Idiopathic delayed-onset edema surrounding deep brain stimulation leads: Insights from a case series and systematic literature review

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Abstract

Introduction
Deep brain stimulation (DBS) is effective for some neurological and psychiatric conditions. Idiopathic delayed-onset edema (IDE) surrounding the leads has been anecdotally reported. The etiology, predisposing factors and prognosis of this complication are unknown.
We present a multicenter case series of patients with IDE, and a systematic literature review, aimed at defining the pathophysiology and identifying appropriate treatment strategies.

Methods
IDE was defined as edema along the DBS lead, occurring ≥72 h postoperatively, in absence of trauma, vascular events or infection. Information on patients with IDE was collected in a standardized way. A systematic search was performed in Pubmed.

Results
Twelve new patients presenting with 14 episodes of IDE are described. From the literature, 38 patients were identified. No common surgical aspects or patient-related factors were identified as risk predictors for the onset of IDE. Symptoms included deterioration of the stimulation effect, seizures and focal neurological signs. Although the condition is self-limiting, with symptoms resolution in 28.5 days on average, three patients underwent surgical revision and seven received antibiotics.

Conclusions
IDE is a rare complication of DBS procedures, presenting from few days to months after surgery. Symptoms can be mild and not-specific, and the condition is self-limiting. The diagnosis of IDE is made after exclusion of vascular events or infections. The pathophysiology is still unexplained. The recognition of this complication can help avoiding unnecessary surgical procedures (system explantation) and antibiotic treatment.

Keywords
Deep brain stimulation; Complications; Edema; Delayed onset

1. Introduction

Deep brain stimulation (DBS) surgery is an increasingly applied, well-established treatment for several neurological and psychiatric disorders [1]. DBS implantation is not risk-free, although intracerebral surgical complications are rare. A number of these, such as intracranial hemorrhage (ICH), ischemia and infectious cerebritis, may be associated with intracranial edema. In a few cases, idiopathic delayed-onset edema (IDE) surrounding the DBS leads has been reported [2], [3], [4], [5], [6] and [7]. At difference with edema associated with lead insertion, which is usually of small size, asymptomatic, and occurs in the perioperative period, IDE presents days to weeks after surgery, and can be fairly large and symptomatic. The etiology, predisposing factors and prognosis of this complication are still unknown.
We present a large multicenter case series of patients who developed IDE surrounding the DBS leads, and a systematic review of the literature, aimed at defining the pathophysiology and identifying appropriate treatment strategies.

2. Methods

Patients presenting with IDE were identified in the participating centers. Information was retrospectively retrieved from medical records and reviewed with standardized forms. Patient characteristics, surgical details, clinical and radiological details, and treatment strategies were recorded.

2.1. Definition of IDE

IDE was defined as edema along the DBS lead, occurring ≥72 h after surgery, in the absence of trauma, vascular events or signs of infection. Patients were not included if: a) postoperative imaging revealed abnormalities or symptoms presented in the first 72 h, b) imaging showed signs of hemorrhage or ischemia before or concomitant to edema onset, or c) patients showed signs of infection.

2.2. Search methods

A systematic search on English-language publications reporting edema after DBS was performed in PubMed using appropriate keywords (Supplementary file 1). Additionally, a cross-referencing check of relevant publications and a rough search were performed using the MeSH-term “Deep Brain Stimulation/adverse effects”. Data extraction was performed using the same definition of IDE and the same standardized form for data extraction applied to gather patient information from our study subjects.

2.3. Statistical methods

Descriptive statistics of retrieved data from medical records and reviewed publications are presented as mean ± standard deviation/range in case of continuous variables, or as frequencies/percentages in case of nominal variables.

3. Results

Of the referred patients, four were not included in this report because symptom onset or scan abnormalities were reported already on the first postoperative day, and thus they did not match the definition of IDE as defined above.

Twelve patients (10 males) from nine centers were included (Table 1). The approximate total number of DBS surgeries in the participating centers at the time of writing was >3000, which would suggest an approximate incidence of 0.4%. The average age at surgery was 51.7 years (range: 23–68). Indications for DBS included PD (eight patients), dystonia (2), ET (1), and chronic post-herpetic trigeminal neuropathy (1). Age at onset ranged from 6 to 56 years and disease duration from 4 to 24 years. One patient had a history of leukemia complicated by graft-versus-host disease and used antiaggregants, two patients had hypertension, and three had known allergies to antibiotics. (Supplementary file 2) Eleven patients underwent bilateral implantation, one with a staged procedure. Lead implantation was performed with local anesthesia in 10 patients. Nine patients received 3389 leads, connected to Activa (5), Kinetra (3) or Soletra (1) implantable pulse generator (IPG - Medtronic, Fridley, Minnesota, USA). The other three patients received the Vercise DBS System (Boston Scientific, Natick, Massachusetts, USA). Two patients underwent IPG implantation 5–8 days after lead implantation, while the others on the same day. Intra-operative microelectrode recordings (MER) were performed in eight patients, with 1–5 tracts per side. In four cases, an intraoperative stun-effect was observed. In seven patients plasma-derived fibrin sealant was used intraoperatively. Early post-operative imaging, available for nine patients, was normal. IDE developed in 18 of the 23 implanted hemispheres, in 14 episodes (simultaneous bilateral IDE in four patients, unilateral in six, and staged bilateral in two). In these hemispheres, the target was the subthalamic nucleus (STN) for 12 leads, internal globus pallidus (GPi) for four, thalamic ventral intermediate nucleus (Vim) for two, and the periaqueductal grey matter for one. In approximately half of the cases the side with (larger) edema was the first implanted side. (Supplementary file 2) Symptoms presented, on average, 84.5 days postoperatively (range: 5–396 days), and included: dysarthria or aphasia (4), confusion (4), deterioration of stimulation effect (4), apathy/depression (3), seizures (3), hemiparesis (2), diminished level of consciousness, headache, diplopia, urine incontinence and agitation. One episode of unilateral IDE, documented four days after the second implant in a staged DBS procedure, was asymptomatic. The maximum axial diameter of edema was on average 35.7 mm (range: 16–100 mm), running along the whole lead track in some cases. (Fig. 1) Contrast-enhancement of small areas was observed in three patients. Bacterial cultures on blood (10 patients), cerebral spinal fluid (CSF – 7 patients) and surgical material (2 patients) were negative. None of the patients showed local or systemic signs of infection. At edema onset, stimulation was on in 14 leads, four of which showed decreased impedance.

4. Management and prognosis

Three surgical revisions were performed. One IPG was replaced in the hypothesis of a malfunction. In another patient, the lead and anchoring system were explanted; a new lead implantation performed 3 months later with perioperative steroid treatment, was uncomplicated. For patients receiving stimulation at edema onset, management included switching stimulation off (10 leads) and increasing amplitude (one lead, due to decreased effect).

In eight episodes (seven patients) antibiotics were used, often in combination, for 7–14 days; in 12 episodes (10 patients) steroids were used; in seven episodes (six patients) steroids and antibiotics were used in combination. One patient was treated conservatively. All episodes were followed by a full and persistent symptom recovery (mean follow-up: 31.8 months, range: 3 months - 8 years). Symptoms resolved over 28.5 days on average (range: 1–70 days) and radiological resolution was documented after an average of 78.5 days (range: 15–122 days, excluding two cases with ongoing edema at last follow-up after 30 and 210 days). The

symptoms recovery duration for the patient treated conservatively was 70 days, while it was on average 24.4 days for those receiving steroids (range 1–60). (Table 1).

4.1. Description of representative patients

4.1.1. Patient 3

A 54-year-old PD patient, with hypertension and allergies to penicillin and acetylsalicylic acid, underwent bilateral STN DBS with local anesthesia, using five MER bilaterally. DBS leads model 3389 and Kinetra neurostimulator were implanted. Postoperative MRI one day postoperatively revealed only small bilateral pneumocephalus. Monopolar stimulation was programmed with contact 1 as cathode at 3.7 V, 60μs and180 Hz on the right and contact 4 as cathode at 2.4 V, 60 μs, and 180 Hz on the left, with satisfying symptoms control. Ten months postoperatively, left limbs tremor reappeared, unrelated to medication changes, and unresponsive to stimulation adjustments. Lower impedances were noticed. Two weeks later, MRI revealed edema surrounding the tip of the right lead (maximum diameter 30 mm, Fig. 2a). The stimulation of the right lead was switched off. CSF and blood cultures were negative. Prednisolone 250 mg was administered intravenously (three days), followed by an oral scheme of descending dosage (three weeks), and antiparkinsonian medication was increased. Edema was still detectable in follow-up MRIs one month after, but was completely resolved 92 days after symptom onset. Resuming stimulation produced a good persistent effect on the symptoms. A 5-year follow-up period was uneventful.

4.1.2. Patient 10

A 62-year-old PD patient underwent bilateral STN DBS with local anesthesia using 4 MER and 2 lead tracks on the left side and 3 MER and 1 lead track on the right. Vercise system was implanted. Routine postoperative CT scan one day postoperatively revealed only bilateral pneumocephalus. Monopolar stimulation was programmed with contact 10 as cathode at 2.4 mA, 60 μs, and 130 Hz on the right and contact 2 as cathode at 1.9 mA, 60 μs, and 130 Hz on the left. Fifteen days postoperatively the patient developed right hemiparesis and global aphasia. A CT obtained that same day, revealed edema without contrast enhancement along the left lead (maximum diameter 58 mm, Fig. 2b). Stimulation was switched off. CSF cultures were negative. Dexamethasone was administered (16 mg/day for 7 days, then 8 mg/day for 5 days), followed by prednisolone (60 mg/day tapered across 3 weeks). Symptom recovery took 7 days. Edema was still detectable in a follow-up CT 12 days after symptom onset, and had completely resolved 60 days after onset. No further events were observed during a 1-year follow-up period.

4.2. Results literature review

A total amount of 35 papers were identified and screened. (Supplementary file 1) Of these, 15 mentioned intracranial edema following DBS surgery. Nine articles were excluded due to an identified edema etiology or perioperative onset. Six papers reported IDE episodes as defined above. No review papers were found.

A total of 38 patients with IDE were identified (Table 2). The average age at surgery was 60.8 years (range: 21–73 years). The indication for DBS treatment included PD (28 patients), dystonia (5), ET (3), and brainstem tremor (1). In 26 patients the STN was targeted, in eight the GPi, and in three the Vim. Sixteen patients underwent bilateral implantation, 14 of which developed unilateral edema. Intra-operative MER were performed in 36 patients, with 1–6 microelectrodes per side. Four patients had early post-operative imaging available, which were all normal. Symptoms presented 4–120 days postoperatively and included: worsening of

pre-existing symptoms (n = 3), headache (n = 3), neurological deficits (n = 2), seizures (n = 2), speech difficulties, confusion, disorientation, behavioral problems. Twenty-five patients were asymptomatic: in these patients imaging was performed in the context of research or staged surgical procedures [2] and [3]. Edema was described along the lead trajectory or lead tip, with a maximum axial diameter of 20–60 mm. No patient showed local or systemic symptoms of infection. Ten patients received steroids, combined with antibiotics in one. All patients experienced a full symptom recovery over 5–21 days, and radiological resolution followed after 7–60 days.

5. Discussion

We describe 12 new patients who developed IDE after DBS surgery, in absence of any sign of hemorrhage, ischemia or infection. Similarly to the cases described in the literature, symptom onset ranged from early to late postoperative period, with a variable clinical presentation. The collection of data from nine different DBS centers, which operated with slightly different techniques and used different management approaches, allowed for the first time to exclude most of the factors potentially associated with the onset of this complication. No common surgical aspects or patient-related factors were identified as risk predictors for the onset of IDE.

The incidence of IDE seems to be rare, although it could be underestimated due to occasional asymptomatic presentation [2] and [3]. In a study [2], 38 patients underwent staged DBS implantation: preoperative imaging prior to the second surgery revealed edema along the DBS track in fifteen asymptomatic patients (39%), all within 3 months from surgery.

Most of our patients (85%) developed edema within 3 months, except two in whom edema occurred afterwards, as also reported in the literature [4]. Although a detection delay could explain this discrepancy, in one of our patients, who developed bilateral edema in a staged manner (patient 6), normal MRI findings up to 7 months after implantation preceded the onset of contralateral edema.

5.1. Differential diagnosis

IDE can present with seizures, diminished consciousness, or different focal neurological signs. Interestingly, in some cases, the only symptom was a deterioration of stimulation effect or worsening of pre-existing symptoms [4], suggesting that brain imaging should always be considered when unexpected worsening of the diseases symptoms occurs.

To define an appropriate management and provide a correct prognosis, IDE should be distinguished from other rare intracranial complications associated with edema, such as ICH (occurring in <2% [8], [9] and [10]), arterial or venous infarction (<1% [8]), and infections (in a series of 447 patients, only one case [11]). While IDE is a self-limiting condition, other complications might require more aggressive treatments, such as large hematomas requiring surgical evacuation, or infections requiring antibiotic treatment often in combination with hardware removal. Clinical presentation of these conditions is similar, but symptoms of ICH or infarction can be permanent [10]. In case of cerebral infection, neurological deficits are associated with systemic symptoms of infection, elevated C-reactive protein and white blood cells, and positive bacterial cultures [12] and [13].

A delayed onset is not expected in case of ICH or ischemia, which usually occur peri-operatively, but it has occasionally been reported following venous infarctions (up to 4 days postoperatively) [14] and infectious cerebritis [13]. Imaging can help distinguishing between these conditions. ICH [9] and [15] and arterial infarctions [14] are usually clearly recognizable

in brain imaging. Venous infarctions are localized at the subcortical level, usually associated with edema and hemorrhage [14]. Infectious cerebritis presents as a hypodense lesion, sometimes accompanied by abscess formation with ring contrast enhancement. No signs of hemorrhage or infection were seen in patients with IDE, although a modest contrast enhancement was reported in some cases.

5.2. Possible pathogenesis

No common surgical aspect (including target, intraoperative use of fibrin sealants, leads model, use of MER tracks, order of implantation), nor patient-related factor (including age, diagnosis, disease duration and characteristics, medication, atopic diathesis, coagulopathies), were systematically identified in our patients.
A direct effect of stimulation can be ruled out since, in some patients, stimulation had not been switched on yet. Moreover, similar delayed reactions (not otherwise explained) have also been described after other intracranial implants, such as catheters for intracranial pressure monitoring [16], Ommaya reservoirs [17] or ventriculo-peritoneal shunts [18] and [19].

Traumatic brain damage due to lead insertion can induce edema, by causing micro-hemorrhages around the track. These can remain unnoticed, due to the lead artefact on imaging. In one of our patients (Patient 7), MRI obtained 62 days after lead removal revealed minimal hemosiderin deposits throughout the lead trajectory after complete resolution of the edema. However, it seems unlikely that micro-hemorrhages can cause the rather large edema observed. Moreover, processes associated with traumatic brain damage are expected to start within hours and thus cannot explain the long delay to onset observed in some cases.
A possible mechanism causing edema is an inappropriate immune reaction to the leads, such as an allergic reaction or a foreign body reaction (FBR).
Lead materials in contact with brain include different metals, polyurethane, nylon, silicone and tin compounds. Biocompatibility of these materials has been confirmed through laboratory and animal testing and clinical experience [20]. Hypersensitivity to silicone components was sometimes reported after implantation of heart pacemakers or cochlear implants [21] and [22]. Possible allergic skin reactions to DBS components, not confirmed by allergy testing and mainly concerning the IPG, were anecdotally reported [23] and [24]. In one patient, a histopathology-confirmed allergic contact dermatitis to the IPG required explantation, despite negative allergy testing [25]. One of our patients (Patient 6) presented with erythema at the burr-hole site, which recovered without system explantation: allergy tests were not performed in this case, but were found negative in other IDE cases in the literature [4].
As opposed to allergic reactions, which are sustained by a specific IgE-mediated immune response, FBR is an acute cytokine response to a foreign body, causing macrophage activation at the biotic-abiotic interface [26]. In the brain, the early inflammatory phase begins during the first week [27]. Symptomatic intracerebral FBR associated with edema has been described for different implants (e.g. stents or aneurysms wrapping materials) [28]. Multinucleated giant cells and reactive gliosis surrounding the leads, indicating minimal FBR, have been also described in DBS leads removed 3 months to 12 years after implant [27] and [29]. These are thought to be caused by a response to the polyurethane coating [30]. The occurrence of repeated episodes in two of our patients suggests a possible role for subject predisposition; however, it must be noticed that unilateral edema formation in cases of bilateral implants, spontaneous recovery, and an uneventful re-implantation in one patient may argue against this.

5.3. Management

Almost all patients in our series and in the literature fully recovered within 3 months, with an event-free follow-up, regardless of the applied treatment, and including patients treated conservatively.
Considering the self-limiting nature of this complication, it appears that explantation of the DBS system and antibiotic treatment are not recommended.
While it seems that steroid treatment shortened the symptoms duration when compared to conservative treatment, data from our series and from the literature are not sufficient to draw firm conclusions [2], [3], [4], [5], [6] and [7]. The recovery time probably also depends on edema volume and symptom severity, and radiological resolution could be accurately defined only with regularly repeated follow-up imaging.
If edema surrounds the stimulating tip of the lead, impedance variations might occur, which would make the delivered current unpredictable when using voltage-controlled stimulation. Switching off the stimulation is the safest option, but is usually uncomfortable for the patient; if the system allows it, a valid alternative could be the use of constant-current stimulation which, by adapting to the impedance changes, could provide a safer and more stable stimulation control.

6. Conclusions

IDE is a rare complication of DBS procedures, with onset ranging from few days to months after leads implantation. Symptoms can be mild and not specific, including deterioration of the stimulation effect, thus brain imaging is recommended in these cases. The diagnosis of IDE can be made after exclusion of other causes of edema, such as vascular events or infections, which might require specific treatment. The condition is self-limiting and the pathophysiology is still unexplained. The recognition of this complication can help avoiding unnecessary surgical procedures (system explantation) and antibiotic treatment. Pooling more cases of this rare complication through multicenter efforts will hopefully provide more knowledge on its pathophysiology and more evidence concerning the most appropriate management strategies.

Authors contributions

CMKEDC and MFC drafted the manuscript. All authors contributed to the collection and interpretation of the data, have revised the article it critically for important intellectual content, and have approved the final version.

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Authors disclosures and conflict of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.09.007

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Fig. 1.
Patient 2. T1, T2 and FLAIR MRI showing large edema surrounding the right DBS lead along the whole trajectory.

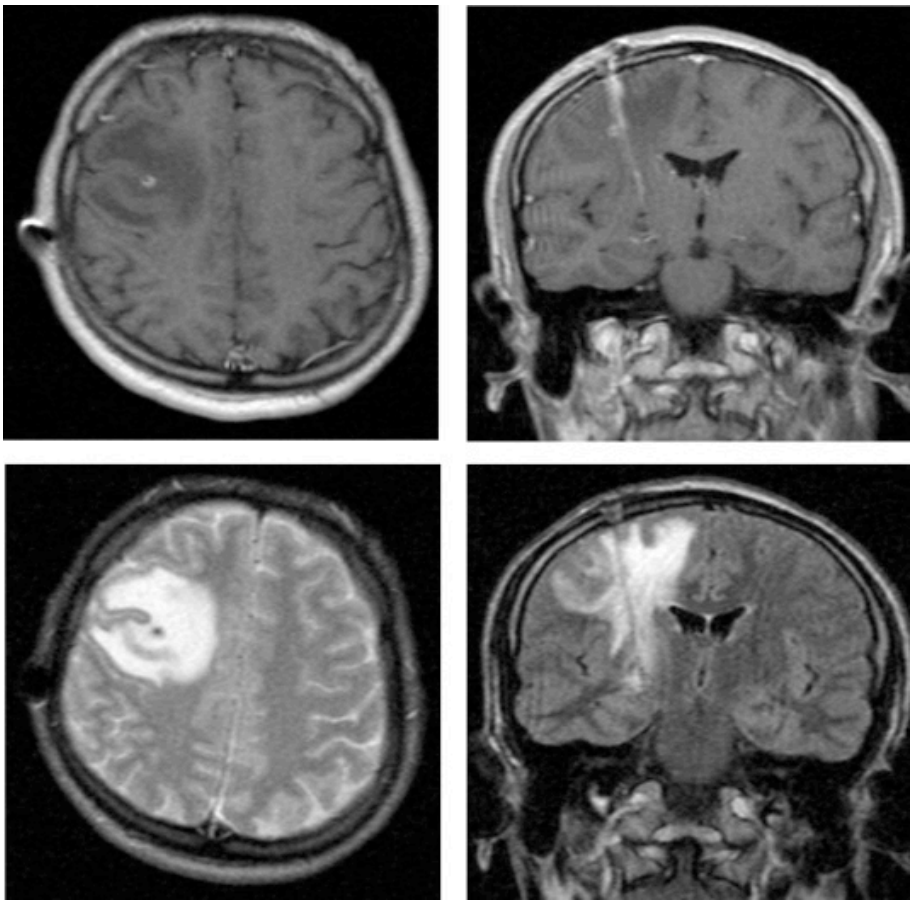

Fig. 2.
(A) Patient 3. Early postoperative routine T2 MRI (Day 1) showing no abnormalities except for minimal pneumocephalus; T2 MRI 305 days after surgery, showing edema along the right lead; T2 MRI 92 days after symptoms onset showing resolution of edema. (B) Patient 10. Early postoperative routine CT showing no abnormalities except for bilateral pneumocephalus; contrast CT 15 days after surgery, showing edema along the left lead; contrast CT 60 days after symptoms onset, showing resolution of edema.

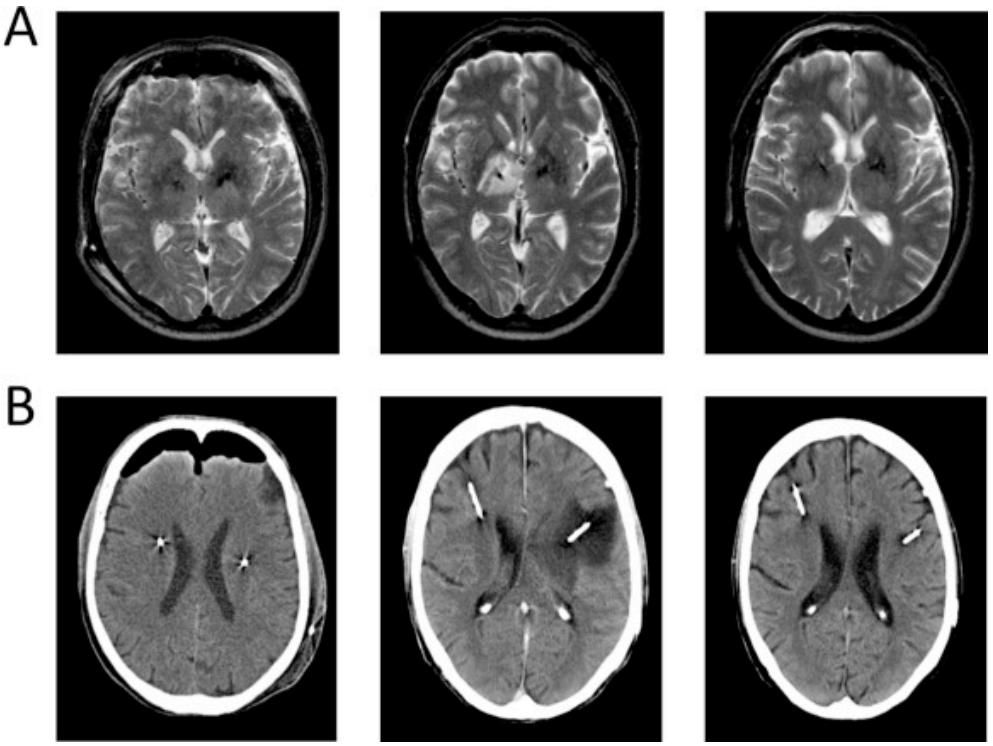

Table 1

Demographic and clinical characteristics of the patients included in the study.

	Age, sex, indication, target	Lead	Micro-electrode recordings	Use of fibrin glue	Normal postop imaging (days)	Symptoms onset (days)	Side edema	Largest diameter (mm)	Bacterial cultures	Stimulation at edema onset	Treatment	Recovery symptoms/ imaging (days)	FU
1. Udine 2003	68, M, PD, Bilateral STN	MDT 3389	L:3/R:3	Yes	1 (CT)	21 (Apathy, reduced L stimulation effect)	R > L	22	Negative (blood, CSF)	ON, no impedance change	AB, steroids, L amp. increased	40/120	9 m
2a. Milan 2006	23, M, Dystonia, Staged bilateral GPi	MDT 3389	2	No	0 (CT)	10 (Seizures, fever, agitation, confusion)	R	100	Negative (blood)	ON, no impedance change	AB, steroids, antiepileptics, stimulation OFF	21/89	8 y
2b. Milan 2007		MDT 3389	2	No	0 (CT)	4 (MRI – patient asymptomatic)	L	26	Negative (blood)	ON, no impedance change	Steroids, stimulation OFF	n.a./15	8 y
3. Kiel 2008	54, M, PD, Bilateral STN	MDT 3389	L:5/R:5	Yes	1 (MRI)	305 (Reduced stimulation effect)	R	30	Negative (blood, CSF)	ON, low impedance	Steroids; R stimulation OFF	30/92	5 y
4. Torino 2009	49, F, PD, Bilateral STN	MDT 3389	L:1/R:2	No	8 (MRI)	60 (Reduced stimulation effect)	L	23	Negative (blood)	ON, low impedance	AB; stimulation OFF, surgical revision, IPG replacement	n.a./122	3 y
5. The Hague 2012	51, M, PD, Bilateral STN	MDT 3389	L:5/R:5	Yes	n.a.	5 (Diplopia, apathy, urine incontinence, diminished LOC)	L	44	Negative (blood, CSF)	L ON/R OFF, no impedance change	Steroids; stimulation OFF	60/51	3 y
6a. Cagliari 2013	55, M, PD, Bilateral STN	MDT 3389	No	Yes	1 (CT)	215 (Scalp erythema)	R	12	Negative (blood, surgical material)	ON, low impedance	AB, steroids, stimulation OFF, surgical revision	n.a./69	2 y
6b.Cagliari 2013		MDT 3389	No	Yes	364 (MRI)	396 (Seizure, confusion)	L	16	Negative (blood)	ON, low impedance	AB, steroids, stimulation OFF	13/>210	2 y
7. Amsterdam 2014	61, M, PHN, L PAG	MDT 3389	No	Yes	1 (CT)	19 (Dysarthria R hemifacial paresis)	L	46	Negative (surgical material)	OFF	AB, steroidsd, lead removal	5/64	10 m
8. Milan 2014	54, F, Dystonia, Bilateral GPi	MDT 3389	L:1/R:1	No	1 (CT)	21 (Dysarthria confusion)	R > L	38	Negative (blood)	ON, no impedance change	AB, steroids, stimulation OFF	7/60	14 m
9. Monza 2014	49, M, PD, Bilateral STN	BSci Vercise	L:3/R:3	No	n.a.	9 (Reduced stimulation effect, apathy, dysarthria, headache)	L > R	40	Negative (blood and CSF)	OFF	Steroids	60/80	16 m
10. Würzburg 2014	62, M, PD, Bilateral STN	BSci Vercise	L:4/R:3	Yes	1 (CT)	15 (Global aphasia, R hemiparesis)	L	58	Negative (CSF)	ON	Steroids, stimulation OFF	7/60	1 y
11. Monza 2015	55, M, PD, Bilateral STN	MDT 3389	L:3/R:3	No	n.a.	5 (Confusion)	L	20	Negative (blood, CSF)	OFF	Conservative	70/90	9 m
12. Udine 2015	40, M, ET, Bilateral Vim	BSci Vercise	L:5/R:5	Yes	1 (CT)	17 (Seizure)	L > R	25	Negative (blood, CSF)	ON, no impedance change	AB, steroids	1/30R/ongoing L	3 m

Table 2.

Demographic and clinical characteristics of the patients available from the literature.

Author & year	Patients (average age)	Indication-target	Lead	MER	Normal postop. imaging (days)	Symptoms onset (average, days)	Side edema	Largest diameter (mm)	Bacterial cultures	Stimulation at edema onset	Treatment	Recovery symptoms/imaging (days)	FU
Ryu et al., 2004	15 (63)	PD-Unilateral STN (13), ET-Vim (1), other (1)	MDT Itrel	3–5	n.a.	<30 (7), <90 (8) (MRI – patients all asymptomatic)	L (13), R (2)	n.a.	n.a.	OFF	Conservative	n.a.	n.a.
Englot et al., 2010	12 (61)	PD-STN (6), PD-GPI (2), ET-Vim (1), Dys-STN (1), BST-GPI (1).	MDT 3387/9	1–4	1 (1 patient); 11 n.a.	5 (disorientation); 8 (gait instability). 10 patients asymptomatic.	L (6), R (5), Bilateral (1)	24–60	n.a.	OFF	Steroids (1 symptomatic patient)	5-15/34 (1 patient)	n.a.
Deogaonkar et al., 2011	8 (55)	PD-STN (4), PD-GPI (1), Dys-GPI (3)	MDT 3387/9	1–6	0 (2 patients); 6 n.a.	4-120: worsening pre-existing sympotms (3), seizure (2), headache (2), neurological def. (1)	R (2), L (1), n.a (5)	20–60	Negative CSF (2), allergy test Negative (1)	n.a.	Steroids (7), Antiepileptics (2) Conservative (1)	n.a./7-60	n.a.
Sikogseld et al., 2011	1 (59)	Dys – Bilateral GPI	MDT 3389	3–5	n.a.	4: motor aphasia and R hemiparesis	L	n.a.	n.a.	ON	AB, steroids, stimulation OFF	14/38	2.5 y
Charles et al., 2012	1 (n.a.)	PD-Bilateral STN	MDT 3389	4	n.a.	n.a.	n.a.	n.a.	n.a.	OFF	n.a.	n.a.	n.a.
Lefaucher et al. et al., 2013	1 (66)	PD – Bilateral STN	MDT 3389	3	2	10: confusion, headache, behavioral problems	R	n.a.	n.a.	n.a.	Steroids	21	6 m