBS-WDS severity: severe (inpatient) – antiparkinsonian therapy ineffective, severe decompensation, dysphagia requiring nasogastric feeding, life-threatening complications requiring hospitalization; moderate (outpatient) – only motor and non-motor parkinsonism worsening without hyperpyrexia, immobility and vital disorders.

Clinical manifestations of severe DBS-WDS include acute rigidity with or without tremor, accompanied by severe akinesia [11, 14, 21–32]. In most cases, this occurs within 1 day after DBS cessation. The most frequent symptom of severe DBS-WDS is dysphagia, which leads to difficulty taking liquids and levodopa. Further, there is a change in mental status (from arousal and mental confusion to stupor) with concurrent development of autonomic symptoms (tachypnea, tachycardia, blood pressure fluctuations, increased sweating, pallor, and urinary incontinence/retention). In some patients, hyperthermia (hyperpyrexia) may be observed over the next few days, probably indicating a more severe course of decompensation. Blood tests in hyperpyrexia reveal leukocytosis, which may lead to misdiagnosis of septicemia. In this case, elevated creatinine kinase levels ranging from 260 to 50,000 U/L may be indicative of rhabdomyolysis [28].

Main characteristics of DBS-WDS:
- DBS-WDS in PD patients is a rare condition caused by abrupt cessation of neurostimulation;
- cessation of stimulation may be due to IPG battery depletion, accidental turn off, DBS hardware failure, or infection in the implantation area;
- abrupt cessation of stimulation does not always lead to DBS-WDS, but always causes worsening of parkinsonism symptoms;
- patients with a disease duration > 15 years and a long period of neurostimulation (> 5 years), elderly patients are at risk;
- hypothetically, DBS-WDS has a different pathogenetic mechanism compared to withdrawal of dopaminergic agents;
- DBS cannot be adequately replaced by DRT, even at the highest doses;
- intensified DRT should be considered as a temporary solution;
- early replacement of the neurostimulator improves clinical outcomes and should be considered as a first-line therapy to prevent lethal outcomes.

Typically, patients develop a medication-refractory akinetic state. A UPDRS motor score decrease is more than 2-fold [11, 14, 21–32]. Despite a significant increase in the levodopa equivalent dose in some patients (10-fold or more, average LED up to 3,200 mg/day), no adequate response to therapy was observed.[14] Thus, DBS withdrawal after long-term stimulation is not fully compensated by DRT, even at high doses [12, 29]. Even intrajejunal administration of levodopa/carbidopa-intestinal gel and subcutaneous administration of apomorphine fail to compensate DBS withdrawal [14, 32]. The reason for this remains unclear.

Complications of DBS-WDS include aspiration pneumonia, rhabdomyolysis-induced acute renal failure, disseminated intravascular coagulation, and venous thromboembolism. The differential diagnosis can be challenging. CJ. Liu et al. reported a clinical case of a patient with a 12-year PD duration, who developed DBS-WDS during the preparation period for routine IPG replacement [28]. The surgery was postponed due to hyperthermia and suspected sepsis. Only after significant worsening of clinical symptoms and despite the administration of broad-spectrum antibiotics, the source of sepsis could not be identified and then DBS-WDS was suspected. Treatment with dantrolene and bromocriptine along with intensive supportive therapy were started, and the dose of dopaminergic agents was increased. The conservative treatment proved ineffective, so the IPG was replaced, which led to regression of hyperthermia.

The outcome prediction in DBS-WDS treatment is complex. Severe DBS-WDS without IPG reimplantation has a high mortality rate. The only efficient treatment option is urgent IPG replacement and restoration of stimulation. In most cases, early IPG reimplantation allows preventing decompensation even in the presence of hyperpyrexia. If the patient survives, recovery may take from a few days to weeks to months. S. Reuters et al. reported that 3 of 4 patients recovered the initial motor level, which they had weeks or months prior to IPG explantation. Nevertheless, one year later, a decrease in daily activities was noted, which could be caused either by prolonged recovery or by disease progression [14]. Even with the earliest possible reimplantation, DBS-WDS treatment may be inhibited by extremely severe condition of the patient due to secondary complications (ischemic brain damage), as described in our clinical case 1.

Risk factors for the severe DBS-WDS are a long-standing PD (> 15 years) and a long-term STN stimulation (> 5 years). Additional risk factors may include advanced age, severe

motor impairment prior to DBS, and progression of disease symptoms since the initial surgery [11, 14, 32].

The exact mechanism of DBS-WDS is yet to be determined. A growing pool of evidence points to an acute neurotransmitter imbalance in the hypothalamus, the nigrostriatal system, and the mesocortical dopaminergic system [26]. Some authors believe that poor response to receptor stimulation by levodopa in patients with advanced PD along with motor improvement after restoration of neurostimulation are suggestive of possible different mechanisms of action in the nigral pathways for the DBS versus oral dopaminergics. Such observations imply possible neuroprotective effect of DBS, which is yet to be confirmed [29].

The mechanism of action of levodopa is aimed at restoring impaired dopaminergic transmission in the nigrostriatal system, while DBS specifically inhibits transmission of electrical signals by hyperactive STN. Electrical stimulation of STN affects cortical activity either by inhibiting activity of indirect pathway or via the hyperdirect pathway of the basal ganglia [33–35]. P. Zsigmond et al. suggested that STN-DBS may indirectly increase dopamine release in the putamen by affecting the pars compacta in the substantia nigra, subsequently reducing the need for levodopa in PD patients receiving neurostimulation [36].

Nowadays, functional MRI (fMRI) studies evaluating the effects of STN-DBS and levodopa, demonstrate modulatory effects of levodopa on brain activity in the putamen during certain motor tests. These effects were not observed in patients receiving DBS [37]. Resting-state fMRI data confirm that modulatory effects of levodopa and STN-DBS on brain connectivity are different. Levodopa increases dopamine availability thereby inducing broad changes in functional brain connectivity both within and outside the motor network [38]. This effect has been confirmed even in healthy volunteers [39]. As to STN-DBS, a simple model was first proposed in which STN inhibition by electrical stimulation leads to a decrease in glutamatergic transmission, supporting activity of the direct pathway of the basal ganglia [40]. More recent studies have shown that the effects of STN-DBS are mediated by complex modulation of brain networks, for example, via antidromic activation of input structures. We have described these mechanisms in detail previously [41].

In any case, poor response to high doses of dopaminergic agents in PD patients after discontinuation of chronic DBS remains an enigma. Could it be caused by postsynaptic changes in dopamine receptor affinity in striatal neurons and degeneration of striatal dendrites with loss of dopaminergic synapses? Understanding the observed changes may be important to improve the results of DBS treatment and to learn more about the pathophysiology of PD. The precise mechanism by which DBS affects neurotransmission in the brain is yet to be elucidated.

Diagnostic algorithm for patients with suspected DBS-WDS is presented in Figure 2. It is important to acknowledge that due to the rarity of DBS-WDS, there is a dearth of vigilance among intensive care physicians and neurologists in diagnosing this condition.

Approaches to DBS withdrawal syndrome therapy

There is a lack of consensus as to whether acute DBS-WDS is the same condition as acute akinesia in PD. Nevertheless, given the similar clinical presentation, it is reasonable to assume that DBS-WDS in PD patients should probably be treated in the same way as akinesia or akinetic-hyperthermic (malignant) syndrome.

According to the literature, the main agents to treat DBS-WDS are dopaminergic agents: levodopa, dopamine receptor agonists – pramipexol, transdermal rotigotine, ropinirole, as well as bromocriptine (7.5–15.0 mg/day), amantadine orally and intravenously, subcutaneous infusions of apomorphine (not available in Russia), methylprednisolone intravenously (1 g), dantrolene sodium (2–3 mg/kg per day intravenously) [42, 43].

Dantrolene is a skeletal muscle relaxant, its mechanism of action is associated with inhibition of intracellular calcium release from sarcoplasm. It is effective in treatment of malignant hyperthermia [44]. Dantrolene can reduce rigidity in individual patients, so it might be used in patients with DBS-WDS accompanied by hyperpyrexia.

Bromocriptine (5–10 mg 3 times a day) is also traditionally recommended for the treatment of acute akinesia, although there are no studies demonstrating its efficacy. However, according to recent publications, bromocriptine has still been prescribed despite the fact that newer non-ergoline dopamine receptor agonists with less side effects are now available. It remains unclear whether a newer generation dopamine receptor agonist or bromocriptine should be preferred [44, 45].

In some cases, patients received parenteral amantadine sulfate (PK-Merz) at a dose of 200 mg (500 mL) 2–3 times daily for 5–14 days. Amantadine sulfate is a blocker of NMDA-type of glutamate receptors, and also exhibits additional dopaminergic effects. These include stimulation of dopamine synthesis in nigral neurons; enhanced release of dopamine (and other monoamine) vesicles into the synaptic cleft and inhibited dopamine reuptake by presynaptic terminals; increase in dopaminergic receptor sensitivity to the neurotransmitter; mild cholinolytic effect [2, 45, 46]. Prior to prescribing amantadine sulfate, it is necessary to assess creatinine, urea levels, and renal function. Amantadine sulfate is contraindicated for patients with acute renal failure.

Hydration, body temperature control, and respiratory support in the ICU should be carried out in a due manner. Undoubtedly,

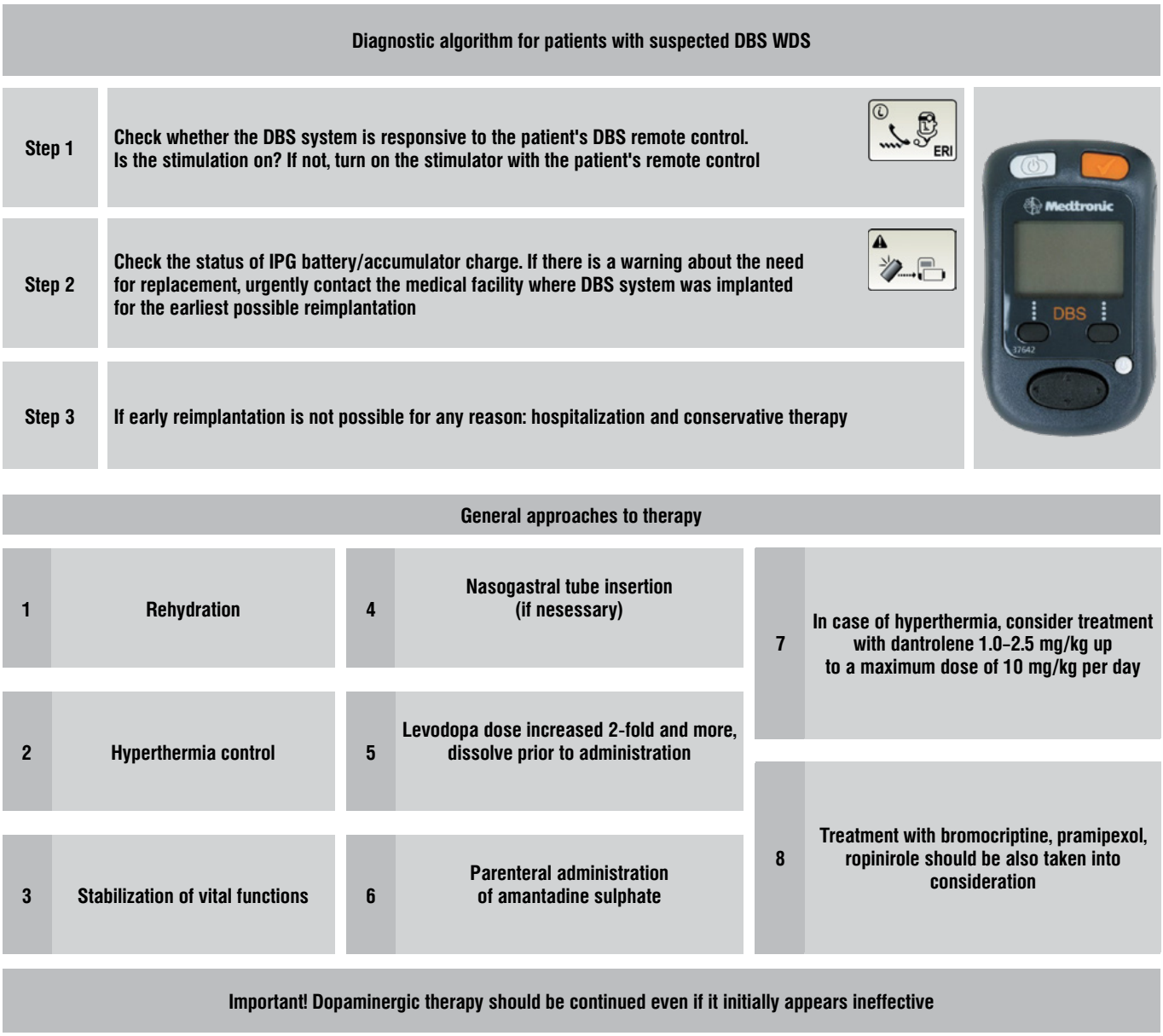

Fig. 2. Diagnostic algorithm for patients with suspected DBS WDS.

reintroduction of agents containing levodopa, which the patient took in the past (if they were withdrawn due to DBS), or the agent dose augmentation is of paramount importance. It is necessary to resume dopaminergic therapy in increased doses (2-fold or more) as early as possible, regardless of the clinical response (a proper response may develop only 7–11 days later or not develop at all) [2].

Nevertheless, in most of the described cases, only early IPG reimplantation promptly reversed akinesia and autonomic instability in patients, which was not achieved with pharmacotherapy. A number of authors believe that dopaminergic therapy during [post-implantation] week 1 may contribute to the favorable outcome [14]. A.K. Helmers et al. suggested that in patients with expected delay in neurostimulation restoration, such pharmacological support can be considered as extreme [17].

When DBS cessation was a result of infections in the IPG area, treatment traditionally includes antibiotic therapy, sanitation of the infection site, and removal of the infected implant with subsequent reimplantation or destructive surgery on deep brain structures. The incidence of such infections is about 2% after primary implantation and ranges from 0.7% to 6% after IPG replacements. In the majority of cases, the infection rate grows with the number of previous IPG replacement procedures, which adds to the benefits of rechargeable neurostimulation systems [47–49]. In this case, a gradual decrease in DBS level and levodopa dose

augmentation prior to neurostimulator removal should prevent the DBS-WDS.

Although early reimplantation would be a logical option, it is often delayed due to the current standards for reimplantation of implantable systems after bacterial infections. Even though the time between explantation and reimplantation is not standardized, reported periods range from 6 weeks to 6 months. It is believed that once the infection is cleared, IPG can be safely reimplanted after 2–3 months [47, 50, 51]. However, if the patient is at high risk of developing DBS-WDS, the infected IPG and extensions can be removed, and a new IPG and extensions on the contralateral side can be implanted during the same surgery with appropriate antibiotic support [14, 17]. For patients with high energy-consuming DBS settings requiring frequent IPG replacement, a switch to rechargeable stimulators is recommended [47, 52].

In the literature, DBS-WDS is described predominantly in patients with STN stimulation. It is assumed that GPi stimulation may be a safer option, because doses of dopaminergic agents for GPi stimulation usually remain high and more stable, in contrast to a significant dose decrease with STN stimulation. At the same time, we presented a clinical case of DBS-WDS in a patient with GPi stimulation (clinical case 2), which suggests the possibility of DBS-WDS development in such patients as well.

Conclusion

Thus, according to the Guidelines on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients with Parkinson's Disease published in 2018, the IPG expiration can be considered a movement disorder emergency [53]. IPG battery drain, accidental turn off, or removal of infected IPGs rapidly worsen parkinsonian symptoms and may cause life-threatening DBS-WDS similar to acute akinesia and hyperthermia. Delayed replacement of subcutaneous IPG should be minimized to avoid potential complications associated with abrupt DBS cessation. If immediate IPG replacement is not possible, the use of intestinal levodopa/carbidopa gel or apomorphine infusion (not available in Russia) may be considered as adjuvant therapy.

Physicians should remain alert to the development of DBS-WDS in high-risk PD patients (long-standing PD, long-term DBS, elderly patients). In these patients, thorough monitoring of battery level is required. The urgent IPG replacement or hardware troubleshooting, especially in high-risk patients, should be the first priority for neurosurgical centers dealing with DBS.

In Russia, IPG replacement is included in Section II of the List of types of high-tech medical care, but not included in the Basic program of compulsory medical insurance. Therefore, urgent IPG replacement in critical situations is challenging. This is why it is advisable to include subcutaneous IPG replacement into the Basic program of compulsory medical insurance (Section I of the List of types of high-tech medical care), in order to increase the availability of this type of medical care, taking into account that rare but potentially dangerous DBS withdrawal syndrome can lead to patient's death.

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