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Vagus nerve stimulation: Outcome and predictors of seizure freedom in long-term follow-up

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ABSTRACT

Objectives: To present long-term outcome and to identify predictors of seizure freedom after vagus nerve stimulation (VNS).
Methods: All patients who had undergone VNS implantation in the Epilepsy Centre Bethel were retrospectively reviewed. There were 144 patients who had undergone complete presurgical evaluation, including detailed clinical history, magnetic resonance imaging, and long-term video-EEG with ictal and interictal recordings. After implantation, all patients were examined at regular intervals of 4 weeks for 6–9 months. During this period the antiepileptic medication remained constant. All patients included in this study were followed up for a minimum of 2 years.
Result: Ten patients remained seizure-free for more than 1 year after VNS implantation (6.9%). Seizures improved in 89 patients (61.8%) but no changes were observed in 45 patients (31.3%). The following factors were significant in the univariate analysis: age at implantation, multifocal interictal epileptiform discharges, unilateral interictal epileptiform discharge, cortical dysgenesis, and psychomotor seizure. Stepwise multivariate analysis showed that unilateral interictal epileptiform discharges (IEDs), $P = 0.014$, HR = 0.112 (95% CIs, 0.019–0.642), cortical dysgenesis $P = 0.007$, HR = 0.065 (95% CIs, 0.009–0.481) and younger age at implantation $P = 0.026$, HR = 7.533 (95% CIs 1.28–44.50) were independent predictors of seizure freedom in the long-term follow-up.
Conclusion: VNS implantation may render patients with some forms of cortical dysgenesis (parietooccipital polymicrogyria, macrogyria) seizure-free. Patients with unilateral IEDs and earlier implantation achieved the most benefit from VNS.

1. Introduction

Despite active pharmacological therapy in the management of epileptic disorders, satisfactory seizure control, even with optimal drug administration, still cannot be achieved in 30–40% of the patients. Some of these patients can benefit from resective surgery.[1] Surgical therapy achieves long-term control in 50–80% of patients.[2–4] Physiological and anatomical limitations such as proximity to the eloquent cortex, false localization of EEG and dual pathology in the remaining patients have been linked to surgical failure. For those who are not candidates for epileptic focus resection, or for those who have not benefited from surgery, VNS-therapy has been shown to be an effective alternative approach.[5] Since the first human implantation of a VNS device in 1988 reported by Penry, more than 55,000 patients have received VNS-therapy worldwide.[6] The efficacy of VNS in treating focal epilepsies and various types of generalized epilepsies, including idiopathic generalized epilepsy and Lennox–Gastaut syndrome, has been demonstrated in numerous studies.[7] The predictors of seizure freedom after VNS implantation are still unknown. Our aim was to assess VNS outcome in a large group of patients and determine the predictors of seizure freedom in long-term follow-up.

2. Methods

2.1. Patient selection

In this retrospective study, all patients with medically refractory epilepsy who had a VNS system implanted at the Bethel Epilepsy Centre from May 2000 to April 2007 were included.

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Table 1
Summary of clinical characteristics and predisposing factors in the patient group.

Variables	All patients $N = 144$	Seizure-free $N = 10$	Non-seizure-free $N = 134$	Sig.
Age at onset (years)	6.3 ± 6.7	3.1 ± 3.2	6.6 ± 6.9	0.114
Age at implantation (years)	23.7 ± 13.4	16.2 ± 10.8	24.3 ± 13.5	0.026
Epilepsy duration (years)	17.4 ± 10.6	13.1 ± 8.1	17.7 ± 10.7	0.189
Follow-up (months)	36.1 ± 12.2	33.4 ± 13.1	36.2 ± 12.1	0.479
Etiology				
MCD	44 (30.6%)	5 (50%)	39 (29.1%)	
Tumour	5 (3.5%)	0 (0%)	5 (3.7%)	
Encephalitis	8 (5.6%)	0 (0%)	8 (6%)	
Lennox-Gastaut syndrome (LGS)	16 (11.1%)	0 (0%)	16 (11.9%)	
Hippocampal sclerosis (HS)	7 (4.9%)	0 (0%)	7 (5.2%)	
Cerebral infarction	3 (2.1%)	0 (0%)	3 (2.2%)	
Unknown	61 (42.4%)	5 (50%)	56 (41.8%)	
Predisposing factors				
Family history	12 (8.3%)	0	12 (9%)	0.407
CNS infection	12 (8.3%)	0	12 (9%)	0.407
Congenital anomaly	14 (9.7%)	3 (30%)	11 (8.2%)	0.059
Febrile convulsion	11 (7.6%)	0	11 (8.2%)	0.440
Head trauma	4 (2.8%)	0	4 (3%)	0.747
History of TLR	11 (7.6%)	1 (10%)	10 (7.5%)	0.560
History of extra TLR	15 (10.4%)	0	15 (11.2%)	0.320

TLR = Temporal lobe resection.

Excluded from our study out of 159 patients were those who had not been followed up for at least 2 years, and patients who had not undergone a complete presurgical evaluation including a detailed clinical history, MRI, and long-term video-EEG with ictal and interictal recordings. Of 144 patients (67 male and 77 female), the mean age at seizure onset was 6.3 ± 6.7 years (range 0.1–44 years) and mean age at surgery was 23.7 ± 13.4 (range 3–65 years), and the mean duration of epilepsy was 17.4 ± 10.6 years (range 5–56 years). The mean follow-up duration was 36.1 ± 12.2 months (range 24–71 months). Table 1 shows a summary of clinical characteristics and predisposing factors in the patient group.

2.2. Presurgical evaluation

In patients who were considered to be possible candidates for epilepsy surgery, a detailed neurological history was taken and the resistance to AEDs was evaluated. A high resolution MRI was carried out on all patients. Patients underwent continuous video-EEG monitoring lasting 2–7 days. In all patients except small children, psychiatric and neuropsychological examinations and a social assessment were undertaken. Findings of the presurgical evaluation were discussed at a multidisciplinary case conference, where decisions were made about the possibility and type of brain surgery or VNS, or alternatively, the need for further investigations.

2.3. Vagus nerve stimulation

Stimulation of the left vagal nerve was carried out using an NCP system (Cyberonics Inc., Houston, TX, USA). Stimulation was initiated in the immediate postoperative period, using the parameters current: 0.25 mA, frequency: 30 Hz, pulse width: 500 μs, 30-s signal on time, 5-min signal off time.

Patients in whom a vagus nerve stimulator had been implanted were examined at regular intervals of 4 weeks for 6–9 months. During this period the antiepileptic medication remained constant. At each visit the current was gradually increased in steps of 0.25 mA and changes of the seizure situation as well as side effects due to VNS stimulation were assessed. The current was gradually increased until seizure freedom or the maximal possible output of 3.5 mA was reached. It was tried to obtain at least 1.5 mA unless the patient did not tolerate this current intensity. The other device parameters were kept unchanged during this period. If patients showed no improvement of their seizures for 0.5–1 year after implantation, despite increasing the output current, the signal on time was changed from 30 to 7 s, the signal off time from 5 min to 30 s As long as the stimulus parameters were adjusted the concomitant antiepileptic drug treatment was altered only if the seizure situation worsened or drug induced side effects occurred. Patients were additionally provided with a magnet allowing stimulation by themselves or by caregiver in the case of an aura or seizure. The output current induced by the magnet was programmed to be 0.25 mA higher than the automatically delivered intensity, and had a pulse width of 500 μs for a period of 60 s.

2.4. Data collection

Demographic data, seizure semiology, EEG (ictal and interictal), neuroimaging data, and epilepsy syndrome were the variables investigated. Data were obtained from the patients' files and medical records. In addition, EEG data were taken from non-invasive continuous video-EEG monitoring. Preoperative 32–64 channel EEG recordings were used; electrodes were placed according to the 10–20 system with the number of electrodes and their placement individually varied depending on the suspected epileptogenic region and side. The location and frequency of IED were assessed by visual analysis of interictal EEG samples of 2-min duration per hour.

2.5. Neuroimaging modalities

Patients underwent MR imaging performed with a 1.5 T magnet, in which a specific protocol for epilepsy patients was used. Additional imaging methods included positron emission tomography, single photon emission computed tomography scanning, and proton MR spectroscopy. However, the results of these investigations were not evaluated in the present study.

2.6. Outcome assessment

Seizure outcome was assessed at regular postoperative visits. The basic follow-up program for all patients was scheduled for 3 months, 6 months, 2 years and then at regular intervals after 2 years. Depending on the effect of VNS, patients were assigned to one of three outcome groups: seizure-free (complete seizure freedom without aura), improvement ($\geq$50% seizure reduction,)

Table 2
Types of seizures, MRI finding and type of IED.

	All patients 144	Seizure-free 10	Non-seizure-free 134	Sig.
Type of seizure				
Presence of auras	54 (37.5%)	2 (20%)	52 (38.8%)	0.202
Psychomotor seizure	38 (26.4%)	0 (0%)	38 (28.4%)	0.042
Tonic seizure	91 (63.2%)	7 (70%)	84 (62.7%)	0.462
Hypermotor seizure	24 (16.7%)	1 (10%)	23 (17.2%)	0.478
Clonic seizure	27 (18.8%)	4 (40%)	23 (17.2%)	0.092
Myoclonic seizure	50 (34.7%)	3 (30%)	47 (35.1%)	0.520
Secondary generalized	88 (61.1%)	5 (50%)	83 (61.9%)	0.335
Atypical absence	29 (20.1%)	2 (20%)	27 (20.1%)	0.676
MRI finding				
Non-lesional	73 (50.7%)	5 (50%)	68 (50.7%)	0.610
Cerebral infarct	4 (2.8%)	0 (0%)	4 (3%)	0.747
Cortical dysgenesis	6 (4.2%)	3 (30%)	3 (2.2%)	0.004
Focal cortical dysplasia	34 (23.6%)	2 (20.0%)	32 (23.9%)	0.566
Tuberous sclerosis	7 (4.9%)	0 (0%)	7 (5.2%)	0.597
Hippocampal sclerosis	7 (4.9%)	0 (0%)	7 (5.2%)	0.597
Brain tumour	5 (3.5%)	0 (0%)	5 (3.7%)	0.694
Encephalitis	8 (5.6%)	0 (0%)	8 (6%)	0.554
Interictal epileptiform discharge (IED)				
Focal	45 (31.2%)	6 (60%)	39 (29.1%)	0.051
Multifocal	76 (52.8%)	1 (10%)	75 (56%)	0.007
Unilateral	55 (38.2%)	8 (80%)	47 (35.1%)	0.005
Generalized	13 (9%)	1 (10%)	12 (9%)	0.624

and no change or <50% seizure reduction. For this study, seizure freedom was defined as a condition in which the patient was seizure-free for a minimum of 1 year prior to the last postoperative visit. If seizures reappeared in an initially seizure-free patient, the outcome was defined as non-seizure-free.

2.7. Statistical procedures

For the single predictive variable analysis using categorical variables, the χ^2, Fisher's exact, and binomial tests were applied. The Mann–Whitney *U*-test was employed to compare continuous variables. A logistic stepwise multivariate regression for variables showing a significant effect in a single predictive analysis was used to identify which variables could predict the outcome independently. Two-tailed error probabilities smaller than $P = 0.05$ were considered significant.

3. Results

3.1. Overall outcome

Overall, 10 (6.9%) of 144 patients remained seizure-free for more than 1 year, in 89 cases (61.8%) seizures improved and in 45 cases (31.3%) seizures did not change. The outcome of treatment in all patients with a follow-up of 3 and 6 months as well as more than 2 years is demonstrated in Table 3, with VNS adjustment correlated with seizure freedom in some patients. Standard cycle parameters were changed to rapid cycle parameters in 35 (24.3%) patients, 5 of whom became seizure-free after the adjustment. The range of current intensity in seizure-free patients was between 1.25 and 3 mA.

Psychomotor seizures showed a significant negative association with outcome ($P = 0.042$). Unilateral interictal epileptiform discharges had been recorded in 80% of patients who later became seizure-free ($P = 0.005$). On the other hand, 1 patient (10%) with multifocal IED became seizure-free. Multifocal IED showed a significant negative association with outcome ($P = 0.007$) (Table 2).

3.2. Outcome in relation to age

In our study, 63 patients were younger than 18 years at the time of implantation. Of these, 8 patients (5.6%) became seizure-free ($P < 0.000$) and the seizures improved in 44 patients (30.6%). Of 81 patients older than 18, 2 of them (1.4%) became seizure-free. Seizures improved for 45 of these patients (31.2%), and for 34 (23.6%) seizures did not change. The outcome after a follow-up of 3 months, 6 months and more than 2 years is demonstrated in Tables 3 and 4. For the factor age at implantation a significant difference could be seen between seizure-free and non-seizure-free patients ($P = 0.026$). The average age at implantation in the seizure-free group was 16.2 ± 10.8 (range 7–36 years), and 24.3 ± 13.5 (3–65 years) in the non-seizure-free patients.

3.3. Outcome in relation to etiologic factors

Various types and degrees of malformation of cortical development were observed in 44 patients (30.6%), 5 (1.5%) of whom became seizure-free after stimulation. The MRI showed a focal cortical dysplasia in 34 patients (23.6%). In 6 cases (4.2%) cerebral dysgeneses such as polymicrogyria, macrogyria, hemimegalence-

Table 3
Overall outcome.

	Seizure-free	Improved	No change	Sig.
3 months (144)	2 (1.4%)	48 (33.4%)	94 (65.3%)	0.056
6 months (144)	5 (3.5%)	74 (51.4%)	65 (45.2%)	0.155
2 years (144)	10 (6.9%)	89 (61.8%)	45 (31.3%)	0.000
More than 2 years (144)	5 (3.5%)	96 (66.6%)	43 (29.8%)	0.012

Table 4
Seizure outcome in adults compared with children.

	Seizure-free	Improved	No change
Adults			
3 months (81)	0 (0%)	23 (16%)	58 (40.3%)
6 months (81)	1 (0.7%)	40 (27.8%)	40 (27.8%)
2 years (81)	2 (1.4%)	45 (31.2%)	34 (23.6%)
More than 2 years (81)	2 (1.4%)	48 (33.3%)	31 (21.5%)
Children			
3 months (63)	2 (1.4%)	25 (17.4%)	36 (25%)
6 months (63)	4 (2.8%)	34 (23.6%)	25 (17.4%)
2 years (63)	8 (5.6%)	44 (30.6%)	11 (7.7%)
More than 2 years (63)	3 (2.1%)	48 (33.3%)	12 (8.3%)

phaly and band heterotopia were observed. Moreover, 2 patients with bilateral posterior parietooccipital polymicrogyria and one with left perisylvian macrogyria became seizure-free ($P = 0.004$). In 3 other patients, 1 patient with hemimegalencephaly became seizure-free for 4 months and 2 patients with bilateral perisylvian polymicrogyria and band heterotopia did not improve after VNS.

3.4. Outcome in relation to AEDs

All patients were examined at regular intervals of 4 weeks for 6–9 months. During this period the antiepileptic medication remained constant. After that AEDs have been added in case of seizure deterioration or presence of side effects. During follow-up the new add-on antiepileptic drug, levetiracetam had been added to the treatment in 2 of the 10 patients who became seizure-free ($P = 0.080$). In the first case levetiracetam was added 2 months after surgery and the patient became seizure-free thereafter. In the second case, levetiracetam was added 1 year after the operation.

3.5. Univariate analysis

Five variables showed a significant association with seizure-free outcome: age at implantation ($P = 0.026$), multifocal IED ($P = 0.007$), unilateral interictal epileptiform discharge ($P = 0.005$), cortical dysgenesis ($P = 0.004$), and psychomotor seizures ($P = 0.042$).

3.6. Multivariate analysis

Stepwise logistic regression was undertaken to investigate in a single predictive variable analysis those five factors found to be significant. Three of the factors correlated independently with successful VNS treatment: age at implantation ($P = 0.026$, HR = 7.533, 95% CIs 1.275–44.494), cortical dysgenesis ($P = 0.007$, HR = 0.065, 95% CIs 0.009–0.481), and unilateral IEDs ($P = 0.014$, HR = 0.112, 95% CIs 0.019–0.642).

3.7. Complications

Some side effects were observed in 43 patients (30.6%). These mostly varied from mild to moderate and disappeared after 4–6 months. Most commonly reported complications were hoarseness in 32 patients (22.2%), coughing in 8 (5.6%) and dizziness in 4 (2.8%). In addition, in two cases the VNS cable was broken 1.5 and 2 years after implantation. These patients underwent reimplantation.

4. Discussion

Despite the increasing amount of clinical data, it is still not possible to predict seizure-free outcome after VNS. In our study, the presence of unilateral IED, cortical dysgenesis, and a younger age at implantation independently predicted a seizure-free outcome. The major finding of this study is the number of seizure-free patients ($N = 10$) with more than 1 year of seizure freedom. A literature review showed that there are only three studies in which more than 1 year of seizure freedom was presented, and fewer patients (2, 3 and 6 patients) were included in all three of these studies.[8–10] In our study, only 2 patients became seizure-free after adding levetiracetam with a non-statistically significant effect on the outcome ($P = 0.08$).

4.1. Unilateral IED

Our study demonstrated that unilateral IED independently predict seizure freedom after VNS implantation. Some studies indicated a relationship between VNS outcome and the electrical seizure pattern.[11] The absence of bilateral IED was shown to have a significant correlation with a seizure-free outcome[12]; in another study it could be seen that patients with an onset of seizure activity in the temporal area had a better outcome than those with frontal or fronto-central seizure activity.[11] Overall, the outcome of epilepsy surgery showed better results when IED occurred ipsilaterally.[13,14]

4.2. Cortical dysgenesis

Cortical dysgenesis encompasses a wide spectrum of brain disorders resulting from abnormal neuronal proliferation, migration or cortical organization.[15,16] A few studies reported the effect of VNS on refractory seizures due to cortical dysgenesis.[17–20] Montenegro et al. described 9 patients with parietooccipital polymicrogyria associated with epilepsy that was intractable in 7 patients.[21] Cortical dysgenesis is often associated with a high degree of epileptogenicity. Seizure generation has been hypothesized to be the consequence of incomplete cellular maturation and pathogenic mechanisms will likely vary in mild and severe cortical dysplastic tissues.[22] With increasingly better MRI resolution, these lesions can be readily detected in patients with cryptogenic epilepsy. In fMRI, these lesions responded actively to simple stimuli or tasks.[23] However, in well-defined epileptogenic areas like cortical tubera or FCD, resective surgery is the preferred treatment option.[24,25] Theoretically, VNS has a widespread inhibitory effect on the brain and, therefore, has a therapeutic role in patients who are not ideal epilepsy surgery candidates.[11] We recommend prospective VNS studies enrolling larger numbers of patients to confirm this result.

4.3. Age at implantation

The relation between the age at implantation and VNS outcome is controversial. In agreement with our study, Wheless and Maggio found that patients younger than 18 years of age at implantation have a better response than those who are over 18. Murphy et al. found that there were few adverse effects in patients younger than age 12.[26,27] These results could be explained by the fact that an immature brain has a higher threshold for excitatory stimuli and seizure-induced changes than an adult one. The inverse correlation between age and the thresholds of after-discharges following cortical stimulation is well known: the younger the patient, the higher the thresholds. Moreover, experimental data showed that kindling and secondary hippocampal damage is less expressed in developing rats compared with adult animals. Moreover, electrical VNS interferes with amygdaloidal kindling epileptogenesis in the cat. Therefore, VNS early in the course of treatment is recommended,[23,28] if other therapeutic options have failed to control seizures.

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