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Adverse events associated with deep brain stimulation in patients with childhood-onset dystonia

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ABSTRACT

Background: Data on pediatric DBS is still limited because of small numbers in single center series and lack of systematic multi-center trials.
Objectives: We evaluate short- and long-term adverse events (AEs) of patients undergoing deep brain stimulation (DBS) during childhood and adolescence.
Methods: Data collected by the German registry on pediatric DBS (GEPESTIM) were analyzed according to reversible and irreversible AEs and time of occurrence with relation to DBS-surgery: Intraoperative, perioperative (<4 weeks), postoperative (4 weeks < 6 months) and long term AEs (>6 months).
Results: 72 patients with childhood-onset dystonia from 10 DBS-centers, who received 173 DBS electrodes and 141 implantable pulse generators (IPG), were included in the registry. Mean time of post-operative follow-up was 4.6 ± 4 years. In total, 184 AEs were documented in 53 patients (73.6%). 52 DBS-related AEs in 26 patients (36.1%) required 45 subsequent surgical interventions 4.7 ± 4.1 years (range 3 months–15 years) after initial implantation. The total risk of an AE requiring surgical intervention was

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7.9% per electrode-year. Hardware-related AEs were the most common reason for surgery. There was a tendency of a higher rate of AEs in patients aged 7–9 years beyond 6 months after implantation.
Discussion: The intraoperative risk of AEs in pediatric patients with dystonia undergoing DBS is very low, whereas the rate of postoperative hardware-related AEs is a prominent feature with a higher occurrence compared to adults, especially on long-term follow-up.
Conclusion: Factors leading to such AEs must be identified and patient management has to be focused on risk minimization strategies in order to improve DBS therapy and maximize outcome in pediatric patients.

Introduction

Childhood-onset dystonia has a severe impact on motor development, activity and participation. In children acquired or formerly so-called "secondary" dystonia is more common than inherited dystonia. Dyskinetic cerebral palsy (CP) is the most common cause of acquired dystonia and manifests at a very early stage of development, often leading to severe functional impairment [1]. Most inherited forms of dystonia entail a progressive disease course with spreading of symptoms to the entire body [1]. Pharmacotherapy has only limited effects [2,3]. Deep brain stimulation (DBS) has become well established as a safe and effective treatment option in adult patients with pharmaco-refractory inherited or idiopathic dystonia [3–5]. Results in patients with acquired dystonia are more heterogeneous [6,7].

DBS has also been increasingly used in children and adolescents during the last two decades [8]. When parents and patients are in the process of decision-making towards DBS, they are mostly concerned about the potential risks and the uncertainty of DBS outcomes [9]. Large series on adult patients with various disease entities have thoroughly investigated acute and long term adverse events (AEs) associated with DBS [10,11]. Published data on effects and AEs in pediatric cohorts is still limited and mainly restricted to single case reports or smaller case series, except one greater cohort from a monocenter setting, showing great variability [7,12–15].

We aim to expand the knowledge of pediatric DBS by providing data on short- and long-term AEs of patients with DBS implantation up to the age of 18 years, generated by a multicenter German registry on pediatric DBS (GEPESTIM). We then discuss challenges of early DBS application and suggestions for reducing the risk of AEs.

Methods

Data collection and documentation

Data were retrospectively collected by the participating DBS centers in Berlin, Cologne, Dusseldorf, Freiburg, Hanover, Kiel, Lubeck, Magdeburg, Munich, and Vienna. For each patient a full chart review was done and all available clinical information on DBS-related AEs were documented in an online database programmed by the *Research Electronic Data Capture (REDCap) system* in cooperation with the Institute of Medical Statistics and Computational Biology of the University of Cologne. The last data documented in the clinical chart record before DBS implantation were considered as preoperative, whereas postoperative data were allocated to certain time periods of follow-up (implantation, 0 - <1 months perioperative, 1–6 months, and >6 months postoperative).

Dystonia was classified based on the current international dystonia classification proposed by Albanese et al. into three groups: *Group 1 isolated inherited and idiopathic dystonia, group 2 combined inherited and idiopathic dystonia*, and *group 3 acquired dystonia* [16].

The GEPESTIM-registry was approved by the ethics committee of the University of Cologne (Nr. 13–168) and by the local ethics committees of the participating centers. Before data collection patients or caregivers were asked for their written informed consent.

Statistical evaluation

Quantitative variables were summarized by mean ± standard deviation and range, qualitative variables by count and percentage. Change over time in quantitative measures was evaluated by the paired *t*-test and Wilcoxon signed-rank test. Comparisons of subgroups were done with the Kruskal-Wallis test (3 or more groups) or the Mann-Whitney *U* test (2 groups). Confidence intervals for incidence rates of AEs were calculated assuming Poisson-distributed counts. Moreover, incidence rates of subgroups were compared using negative binomial regression adjusted for clustering by patient. All statistical calculations were done with the software SPSS Statistics (IBM Corp., Armonk, NY, USA) and Stata (StataCorp LLC, College Station, TX, USA).

Results

Demographics

10 DBS centers from Germany and Vienna/Austria provided data on 72 patients who underwent DBS until the age of 18 years between the years 1998–2018. The average age at operation was 12.3 ± 3.4 years (range 4–18 years). 16 patients were classified into *group 1 isolated inherited and idiopathic dystonia*, 34 patients into group 2 *combined inherited and idiopathic dystonia*, and 22 patients into group 3 *acquired dystonia*. Groups 1 and 2 showed a significant improvement in the mean Burke-Fahn-Marsden Dystonia Rating Scale movement score (BFMDRS-M) compared to preoperative baseline scores, whereas group 3 showed only mild improvement without reaching statistical significance. For further details on aetiology, clinical characteristics and DBS targets see Table 1 and Supplementary Table 1.

Operative details

72 patients received a total number of 173 DBS electrodes and 141 IPGs in 166 surgical procedures (details about hardware see Supplementary Table 2). During time of follow-up, 24 DBS electrode revisions in 11 patients (15.3%), 16 extension lead revisions in 12 patients (16.7%), and 68 IPG replacements in 35 patients (48.6%) were performed in this cohort with 47 being scheduled IPG replacements due to battery failure. The IPG was placed in a subcutaneous pocket either below the clavicle or at the abdomen. In 26 DBS-procedures (56 electrodes) in 25 patients (34.7%), the IPG was implanted during the same session as the electrodes, and in 62 procedures (70 electrodes) the IPG was replaced and connected to a preexisting electrode. 19 IPGs in 18 patients (25%) were implanted

Table 1
Demographics, DBS-targets and pre- and postoperative Burke-Fahn-Marsden-Dystonia Rating Scale movement scores (BFMDRS), (** = $p < 0.05$). Patients, who underwent repeated electrode replacements are marked with numbers and referred to in the legend. GPi = Globus pallidus internus, STN=Subthalamic nucleus, VIM=Nucleus ventral intermediate nucleus of the thalamus, VOA=Nucleus ventralis oralis anterior of thalamus.

	All	Group 1 isolated inherited and idiopathic N = 16	Group 2 combined inherited and idiopathic N = 34	Group 3 Acquired N = 22
Number of patients	72	16 (22.2%)	34 (47.2%)	22 (30.6%)
Gender (male/female)	46 (63.9%)/26 (36.1%)	11 (68.8%)/5 (31.2%)	21 (61.8%)/13 (38.2%)	14 (63.4%)/8 (36.2%)
Age at onset (mean year, SD)	4.4 ± 3.5[a]	6.6 ± 2.3	4.7 ± 3.4	2.6 ± 3.5
Age at first DBS (mean year, SD)	12.3 ± 3.4	12.1 ± 3.3	12.3 ± 3.3	12.6 ± 3.7
GPI (unilat./bilat./not known)	0/70/3[b]	0/16/1[c]	0/34/1[d]	0/20/1[e]
STN (unilat./bilat.)	1/2	0	0/1[f]	1/1[g]
VIM (unilat./bilat.)	0/4	0	0/1[h]	0/3[i]
VOA (bilat.	1	0	1	0
not known (after revision)	1	1	0	0
Mean BFMDRS preoperative±SD (mean follow-up 4.6 ± 4 years)	65.9 ± 30.2	57.4 ± 23.4	67.7 ± 33.6	71.0 ± 28.3
Mean BFMDRS postoperative±SD (mean follow-up 4.6 ± 4 years)	52.1 ± 33.8**	27.6 ± 16.3**	56.2 ± 36.3**	59.9 ± 30.7
Missing pre and/or post BFMDRS scores	30	7	12	11

[a] 11 patients with missing data.
[b] Nine patients with 2nd GPi implantation (eight bilateral/two unilateral) and one patient with 3rd GPi implantation after initial GPi-DBS.
[c] One patient with 2nd GPi implantation bilateral and with 3rd GPi implantation unilateral after initial GPi-DBS.
[d] Five patients with 2nd GPi implantation (one unilateral/four bilateral) after initial GPi-DBS.
[e] One patient with GPi implantation after initial STN implantation, two patients with 2nd GPi implantation after initial GPi-DBS.
[f] One patient with STN and VOA implantation after initial GPi and VIM implantation.
[g] One patient with GPi and STN DBS.
[h] One patient with GPi and VIM.
[i] One patient with GPi and VIM DBS and one patient with 2ndVIM implantation after initial VIM implantation.

in a second surgical session a few days after implanting the electrodes (missing data for 29 patients). At initial DBS implantation 28 patients (38.9%) received a rechargeable IPG, whereas 35 patients (48.6%) were implanted by a non-rechargeable IPG. 13 patients (18.1%) received a rechargeable device for revision surgery and 21 patients (29.2%) received a non-rechargeable IPG (missing data for 23 patients).

Adverse events

The mean follow-up duration was 4.6 ± 4 years after initial implantation (range 1 month–15 years). Adverse events were classified into reversible and irreversible AEs, requiring surgical intervention, and according to different peri- and postoperative time categories. Fig. 1 and Table 2 provide a detailed overview of the type of event and its occurrence within these categories.

IPG replacements due to battery failure are excluded in the following as they are classified as expected and scheduled surgical interventions. Overall, 184 AEs were documented in 53 of 72 patients (73.6%) including 61 transient programming-induced side effects in 22 patients (30.6%), and 27 AEs in 17 patients (23.6%) not related to the DBS system. Seven patients (9.7%) were documented to have lack or loss of effect, categorized as non-responders. In four of these patients the whole DBS-system was explanted, whereas the sole removals of IPGs and extension leads were performed in two patients. One patient refused any further intervention (Fig. 1).

Excluding scheduled IPG replacements, stimulation-induced side effects, non-DBS related AEs, and lack or loss of effect-related events, the total number of unexpected DBS-associated AEs was 89 in 39 patients (54.2%), of which 36 events were reversible and 53 were irreversible. 52 irreversible AEs in 26 patients (36.1%) required 45 subsequent surgical interventions 4.8 ± 4.1 years (range 3 months – 15 years) after initial implantation. One patient refused

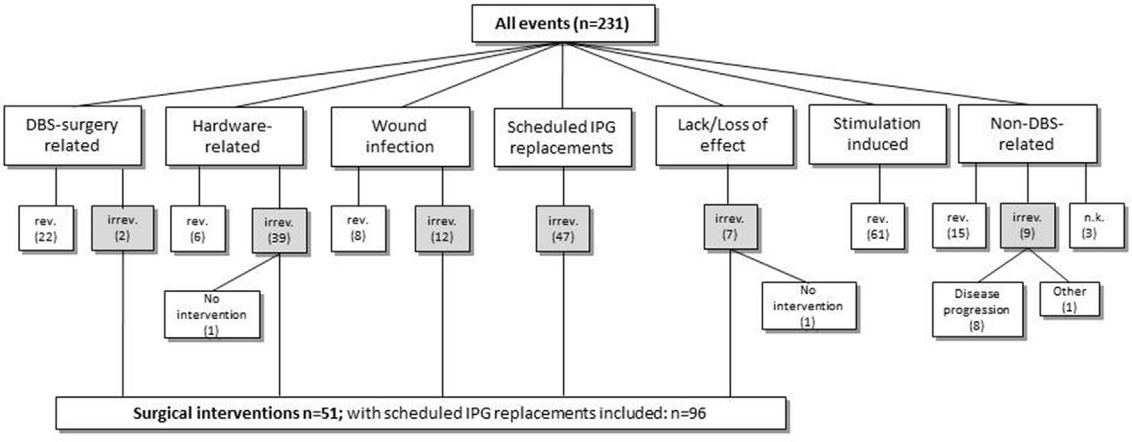


Fig. 1. Overview of all documented adverse events with scheduled IPG replacements included.

Table 2
Short and long term adverse events (AEs) associated with DBS. Ongoing AEs are listed in all time intervals during which they were documented. Note, that they were only counted once when calculating the absolute number of AEs per patient (see section on results). IPG = implanted pulse generator, DBS = deep brain stimulation, CSF = cerebrospinal fluid.

Perioperative (<4 weeks)		
DBS-surgery related complications	AE/patient	Intervention
1. reversible		
CSF collection[b]	7/7	
Fever[b]	3/3 (1 after DBS explant)	
Stridor after IPG revision/respiratory distress[a]	2/2	
Paraesthesia/sensory dysfunction[b]	2/1	
Impaired wound healing[b]	1/1	
Pneumonia[a]	1/1	
Swallowing problems/dysarthria[b]	1/1	
Agitation[a]	1/1	
Vertigo[a]	1/1	
Seizure (known epilepsy)[c]	1/1	
Intracranial haemorrhage after pallidotomy and DBS explantation[b]	1/1	
Increased hyperkinesia[b]	1/1	
2. irreversible		
Wound infection[b]	2/2	Intervention 8 weeks after implantation (see next interval)
All	**24 (10.1%)/17 (23.6%)**	

Short-term postoperative (1–6 m)		
Adverse Event	**AE/patient**	**Intervention**
Wound complications		
1. reversible		
Wound infection	3/3	
Papilloma	1/1	
Seroma	5/5[d]	
2. irreversible		
Wound infection	3/3[e]	IPG and/or lead extension removal/replacement
	1/1[e]	DBS-System removal/replacement
Seroma	1/1	IPG and/or lead extension removal/replacement
Hardware complications		
1. reversible		
IPG accidental arrest	0	
2. irreversible		
IPG		
IPG technical defect	1/1	IPG removal/replacement
Extension lead		
Extension lead technical defect	1/1	Lead extension removal/replacement
Extension lead dislocation/migration	1/1	Lead extension removal/replacement
Lack or loss of effect-related complications		
Lack or loss of efficacy	1/1	No intervention
All	**18 (7.6%)/16 (22.2%)**	

Long-term postoperative (>6 m), mean follow-up 4.6 ± 4 years		
Adverse Event	**AE/patient**	**Intervention**
Wound complications		
1. reversible		
Wound infection	2/2	
2. irreversible		
Wound infection	5/3[f]	IPG and/or lead extension removal/replacement
	6/5[f]	DBS-System removal/replacement
Hardware complications		
1. reversible		
IPG accidental arrest	6/6	
2. irreversible		
IPG		
Technical defect	10/7	IPG removal/replacement
Dislocation	4/3	IPG removal/replacement
Extension lead		
Technical defect	1/1	Lead extension removal/replacement
Fracture	3/2	Lead extension removal/replacement
Dislocation	1/1	Lead extension removal/replacement
Migration	1/1	Lead extension removal/replacement
Shortness due to growth	5/5	Extension lead revision
Discomfort/pain	3/1	Extension lead revision and/or change of IPG position

Table 2 (*continued*)

Perioperative (<4 weeks)			
DBS-surgery related complications	AE/patient	Intervention	
DBS electrode			
Technical defect	2/2	DBS-system removal/replacement	
	1/1	No intervention	
Dislocation/migration/malposition	5/4	DBS-system removal/replacement	
Lack or loss of effect-related complications			
Lack or loss of efficacy	4/4	DBS-system replacement/removal	
	2/2	IPG and/or extension lead removal/replacement	
Battery expiry	**47/26**	**Scheduled IPG removal/replacement**	
All	**108 (45.4%)/44 (61.1%)**		
Stimulation-induced side effects[g]	Perioperative (<1 month)	1–6 months	>6 months (mean follow-up 4.6 ± 4 years)
Occurrence of/worsening of dystonia	2/2	9/7	13/13
Pain		3/3	2/2
Swallowing/dysarthria		3/3	12/7
Coordination problems		1/1	
Muscle cramps/fasciculations		1/1	3/2
Increased seizure frequency			1/1
Weakness		1/1	
Paraesthesia			4/4
Sleep disorder			2/2
Vertigo		1/1	1/1
Psychiatric comorbidity		1/1	1/1
All	**2 (0.8%)/2 (2.8%)**	**20 (8.4%)/9 (12.5%)**	**39 (16.4%)/17 (23.6%)**
Non-DBS associated disease-related complications			AE/patient
1. reversible			
Spread of dystonia in new body parts, reversible after stimulation adjustment			5/5
Weakness			2/2
Sleep disorder			1/1
Vertigo			1/1
Worsening of Cognition			1/1
Pain/headache			5/4
2. irreversible			
Worsening of dystonia due to disease progress (independent to stimulation parameters)			8/7
Increased frequency of seizure			1/1
3. not known			
Pain/Headache			1/1
Dystonia in new parts			2/1
All			**27 (11.3%)/17 (26.6%)**

[a] Associated with anesthesia.
[b] Associated with surgical intervention/DBS implantation.
[c] Unknown association.
[d] Ongoing AEs are counted for all time intervals.
[e] Two patients with ongoing wound infection.
[f] Two patients with impaired wound healing and infection.
[g] Reversible after stimulation adjustment.

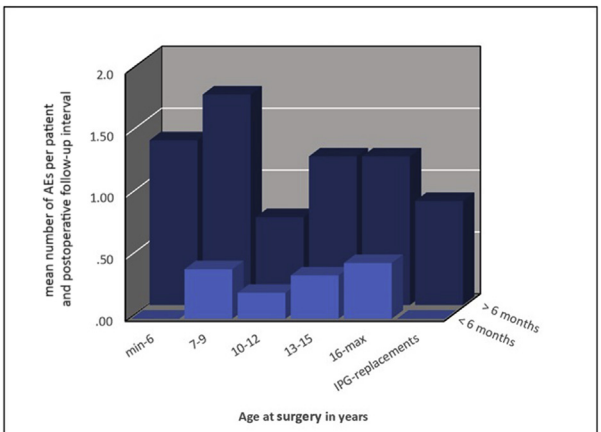
intervention. Note, that in six patients (8.3%) more than one DBS-related complications were revised within the same surgical session.

26 patients (36.1%) underwent at least one surgical intervention due to wound infections or hardware problems, with hardware-related AEs being more common (n = 38 in 19 patients/26.4%), including 16 AEs associated with lead extensions, 15 AEs with IPGs and seven AEs with DBS electrodes (for further details see below). The number of DBS-related wound infections requiring surgical interventions was n = 14 in nine patients (12.5%) (Table 2). Differentiating between the different groups with regard to aetiology and clinical phenotype, 19 AEs (36.5%) in seven patients requiring surgical intervention were documented in group 1 (isolated inherited or idiopathic dystonia), 19 AEs (36.5%) in 11 patients in group 2 (combined inherited or idiopathic dystonia), and 14 AEs (26.9%) in eight patients in group 3 (acquired dystonia). Comparing the rate of AEs between these groups, there were no statistically significant differences.

With relation to the surgical procedure, there was a higher rate of perioperative AEs in patients, who underwent electrode and IPG implantation whithin the same surgical session (n = 16), compared to patients with two-staged surgery (n = 14) during the first six months postoperative ($p < 0.05$, 95% CI 0.03 to 0.47). However, none of these AEs were infections.

There was a trend towards a positive correlation between severity of dystonia and rate of adverse events. The higher the preoperative BFMDRS score was, the more AEs could be documented, but without reaching statistical significance ($p > 0.05$) (Supplementary Fig. 1).

Age had a relevant impact on the complication rate. The following paired comparisons of different age groups in terms of complication rate were significant: Comparing patients aged 7–9 years with 10–12 year-old patients ($p < 0.05$) and comparing patients aged 7–9 years with 15–18 year-old patients ($p < 0.05$). Patients aged 7–9 years had the highest complication rate per follow-up year, whereas patients aged 10–12 years had the lowest (Fig. 2).



		Age at surgery in years					
	Number events/ number patients	min-6	7-9	10-12	13-15	16-max	IPG replace-ments
Treatment time	< 6 months	0/3	4/10	3/14	6/17	5/11	0/55
	> 6 months	4/3	17/10	10/14	21/17	13/11	45/55

Fig. 2. Mean number of adverse events per patient (z-axis) according to different age groups (x-axis) during the follow-up intervals of 0–6 months (light blue) and 6 months till max. time after implantation (dark blue) (y-axis) (excluding stimulation-induced and non-DBS related events). Analysis was restricted to patients with at least two years of follow-up (n = 55). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Gender did not have any impact on the rate of AEs.

All these analyses were restricted to patients with at least two years of follow-up (n = 55).

In terms of electrode-year (EY), implying the number of initially implanted electrodes multiplied by years of follow-up, the total risk of a complication requiring surgical intervention was 7.9% per EY (95% CI 5.9 to 10.3) (excluding system removals due to loss or lack of effect (n = 6) and scheduled IPG replacements due to battery expiry (n = 47)). Looking at the two categories separately (wound-related and hardware-related AEs), the risks for a wound-related AE requiring surgical intervention was 2.1% per EY (95% CI 1.2%–3.6%) and for an irreversible hardware-related AE 5.8% per EY (95% CI 4.1%–7.9%).

In the following, AEs are listed according to different follow-up intervals (Fig. 3):

Intraoperative adverse events

There were no intraoperative AEs documented.

Perioperative AEs (<4 weeks after implantation)

26 AEs were documented in 18 patients (25.5%) during the first four weeks after implantation, either during hospitalization or during outpatient consultation after discharge (Table 2). In one patient with GPi-DBS an asymptomatic right-sided intracranial bleeding was identified on postoperative imaging two days after pallidotomy via DBS electrodes and subsequent incomplete removal of the DBS electrode on the same side and complete removal of the left electrode, all within the same surgical session. One patient with known epilepsy had a generalized seizure seven days postoperatively.

Irreversible wound infections were documented in two patients. All other AEs (20 AEs in 15 patients) during the perioperative period were self-limiting. The most common reversible AE was a transient CSF collection in seven patients, either around the IPG pocket or around the burr holes on the scalp.

In two patients successive stimulation-induced worsening of dystonia was documented.

Postoperative AEs (1–6 months after implantation)

During the interval between 1 and 6 months after first DBS-Implantation or revision surgery, 36 AEs in 18 patients (25.5%) were documented. 12 AEs could be categorized into *wound- and hardware-related AEs* with six being reversible and six being irreversible events. One patient was reported to have loss of effect without any intervention.

Wound-related AEs were documented in nine patients (12.5%), including wound infections in two patients, seroma around the IPG or the scalp in three patients, and one papilloma on the IPG pocket, which were all reversible.

Irreversible wound AEs were documented in three patients, including wound infections in two patients and a seroma in one patient, all requiring surgical interventions.

In terms of *hardware-related AEs* there was one patient with an IPG replacement due to a technical defect. Replacements of extension leads were necessary in two patients due to technical defects, respectively migration of the retro-auricular part.

In total, there were six patients (n = 8.3%) undergoing surgical interventions due to irreversible AEs associated with wound infections or hardware problems 3.4 ± 1.1 months (range 3–6 months) after implantation, including two patients with ongoing wound infections already documented in the perioperative period (0-<4 weeks).

20 stimulation-induced transient AEs were documented in nine patients and three events could be classified as not DBS-related.

Postoperative long-term adverse events (>6 months after implantation)

In total, 122 adverse events (66.3% of all AEs) in 42 patients (58.3%) were documented, which occurred more than six months after first implantation or revision surgery, including 39 stimulation-induced, and 24 not DBS-related events. Excluding the two latter, 59 AEs in 30 patients could be categorized into *wound-, hardware- and loss or lack of effect-related AEs*, with eight AEs being reversible and 51 being irreversible.

Wound associated AEs were documented 11 times in nine patients. In two patients two wound healing problems were self-limiting, whereas seven patients suffered of irreversible infections necessitating surgical interventions: In total, four IPG or lead extension removals/replacements in three patients after a mean time of 36 ± 13.15 months (range 24–48 months) and five DBS-system removals/replacements in five patients after a mean time of 33.6 ± 19.7 months (range 12–48 months) were documented. Explantation of the DBS-system due to recurrent wound infections was performed one year (two patients) and four years (three patients) after initial implantation. One of these five patients was re-implanted.

In total, seven patients (9.7%) underwent surgical interventions due to wound infections 34.7 months ± 16.4 (range 12–48 months) after initial implantation.

Hardware-related adverse events were most common with a frequency of 42 in 21 patients (29.2%). Six accidental arrests of the IPG were documented in six patients as reversible events.

Unscheduled IPG replacements were performed in seven patients due to technical defect (10/7) or dislocation (4/3) after a mean time of 73.7 months ± 45.6 (range 24–180 months) after initial implantation. Lead extension replacements were performed

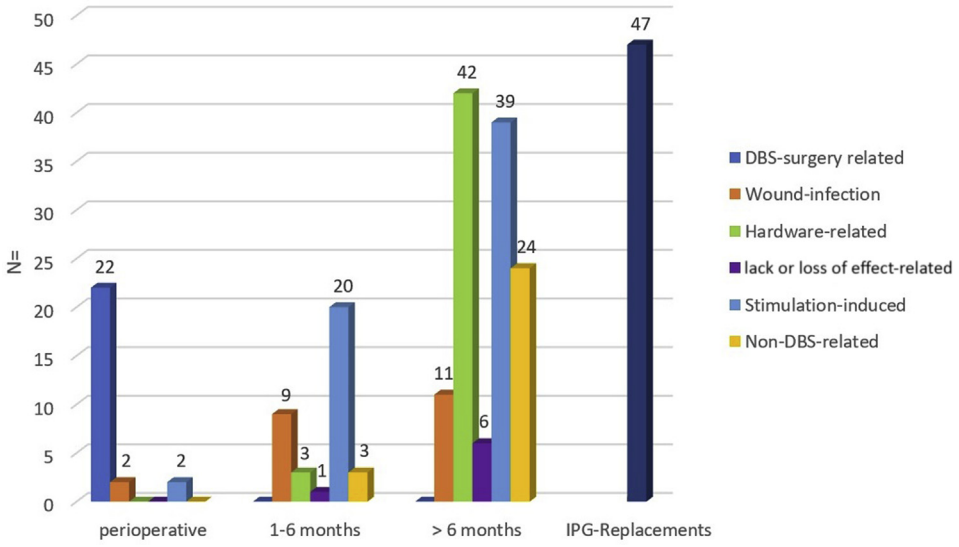


Fig. 3. The number of all adverse events in each time category.

14 times in 10 patients due to a technical defect indicated by repeatedly measured high impedances on the connecting sites (1 replacement), lead fracture (3 replacements/2 patients), lead migration (2 replacements/2 patients), shortening due to growth (5 replacements/5 patients) or discomfort/pain (3 replacements/1 patients). The mean time of lead extension revision was 62.6 months ± 45.4 after initial implantation (range 24–168 months). Seven DBS-system removals had to be performed in six patients due to technical defects according to high impedances on the connecting sites (2/2), dislocation (4/4), or malposition (1/1) of the DBS electrode after a mean time of 56.6 months ± 40.2 (range 24–120 months) after initial implantation. One patient refused intervention despite a documented technical defect.

In total, 35 AEs in 16 patients (22.2%) were due to hardware defects requiring surgical interventions after an average time of 65.8 months ± 43.7 (range 1–15 years) after initial implantation.

Loss or lack of effect-related adverse events were documented in six patients. Four patients wished for complete removal of their DBS-system and two patients only of their IPG plus extension lead because of ineffectiveness or loss of effect after a mean time of 48 months ± 21.5 (range 24–48 months) after initial implantation.

47 scheduled IPG replacements due to battery expiry were documented in 26 patients (36.1%) 40.6 months ± 21.9 (range 12–96 months) after initial implantation or last revision. 39 stimulation-induced side effects were documented in 17 patients (23.6%) during the long-term follow-up. 24 events were documented as non-DBS related, whereas nine irreversible AEs were interpreted as part of the underlying diseases. Due to incomplete documentation, it was not clear whether worsening of dystonia in one patient was stimulation-induced or an irreversible phenomenon, and whether pain was reversible or irreversible in one patient.

Overall, patients were more likely to encounter AEs on the long-term follow-up as most AEs were documented beyond 6 months after initial surgery: 18 AEs (21.7% of all AEs) documented in 11 patients (20%) during 0–6 months versus 65 AEs (78.3%) in 31 patients (56.4%) >6 months ($p < 0.05$). This analysis was restricted to patients with at least two years of follow-up, too ($n = 55$).

Discussion

Generally, DBS is an elective procedure. The selection of suitable patients can be difficult, as there is a great variability in outcome [6,7]. Patients with inherited isolated dystonia such as DYT-TOR1A often have beneficial effects, whereas outcome of patients with acquired forms is less pronounced and more heterogeneous. Here, a definite prediction of outcome is difficult to make. When considering DBS in pediatric patients, weighing up the risks against the potential benefits is therefore challenging in most of the cases. DBS is regarded as a safe and effective treatment option, but large controlled trials are limited and most reports only briefly mention DBS-related AEs with varying information concerning frequency and severity. This variability may be due to several reasons such as differences in the definitions of AEs, the inclusion or exclusion of self-limiting AEs, or to differences concerning the length of follow-up. Long-term case series, especially for pediatric cohorts, are lacking, which is critical for the interpretation of the data as we could demonstrate that patients are more likely to encounter AEs beyond six months after implantation.

Almost all AEs, which are documented as intraoperative or perioperative, immediately related to DBS implantation, were transient, except one asymptomatic intracerebral haemorrhage (ICH) in a patient with GPi-DBS after pallidotomy and subsequent incomplete removal of the DBS lead. ICH can be a devastating complication associated with DBS implantation, but seems to be far less frequent than infections. It can be easily detected by computed tomography (CT), which is performed postoperatively in many centers to evaluate location of the electrodes and exclude ICH. In a large cohort of 272 adults who underwent 448 DBS lead implantations, the ICH rate was 2.9% per lead and 4.8% per patient, whereas only one patient showed a large ICH requiring surgery [17]. Fenoy et al. report only one symptomatic postoperative ICH in a cohort of 720 patients [18]. Besides the rate of symptomatic ICH, there was a higher number of asymptomatic ICH, which became evident on postoperative CTs [11,19,20]. In the largest pediatric population reported so far, the rate of perioperative ICH was below 1% [21], which is in accordance with our data suggesting a very low risk of vascular events associated with DBS, especially in young patients. This might be due to the rare use of multiple test trajectories for microelectrode recordings and the lack of any cardiovascular co-morbidity in the pediatric population [22]. However, it is of note that in children the postoperative CT scan is most often performed immediately after implantation in order to avoid a second anesthesia, whereas in adults CT scans are most preferably

performed one day after surgery. Therefore, cases with asymptomatic late ICH may be underreported [17].

Wound or hardware infections were common AEs documented in our cohort, affecting 12.5% of the patients, which is higher compared to most of the previous reports on adult cohorts [18,23,24]. Postoperative surgical-site infections seem to be the most common problem during follow-up, varying among authors between 1 and 10% in adult cohorts [25,26]. Most infections seem to occur within the first months after surgery, with coagulase-negative staphylococci (40–60%) being the most common causative organism [11,26,27], whereas in our cohort DBS-related infections were more common beyond six months of treatment. Only four out of 17 documented infections could be effectively treated by non-invasive procedures. All others required hardware removal or replacement. Wound infections associated with DBS surgery are particularly challenging, because of its association to the implanted hardware, mainly the IPG and the extension cable, requiring hardware removal in most of the cases despite extensive antibiotic treatment [21,28,29]. Most of the data suggest that children undergoing DBS have a higher infection rate compared to adults, especially with acquired forms of dystonia such as cerebral palsy [7,13]. However, the rates of infections vary among authors. Air et al. reported infections in 57% of the children implanted younger than 10 years of age [7], which is in line with our findings in the group of patients aged 7–9 years at time of surgery and the highest rate of AEs per follow-up year, whereas Kaminska et al. recorded a distinctively lower rate of 7.6% in patients younger than 7 years from a 10 years-experience, with an even lower rate of 4.7% in those patients with new rechargeable implants, comparable to the rates reported in adult cohorts [2,12,15,30–32]. The authors postulate that the low infection rate in this group could be attributed to the favorable small size of the generator facilitating accommodation within the surrounding tissue [21]. In the multicenter setting of the registry several factors may influence frequent infections after DBS implantation among children, such as the severe physical impairment and underweight of most of the patients implanted at a young age, making them vulnerable for infections, the nature of the hyperkinetic movement disorder causing mechanical irritation of the skin covering the hardware, and not least the surgeon's experience and the length of surgery [23]. Therefore, the development of clinical guidelines addressing peri- and postoperative antibiotic treatment regimens, a sensible duration for postoperative inpatient monitoring as well as follow-up visits enabling a thorough clinical follow up of these patients would be desirable.

We found a significant number of non-infectious, hardware-related adverse events in 29.2% of the patients, with technical defects being the most common indication for surgery. The group of patients with severe hyperkinesia such as in dyskinetic cerebral palsy is particularly vulnerable to hardware defects such as lead fracture or IPG dislocation because of the mechanical strain caused by involuntary movement. Impedances should therefore be checked regularly, because there is a risk of worsening of dystonia due to lack of efficient stimulation. In case of high impedances, an X-ray of the whole DBS system should be performed to rule out lead or extension lead fracture [21]. Sufficient peri- and postoperative pain management should also be implemented for pediatric patients in order to avoid deterioration of dyskinesia triggered by pain. According to our own clinical experience, starting the stimulation too early with rapid increase of stimulation parameters, though still far below the therapeutic ranges, can also increase dyskinesia in some patients.

In six children the IPG switched off accidentally, not related to battery failure. This might be attributed to neglected recharging or by incorrect use of the patient's control device, which can lead to acute deterioration of dystonia. Therefore, a regular clinical follow-up of patients and families in combination with repeated training on device maintenance is highly recommended, especially in patients with poor compliance [14].

In 26 patients the IPG had to be replaced 47 times due to battery expiry, classified as an expected event. Repetitive admission for surgery requiring full anesthesia and the increased risk of infections could be avoided by implanting rechargeable devices, especially in young children [33]. Most of the patients and caregivers regard rechargeable IPGs as a suitable option [14].

In six patients (8.3%) the whole system was removed due to lack or loss of effect. The most frequent reasons for lack of effect, categorized as "non-responder" patients, are poor lead location or dystonia aetiology other than idiopathic or isolated inherited dystonia [34]. Even in patients classified as idiopathic dystonia, DBS is not always beneficial, because they may have heterogeneous aetiologies for dystonia. Many of them may carry a monogenetic disease-causing mutation in undiscovered or recently discovered new genes associated with dystonia, which can be associated with rapid disease progression [35]. Therefore, DBS not always alleviates symptoms in so called idiopathic dystonia as often referred to. In order to improve the DBS service, a "personalized medicine approach" by the implementation of next generation sequencing is encouraged before implantation. Identifying the genetic defect of the underlying disease can help to predict the therapeutic response.

The phenomenon of decreasing effect over time is mostly attributed to the progression of disease in patients with inherited forms of isolated or neurodegenerative dystonia and seems to be more commonly observed in younger patients [36–38]. Multiple electrodes within the GPi or different targets might be helpful in controlling progressive symptoms [36]. In our cohort additional electrodes were rarely implanted. The removal of the total system was preferred giving up DBS as a therapeutic option.

Stimulation-induced side effects limiting the effective use of DBS in some patients can be another reason for loss or lack of effect [11].

Conclusion

DBS can be a powerful treatment option in children suffering from dystonia. Data provided by a multicenter cooperation demonstrate a noticeable rate of AEs associated with DBS during childhood, with hardware-related AEs being the most common AEs. Each complication is challenging and mostly necessitates hospital admission with great impact on the patients' quality of life. This has to be taken into account when counselling patients and their families about this therapeutic option. There is a trend of a higher complication rate in very young children, which has to be considered for DBS evaluation at a young age, when cerebral plasticity for neuromodulation is highest.

Being aware of potential AEs associated with early DBS application, standardized treatment and follow-up algorithms would be desirable to improve the medical and surgical management for this vulnerable population and to maximize the therapeutic benefit.

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Appendix A. Supplementary data

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