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Complications of vagal nerve stimulation for drug-resistant epilepsy A single center longitudinal study of 143 patients

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ABSTRACT

Purpose: To longitudinally study surgical and hardware complications to vagal nerve stimulation (VNS) treatment in patients with drug-resistant epilepsy.
Methods: In a longitudinal retrospective study, we analyzed surgical and hardware complications in 143 patients (81 men and 62 women) who between 1994 and 2010 underwent implantation of a VNS-device for drug-resistant epilepsy. The mean follow-up time was 62 ± 46 months and the total number of patient years 738.
Results: 251 procedures were performed on 143 patients. 16.8% of the patients were afflicted by complications related to surgery and 16.8% suffered from hardware malfunctions. Surgical complications were: superficial infection in 3.5%, deep infection needing explantation in 3.5%, vocal cord palsy in 5.6%, which persisted in at least 0.7% for over one year, and other complications in 5.6%. Hardware-related complications were: lead fracture in 11.9% of patients, disconnection in 2.8%, spontaneous turn-off in 1.4% and stimulator malfunction in 1.4%. We noted a tendency to different survival times between the two most commonly used lead models as well as a tendency to increased infection rate with increasing number of stimulator replacements.
Conclusion: In this series we report on surgical and hardware complications from our 16 years of experience with VNS treatment. Infection following insertion of the VNS device and vocal cord palsy due to damage to the vagus nerve are the most serious complications related to the surgery. Avoiding unnecessary reoperations in order to reduce the appearances of these complications are of great importance. It is therefore essential to minimize technical malfunctions that will lead to additional surgery. Further studies are needed to evaluate the possible superiority of the modified leads.

1. Introduction

The prevalence of epilepsy is 0.5–1%.[1] After adequate antiepileptic drug-therapy, approximately one third still suffer from seizures.[2] Resective surgery, where the cortical location of the onset of the seizures is resected, is one approach to decrease seizure frequency in patients with partial epilepsy. In order for this to be applied, the focus of the onset of the seizures needs to be identified, dispensable and accessible for surgery. In cases when this has proven not possible vagal nerve stimulation (VNS) has emerged as a therapeutic option. The first VNS implantation for the treatment of drug-resistant epilepsy not suitable for resective surgery was conducted in 1988.[3] Over the years, patients with primary generalized epilepsy which has been proven to be drug-resistant have also become candidates for VNS treatment. The positive effect of VNS in reducing seizure frequency has been shown extensively.[4,5] Complications due to surgery and hardware malfunctions have not been evaluated as thoroughly. Vocal cord palsy, transient bradycardia and infection are some of the complications associated with the surgical procedure that have been reported.[6–8] Hardware malfunctions such as lead fracture, disconnection between lead and stimulator, and stimulator malfunction have previously been observed.[6,9,10] VNS has been an integrated tool in the management of drug-resistant epilepsy in the epilepsy surgery program at Umeå University Hospital since 1994. The aim of this study is to describe surgical and hardware complications related both to the implantation and to the treatment course in patients with drug-resistant epilepsy receiving VNS treatment at our department since 1994.

2. Methods

In a longitudinal retrospective study, we identified the patients who between 1994 and 31 December, 2010, underwent implantation of a VNS device (Cyberonics Inc., Houston, TX, USA)

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for drug-resistant epilepsy at our department and analyzed the occurrence of surgical and hardware complications. The definition of surgical complication used is that of Sokol and Wilson: "A surgical complication is any undesirable, unintended, and direct result of an operation affecting the patient, which would not have occurred had the operation gone as well as could reasonably be hoped".[11] Infection is a condition that led to an active treatment with antibiotics. Hoarseness that persisted 15 days post surgery is considered vocal cord palsy. Hardware complication is defined as an incident that meant that the device did not work properly.

2.1. Patients

All patients were worked up within the multidisciplinary epilepsy surgery program at the Departments of Neurology, Pediatrics, Neurophysiology, Neuroradiology and Neurosurgery at the Umeå University Hospital, Sweden. They were all diagnosed with drug-resistant epilepsy, either not suitable for resective surgery or failure of the same.

2.2. Surgical procedure

Antibiotics are administered before skin incision. We used cefuroxime (30 mg/kg or 3 g) until the end of 2010 when we changed to cloxacillin (2 g). We use three different approaches, for the placement of the stimulator, depending on the patient. The most commonly used is a transverse incision approximately 3 cm below the collarbone. An incision just behind the anterior axillary line can be used to hide the scar. In one patient, we used a cranio-caudal incision along the course of the bra strap. For the implantation of the electrodes we used, in the very first patients, an incision along the sternocleidomastoid muscle. We soon changed to a partial collar incision. With blunt and sharp dissection the carotid sheath is entered. The nerve is identified and prepared for approximately 4–5 cm. A vessel loop is run beneath the nerve and used to hold the nerve while the electrode and anchor helices are being applied around the nerve. The electrode is secured with one anchor to the fascia of the medial muscles. The stimulator is tested and connected to the electrode followed by another test to verify that the system is functioning properly. The stimulator is usually not anchored to the fascia of the pectoral muscle. Stimulator replacements are done under local or general anesthesia and with prophylactic antibiotics. Leads are replaced under general anesthesia and with antibiotics.

2.3. Follow up

If no complications occurred the patient revisited the hospital two weeks post surgery for initiation of the stimulation. This was accomplished in three days by either the senior author or by a single epilepsy nurse. The adjustment to our standard parameter setting of 1.25 mA was reached in a great majority of the patients. Patients were evaluated at our clinic for outcome and the occurrence of complications every three months the first year, followed by yearly assessments. Medical charts from local hospitals were collected from the time in which the patients received treatment.

2.4. Statistics

Continuous variables are reported as means ± standard deviations. The median and range are also presented. Chi-squared is used for the comparison of proportions. A Kaplan–Meier plot was used to illustrate and analyze difference in lead survival time. A p-value of <0.05 is considered to be statistically significant. The statistical software used is JMP 9.0.0 (SAS Institute Inc.)

2.5. Complication frequency

Complication frequency is reported as percentage in relation to number of relevant procedures (npr) as well as the proportion of patients that suffered from complication (npts). Calculation basis npr or npts is shown after the percentage figure. The relevant procedures chosen for the different complications are presented in Table 3.

2.6. Ethics

The study was approved by the Regional Ethical Review Board Umea, dnr 2011-214-31.

3. Results

We identified 143 patients who had had a VNS device implanted between 1994 and 2010. Previous resective epilepsy surgery had been done in 27 of these patients. Patient characteristics are shown in Table 1.

The median follow-up time was 55 months (1–193) and the mean follow-up time was 62 ± 46 months. This corresponds to a total treatment time of 738 years. 110 patients were still receiving stimulation on 31 December 2010. Table 2 shows a summary of the 251 surgical procedures performed. The mean time to stimulator replacement was 58 ± 20.2 months and the median time 62 months (0.25–98). For the stimulators that were replaced before end of power the mean time to replacement was 66 ± 9.8 months and for the stimulators that were replaced because of end of power 62 ± 13.5 months. We used a skin incision below the collarbone in the midclavicular line in 79 patients and an incision in the anterior axillary line in 63. The system was implanted on the left side in all cases but two. Previous lymphoma on the left side of the neck was the reason in one patient. The other presumably had extensive tissue adhesions around the left vagus nerve as a result of infection during earlier left VNS treatment. We noted 28 surgical (11.2% npr) and 25 hardware (10.4% npr) complications in 40 patients (28% npts). 24 patients (16.8% npts) were afflicted by complications related to surgery and 24 patients (16.8% npts) suffered from hardware malfunctions. The total number of individual patients who experienced any complication leading to a surgical intervention was 25 (17.5% npts).

Table 3 summarizes all the complications.

Table 1
Patient characteristics.[a]

	Mean age, SD, at implantation, years	Median age (range) at implantation, years	PG	P	Unclear classification of seizures	Total
Men	25.4 ± 15.4	22.9 (2.2–64.2)	25	56	0	81
Women	30.7 ± 15.6	31.7 (4.1–72.7)	15	46	1	62
Adults	35.8 ± 11.9	34 (18.1–72.7)	30	67	1	98
Children	10.1 ± 4.3	9.4 (2.2–17.8)	10	35	0	45
Total	27.7 ± 15.7	27.8 (2.2–72.7)	40	102	1	143

[a] P, partial onset seizures; PG, primary generalized seizures.

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Table 2
Summary of surgical procedures.

Surgical procedure	*n*
VNS implantation	143
Plain stimulator replacement in one session	66
System replacement in one session (stimulator and lead)	6
Plain lead replacement in one session	9
Intentional lead replacement discontinued	1
Reconnection of lead to stimulator	4
Reposition of stimulator	2
Explantation of system (stimulator and lead)	9
Explantation of stimulator	5
Explantation of lead	2
Reimplantation of system (stimulator and lead)	3
Reimplantation of stimulator	1
Total surgical procedures	251

Table 3
Summary of the complications.[A]

Complications	Numbers	Incidence/ procedure (%)	Proportion of the patients (*n* 143) with complication (%)
Surgical complications	28	11.2[a]	16.8
Infection (all)	12	5.0[b]	7.0
Explantation required	7	2.9	3.5
Vocal cord palsy (all)	8	4.6[c]	5.6
Post first insertion	7	4.9[d]	4.9
Post lead explantation or replacement	1	3.8[e]	4.2
Bradycardia	1	0.4[f]	0.7
Puncture of jugular vein	3	1.7[g]	2.1
During first time insertion	1	0.7	0.7
During lead explantation or replacement	2	7.7	8.3
Hematoma	1	0.4[h]	0.7
Large subcutaneous nerve cut-off	1	0.4[i]	0.7
Keloid development	1	0.4[j]	0.7
Horner syndrome	1	0.6[k]	0.7
Technical complications	25	10.4[l]	16.8
Lead fracture	17	10.5[m]	11.9
Device malfunction	2	0.9[n]	1.4
Lead disconnection	4	1.8[o]	2.8
Spontaneous VNS turn off	2	0.9[p]	1.4

[A] a, relative frequency of incidents of complications among all surgical procedures; b, relative frequency of incidents of infection among all procedures excluding ex-plantations of parts of the device due to infection and ex-plantations of the entire system; c, relative frequency of incidents of voice alteration that remained for at least 15 days post surgery among all procedures on the neck excluding procedures where voice alteration already existed; d, relative frequency of incidents of voice alteration that remained for at least 15 days post first time insertion among all first time insertions; e, relative frequency of incidents of voice alteration that remained for at least 15 days post lead ex-plantation and replacement among all lead ex-plantations and replacements; f, relative frequency of incidents of bradycardia intra-operatively among all implantations, replacements and reconnections; g, relative frequency of incidents of hemorrhage among all procedures on the neck; h, relative frequency of incidents of hematoma among all surgical procedures; i, relative frequency of incidents of nerve cut-off among all surgical procedures; j, relative frequency of incidents of keloid development among all surgical procedures; k, relative frequency of incidents of Horner syndrome among all procedures on the neck; l, relative frequency of incidents of technical complications among all surgical complications excluding explantations where all parts were explanted; m, relative frequency of incidents of lead fracture among all procedures where a new lead was inserted; n, relative frequency of device malfunction among all stimulators inserted; o, relative frequency of incidents of disconnection between stimulator and lead among all procedures excluding explantations; p, relative frequency of incidents of systems spontaneously turning off among all stimulators.

3.1. Surgical complications

Twelve incidents of infections were reported in ten patients (7.0% npts), i.e. two patients were affected twice by an infection. Each infection exclusively affected the region close to the stimulator with two exceptions where the location of the lead, close to the vagus nerve, was infected. Fig. 1 illustrates infection frequencies in relation to the number of surgeries and patient age. The differences in these infection frequencies are not statistically significant. Of the twelve infections seven (3.5% npts) had to be treated with surgical removal of the device. After first time insertion three (2.1% npts) deep infections needing removal of the generator occurred, and three (2.1% npts) superficial infections, only needing antibiotics, were identified. An infection needing surgical intervention after stimulator replacement was found in 3 patients (3.9% of the replacements). After one case of stimulator replacement (1.3% of the replacements) a superficial infection was observed and later successfully treated with antibiotics. In one patient who experienced a deep infection around the stimulator the stimulator was removed but the lead left in place and the patient was treated with antibiotics. This patient was after the treatment re-implanted with a new stimulator but soon after developed a new infection which led to the explantation of the entire system. The median time to the appearance of infection was 13 days (1–930) after the last surgery. Of the infections three presented later than 3 months after surgery (182, 435, 930 days after surgery), two of them needed surgical treatment. The mean age of the patients with infection was 29.1 ± 16.1 years. There was no statistically significant difference in infection frequency related to the skin incision used.

Postoperative vocal cord palsy was seen in eight patients (5.6% npts), as shown in Table 4.

One patient (0.7% npts) experienced an episode of bradycardia during the intra-operative testing. Atropine was administered intravenously and within one minute the cardiac rhythm had normalized. Bradycardia did not occur during the initiation phase two weeks later. The patient had no history of cardiac disorder prior to the surgery. In three patients (2.1% npts), the jugular vein was injured causing peroperative bleeding. One was a first time insertion and two occurred during lead revisions. In two cases, the vein was repaired and the operation continued. In one case of lead replacement, the procedure was interrupted and performed six months later. In one case (0.7% npts), a superficial cutaneous nerve branch was cut. This patient suffered from hypoesthesia on the left side of the neck after surgery. In one patient (0.7% npts), keloid development was seen at the site of the incision on the neck. Signs of Horner syndrome appeared in one patient (0.7% npts) in whom left-sided miosis and ptosis were present subsequent to surgery. The surgery was a first time insertion and the symptoms arose before the initiation of stimulation. Computed tomography angiography revealed no carotid dissection. The condition was temporary but its duration could not be ascertained.

3.2. Technical complications

Totally 161 leads of 4 different types have been implanted. We noted 17 lead breakages (11.9% npts and 10.5% of the leads). All lead breakages affected the primary implanted lead. Of the first introduced lead model (300) 64 have been implanted. We changed to lead model 302 in the midst of 2003 of which 92 have been implanted. In 2010 two new models were introduced, 303 and 304, of which we have implanted 3 and 2, respectively. Median time, from implantation until explantation or end of study, was 93.5 months (3–192) for lead model 300 and for the model 302 the corresponding time was 39 months (0–86). The number of lead breakages noted in the 300 model was 13 (20.3% of the 300 leads) and in model 302 4 (4.4% of the 302 leads) ($p = 0.0016$, Chi-square). Looking at a survival analysis (Fig. 2), there was no statistically significant difference in the survival time between the two lead

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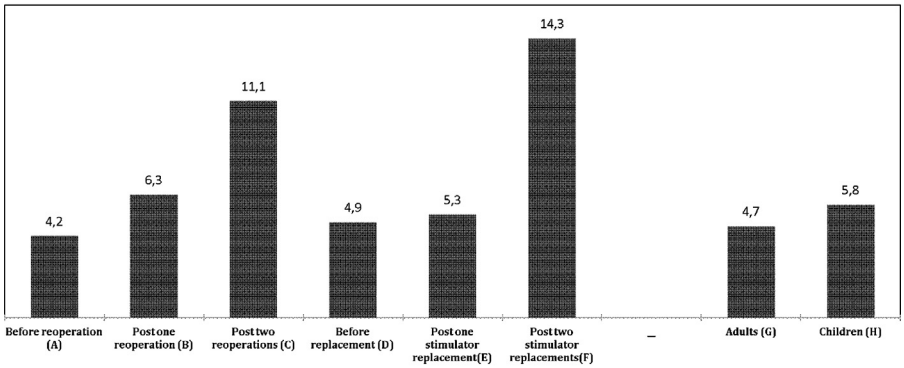

Fig. 1. Bar graph demonstrating the infection frequencies (%) before and after one and two reoperations and stimulator replacements respectively, and the difference in infection frequencies (%) between adults and children. (A) Relative frequency of infections occurring before replacement, reconnection, or repositioning among all patients with a VNS implant. 6/143. (B) Relative frequency of infections occurring after one procedure (replacement, reconnection, or repositioning) among all patients that have undergone at least one of these procedures. 4/63. (C) Relative frequency of infections occurring after two procedures (replacements, reconnections or repositionings) among all patients that have undergone at least two of these procedures. 2/18. (D) Relative frequency of infections occurring before stimulator replacement among all patients with a VNS implant. 7/143. (E) Relative frequency of infections occurring after one stimulator replacement among all patients who had undergone at least one stimulator replacement. 3/57. (F) Relative frequency of infections occurring after two stimulator replacements among all patients who had undergone at least two stimulator replacements. 2/14. (G) Relative frequency of infections occurring in patients who were over 18 years old when the last procedure was done among all procedures on patients over 18 years old excluding explantations of parts of the device due to infection and explantations of the entire system. 8/170. (H) Relative frequency of infections occurring in patients who were under 18 years old when the last procedure was done among all procedures on patients under 18 years old excluding explantations of parts of the device due to infection and explantations of the entire system. 4/69.

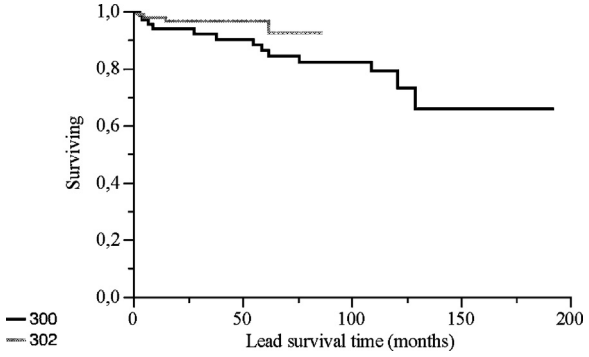

Fig. 2. Kaplan–Meier plot over survival time of different models of leads.

models. Lead replacements due to presumed breakages were preceded by plain X-ray to identify lesions in 10 cases. Lesions could be verified in 4 of these. No stimulator replacement had been made prior to 14 of the 17 cases of lead breakage. In instance of stimulator replacement, a breakage occurred while the electrode pins were being removed from the stimulator. This lead had been inserted 129 months before and corrosion between lead and stimulator was observed. The mean time to lead breakage after insertion was 42.9 ± 41 months, median 37 months (0.6–129). The median age of the patients when the breakage occurred was 25.8 years (6–59). There was no statistically significant difference in lead breakage depending on the type of skin incision used. Two devices (1.4% npts) appeared not to be working shortly after insertion. Subsequent tests verified that these were non-functional devices. One was a first time insertion and the other occurred after replacement. The stimulators were replaced after 8 and 29 months respectively resulting in properly working devices. The reason for these malfunctions is unclear. Disconnection between lead and stimulator was seen in four cases in four patients (2.8% npts). No stimulator or lead replacements had been made prior to these incidents. After reconnection, all four systems worked properly. The times from VNS insertion to disconnection were 24 days, 6, 7, and 11 months. The ages of these patients at disconnection were 9, 39, 18, and 10 years respectively. Two systems (1.4% npts) turned off spontaneously during treatment. This occurred once in one patient, and twice in another. They were both restarted and no explanation for these malfunctions could be found.

Table 4
Summary of the vocal cord palsies.[a]

Vocal cord palsy, no	Post system implantation or lead-explantation	Verified at the Department of Otolaryngology	Duration (months)
1	SI	Y	1.5
2	SI	Y	12
3	SI	Y	6
4	SI	Y	Subsided after 3
5	SI	Y	?
6	SI	N	1
7	SI	N	1
8	LE	N	Prevalent after 12

[a] SI, implantation; LE, lead-explantation; N, no; Y, yes.

4. Discussion

VNS treatment is considered to be a relatively safe approach to improve the condition of individuals suffering from drug-resistant epilepsy. Various side effects are related to the actual stimulation and adjusting the stimulation settings can reduce these. However, being a surgical procedure, VNS implantation involves certain risks. Inserting a foreign body adds to these risks. Published surgical and hardware complication frequencies are most often reported as the relative frequency of patients that suffered from complications. The number of additional surgeries patients undergo may influence some of these frequencies. Stimulator replacements are inevitable since stimulators run out of power. We believe that a long follow-up time tends to increase certain complication frequencies. In order to obtain more accurate numbers, a different way of calculating these frequencies has been used, as in Table 3. To be able to compare our data with previous data, we also present figures as the proportion of patients that suffered from complications.

In our study, 16.8% of the patients were affected by complications related to the surgery. With few exceptions, previous studies present frequencies ranging from 2.5 to 12.5%.[5,6,8–10,12–17] One report noted that at least 23.5% of their patients suffered from complications from the surgery.[18] Cervical hypoesthesia was the

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main reason for the high frequency in that study. The reason for our relatively high surgical complication frequency is most likely multifactorial. As described above, a long follow up time will most certainly increase the numbers of complications. Our mean follow time of 62 months is within the higher range of previous studies.[5,6,8–10,12–17] Scrutinizing the complications that appeared in our material and comparing these with previous described one can notice that apart from vocal cord palsy, of what we had a higher frequency, our complication rates for specific complications were within the same range as other studies. However, we report of certain complications not previously described, e.g. puncture of the jugular vein and keloid development. Noticeable was also the vast number of different complications that was prevalent in our series. We encountered 8 different types of complications related to surgery. Previous studies report numbers ranging from 1 to 5 with a mean rate of 1.9.[5,6,8–10,12–17] Adjusting these figures to the number of patients these studies comprehended there were 28.6 patients to every new type of complication compared to our 17.9. We have no explanation for this finding. The criteria set for the various complications may differ in the literature. Regarding the cases of infections we included conditions that led to an active treatment. This approach may overestimate the infection frequency. One patient received antibiotics in an outpatient clinic 930 days after surgery for a suspected infection around the system. The symptoms of the claimed infection allegedly then vanished. It can be questioned whether or not this was an infection related to the system.

In terms of hardware complications, reports of relative incidences are between 0 and 20.8%.[5,6,8,10,12,14–17,19] Our results (16.8% npts) are consistent with these studies.

4.1. Surgical complications

4.1.1. Infection

We report 12 cases of infection in 10 (7.0% npts) of the patients. Previous studies report infection rates from 0 to 10.9%.[5,6,8,9,12,13,16–18,20–24] We treated superficial infections successfully with oral antibiotics, but in the deeper infections, device explantation was unavoidable. Prophylactic antibiotics were administered only during implantation. Prolonged antibiotic treatment subsequent to surgery might be feasible to reduce the incidence of infection. One study implementing this regime reported an infection frequency of 0% in 36 patients treated.[6]

Whether or not the frequency of infection is higher after additional surgery has not to our knowledge been assessed before. Among our patients, we recognized a higher frequency of infection after one reoperation and an even higher frequency after a second than in patients with no reoperation. We made the same observation with regard to stimulator replacements. This outcome could imply that the absolute risk of infection at the site of the stimulator is enhanced after every reoperation at this location. This emphasises the need for stimulators with a longer battery life or rechargeable stimulators.

With two exceptions, all our infections occurred at the location of the stimulator. A concern of ours has been the risk of reinfection after reimplantation if previous explantation due to infection included only the stimulator and not the entire system. We noted a higher risk of infection if only the stimulator was removed. Our material is too small for conclusions to be drawn, but it nevertheless suggests that the removal of the entire system is necessary in order to reduce the risk of reinfection. Patel and Edwards encouraged the same regime based on their own experiences of reinfection and a review of present literature.[25] In contrast to these reports, Wozniak et al. showed that early removal of the stimulator and concealing the proximal end of the lead in unaffected tissue followed by three to four weeks of antibiotic treatment cured the infection and led to subsequent successful reimplantation in three out of four patients.[26] Although the number of patients is small, these later results are promising as they indicate that two additional interventions in the vicinity of sensitive structures in the neck can be avoided in some cases of infection. Further studies implementing this approach are needed to determine its value.

4.1.2. Vocal cord palsy

Vocal cord palsy has previously been reported to affect 1–2.7% of the patients and has usually been transient.[5,6,12,21,22,24,27,28] Higher frequencies of this complication have been reported in studies with small materials.[3,19,29] Zalvan et al. presented two cases of vocal cord palsy attributed to the surgery.[30] Dissection in order to reveal the vagus nerve, leading to disruption of the blood supply in the area as well as clamping, heating and traction to the nerve were mentioned as possible explanations of the symptom. We experienced eight cases (5.6% npts) of vocal cord palsy. As previous studies have suggested, the tendency for voice alteration to normalize with time also applied to most of our patients. Although studies have demonstrated the safety in removing leads,[31,32] complications following this intervention can occur. Fibrosis in this region, subsequent to earlier lead insertion, makes additional surgery here troublesome. We experienced one case of vocal cord palsy after a lead replacement (3.8% of the lead explantations and lead replacements), which persisted for at least a year. Other studies have reported the same complication.[27,33] Spuck et al. speculated that vocal cord palsy arising after surgery could be age-dependent and predominantly affect adults.[12] We can add support for this hypothesis as all our cases of vocal cord palsy appeared in adults. Among the three cases of damage to the jugular vein in our series, two appeared while attempting to remove leads. With these experiences in mind, it might be favorable to leave the old electrodes in place in cases where extensive scarring or fibrosis is prevalent. New electrodes can be inserted cephalad to the old.[34]

4.1.3. Cardiac complications

We report one intra-operative episode of bradycardia (0.7% npts). The presence of cardiac branches emanating from the vagus nerve has led to a concern that the treatment by vagus nerve stimulation may affect the cardiac function. The VNS-system has been tested under ECG surveillance intra-operatively and, although they seldom occur, bradycardia and asystole are occasionally reported during this session. The estimated incidence is 0.1%.[35] Cardiac rhythm normalizes, either spontaneously or after decreasing/discontinuation of stimulation and in some cases after the administration of atropine.[12,35,36] In spite of a previous event of bradycardia/aystole during intra-operative testing, stimulation has been observed to be well tolerated during subsequent treatment.[7,12,24] Increased sensitiveness to VNS under anesthesia is one theory of this occurrence.[36]

Cardiac branches sprouting from the left vagus nerve predominantly modulate activity in the atrioventricular node whereas the sinoatrial node receives branches mainly from the right.[37] This is the reason for stimulation of the left vagus nerve. Situations exist where left vagus nerve stimulation is not possible, usually because of previous infection in the area with subsequent tissue adhesion around the vagus nerve. Although there are few data available, right vagus nerve stimulation has been suggested as a viable option in these cases.[37–39] In our series, two devices were implanted around the right vagus nerve and subsequent VNS treatment was uneventful.

4.1.4. Other surgical complications

During the surgery, the surgeon must be aware of cutaneous nerve branches that may transverse the surgical field. Even though

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they have minor functions, any loss of sensation is bothersome for the patient and care should be taken to avoid this kind of complication. As mentioned, we encountered one patient with hypoesthesia post surgery (0.7% npts). This complication has previously only rarely been described in the literature.[18]

In 2001, a case report was published of a patient developing Horner syndrome after insertion of a vagus nerve stimulation device.[40] It was suggested that this condition was the result of a transient dysfunction of third-order oculosympathetic fibers within the carotid sheath. The condition has since been described only once more.[18] We here report a third case of Horner syndrome after vagus nerve stimulator insertion.

4.2. Technical complications

Among the technical complications, lead fracture is the most common. This is a serious complication as it inevitable leads to surgery to replace the lead. The surgery is technically challenging, as it is necessary to proceed in scar tissue toward the nerve, with the risk of damaging the nerve and other structures in this region. We report 17 cases (11.9% npts) of lead fracture. Other authors have presented figures ranging from 0.5 to 20.8%.[6,9,12,14,15,20–22,29] Analysing all lead fractures and patients included in these studies we calculated that 3.9% of the patients treated suffered from this incident. Spuck et al. suggested that this complication is age-dependent, as all their lead fractures occurred in children.[12] This was not the case in our results. All but five leads implanted were of lead models 300 or 302. In our analysis of these two leads, no statistical significant difference in survival time was found. Looking at the survival curve, the 300 lead seems to be more susceptible for breakage though. The difference in observation time between the two leads could be a contributing factor to the reason that no statistical significant difference was found. This analysis can be redone in a couple of years to find out if a difference exists. Hopefully, the recently introduced new lead models will reduce this serious complication.

Stimulators are usually solid and have only rarely been reported as being the cause of non-functional devices.[5,10,16] In our series, we had to replace two stimulators which did not work properly (1.4% npts). No trauma was mentioned prior to the malfunction. However, a recently published article described one case of post-traumatic stimulator dysfunction.[12]

4.3. Generally remarks and comparison

It is always difficult to discuss complications to surgical procedures. We have chosen to report every complication irrespectively of its magnitude, as there is no general agreement of what kind of an event constitutes a complication to a surgical procedure or treatment. In the National Swedish Epilepsy Surgery Register (NSESR), which compiles data from all Swedish epilepsy surgery, complication is defined as "an unwanted, unexpected, and uncommon event after a diagnostic or therapeutic procedure".[41] The complications are here graded as minor or major. A minor complication is an event that resolves within 3 months and a major complication is an event that affects activity of daily living and lasts longer than 3 months. In the major complication group is also included any significant neurological deficit even if it does not affect activities of daily living. In correspondence to this definition the infections could be regarded as minor complications but the vocal cord palsies lasting longer than 3 moths ($n = 4$, 1.6% of procedures) should be regarded as major complications. The infection rate for therapeutic procedures reported in the study from the NSESR was 5.3% and the total number of surgical complications was 7.8% in relation to number of procedures, which would be in the range of our 11.2% surgical complication rate in relation to number of procedures. The number of major complications would also be comparable between the paper by Rydenhag and Silander,[41] and our material (3.1% cf. 1.6%)

A comparable surgical procedure in neurosurgery would be the implantation of deep brain stimulation (DBS). The DBS system consists of an electrode, which is stereotactically introduced to a certain point in the brain through a burr hole, then connected with a cable, which is tunneled subcutaneously to a stimulator placed in a subcutaneous pocket usually on the chest. In the literature we have found a few recent papers specifically dealing with complications to DBS surgery.[42–47]

The percentage of infection reported in these studies is in the range of 2.5–8.5%. It is not explicitly formulated that the reported infection frequencies are based on the number of primary implantation, though reading the papers this seems to be the case. This would mean that the reported infection frequencies are in the same range of what we report in our primary implants.

The frequency of lead breakage in DBS surgery is reported to be in the range of 0.9–6.7%[42,44] which can be compared with the range of what is reported for VNS 0.5–20.8%.[6,9,12,14,15,20–22,29] This could signal a definite need for improvement of the leads, which may have been met by the introduction of new leads on the market. It might also illustrate a need for changed surgical practice, as Blomstedt and Hariz showed in their paper that with a change of surgical practice the number of lead breakages seemed to be reduced.[42]

It is not easy to evaluate complications to vagal nerve stimulation in patients with refractory epilepsy. Many of the patients are mentally disabled and are not able to describe certain symptoms. The frequency of vocal cord palsy with subsequent hoarseness could be underreported in the literature, as many patients receiving treatment are not using their voice in a manner that would permit the detection of vocal cord palsy. We are also aware of the inherited weaknesses of a retrospective designed study when analyzing long-term complications. Determining the time at which a hardware complication occurs is prone to inaccuracy and the same applies to the duration of vocal cord palsies. One may suppose that complications might have been missed as people seek medical care at other hospitals and consequently, frequencies must be considered minimum estimates. We would like to argue against this last assumption as the patients have been assessed at our hospital at least once a year and also because medical charts from local hospitals were collected for the study.

5. Conclusions

In this series we report on surgical and technical complications from our 16 years of experience with VNS treatment. Infection following insertion of the VNS device and vocal cord palsy due to damage to the vagus nerve are the most serious complications related to the surgery. Avoiding unnecessary reoperations in order to reduce the appearances of these complications are of great importance. There seems to be an increased infection frequency with increasing number of stimulator replacements. This emphasizes the importance of longer battery times or the need for rechargeable devices. We noted that 10.5% of our leads between the electrodes and the stimulator suffered from fracture. This rate is too high to be considered acceptable. The leads have been modified several times since the introduction of the treatment in attempts to minimize this occurrence. In our material we noticed a tendency for an old model of lead to be more susceptible to fracture than a later model. Further studies are needed to evaluate the possible superiority of the modified leads. Considering that VNS therapy is a lifelong therapy, the importance of long-term follow-up must be stressed.

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Disclosure

Magnus Olivecrona is since 2010 an independent consultant for Cyberonics. This includes giving lectures on VNS including its indications, patient selection and surgical techniques in VNS surgery.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.06.011.

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