Complications and safety of vagus nerve stimulation: 25 years of experience at a single center

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OBJECTIVE The goal of this paper was to investigate surgical and hardware complications in a longitudinal retrospective study.

METHODS The authors of this registry study analyzed the surgical and hardware complications in 247 patients who underwent the implantation of a vagus nerve stimulation (VNS) device between 1990 and 2014. The mean follow-up time was 12 years.

RESULTS In total, 497 procedures were performed for 247 primary VNS implantations. Complications related to surgery occurred in 8.6% of all implantation procedures that were performed. The respective rate for hardware complications was 3.7%. Surgical complications included postoperative hematoma in 1.9%, infection in 2.6%, vocal cord palsy in 1.4%, lower facial weakness in 0.2%, pain and sensory-related complications in 1.4%, aseptic reaction in 0.2%, cable discomfort in 0.2%, surgical cable break in 0.2%, oversized stimulator pocket in 0.2%, and battery displacement in 0.2% of patients. Hardware-related complications included lead fracture/malfunction in 3.0%, spontaneous VNS turn-on in 0.2%, and lead disconnection in 0.2% of patients.

CONCLUSIONS VNS implantation is a relatively safe procedure, but it still involves certain risks. The most common complications are postoperative hematoma, infection, and vocal cord palsy. Although their occurrence rates are rather low at about 2%, these complications may cause major suffering and even be life threatening. To reduce complications, it is important to have a long-term perspective. The 25 years of follow-up of this study is of great strength considering that VNS can be a life-long treatment for many patients. Thus, it is important to include repeated surgeries such as battery and lead replacements, given that complications also may occur with these surgeries.

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KEY WORDS epilepsy; treatment; neurosurgery; vagus nerve stimulation; VNS; implants; complications

VAGUS nerve stimulation (VNS) is a therapy that has been available for the treatment of refractory epilepsy since 1994 in Europe and 1997 in the US. VNS was also approved for treating depression in 2001 in Europe and 2005 in the US. Our department was one of the very first to begin VNS implantation in 1990 when the first trials (EO3) were initiated^{8,32} and has continued to perform implantations ever since, with a relatively stable number of operations every year. Despite over 20 years of availability, discussion of safety and efficacy is still ongoing. The new evidence-based guidelines from the American Academy of Neurology (AAN) (2013) that analyzed all VNS studies until 2012 emphasized the need for further

safety information. The major safety questions from the evidence-based analysis that still need to be clarified are if new safety concerns have emerged over time for sudden unexpected death in epilepsy (SUDEP), cardiac arrhythmias during and after implantation, and sleep apnea.²⁶ A recent review presents safety data from clinical trials and databases,⁹ and results concerning SUDEP and patients with VNS from a single center were also reported recently.¹⁶ The long-term follow-up is limited in most studies; however, Kahlow and Olivecrona²¹ presented data over a 17-year period between 1994 and 2010.

Safety concerns must be seen in long-term perspectives. Many patients receive their VNS when they are young and

ABBREVIATIONS AAN = American Academy of Neurology; EEG = electroencephalography; IQR = interquartile range; SUDEP = sudden unexpected death in epilepsy; VNS = vagus nerve stimulation.

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are expected to use it for many years. At our center, all VNS patients have been recorded in a local registry since the start of VNS implantation. Thus, we have the possibility of analyzing long-term safety and efficacy aspects up to 25 years after implantation. Unique to our patient population are the very old patients who received VNS during a pilot study on Alzheimer's disease and clinical symptoms.²⁵

Methods

All patients in this case series suffered from refractory epilepsy of different etiologies and syndromes. Patients whose epilepsy is refractory, irrespective of syndrome, were evaluated by the multidisciplinary epilepsy team at Sahlgrenska University Hospital, Gothenburg, Sweden, as potential suitable candidates. In the preimplantation evaluation, all patients were evaluated with respect to possible resective or palliative epilepsy surgery, i.e., callosotomy. This evaluation includes history, semiology, imaging (MRI since 1994), electroencephalography (EEG), and, for some patients, video-EEG monitoring. In total, 247 patients with epilepsy (age range 4–71 years; mean 29.5 years) were implanted with VNS between 1990 and 2014. They had either not been considered as candidates for epilepsy surgery or had undergone failed epilepsy surgery.

For the subgroup analyses, patients were divided into adults and children, male and female, and procedures performed between 1990 and 1999 or 2000 and 2014.

All patients underwent the implantation of a VNS device (Cyberonics Inc. [$n = 242$] or BioControl Medical [$n = 5$]), mainly for drug-resistant epilepsy, at our department between January 1990 and December 2014. Apart from primary surgery, all replacements due to battery failure were analyzed to determine the occurrence of surgical and hardware complications.

Standard preoperative chlorhexidine scrubbing and blood work were performed on all patients. If body temperature and C-reactive protein were considered pathologically elevated, the procedure was postponed. After the administration of antibiotics (either 1.5 g cefuroxime or 2 g cloxacillin), the left vagus nerve was exposed via a transverse incision at a midcervical level. Initially the incision was longitudinal, but this technique was abandoned in 2003. As a standard procedure, a 2-mm lead was placed around the vagus nerve, tunneled, and connected to the stimulator. Three-millimeter leads were used only during lead revision with prominent nerve fibrosis. The stimulator was then placed in a subcutaneous pocket over the left major pectoral muscle, and the wounds were closed. All patients who underwent any kind of revision, replacement, or extraction of the VNS received prophylactic antibiotics preoperatively, as is the custom at our center. The patients were under continuous surveillance the first night after surgery and most went home the following day. There were no outpatient procedures. All patients, children and adults, underwent the same surgical procedure.

If no immediate complication occurred postoperatively, the patient was discharged the day after surgery. The patient revisited the hospital 1–2 weeks after surgery for initiation of the stimulator either by the epilepsy physician or epilepsy nurse. Patients were continuously evaluated at

our clinic as well as the pediatric neurology department for outcomes and complications every 3 months for the 1st year, followed by 6-month or yearly assessments. A few patients moved from the Gothenburg region and were lost to follow-up ($n = 3$).

The generator was usually started after 2 weeks. The rationale for the time delay was the concept of nerve swelling following surgery that was later confirmed in the study by El Tahry et al.¹³ The device was started at 0.25 mA, 30 Hz, and 500- μ sec pulse width for 30 seconds on and 5 minutes off. This was later changed if patients complained of vocal side effects, whereby the frequency was reduced to 20 Hz and the pulse width to 250 μ sec. To improve efficacy, the settings were adjusted in some patients to 30 seconds on and 1.8 or 3 minutes off. Rapid cycling was tried in some patients (7 seconds on and 21 seconds off), but because of the shortened battery life and lack of improved efficacy, all patients were reverted back to 30 seconds on and 1.8–5 minutes off. Invariably, the magnet settings were 1 notch more than the regular stimulation.

Statistical Analysis

The continuous variables are presented both as the mean with standard deviation (SD) and as the median with interquartile range (IQR). The chi-square test was used for the comparison of proportions between groups. A p value < 0.05 was considered to be statistically significant. All statistical calculations were performed using SPSS version 22 (IBM Corp.).

Results

Between January 1990 and December 2014, 260 patients were implanted with a VNS device. Thirteen of these patients were implanted with VNS as part of study on Alzheimer disease (age range 58–81 years),²⁵ and the remaining 247 patients were diagnosed with epilepsy. Fifty-five of the patients were children (age range 4–18 years). Previous resective surgery had been performed in 52 of these patients (29 children). Patient characteristics are shown in Table 1.

The median follow-up time was 11.8 years (IQR 6.9–17.7), and the mean follow-up time was 12.0 years (SD 6.5). Table 2 shows a summary of the 497 surgical procedures performed. The mean time to stimulator replacement in all models was 5.6 years (SD 2.1), and the median time was 5.1 years (IQR 4.1–6.9). In all patients, the stimulator replacement was performed in the same pocket as was previously used in the primary implantation. Table 3 shows time to replacement in different models.

In total, there were 37 surgical complications and 16 hardware complications in 47 different patients. Surgical complications occurred in 6.8% of the procedures performed in children and 9.1% in adults. The difference was not significant ($p = 0.67$). No technical complications were reported in children. All complications are summarized in Table 4.

A total of 8 incidents of postoperative hematomas were reported. One child in the second cohort suffered from a postoperative hematoma. Seven of the hematomas occurred after primary implantation, including the hemato-

TABLE 1. Patient demographics

Variable	Total	Children	Adults	Female	Male
No. of patients	247	55	192	125	122
Mean age, yrs (SD)	29.5 (14.8)	11.8 (3.6)	34.6 (12.7)	29.3 (14.8)	29.8 (14.9)
Median age, yrs (IQR)	27 (19–39)	12 (9–15)	32 (24–43)	26 (19–38)	28.5 (18–41)
No. of males (%)	122 (49.4)	30 (54.6)	92 (47.9)		
No. of adults (%)	192 (77.7)			100 (80.0)	92 (75.4)

TABLE 2. Summary of surgical procedures

Surgical Procedures	Total	Children	Adults	Female	Male	1990–1999	2000–2014
VNS implantation	247	55	192	125	122	89	158
Plain stimulator replacement in 1 session	161	29	132	68	93	29	132
System replacement in 1 session (stimulator & lead)	8	2	6	3	5	2	6
Plain lead replacement in 1 session	9	1	8	4	5	4	5
Reimplantation of stimulator	4	1	3	2	2	0	4
Explantation of stimulator	45	9	36	21	24	14	31
Lead exploration	5	0	5	2	3	4	1
Wound revision	5	0	5	2	3	1	4
Explantation of lead	4	1	3	3	1	0	4
Intentional stimulator replacement discontinued	1	0	1	0	1	0	1
Intentional lead replacement discontinued	1	0	1	1	0	1	0
Reconnection of lead to stimulator	2	0	2	0	2	0	2
Repositioning of lead	1	0	1	1	0	1	0
Reposition of stimulator	2	0	2	2	0	1	1
Removal of postoperative hematoma	2	0	2	1	1	0	2
Total surgical procedures	497	98	399	235	262	146	351

ma in the child. Two adults needed immediate hematoma evacuation due to compression of the trachea and risk of desaturation. Neither of these patients suffered any damage related to the reoperations. The remaining patients who experienced a postoperative hematoma were treated conservatively. One patient had a postoperative hematoma that occurred after stimulator replacement. This was followed by a postoperative infection, resulting in explantation of the stimulator. To monitor any deterioration due to the hematoma, the patients stayed in the postoperative ward overnight and, if they were stable the day after, they were discharged; thus, all postoperative hematomas were considered a surgical complication.

Eleven incidents of infection were reported in 10 patients (4 children), where 1 adult patient was reinfected after stimulator reimplantation. Eight infections occurred after primary implantation and 2 after stimulator replacement. All patients suffering from infection received oral antibiotics as the first line of treatment. Two patients (1 child) suffered from superficial infection and responded to oral antibiotics. The remaining patients (3 children) were treated with surgical removal of either the stimulator only, or both the stimulator and lead. The surgical treatment regimens and time frames are presented in Table 5. Mean time from implantation to surgery due to infection, wound revision or explantation was 99 days (SD 68; median 86

days). The mean age of the patients with infection was 22.1 years (SD 12.8; median 20.5 years). The infection rate between 1990 and 1999 was 0.8% and 3.3% between 2000 and 2014. The difference was, however, not statistically significant, with a *p* value of 0.057.

Postoperative vocal cord paralysis was seen in 5 patients (no children), 4 after primary implantation and 1 after lead revision, and lower facial weakness in 1 patient. One patient suffered from facial tingling after surgery. All of these patients recovered from their initial symptoms after 2–14 months.

Five patients (no children) suffered from postoperative pain in the implantation area. Three of these patients recovered spontaneously, 1 underwent removal of the stimulator, and 1 had a surgical repositioning of the stimulator. In 1 case the pocket size was reduced when the stimulator

TABLE 3. Stimulator durability

Model	No. of Patients	Mean Yrs (SD)	Median Yrs (IQR)
100	32	3.7 (1.4)	3.7 (2.8–4.5)
101	30	4.3 (1.0)	4.4 (3.9–4.7)
102R	71	6.8 (2.0)	6.7 (5.1–8.4)
102	15	6.5 (1.5)	6.7 (5.1–8.4)

TABLE 4. Summary of complications

Complications	Total	Children	Adults	Female	Male	1990–1999	2000–2014
Surgical complications (total)	37 (8.6%)	6 (6.8%)	31 (9.1%)	25 (12.4%)	12 (5.3%)	11 (8.9%)	28 (9.2%)
Hematoma	8 (1.9%)	1 (1.1%)	7 (2.1%)	6 (3.0%)	2 (0.9%)	2 (1.6%)	6 (2.0%)
Post–primary implantation	7 (2.8%*)	1 (1.8%*)	6 (3.1%*)	6 (4.8%*)	1 (0.8%*)	2 (2.2%)	5 (3.2%)
Post–stimulator replacement	1 (0.6%†)	0 (0%†)	1 (0.7%†)	0 (0%†)	1 (1.0%†)	0 (0%)	1 (0.7%)
Infections (all)	11 (2.6%)	4 (4.5%)	7 (2.1%)	5 (2.5%)	6 (2.6%)	1 (0.8%)	10 (3.3%)
Post–primary implantation	8 (3.2%*)	4 (7.3%*)	4 (2.1%*)	4 (3.2%*)	4 (3.3%*)	0 (0%)	8 (5.1%)
Post–stimulator replacement	2 (1.1%†)	0 (0%†)	2 (1.4%†)	0 (0%†)	2 (1.9%†)	1 (2.9%)	1 (0.7%)
Post–stimulator reimplantation	1 (NA)	0 (NA)	1 (NA)	1 (NA)	0 (NA)	0 (0%)	1 (0.3%)
Vocal cord palsy (all)	6 (1.4%)	0 (0%)	6 (1.8%)	5 (2.5%)	1 (0.4%)	3 (2.4%)	3 (1.0%)
Post–primary implantation	5 (2.0%*)	0 (0%*)	5 (2.6%*)	4 (3.2%*)	1 (0.8%*)	2 (2.2%)	3 (1.9%)
Post–lead explantation or replacement	1 (NA)	0 (NA)	1 (NA)	1 (NA)	0 (NA)	1 (NA)	0 (NA)
Lower facial weakness	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0 (0%)	1 (0.8%)	0 (0%)
Pain & sensory-related complications	6 (1.4%)	1 (1.1%)	5 (1.5%)	4 (2.0%)	2 (0.9%)	2 (1.6%)	4 (1.3%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Puncture of jugular vein	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Large cutaneous nerve cutoff	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Aseptic reaction	1 (0.2%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.3%)
Cable discomfort	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0 (0%)	1 (0.8%)	0 (0%)
Surgical cable break	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0 (0%)	1 (0.8%)	0 (0%)
Oversized stimulator pocket	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.3%)
Battery displacement	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.3%)
Technical complications (total)	16 (3.7%)	0 (0%)	16 (4.7%)	5 (2.5%)	11 (4.8%)	9 (7.3%)	7 (2.3%)
Lead fracture/lead malfunction	13 (3.0%)	0 (0%)	13 (3.8%)	4 (2.0%)	9 (4.0%)	8 (6.5%)	5 (1.6%)
Spontaneous VNS turn-on	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.3%)
Lead disconnection	2 (0.5%)	0 (0%)	2 (0.6%)	0 (0%)	2 (0.9%)	1 (0.8%)	1 (0.3%)

NA = not applicable.

* Percentage of all primary VNS implantations (247 primary VNS implantations were performed on 55 children, 192 adults, 125 female patients, 122 male patients, 89 in 1990–1999, and 158 in 2000–2014).

† Percentage of all plain stimulator replacements in 1 session, system replacements in 1 session (stimulator and lead), plain lead replacements in 1 session, and reimplantations of the stimulator (182 procedures were performed on 33 children, 149 adults, 77 female patients, 105 male patients, 35 in 1990–1999, and 147 in 2000–2014).

was changed and 1 case underwent exploration because the stimulator had turned in its subcutaneous pocket.

One 29-year-old patient underwent reoperation 3 months after primary implantation with lead placement correction because of discomfort and tightness on the throat. One aseptic reaction with fluid collection around the stimulator was reported. Although cultures were taken, no infectious microorganism was found when explanting the device. This occurred 6.2 years after primary implantation.

Thirteen lead malfunctions in 12 patients (no children) were reported. Lead exploration to try to salvage the lead was required in 5 cases, 1 was successful and the remaining resulted in replacements. Table 6 summarizes the surgical revisions performed after lead malfunction. The rate of lead breaks between 1990 and 1999 was 7.3% and 2.3% between 2000 and 2014. The difference was statistically significant ($p = 0.049$).

In 2 adult patients, an immediate postoperative lead disconnection was suspected, resulting in an early surgical reconnection. This was probably due to unsuccessful con-

nection between the lead and stimulator during primary surgery. It is unclear if the surgeon performed a proper lead test in these cases. In 1 patient, the stimulator was turned on immediately after surgery despite being set to off-mode in the operating room. Thirty stimulators were removed due to the lack of efficacy in combination with discomfort from the stimulator or patient desire.

Discussion

The aim of this long-term follow-up study of all patients implanted with VNS since 1990 is to describe the panorama of complications to VNS implantations since its introduction in clinical trials at a single center. The Phase III clinical trials for VNS began in 1990, and our center was one of the first to participate in Europe. Initially, 18 patients were included, and since then a total of 245 patients have been implanted, including the patients in the Alzheimer study³⁶ and the 3 patients lost to follow-up. This case series is, to our knowledge, the first longitudinal series dealing with complications to vagus nerve stimulation that ranges up to 25 years. Most long-term studies have

TABLE 5. Infections

Patient Sex (age in yrs)	Reoperation No.	Surgical Procedures Performed & Time Btwn Surgeries
Infections needing surgical revision following primary implantation		
Female (6)	1st	Lead removal after 26 days
Female (11)	1st	Stimulator removal after 34 days
Male (11)	1st	Complete system removal after 106 days
Male (24)	1st	Complete system removal after 155 days
Male (26)	1st	Wound revision after 37 days
	2nd	Wound revision after 44 days
	3rd	Stimulator removal after 49 days
	4th	Lead removal after 309 days
Female (30)	1st	Stimulator removal after 181 days
	2nd	Reimplantation of stimulator after 168 days
	3rd	Stimulator removal & subtotal lead removal due to infection after 50 days
	4th	Wound revision after 40 days
	5th	Wound revision after 10 days
	6th	Removal of remaining lead after 24 days
Infections needing surgical revision following stimulator replacement		
Male (37)	1st	Wound revision after 186 days
	2nd	Stimulator removal after 145 days
Male (40)	1st	Stimulator removal after 65 days
	2nd	Reimplantation of stimulator after 141 days

safety data ranging from 1 to 5 years.^{6,14,19,20,34,37–39} Considering that VNS can be a life-long treatment for many patients, it also involves repeated surgeries with multiple (up to 4) battery replacements that we account for in our series.

The AAN guidelines on VNS were recently published and emphasized the lack of information or gaps in knowledge concerning the side effects of VNS, especially in the pediatric population.^{15,30,43} Therefore, we deem it important to present our comprehensive long-term data to help answer some of the concerns. Since the start of VNS implantation in 1990, a local registry of all VNS patients has been maintained. We have registry data concerning the efficacy and tolerability as well as side effects and implantation data, including difficulties encountered with a median follow-up time of 12 years, that, to our knowledge, is twice as long as any other report.^{14,21}

The overall complication rate was 12.4%, including both surgical and hardware complications. Most previous studies present frequencies ranging from 2.5% to 12.5%.^{2,11,15,18,22,23,34,38,39} It is reasonable to believe that the complication frequency increases with a longer follow-up time, considering the repeated surgeries needed due to depleted batteries and hardware being worn out. Kahlow and Olivecrona²¹ recently presented a single-center longitudinal study of 143 patients with a mean follow-up time of 62 months.²¹ The surgical complication frequency was 16.8%, including 3 cases of perioperative jugular vein puncture. In the study by Elliott et al.¹⁴ with a mean follow-up time of 4.1 years, 12 patients experienced some degree of permanent vagus nerve injury, and there was also 1 case of pneumothorax. These unusual complications have

never occurred at our site during the 25 years of follow-up. Others have reported vocal cord paralysis in 1%–5.6% of patients.^{7,17,21,23,32,34,37,38,41} The surgical complication rate for all procedures was 8.6%, and 1.4% of the patients experienced vocal cord paralysis and all recovered completely. In a recent study by Robinson and Winston,³³ vocal cord paralysis occurred at almost twice the rate with leads that had a 2-mm inner diameter in comparison with 3-mm inner diameter in patients 18 years of age and older. In our series, all patients were initially implanted with 2-mm inner-diameter leads. Only patients who underwent lead revision received a 3-mm inner-diameter lead if fibrosis around the nerve was apparent. Lower facial weakness is a rare complication and is probably caused by high surgical incisions. The only case that occurred in our series was after a longitudinal skin incision at the time of implantation. Horizontal skin incision probably reduces the risk of lower facial weakness.

None of our patients experienced asystole during or after the implantation. Arrhythmia, including asystole and bradycardia, is an important but rare complication that has been reported in the literature.^{3–5,35,40} Possible reasons for this phenomenon could be polarity reversal of the leads during implantation causing efferent instead of afferent stimulation,⁴⁴ indirect stimulation of the cervical cardiac nerves, technical malfunction of the device, or accidental over-manipulation of the nerve since placing the spiral (Cyberonics) lead around the nerve can be difficult due to anatomical variations. The CardioFit cuff lead is subjectively easier to apply because of its design and requires less manipulation of the vagus nerve as a whole.¹⁰ On the other hand, only a handful of CardioFit systems have been

TABLE 6. Lead malfunctions

Patient Sex (age in yrs)	Reoperation No.	Surgical Procedures Performed & Time Btwn Surgeries	Model	Lead Model
Lead malfunctions following primary implantation				
Female (21)	1st	Lead exploration after 200 days	100	300
	2nd	Complete system replacement in 1 session after 3.9 yrs	100	300
Male (45)	1st	Lead exploration after 1.9 yrs	100	300
	2nd	Plain lead replacement after 48 yrs	100	300
Female (59)	1st	Plain lead replacement after 3.7 yrs	100	300
	2nd	Plain lead replacement after 132 days	100	300
Male (63)	1st	Complete system replacement in 1 session after 3.4 yrs	102	304
Male (70)	1st	Plain lead replacement after 3.7 yrs	100	300
Lead malfunctions following stimulator replacement				
Male (19)	1st	Complete system replacement in 1 session after 9.6 years	101	300
Female (21)	1st	Plain lead replacement after 85 days	101	300
	2nd	Plain lead replacement (at 29 yrs of age, after another ordinary replacement)	101	300
Male (42)	1st	Plain lead replacement after 13 days	101	300
Male (49)	1st	Lead exploration after 1.6 yrs	100	300
Male (53)	1st	Plain lead replacement after 112 days	100	300
Male (56)	1st	Lead exploration w/in a year (date of previous surgery unknown)	100	300
	2nd	Complete system replacement in 1 session after 28 days		
Male (59)	1st	Plain lead replacement after 291 days	101	300

implanted thus far, and it is too early to draw any conclusions about the complications rates. One can speculate that less manipulation of the nerve would decrease the number of instances of postoperative vocal cord paralysis.

Not all lead fractures were visible on radiography, and the lead failures were mainly detected by diminished function, e.g., increased seizure frequency and increased impedance measurement leading to revision or replacement of the lead. Only a few were detected on radiography, and the etiology of high impedance is not entirely clear. Some have described lead failure in the absence of visible fractures as “microlesions” within the lead cable.^{12,42} Others have presented significant scar tissue around the lead as a possible cause of high impedance.²⁹ We report 13 cases (3.0%) of lead malfunction, of which no children were involved. Previous studies report 0.5% to 20.8%.^{11,15, 20,21,24,27,34,37,38} Of the 13 lead malfunctions, all but 1 was of the Cyberonics model 300, which suggests that this model is more susceptible to breakage. This product is no longer distributed by Cyberonics, and lead failure has decreased significantly since the introduction of newer models. Some of our patients still have the original leads that were implanted between 1990 and 1994. It is interesting that most of the leads now show high impedance on “device diagnostics.” However, these patients feel the stimulation especially during the use of the magnet, and the initial reduction of seizure frequency in the early years has remained stable. Because of the difficulties of replacing a lead, we have continued to stimulate with the original lead as long as the patient does not experience an increase in seizure frequency and/or severity. Explantation of the lead can be a challenge because of fibrosis around the nerve,⁷ and replacing the Cyberonics lead can take several hours using microscopic dissection. Postoperative hoarseness after

lead replacement occurred in 1 patient. We have no experience of lead change with the CardioFit, as the oldest implanted device is just 3 years old.

The absolute majority of hardware complications occurred in the early years of implantation. This is probably due to both the learning curve and development of the equipment, both the leads and stimulators. In the early years, the same surgeon made all implantations. Since then, an additional 5 surgeons have learned the implantation technique. Lead quality and stimulator lifetime have increased and the stimulator size has decreased. This has resulted in fewer lead revisions and longer periods between stimulator replacements. When it comes to surgical techniques, the only difference in standard protocol is that the neck incision was longitudinal originally and today all neck incisions are transverse, which is more cosmetically appealing. The preoperative protocol has remained unchanged since the start of implantation.

Implantation in children has been carried out since 1994. No complications exclusive to this population have been encountered, except for an infection rate that was nearly twice as high as that in adults (4.5%), which is in line with other previous studies.^{1,26} We speculate that the cause of this is excessive wound manipulation, especially in children with intellectual disabilities, which is common in this patient group. Close postoperative monitoring of this patient group might resolve this problem. No hardware complications were reported in the pediatric population, probably due to the fact that only 4 children were implanted between 1990 and 1999. The overall rate of infection was 2.6%, and this is in the lower range compared with most previous complication studies where the infection rates are reported as 3%–8%.^{31,34,37,38} When looking at the infection rates after battery replacement it was

only 1.1%, suggesting that this is a fairly low-risk procedure compared with primary implantation. In contrast to the recommendations from Air et al.¹ to treat all deep infections with intravenous broad-spectrum antibiotics as the first-line treatment, our patients received oral antibiotics and all but 2 patients with infection had to have their stimulator removed. The incidence of infection was higher between 2000 and 2014. Even if not statistically significant, the higher infection rate in the later period might be due to the involvement of several surgeons.

Thirteen elderly patients (< 81 years old) also underwent implantation as part of a study on Alzheimer disease.²⁵ None of these patients had epilepsy. Apart from 1 case of recurrence paralysis that recovered over a few months, no other complications were observed. Postoperative recovery was unremarkable. The follow-up time was relatively short compared with the epilepsy patients. They all died within 5 years due to their underlying disorder and are therefore not included in the mortality analysis for epilepsy patients. This implies that the implantation of VNS is well tolerated by all age groups.

Battery life has been extended but still varies between 2.8 and 8.2 years depending on the settings and the battery itself, with the Cyberonics 102R having the longest battery life.

Twenty-five patients treated with VNS for epilepsy have died over the 25 years of implantation at our center. When analyzing the cause of death, 2 patients were found to be definite SUDEP deaths and 5 others were possible SUDEP deaths. However, the cause of death was not traceable in some cases due to the fact that the patients had been treated at different hospitals. Excess mortality in patients with epilepsy has long been recognized,²⁸ but the question still remains if the death rate as a result of SUDEP is lower in the VNS-treated population than in similar groups of patients with refractory epilepsy not treated with VNS.

Analyzing registry data over long time periods can be difficult, especially as surgeries performed before 1997 were not registered automatically in the electronic charts at our hospital. Some data may have been lost in the process of digitalizing the paper charts.

Conclusions

Currently, more than 100,000 VNS devices have been implanted in more than 80,000 patients. VNS implantation is a relatively safe procedure but it still involves certain risks. The most common complications are postoperative hematoma, infection, and vocal cord paralysis. Although their occurrence rates are rather low at about 2%, these complications may cause major suffering and even be life threatening. To reduce complications it is important to have a long-term perspective. The 25 years of follow-up of this study is of great strength considering that VNS can be a life-long treatment for many patients. Thus, it is important to include repeated surgeries, such as battery and lead replacements, given that complications also may occur with these surgeries. Children may have a greater risk for wound infection than adults due to behaviors more common in children. As concluded in the AAN guidelines, extra vigilance in monitoring for the occur-

rence of site infection in children should be undertaken. Our general opinion is that VNS implantations should be restricted to neurosurgeons with detailed familiarity with the procedure at hand and attention to detail in order to minimize surgical complications.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Révész, Rydenhag. Acquisition of data: Révész. Analysis and interpretation of data: Révész. Drafting the article: Révész, Rydenhag. Critically revising the article: Rydenhag, Ben-Menachem. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Révész. Statistical analysis: Révész. Administrative/technical/material support: Révész. Study supervision: Rydenhag, Ben-Menachem.

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