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ORIGINAL ARTICLE

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Complications of vagal nerve stimulation for epilepsy in children

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Abstract Vagal nerve stimulation (VNS) is a surgical option to treat drug-resistant epilepsy. A few side effects have been described, mainly as anecdotal reports. We analysed our material concerning a juvenile population to identify the most common and most important complications, discussing them with the literature. Thirty-six patients were studied (18 months–18 years old). The children were assessed before the VNS implant and 3, 6, 12, 24 and 36 months after surgery. The mean follow-up was 30 months. Four patients required a second surgery: two for changing the device 3 years after implant; one for revision of an imperfect implant; one for removing a non-functioning device. In one patient a transient vocal cord paralysis was observed. Hoarseness was the main complaint (38.8%). More infrequent was mild sleep apnoea (8.3%), sternocleidomastoid muscle spasm, drooling and snoring in one patient each. Skin scars were reported with a different frequency according to the surgical technique. At variance with the literature reports, we did not observe infections. Side effects of VNS can be minimised, but not avoided completely, with a correct technical procedure, which in turn depends upon a thorough knowledge of vagus nerve anatomy.

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Introduction

Vagal nerve stimulation (VNS) has emerged during the last 10 years as a viable surgical option for treating drug resistant epilepsy not eligible for resective epilepsy surgery [1]. VNS has mostly been used to treat adult patients with severe partial seizures. This technique has also been used in children with medically refractory encephalopathic seizures, idiopathic seizures, primary generalized epilepsy and Lennox-Gastaut syndrome [8, 11, 13, 16, 18, 20, 26]. Past studies have proposed that the antiepileptic action of VNS is related to the effect on the brainstem reticular activating system and is mediated largely by the widespread release of two inhibitory agents [gamma aminobutyric acid (GABA) and glycine] but the exact mechanism by which this procedure reduces seizure frequency is largely unknown. For this reason, it is difficult to define precisely the selection criteria for patients more likely to benefit from VNS therapy. Nevertheless, results from small observational studies suggest that VNS is more effective in children [13, 16, 28].

Although there are many published series concerning efficacy and quality of life (QOL), relatively few data have been published about surgical complications in both adults and children [6, 14, 21, 25]. Voice alteration, hoarseness, dysphonia, cough, pain, dyspnea, vomiting, nausea, hiccup, paresthesia, fever, local infection, accidental injury, aspiration and bradycardia have been quoted as side effects. [6, 17, 24]. The likelihood of bradycardia is reduced by placing the stimulator on the left vagal nerve. However, even with this precaution, asystoly is more frequent than in other patients with medication resistant epilepsy [3, 15]. The sudden death of VNS-treated patients is not greater than in other epileptic patients [2].

Overall, VNS is regarded as a safe therapy, the most common side effects occurring only during stimulation and becoming less severe over time. However, there are a

number of rare but serious complications that must be known when discussing this surgical procedure. The aim of this study was to better define the incidence of surgical complications and to identify the long-term side effects of chronic VNS in a series of children with drug-resistant epilepsy.

Clinical material and methods

Patients

The present study consists of 36 consecutive children (22 male, 14 female), 18 years or younger (range: 18 months–18 years; mean age: 11.5 years) submitted to implantation of a left vagal nerve stimulator at a single institution between 2000 and 2004.

Inclusion criteria were already described in a previous report [28]. In all cases, treatment with at least two antiepileptic drugs in variable associations had been tried unsuccessfully.

Patients with severe swallowing difficulties, severe self-mutilating behaviour, recent onset epilepsy, progressive metabolic or degenerative disease, congenital heart defects, gastrointestinal diseases (mainly gastroesophageal reflux), obstructive sleep apnoeas or with poor parental compliance, were not included.

Data collection forms were designed for data aquisition regarding patient history, seizures, drug therapy , implant, device settings and side effects.

Patients were assessed prior the implant and 3, 6, 12, 24 and 36 months after surgery. The mean follow-up time was 30.8 months (range: 3–51.8 months), mean epilepsy duration was 9.3 years.

Nine patients suffered from Lennox-Gastaut Syndrome and 27 children suffered from partial epilepsy. All but three patients had multiple seizures [partial complex motor seizure (PCS), partial seizure with complex secondary generalisation (PSSG)]; in 18 cases, tonic or atonic drop attacks were present. Twenty-nine patients had daily seizures up to a maximum of 40 seizures/day.

All but five patients showed severe mental retardation. Focal neurological disorders were present in 23 cases. School attendance, with the support of a personal teacher, was possible in all school age children.

At 2 years follow-up, 71% of patients experienced an improvement in seizure frequency by more than 50%; three patients were seizure-free.

Surgical procedure

The first ten patients of our series underwent a standard VNS procedure, with a chest incision for the pulse generator and a neck incision for electrode positioning. Since 2001, the surgical technique has been modified by using a single cervical incision, as described by Glazier et al. [9]. The patient is placed in a supine position with a shoulder roll beneath the scapulae to provide mild neck extension. With the head straight, a 5–6 cm transverse neck incision is made 2 cm above the clavicle and the deep cervical fascia is identified after separating the platysma.

The underlying fat and pectoralis fascia are dissected to create a subcutaneous pocket for the pulse generator. Subsequently the deep cervical fascia is opened and the neurovascular bundle identified. The left vagus nerve is generally encountered deep and medial to the internal jugular vein, encased in a firm areolar tissue lateral to the common carotid artery. Approximately 4 cm of the nerve trunk is dissected and superficialised with the help of a plastic sheet.

Positioning the three electrodes coils around the nerve is more easily performed using a microscope.

Once the cables are connected to the generator, the lead test is carried out to evaluate the impedance and the output current. A tension relief loop is made in the electrodes and sutured with non-absorbable material to the sternocleidomastoid muscle, followed by a standard layer closure. The device is tested for function and the electrode impedance is checked prior to leaving the operating suite. Usually it is activated 3 days after the implantation. Prophylactic antibiotics are administered preoperatively and 7 days postoperatively.

Results

Overall surgical complications are reported in Table 1.

Of the 36 patients treated, four required a second surgery. Two had a complication necessitating device replacement; one required device revision; and in one patient a non-functioning device was finally removed. In the first two children the devices were revised because of lead fracture, which occurred more than 3 years after implantation. In both cases the device malfunction was suspected for the high values of impedance found during a lead check and confirmed by X-ray examination (Fig. 1). It is of note that we did not observe a worsening of seizures at that

Table 1 Surgical complications

Surgical complications during 40 procedures		
Complication	Incidence	Treatment
Hypertrophic chest scars	6/10 (60%)	Change in operative technique
Electrode fracture	2/36 (5.5%)	Lead and generator replacement
Device intolerance and lack of efficacy	1/36 (2.7%)	Device removal
Bad contact electrodes-generator	1/36 (2.7%)	Device revision
Vocal cord paresis	1/36[a] (2.7%)	
Tonsillar pain, adverse changes in respiration during sleep, cough	1/36[a] (2.7%)	Stimulation parameters adjustment

[a]All occurred in the same patient

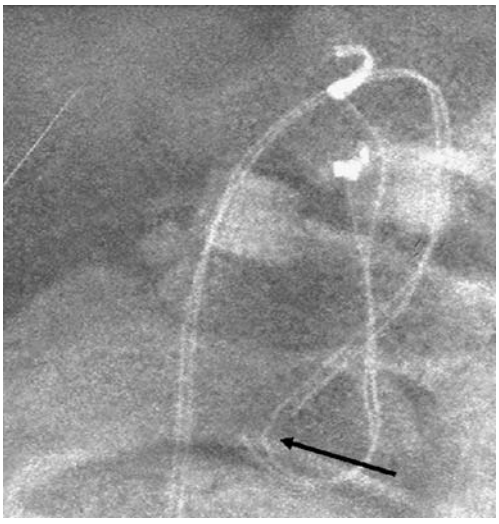

Fig 1 X-ray examination showing lead fracture

moment. A direct trauma on the electrode was not reported. The electrodes and the generator were removed and replaced. The surgery was performed under general anaesthesia with microscope magnification; after re-opening the cervical skin and deep cervical fascia, the silicon tie-downs and electrode leads were identified with some difficulties superficial to the carotid sheath, covered by fibrous tissue.

Once the vagus nerve was identified, the spiral electrodes were removed, unwinding them in the first case and cutting in several pieces in the other case. At the end of the procedure the nerve was intact in both cases. New electrodes were easily re-applied with good electrode contact. The surgical procedure was performed in 90–120 min; both patients received antibiotic and steroid therapy. No immediate complications were observed in either patient. Surprisingly, in the first case, 45 days after surgery, voice alteration was noticed, associated with cough, hoarseness and snoring. Flexible laringoscopy showed a left vocal cord paresis. The patient regained normal voice within 3 months and a second laringoscopy performed at this time showed the disappearance of the vocal cord paresis.

The third patient, three weeks after implant, experienced a loss of perceived stimulation. The lead test showed high electrode impedance. Bad contact between one connector pin and the generator was found at the surgical revision. The full insertion of the pin in the receptacle of the generator and the tightening the setscrew were enough to obtain normal function.

Finally, the generator was removed, on demand, in a 18-year-old boy because of lack of efficacy and subjective intolerance. In this case, we decided to cut off the distal leads and not remove the electrodes from the vagus nerve.

Hypertrophic chest scars developed in six of our first ten patients, four of whom were females. This problem, poorly acceptable from an aesthetic point of view convinced us to perform a single cervical incision that obtained better cosmetic results compared with the two incision technique.

Table 2 Side effects related to chronic VNS stimulation

Chronic VNS side effects	
Side effects	Incidence (%)
Mild hoarseness	14 (38.8%)
Cough	2 (5.5%)
Mild sleep apnoeas	3 (8.3%)
SCM spasm	1 (2.7%)
Shortness of breath	1 (2.7%)
Drooling	1 (2.7%)
Snoring	1 (2.7%)

All side effects related to chronic VNS stimulation were well tolerated and did not cause discontinuation of the treatment.

Mild hoarseness developed in 14 of the 36 patients (38.8%) during the ramp up process. A severe hoarseness associated with cough and vomiting affected two patients after electrode replacement also at a low threshold of stimulation. In these two cases we changed the ramping up procedure using lower values of output current and longer intervals to reach higher stimulation values.

Minor side effects were represented by mild sleep apnoeas in three cases (8.3%), sternocleidomastoid muscle spasm in one (2.7%), shortness of breath in one (2.7%), drooling in one (2.7%) and snoring in one (2.7%) (Table 2).

Discussion

Although VNS has been shown to be a safe therapy, adverse events can occur during Neuro-Cybernetic Prosthesys system (Cyberonics, Houston, Tex., USA) implantation and during chronic stimulation. In published trials, infection was the most commonly observed surgical complication of either the generator site or lead implantation site. The overall infection rate was 3%, but only about 1% required explantation of the device; the other patients being successfully treated with antibiotic therapy only. In our experience, no infection was observed, perhaps due to the use of prolonged antibiotic therapy [4].

Lead breakage occurred commonly in the early history of VNS, with a rate of 0.12–2.7%. It was due to fatigue at the junction between the lead wire and the electrode contact. This problem seems to have corrected by the redesign of the electrode with quadrifilar wire [14]. Some unusual circumstances may rarely cause lead breakage, such as drop attacks, trauma, self-manipulation, excessive generator movement, and suturing directly to the lead body [5, 14, 25]. In addition, normal growth during childhood could place additional strains on the leads and damage them. The generator device may be easily taken away, but removal of the electrodes would cause injury to the vagal nerve because they are wrapped around the nervous trunk; therefore a common option is to cut off the distal leads rather than remove the electrodes from the nerve. The placement of new electrodes on the remaining free space on the vagus

nerve when old electrodes were retained could be difficult because of the limited space [5]. Previous experiences showed that the spiral electrodes may be safely removed from the vagus nerve even after several years [5, 14]. In our series, electrode breakage occurred in two patients 3 years after surgical implantation without a history of trauma or drop-attacks. The breakage was discovered accidentally while performing a lead test that showed high impedances and did not present as an absence of perceived stimulation.

In both patients that were operated on with the NCP100 Generator model and 300 Lead model, a new device has been implanted after removing the previous vagal electrode coils and generator. Our experience confirms that stimulation electrodes may be removed even after a prolonged period of implantation in spite of the presence of a marked fibrosis of the region. In this circumstance we found that it is less traumatic to cut the spiral electrodes than to unwind them from the nerve. A few cases of early temporary vocal cord paralysis have been reported in the literature. Fortunately, it is a rare event that occurs in about 1% of the treated cases and could be related to the mechanical trauma to the vagus nerve and to the stimulation setting [14, 25–27].

The physical characteristics of the stimulus (frequency and intensity of stimulation) could be involved in laryngeal side effects of VNS [12].

We think that vocal cord dysfunction could be minimised by careful manipulation of the vagus nerve, with care not to disrupt the vascular supply to the vagus nerve and by output currents values of 2 mA or less.

Some authors pointed out that the position of the electrode on the vagus nerve may be relevant for the frequency of this side effect. In the case of a stimulation positioned high on the vagus nerve, 63% of the patients experienced voice problems, while in the case of low stimulation, only 31% experienced voice problem [10]. Up to now, there is only one report of delayed vocal cord paralysis as a result of removal of the VNS leads. This is a very unusual complication and the exact mechanism is unclear: it is possible that injury to the vagus nerve, either via surgical manipulation or inflammation, may not manifest until a certain degree of demyelination occurs [26]. Another explanation could be that the surgical removal and the new implantation of electrodes can minimally injury the recurrent laryngeal branches by mechanical trauma so that a normal stimulation current amplitude could become an “excitotoxic” overstimulation.

These adverse events can be minimised by postponing VNS therapy until 2 weeks after surgery. The stimulation should be increased at 0.25 mA increments to avoid hoarseness, coughing or vomiting, but the tolerated re-implant current is less than preoperative output current in most cases.

The aesthetic damage related to the size of the stimulator was acceptable in all the cases, the modification of the surgical procedure using a single transverse cervical incision combined with a sub-pectoral placement of the pulse generator offered a safe and cosmetically favourable method for the implantation of the VNS in our series.

Transient side effects of chronic VNS occurred frequently and include hoarseness, cough, voice changes, dyspnoea, headache, nausea and neck spasms. They are usually parameter-dependent and occur during stimulus delivery only. All these side effects are reversible, well tolerated and did not precipitate discontinuation of the treatment.

Recently, different adverse events have been reported, such as the effects of VNS on sleep-related breathing and heart rate. Therefore, a more accurate selection of candidates for VNS is needed [7, 19]. Respiratory pattern changes during sleep with VNS were seen in seven of eight children reported by Nagarajan [22], but the changes did not meet the criteria for apnoea/hypopnoea and there were no significant hypoxia or hypercapnia. We believe that further investigations are required to explore respiratory pattern changes in sleep with VNS, especially in children with sleep apnoeas or compromised respiratory functions.

Conclusions

The VNS surgical implantation is safe, even in small children, but requires thorough knowledge of the anatomy of the vagus nerve and its branches. An appropriate surgical technique can minimise potential mechanical injury, also in the cases of lead removal and re-implantation. The reversibility of the procedure increases the attractiveness of VNS, because complete removal of leads and electrodes may be more satisfying to the patients, since they would not retain unnecessary hardware.

In our experience, a lead fracture in two of the first eight patients of our series and an intermittent vocal cord paresis were the only surgical complications. The most frequently encountered adverse effects typically occur during stimulation, are usually of mild severity and resolve spontaneously over time.

References

1. Aldenkamp AP, Van de Veerdonk HA et al (2001) Effects of 6 months of treatment with vagus nerve stimulation on behaviour in children with Lennox Gastaut Syndrome in an open clinical and nonrandomized study. Epilepsy Behav 2:343–350
2. Annegers JF, Coan SP, Hause WA, Leestma J, Duffel W, Tarver B (1998) Epilepsy, vagal nerve stimulation by NCP system, mortality and sudden, unexpected, unexplained death. Epilepsia 39:206–212
3. Asconapé J, Moore, Zipes D, Hartmann L, Duffel WH (1999) Bradycardia and asystole with the use of vagus nerve stimulation the treatment of epilepsy: a rare complication of intraoperative device testing. Epilepsia 40:1452–1454
4. De Giorgio CM, Amar A, Apuzzo MLJ (2001) Surgical anatomy, implantation technique, and operative complications. In: Schmidt D, Schachter SC (ed) Vagus nerve stimulation. Martin Dunitz, London, pp 31–50
5. Espinosa J, Aiello MT, Naritouku DK (1999) Revision and removal of stimulating electrodes following long term therapy with the vagus nerve stimulator. Surg Neurol 51:659–664
6. Fisher RS, Krauss GL, Ramsay E et al (1997) Assessment of vagus nerve stimulation in epilepsy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 49:293–297

7. Frei MG, Osorio I (2001) Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effexts on heart rate and on its variability in humans. Epilepsia 42:1007–1016
8. Frost M, Gates J, Helmers SL, Wheless JW et al (2001) Vagus nerve stimulation in children with refractory seizures associated with Lennox Gastaut Syndrome. Epilepsia 42:1148–1152
9. Glazier SS, O'Donovan A, Bell WL et al (2000) Placement of the vagus nerve stimulator and electrodes through a single transverse cervical incision: experience with 25 patients. Epilepsia 41:221
10. Handforth A, De Giorgio CM, Schachter SC et al (1998) Vagus nerve stimulation therapy for partial onset seizures. Neurology 51:58–55
11. Hornig GW, Murphy JV, Schallert G (1997) Left vagal nerve stimulation in children with refractory epilepsy: an update. South Med J 90:485–488
12. Kersing W, Dejonckere PH,Van der Aa HE, Buschman HPJ (2002) Laryngeal and vocal changes during vagus nerve stimulation in epileptic patients. J Voice 16:251–257
13. Labar D (2000) Vagus nerve stimulation for intractable epilepsy in children. Dev Med Child Neurol 42:496–499
14. Landy HJ, Ramsay RE, Slater J, Casiano R, Morgan R (1993) Vagus Nerve stimulation for complex partial seizures: surgical technique, safety and efficacy. J Neurosurgery 78:26–31
15. Lesser RP (2000) Ventricular asystole during vagus nerve stimulation for epilepsy in humans. Neurology 54:776
16. Lundgren J, Amark P, Blennow G, Strombald LG (1998) Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 39:809–813
17. Lundgren J, Ekberg O, Olsson R (1998) Aspiration: a potential complication to vagus nerve stimulation. Epilepsia 39:998–1000
18. Majoie HJM, Berfelo MW, Aldenkamp AP, Evers SMAA, Kessels AGH, Renier WO (2001) Vagus nerve stimulation in children with therapy–resistant epilepsy diagnosed as Lennox Gastaut Syndrome. Clinical results, neuropsychological effects, and cost effectiveness. J Clin Neurophysiol 18:419–428
19. Marzec M, Edwards J, Sagher O, Fromes G, Malow BA (2003) Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia 44:930–935
20. Murphy JV, Pediatric VNS Study Group (1999) Left vagal nerve stimulation in children with medically refractory epilepsy. J Pediatr 134:563–566
21. Murphy JV, Hornig GW, Schallert GS, Tilton CL (1998) Adverse events in children receiving intermittent left vagal nerve stimulation. Pediatr Neurol 1:42–44
22. Nagarajan L, Walsh P, Gregory P, Stick S et al (2003) Respiratory pattern changes in sleep in children on vagal nerve stimulation for refractory epilepsy. Can J Neurol Sci 30:224–227
23. Parker APJ, Polkey CE, Binnie CD et al (1999) Vagal nerve stimulation in epileptic encephalopathies. Pediatrics 103:778–782
24. Ramsay RE, Uthman BM, Augustinsson LE et al (1994) Vagus nerve stimulation for treatment of partial seizure. 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Group. Epilepsia 35:627–636
25. Smyth MD, Tubbs RS, Bebin EM, Grabb BA, Blount JP (2003) Complications of chronic vagus nerve stimulation for epilepsy in children. J Neurosurg 99:500–503
26. Vassilyadi M, Strawsburg RH (2003) Delayed onset of vocal cord paralysis after explantation of a vagus nerve stimulator in a child. Childs Nerv Syst 19:261–263
27. Zalvan C, Sulica L, Wolf S, Cohen J, Gonzalez-Yanes O, Blitzer A (2003) Laryngopharyngeal dysfunction from the implant vagal nerve stimulator. Laryngoscope 113:221–225
28. Zamponi N, Rychlicki F, Cardinali C, Luchetti A, Trignani R, Ducati A (2002) Intermittent vagal nerve stimulation in paediatric patients: 1-year follow-up. Childs Nerv Syst 18:61–66