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Vagus nerve stimulation: Clinical experience in drug-resistant pediatric epileptic patients

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Summary

Introduction: Vagus nerve stimulation (VNS) is an effective alternative treatment for patients with partial refractory epilepsy. Nevertheless, information regarding VNS in children is still limited.
Materials and methods: The clinical efficacy, safety and neuropsychological effects of VNS in 34 children (mean age 11.5 years) with drug-resistant epilepsy were studied. Mean follow-up was 30.8 months.

Nine patients have been diagnosed with Lennox—Gastaut Syndrome, nine patients were affected by severe partial epilepsy with bisynchronous EEG and drop attacks, and 16 patients suffered from partial epilepsy without bisynchronous EEG and fall seizures. Forms were designed for prospective data collection on each patient's history, seizures, implants, device settings, quality of life (QOL), neuropsychological assessment and adverse events. Surgical technique was performed both by standard two incisions and single neck incision.
Results: Mean reduction in total seizures was 39% at 3 months, 38% at 6 months, 49% at 12 months, 61% at 24 months and 71% at 36 months. Significant better results were obtained in partial epilepsy, with and without drop attacks, than in Lennox—Gastaut syndrome—three patients being seizure-free. No operative morbidity was reported. Side-effects were minor and transient—the most common were voice alteration and coughing during stimulation. In two patients, electrode breakage occurred 3 years after surgical procedure; in both cases, a new device was implanted after removing the vagal electrode coils and generator.

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Conclusion: VNS can be considered an appropriate strategy as an add-on treatment in children affected by drug-resistant partial epilepsy and ineligible for resective epilepsy surgery.

Introduction

Vagus nerve stimulation (VNS) can be considered a non-pharmacological therapy for patients with intractable epilepsy who are ineligible for resective epilepsy surgery.[1]

Over the last decade, the advent of VNS has aroused renewed interest in neurostimulation and opened up new perspectives in the treatment of epilepsies.[2] It is evident that VNS offers substantial therapeutic benefit to some patients without causing major side-effects. In most situations, VNS is considered a palliative treatment with the goal of reducing the frequency and severity of seizures, although a small proportion (about 5%) of patients with VNS implants have been reported as seizure-free.[2,3–5]

In adults, the technique has been used on a wide scale, but little data are available on the use of VNS therapy in children with refractory epilepsy. Results from small observational studies suggest that the therapeutic effect of VNS is better in children than in adults, and the benefit in children is achieved more rapidly.[1,3,6,7–17]

In a recent study on 60 children (mean age: 15 years), the median reduction in seizure frequency was 44%.[10]

A retrospective study in six epilepsy centers evaluating the effectiveness of VNS therapy in 125 children with Lennox–Gastaut Syndrome (LGS), reported an average seizure reduction of 36.1% at 3 months and 44.7% at 6 months.[18]

This clinical, non-randomized, prospective study of a series of pediatric patients reports our clinical experience in evaluate the effectiveness and safety of VNS, especially in the most severe and advanced cases, such as LGS, and to identify any variations that may exist in responses among different epileptic syndromes.

We also provide preliminary data on the effects of different stimulation conditions (standard versus intermediate cycle).

Material and methods

Patients

Thirty-four patients (21 male and 13 female) with drug-resistant epilepsy were included.

Patients were eligible for the study if they met the following criteria:

(1) Lennox–Gastaut Syndrome;
(2) partial epilepsy with multiple seizure types, bisynchronous EEG and drop attacks;
(3) partial epilepsy with multiple seizures, without bisynchronous EEG and drop attacks;
(4) absence of progressive or systemic diseases;
(5) seizure frequency higher than 10 per month with interictal period shorter than 3 weeks, despite maximal drug treatment regimens;
(6) epilepsy history lasting more than 3 years or catastrophic epilepsy of infancy.

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), or with poor parental collaboration, were not included.

Patient's age ranged from 1.4 to 18 years (mean age: 11.5 years).

Nine patients suffered from Lennox–Gastaut Syndrome, nine patients suffered from partial epilepsy with drop attacks and secondary bisynchronism on the EEG and 16 patients had partial epilepsy without drop attacks.

Etiology of epilepsy was cryptogenic in 14 patients and symptomatic in 20.

The etiology of symptomatic forms includes five patients with neurological damage secondary to prematurity and perinatal anoxic/ischemic lesions, three patients with herpethic encephalitis, four patients with neurological sequels of bacterial meningoencephalitis, three patients with cortical dysplasia, two patient with Bourneville tuberous sclerosis, one patient with vascular malformation of the middle cerebral artery, one patient with neurological sequels of near SIDS and one patient with chromosomopathy.

All but three patients had multiple seizures—in 18 cases, tonic or atonic drop attacks were present. Overall, mean seizure frequency was always very high. Twenty-seven patients had daily seizures up to a maximum of 40 seizures per day. Seven patients had 8–20 seizures per month (average seizure frequency per month: 297.5).

In all cases, treatment with at least two antiepileptic drugs, in variable associations, had been tried unsuccessfully.

Interictal and ictal EEGs were available in all patients. The seizure characteristics were assessed by video-EEG recordings in 27 patients.

Neuropsychological assessment showed severe mental retardation in 22 cases, moderate in seven cases and mild mental retardation in four. One patient had a normal intelligence quotient (IQ). Focal neurologic disorders, including hemiparesis or tetraparesis, were present in 22 cases.

School attendance, with the support of a personal teacher, was possible in all school-age children.

Lennox—Gastaut Syndrome

Nine patients (8 male/1 female) have been diagnosed with Lennox—Gastaut Syndrome.

They showed the typical electroclinical pattern of the syndrome and in eight patients spasms were present in the first 5 months of life.

Mean age at implant operation was 11.1 years, with a mean epilepsy duration of 9.6 years.

Multiple seizures (atypical absences, tonic seizures, tonic—clonic generalized seizures) were present, with frequent and very disabling tonic or atonic drop attacks (average seizure number: 330.6 per month)

All patients showed neurological focal deficits and mental retardation—severe in seven cases and moderate in two cases.

Partial severe epilepsy with drop attacks and bisynchronous EEG (Pseudo-Lennox Syndrome)

Nine patients (4 male/5 female) were affected by partial epilepsy with multifocal frontal or frontotemporal EEG abnormalities and important secondary bilateral synchrony. Multiple seizures were present, mainly partial complex or secondary generalized and drop attacks. Usually, falls followed a tonic asymmetric contraction of axial and leg muscles leading to a loss of balance.

Mean age at implantation was 8.53 years, with a mean epilepsy duration of 7.8 years and an average seizures number per month of 457.8.

Severe ($n = 8$) or moderate ($n = 1$) mental handicaps were present in all patients.

Partial epilepsy without drop attacks

Sixteen children (9 male/7 female) had partial epilepsy with polymorphic seizures, mainly complex partial or secondary generalized without tonic seizures and drop attacks.

The EEG pattern was characterized by focal or multifocal discharges without secondary diffusion.

Mean age at surgery was 13.5 years, with a mean epilepsy duration of 9.2 years and an average number of seizures per month of 188.8.

Severe mental retardation was present in seven patients—four children showed moderate mental retardation, four mild and one had a normal IQ.

Study design

Forms were designed for prospective data collection on each patient's history, seizures, drug therapy, implant, device settings and side-effects.

Patients were assessed prior to implantation and 3, 6, 12, 24 and 36 months after surgery. The mean follow-up time was 30.8 months (range: 3—51.8 months).

Medical outcome measures

Once the definitive target parameters of stimulation were reached, the follow-up was extended to every 3 months in the first year and to every 6 months in subsequent years to evaluate the degree of tolerance and clinical efficacy of VNS.

Clinical efficacy was determined by comparing the seizure frequency during the last 3 months of follow-up with the seizure frequency during the preimplantation period, using the following equation: [seizures/month on VNS—baseline seizures/month]/[baseline seizures/month] $\times$ 100.[3]

Seizures were encoded, according to the International League against Epilepsy classification, as follows: complex partial seizures (CPS), complex partial secondary generalized (CPSG), myoclonic seizures, tonic seizures, tonic—clonic seizures, absence, drop attacks.[12]

Complex partial seizures and the drop attacks were scored separately.

The antiepileptic therapy was not changed during the first 6 months after surgery, with exception of three patients who presented a status epilepticus.

2.2.2. Neuropsychological outcome measures

QOL was assessed by using the Vineland adaptive behavior scale (VBAS). VBAS is a well-standardized measure of functional behavior and can be used on all children with epilepsy and learning disabilities. VBAS evaluates the social and personal grade of autonomy of an individual. Because it is administered by interview of parents or carers, it does not require the presence or collaboration of the patient and also provides a global functional assessment in subjects with severe neuropsychological disorders. It is divided into five general areas, including communication, socialization, daily living skills, movement abilities and disturbed behaviours.[19]

The test was administered to the 21 treated patients before VNS (baseline) and after 18 months, and to a homogenous control group of 21 epileptic subjects.

Mental age was assessed using a battery test consisting of three different cognitive tests: WISC-RN or Stanford—Binet (Terman—Merrill) scales or Brunet—Lezine scale, depending on the level of mental functioning

Statistical analysis

Seizure frequency changes in the pre- and post-implant period were verified by the *t*-test for paired samples. Comparison between two or more groups was performed by an unpaired *t*-test and one-way factorial ANOVA.

The correlation between some clinical parameters, such as epilepsy duration, chronological age at implant, seizure number pre-VNS, mental retardation, etiology, epileptic syndrome and VNS response were evaluated by Fisher's exact test from 2×2 contingency tables.

P-values < 0.05 were considered to be statistically significant.

Surgical procedure

Implantation technique has been described elsewhere.[14]

The first 10 patients in our series underwent a standard VNS procedure with neck and chest incisions.

Since 2001, the surgical technique has been modified by using a single cervical incision. The upper retraction of the wound allows exposure of the vagal nerve, while the lower retraction is used to create a subclavicular pocket to host the stimulating unit at a distance of about 7 cm from the electrodes. The pulse generator is placed underneath the pectoralis major muscle and secured to the fascia of the intercostal musculature.

Stimulation parameters

Children were discharged 72 h after surgery. On post-operative day 3, the neurostimulator was switched on and, thereafter, the children were re-evaluated as outpatients every week for 1 month for the ramp-up.

The intensity of stimulation, beginning 0.50 mA, was increased, in steps of 0.50 mA, until the stimulation parameters reached 2 mA at a frequency of 30 c/s, with an OFF-period of 5 min alternating with an ON-period of 30 s (standard stimulation setting). During this adjustment period, ECG-coupled polygraphic EEG was systematically performed at the beginning of activation and while the intensity of stimulation reached 1 and 2 mA. In 17 cases, the standard stimulation setting was switched to an intermediate stimulation pattern (ON period 30 s and OFF period 3 min) after 3 months for an unsatisfactory clinical response.

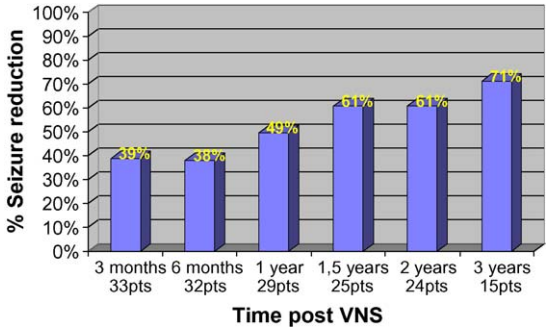

Fig. 1 Summary of seizure-frequency reduction rate in all patients.

Results

Effectiveness

All patients

Data are available for 33 patients at 3 months of treatment. In this period, VNS produced a mean seizure rate reduction of 39% ($P = 0.004$)

At 12 months, data are available for 29 patients. The seizure reduction rate was 49% ($P = 0.003$). Twenty-four patients had a 2-year follow up, with a mean seizure reduction rate in this group of 61% ($P = 0.008$). Seizure reduction rate in the 15 patients with a 3-year follow-up was 71% ($P = 0.002$) (Fig. 1).

At 3 months follow-up, 48% of treated patients were considered responders. The percentage increased to 55 and 71% at 1 and 2 years, respectively (Fig. 2).

Ten of 29 patients with a 12-month follow-up had a reduction in seizure frequency exceeding 70%.

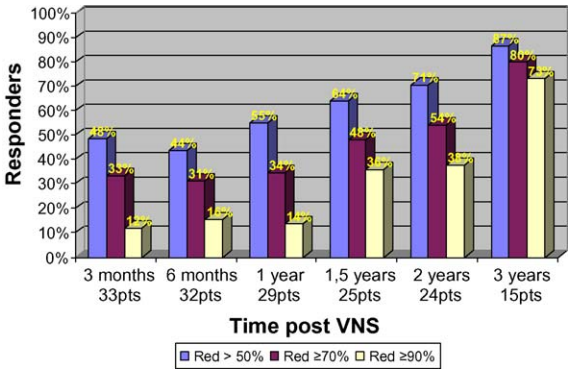

Fig. 2 Percentage of patients with >50% seizure reduction over the follow-up period.

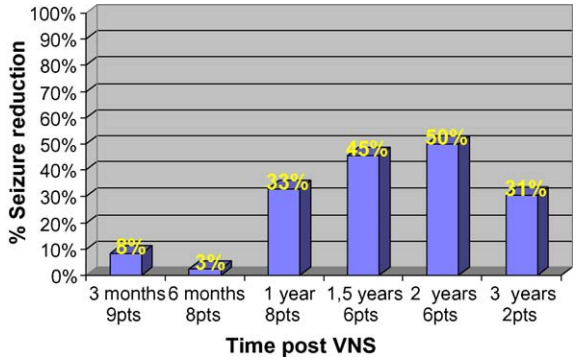

Fig. 3 Seizure-frequency reduction rate in Lennox—Gastaut Syndrome.

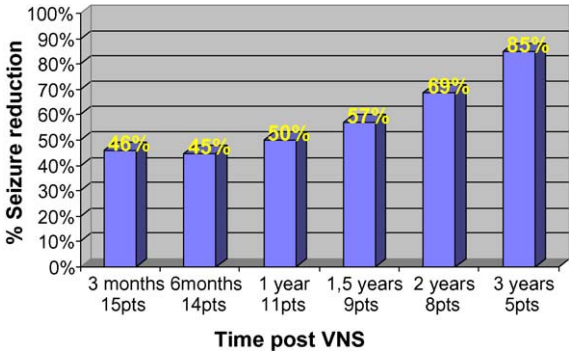

Fig. 5 Seizure-frequency reduction rate in partial epilepsy.

In 19 patients (55.8%), the clinical response was achieved early after surgery with stimulation intensities between 0.75 and 1.25 mA.

Three patients showed a transient worsening of seizure pattern during the first 3 months of treatment.

In eight patients, clusters of seizures, alternating with prolonged seizure-free periods during the first 6 months of treatment, were also observed.

At present, three patients (8.8%) reported a seizure-free period lasting more than 1 year. All of them were affected from partial epilepsy without drop attacks.

Lennox—Gastaut Syndrome

Among patients with Lennox—Gastaut Syndrome, the mean reduction in seizure frequency was 8% at 3 months (n.s.) 33% at 12 months (n.s) and 50% at 2 years (n.s.) (Fig. 3).

Severe partial epilepsy

The average reduction in seizure frequency among patients with severe partial epilepsy with drop attacks was 58% ($P = 0.02$) and 65% at 3 and 12 months, respectively ($P = 0.02$). Only eight patients had more than 2 years follow-up—the mean seizure reduction rate in these children was 59% ($P = 0.02$) (Fig. 4).

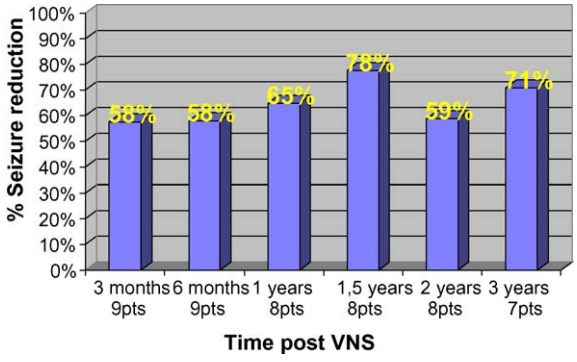

Fig. 4 Seizure-frequency reduction rate in Pseudo-Lennox—Gastaut Syndrome.

Partial epilepsy

Patients with partial epilepsy had a mean reduction in seizure frequency of 46% at 3 months ($P = 0.09$) and 50% at 12 months ($P = 0.02$). At 2 years follow-up, mean reduction was 69% ($P = 0.01$) (Fig. 5).

Clinical effectiveness differed significantly among the three considered groups ($P = 0.001$).

Factors strongly correlated with a better clinical response were:

- age at implantation less than 12 years ($P = 0.009$);
- epileptic syndromes, such as partial epilepsy versus the others ($P = 0.01$);
- epilepsy duration less than 6 years ($P = 0.05$).

Other suggested variables, i.e. etiology, number of seizures and mental retardation, have not been shown statistical significance.

Drop attacks and other seizure types

Data were further analyzed by seizure type.

Drop attacks, present in 18 patients, decreased by 38% at 1 year and 53% at 2 years. Partial seizures, present in 25 patients, decreased by 58 and 67% at 1 and 2 years respectively. No significant difference in clinical response exists between the two seizure types.

Device setting

All the patients were initially set on standard stimulation conditions (2 mA, 30 c/s, OFF time 5 min, ON time 30 s) Vagus nerve stimulation parameters were switched to intermediate cycle (OFF time 3 min, ON time 30 s) in 17 of 34 patients owing to low efficacy of the previous treatment. After a mean period of 8 months, six patients (35.2%) reported a further mean seizure reduction of 21% without side-effects.

Therapy

Patients consumed an average of 2.9 antiepileptic drugs (AEDs) before operation. At the cut-off date, the mean number of AEDs was reduced to 1.8.

At 2 years follow-up, 8 of 24 patients were able to simplify their drug therapy. In five children, the AED number was reduced, while in three there was a dosing reduction without compromising seizure control.

Nine patients received psychotropic medications for concomitant autistic spectrum disorders. At 2 years follow-up, the therapy was discontinued in five children.

Twelve patients received levetiracetam in add-on therapy. Only four patients showed a further seizure reduction of 26%. The occurrence of psychotic behavior required the discontinuation of the drug in two patients.

Neuropsychological outcome

Data are available for 21 patients followed for more than 18 months and for 21 control subjects. No clear cognitive improvement, but also no major disruption, was evident on the clinical sample. On the VABS scores, there was a positive trend, especially in the motricity ($P = 0.04$) and the sociability domains ($P = 0.05$). For three patients, the improvement was significant. The control group showed a significant decrease in the adaptive behavior score ($P < 0.01$), particularly in the communication and daily living skills domains. In the treated group, parental satisfaction and subjective QOL, evaluated by analogical scale, showed a significant improvement—seemingly related to seizure and AEDs reduction and the entity of mental retardation pre-VNS.

Side-effects

The surgical procedure was well tolerated in all cases without noticeable complications.

The aesthetic damage, related to the size of the stimulator, was acceptable in all the cases. Hypertrophic chest scars developed in six of our first 10 patients. The recent implantation modification procedure, using a single cervical incision, reduced this discomfort, particularly in small children with small muscular mass.

In four cases, transient pain was reported at the neurostimulator implantation site.

Fifteen patients reported hoarseness and coughing during the setting phase, i.e. when increasing the stimulation parameters. Both these events resolved in 1—2 days after stimulation adjustments.

A change in the vocal timbre was reported in all patients during the stimulation period; however, this never represented a significant problem.

In two patients, electrode breakage occurred 3 years after surgical implantation. In both cases, device malfunction was suspected for the high values of impedance occasionally found during a lead check and was subsequently confirmed by X-ray examination. It is noticeable that we did not observe worsening of seizures at that time. Drop attacks or trauma were not reported in the two children who received the first lead model of the neurocybernetic prosthesis. A new device was implanted after removing the vagal electrode coils and the generator.

Discussion

The global outcome of VNS treatment in our pediatric patient series confirms earlier reports.[7,9,10,18,20] Moreover, our data showed that seizure-free patients, or those who experienced a >75% seizure reduction, are a more consistent group. Literature data show that seizure-free patients are 2—3% of all treated patients and those with a >75% seizure reduction are about 20%.[4,5]

The aim of this prospective study was to evaluate the effectiveness and safety of VNS therapy in children and to identify the type of epileptic syndrome related to the best results.

At present, literature data does not characterize which type of epilepsy is most suitable for surgical treatment by VNS.

Pediatric series are often heterogeneous and include several different types of epileptic syndromes. Owing to the limited number of cases in each study, no stratification can be performed to achieve a more homogeneous group. In addition, the duration of the follow-up periods and changes in drug regimens are frequently not specified.[8—12,16,18]

Our series includes two types of epileptic syndrome, i.e. Lennox—Gastaut Syndrome and partial epilepsy. In this last group, we analyzed a subgroup of children with a peculiar electroclinical pattern characterized by multifocal, mainly frontal, EEG abnormalities and important bilateral synchrony associated with polymorphic seizures, mainly tonic and drop attacks. These patients developed a progressive mental deterioration so that they look like children with Lennox—Gastaut Syndrome.

Seizures become more and more frequent and disabling so that callosotomy is sometimes considered the correct surgical therapy.[21]

Our results also indicate that, in this group of patients, in which drop attacks are the most important type of seizures, VNS can provide a significant improvement in seizure control. In spite of the small number of patients in the study, the clinical effectiveness of the VNS seems greater in the group of patients with partial epilepsy and drop attacks than in the group of patients with Lennox—Gastaut Syndrome.

This result is similar to that reported in two neurosurgical studies where callosotomized patients with an EEG pattern of secondary bilateral synchrony, drop attacks and partial seizures had a better outcome than patients with generalized epilepsies.[13,21]

At present, VNS is considered the first surgical option for treatment of Lennox—Gastaut and related syndromes and takes precedence over callosotomy because it is less invasive, reversible and with few serious side-effects.[13]

As regards patients with Lennox—Gastaut Syndrome, some studies indicate that VNS can produce satisfactory seizure control while others studies have failed to demonstrate significant efficacy.[7,8,11] Our results are consistent with the latter consideration.

The results in patients with partial epilepsy, without drop attacks and independent EEG abnormalities, confirm previous studies.[3,22]

In these patients, where multiple seizures are not associated with encephalopathy, the treatment with VNS allows prolonged seizure-free periods, suggesting a positive correlation between efficacy and preserved mental function level.[12]

In our series, the positive response was achieved very early after surgery and progressively improved with time, confirming that the duration of stimulation is the most important factor in clinical long-term improvement, due to the cumulative effect of continuous electrical stimulation on the vagus nerve.[20,23]

Initial seizure reduction can be obtained with an amplitude of stimulation, which is usually considered 'non-therapeutic'. This observation supports the hypothesis that, at least for pediatric patients, intensities of stimulation lower than those commonly used in clinical practice for adults can be therapeutic.

The role of the stimulation parameters is still controversial. Currently, it is established that amplitude not higher than 2 mA and a standard cycle (OFF 5 min, ON 3 min) is more effective than a duty cycle (OFF 20 s, ON 7 s).

The role of the intermediate cycle (OFF $\leq$3 min, ON 30 s) is still not clear.[13,17,18,22] Our cases and other sporadic reports in the literature suggest that some patients may benefit from a reduction in OFF time of 1—3 min.[13,23]

It has been recently suggested that the association with some AEDs, mainly levetiracetam, could have a synergic effect with VNS.[24]

This data was not confirmed in our experience.

The side-effects of short- and long-term VNS are mild. Common adverse effects, such as cough, hoarseness, voice alteration, tend to improve and disappear with time. Lead breakage must be considered an important complication rarely reported in the literature.[25] In this case, it became mandatory to perform a new surgical procedure after removing all previous devices, but sometimes it is not possible to remove the coils without damaging the vagus nerve, while it is not so easy to find a free nerve tract to host the coils.

Conclusions

Vagus nerve stimulation is an effective palliative treatment for patients with refractory epilepsy.

In the present study, about 55% of patients showed a considerable improvement in seizure control, with a reduction in seizure frequency of at least 50%.

Clinical response was evident early and efficacy progressively improved with the duration of treatment up to 24 months post-operatively.

The best responders can be considered children with highest mental age affected with partial epilepsy with and without drop attacks.

A small number of patients with partial epilepsy experienced long-term complete freedom from seizures and, during this time, the patients may function at a higher level in daily activities and obtain considerable improvement in QOL and neuropsychological performances.

Clinical effectiveness seems higher in younger children with a short epilepsy history, suggesting a precocious useful role for VNS.[26]

Long-term clinical studies, with larger homogeneous series of patients, are needed to further define the best responders and to direct the search for optimal stimulation parameters and operation time.

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