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ORIGINAL ARTICLE

Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children

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Abstract The objective of this study is to evaluate the safety and efficacy of vagus nerve stimulation (VNS) in very young children suffering from catastrophic epilepsy and status epilepticus. We reviewed files of 60 VNS-implanted children at our institution and we selected six very young patients, less than 3 years old (mean age at implant 1.6 years). All patients suffered from severe cognitive impairment and catastrophic epilepsy with underlying diagnosis of hemimegalencephaly (1), hypoxic-ischemic encephalopathy (1), tuberous sclerosis complex (1), and malignant migrating partial epilepsy of infancy (3). Three patients were VNS-implanted during admission at intensive care unit (ICU) after developing life-threatening status epilepticus. The mean follow-up time was 41.6 months. The VNS was implanted using a single cervical incision. No surgery-related complications were observed. Four of six children have shown a significant, persistent improvement in seizure control (range, 60–90%). In patients with status, insertion of the vagal nerve stimulator allowed early cessation of status and discharge from ICU. Quality of life and parental satisfaction improved and for three children there was some milestone evolution. Catastrophic epilepsy in infancy can be devastating and difficult to treat with drugs and surgery. If resective surgery is inappropriate or refused, VNS can be considered as a well-tolerated and effective procedure even in toddlers affected by severe epilepsy and multiple developmental disabilities.

Keywords VNS · Very young · Catastrophic epilepsy · QOL

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Introduction

The use of vagus nerve stimulation (VNS) therapy (Cyberonics, Inc, Houston, Texas, USA) was approved by the Food and Drug Administration (FDA) in 1997 as an alternative treatment to medications in patients older than 12 years, to help control or reduce seizures that occur because of drug-resistant epilepsy. Unlike medications, it does not negatively impact mental awareness and quality of life (QOL) and interestingly, the efficacy of treatment increases over time.No randomized double-blind controlled trials were performed exclusively on children younger than 12 years. Until now, VNS has been used with varying success for patients younger than 12 years who have severe symptomatic epilepsy, just as off-label antiepileptic drugs (AED) have been used in difficult clinical situations. Several class II and III studies that included children and adolescents have indicated that VNS is useful in managing partial and generalized seizures. It has been found to significantly lessen the intensity and frequency of seizures greater than 50% in over half the patients that are treated [2, 3, 6, 8, 10, 13, 15].

Complications related to the surgical implantation (vocal cord paralysis, prosthesic infection) rarely occur. Some complications such as cosmetic adverse effects are more likely to occur in children because of their body habitus, but a single cervical incision and subpectoral implantation reduce the prevalence of these complications [14, 16].

In addition to the efficacy of VNS in treating seizures, paediatric studies have shown considerable improvement in global evaluation scores of QOL in up to 50% of children that are treated. VNS therapy was found to improve independence, learning, and mood, at times independently from its antiepileptic effect [1–3, 5, 7–10, 12, 13, 17].

The experience with VNS in very young children is limited, and mainly in those younger than 5 years. Some reports, based on a small patient cohort, showed that VNS in very young children with life-threatening epilepsy could be safe and efficacious [4, 18].

In the present study, we report our experience about the safety and effectiveness of VNS therapy involving six very young children (less than 36 months old) affected by catastrophic epilepsy.

Materials and methods

Data collection

We reviewed files of 60 children and adolescents with VNS implant at the G. Salesi Children's Hospital in Ancona, Italy, between 2000 and 2006 and we selected six very young patients suffering from catastrophic epilepsy with pluridaily seizures and severe progressive psychomotor milestones impairment.

The group of patients was composed of six children under the age of three, with the mean age of 1.6 years at implant (range, 8–31 months). Body weight ranged from 8 to 12 kg.

All patients suffered from severe cognitive impairment and catastrophic epilepsy with underlying diagnosis of hemimegalencephaly (1), hypoxic-ischemic encephalopathy (1), tuberous sclerosis complex (1), and malignant migrating partial epilepsy of infancy (3). One of them refused surgical option and the other five were not candidates for surgery.

The mean follow-up (FU) time was 41.6 months (range, 14.3–81.3 months) Clinical and electroencephalogram (EEG) details are summarized in Table 1.

Patients

Case 1 (CC) was a male, second-born from healthy parents after an uneventful pregnancy and delivery. Short partial seizures started when he was 11 days old. Spasms, asymmetrical tonic posturing, partial complex, and unilateral hemiclonic seizures with secondary tonic-clonic generalization appeared since he was 3 months old. These events required frequent emergency admissions to the intensive care unit (ICU). Seizure frequency was high from the beginning (5–40/day) and severe drug resistance to mono- and politherapy developed. Neurological evaluation showed right hemiparesis and progressive and psychomotor delay.

Magnetic resonance imaging (MRI) at the age of 17 days and later at 16 months showed left hemisphere and left ventricle enlargement and wide cortical dysplasia in the left hemisphere, mainly in the frontal region with abnormal signal and thickening of WM and periventricular band heterotopia. Hemispherectomy was considered as the first surgical option, but the parents refused it. VNS implant was performed at 19 months of age with a weight of 9 kg.

Case 2 (MF) was a female, first-born from healthy parents by caesarean section because of perinatal anoxia. Since the age of 8 months she presented medically refractory seizures daily characterized by brief sudden flexion of the head and flexion and adduction of the upper extremities with purple discoloration of the face. Seizure frequency was 20–30/day. The evolution showed the appearance of complex focal seizures with generalization and status epilepticus. Neurological evaluation showed global developmental delay, microcephaly, central hypotonia, and dysmorphic features. Brain MRI showed hypoxic-ischemic brain damage. VNS implant was performed at 26 months of age at a weight of 11 kg.

Case 3 (PA) was a female, first-born from healthy parents after an uneventful pregnancy. Partial, brief, right versive seizures with vegetative symptoms appeared at the age of 7 months. EEG showed multifocal paroxysmal abnormalities. Neuroradiological, clinical, and genetic investigations led to the diagnosis of tuberous sclerosis complex. Vigabatrin therapy led to a 6-month seizure-free

Table 1 Clinical and EEG details

Case	Etiology	Seizures/month	Age at onset	Age at VNS implant (years; months)	Follow-up (in months)	EEG
1 (CC)	Left hemimegalencephaly	120	11 days	1.7	81.3	Left focal
2 (MF)	Anoxo-ischemic encephalopathy	600	8 months	2.2	77.7	Multifocal with bysinchronism
3 (PA)	Bourneville TS	120	7 months	2.7	14.3	
4 (AC)	Malignant partial epilepsy of infancy	600	18 days	1.4	37.5	Multifocal
5 (ML)	Malignant partial epilepsy of infancy	600	6 months	0.9	21.6	Multifocal
6 (GN)	Malignant partial epilepsy of infancy	600	2 months	0.7	17.2	Multifocal

period; then, flexion spasms associated with pluridaily complex partial seizures appeared despite several AED.

Cognitive level was not affected and permanently adequate. Ictal video EEG recordings showed multiple, independent sources of seizures. VNS implant was performed at 31 months of age, at a weight of 12 kg.

Case 4 (AC) was a male, first-born from a heroin-dependent mother by caesarean section at 37 weeks of gestation, after heroin abuse during pregnancy. Focal unilateral seizures started at 18 days followed by migrating focal seizures. Since the beginning, frequency of seizures was high (up to 50/day) and severe drug resistance progressively developed. Recurrent status epilepticus led to frequent emergency admissions to the ICU. Neurological evaluation showed severe psychomotor delay and dyskinesia (abnormal involuntary movements that primarily affected the extremities and trunk). Complete biochemical and morphologic evaluation failed to demonstrate any metabolic or degenerative disorders. MRI showed diffuse atrophy. Clinical and EEG findings led to the diagnosis of malignant migrating partial epilepsy of infancy. VNS implant was performed at 16 months of age at a weight of 11 kg.

Case 5 (ML) was a male, first-born by caesarean section due to maternal hypertension in the 40th week of pregnancy. Seizures started at the age of 6 months: the semeiology included eyes and right deviation of the head, right clonic jerks, flushing, salivation, apnoea. Subsequently, similar seizures appeared on the left side of the body. Subclinical seizures characterized by vegetative symptoms, were also present and mixed with the other one.

Ictal EEG showed apparently random involvement of various areas of the brain, each seizure consisting of rhythmic theta activity starting in one region and progressively affecting adjacent areas. On the ictal EEG, consecutive seizures overlapped, that is, a seizure started before the preceding one had finished.

Frequent convulsive status required emergency admission to the ICU. Pharmacoresistance was severe and neurological evaluation showed progressive microcephaly and psychomotor retardation. Complete metabolic, viral, genetic, and neuroradiologic investigations led to negative results. Malignant migrating partial epilepsy of infancy was diagnosed.

The boy was hospitalized at the ICU, EEG recorded subcontinuous critical activity migrating from the left to the right hemisphere when VNS was implanted. His age was 9 months and weight was 8.6 kg.

Case 6 (GN) was a male, fifth-born after regular pregnancy from healthy parents. Seizures began when he was 2 months old with staring, upper limb clonic jerks, apnoea, cyanosis, and severe oxygen desaturation. Since epilepsy onset, seizure frequency was very high (reaching 20–30 seizures/day). He showed pharmacoresistance to old and new AED. The course of the illness showed almost continuous seizures, mainly characterized by vegetative phenomena, apnoea, cyanosis, and partial alternating motor seizures. General and neurological conditions progressively worsened and parenteral feeding became necessary. Psychomotor development arrested, microcephaly and severe muscular hypotonia developed. In the beginning, interictal EEG was normal, ictal EEG was characterized by rhythmic theta activity discharges in the fronto-temporal regions of the two hemispheres with alternating prevalence of side. Biochemical assessments for genetic, metabolic or degenerative and viral diseases were negative and neuroradiological investigations were not conclusive. Diagnosis of partial migrating epilepsy of infancy was performed.VNS was implanted at 7 months of life and, at that time, the child was admitted at the ICU after convulsive epilepticus status that required general anaesthesia. Body weight was about 9 kg.

Neurostimulator implant and stimulation paradigms

The VNS was implanted using a single cervical incision. The upper retraction of the wound allowed exposure of the vagal nerve while the lower retraction was used to create a subclavicular pocket to host the stimulating unit at the distance of about 7 cm from the electrodes. The pulse generator was placed underneath the pectoralis major muscle and secured to the fascia of intercostal musculature.

The neurostimulator was switched to the 'ON' position on the third postoperative day and thereafter the children were revaluated every week for the ramp-up. The intensity of stimulation, started at 0.25 mA, was increased step-by-step by 0.25 mA until the stimulation parameters reached 1.50–2 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).

Seizure reduction

The clinical efficacy of VNS 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 formula:

$$[\text{seizures/month on VNS} - \text{Baseline seizures/month}]/[\text{baseline seizures/month}] \times 100.$$

The patients with seizure reduction >50% were considered responders.

Quality of life

Quality of life was assessed using the Vineland Adaptive Behavior Scale (VABS) and by an analogical scale of

parental satisfaction. We selected the VABS for QOL evaluation as it measures different behavior domains [17].

This instrument is a standardized and widely used semistructured interview addressed to parents or caregivers. It assesses personal and social sufficiency; it is applicable to individuals with or without disabilities and it is particularly well-indicated for evaluation and diagnosis of mentally retarded patients or patients with other handicaps. It assesses QOL in composite and individual domains: communication, daily living skills, socialization, and motor skills. Each domain is composed of a series of items reflecting the continuous presence or sporadic presence, or absence of a specific skill or behavior. Domain scores are given by the sum of the score (0, 1, or 2) for each item of each specific domain. The total score (Adaptive Behavior Standard Score) is given by the sum of the score of all domains.

Finally, to evaluate children's behavioral changes and parental emotional distress related to child pathology, we selected an analogical scale that evaluates children, using parameters such as vigilance, impulsivity, independence, anxiety, and attention, or concentration.

Results

Surgery

No surgery-related complications were observed in our patients. A single cervical incision rather than the two classical incisions at the neck and at the thorax reduced cosmetic effects due to low weight and slight muscular mass.

Seizure reduction

One patient was seizure-free at last follow-up time. Four of six children showed a significant improvement in seizure control (range, 60–90%). In three children with convulsive status at implant, VNS led to early improvement of seizure frequency and severity with discharge from the ICU (from 7–12 days postimplant).

In detail, long-term post-VNS evaluation showed the following results:

In Case 1, 3 days after VNS implant, a fast ramp-up program was started to reach the standard stimulation parameters by 0.25 mA steps every 2 days until 1.75 mA with OFF time 5 min and ON time 30 s Since 0.75 mA amplitude, seizures reduced in intensity and frequency with 60 days of seizure-free time (from third to fifth month after implant). At follow-up, seizure reduction persisted with clusters of seizures that demanded few hospital medical treatments without ICU admissions. At the end of the 2nd year of follow-up, a 75% seizure reduction was achieved with stable AED. Subsequently new AED have been introduced (Sultiame, Zonisamide, Pregabalin) without further improvements. Progressive improvement in psychomotor functions has been observed.

In Case 2, (6 years follow-up), we observed persistent, significant reduction in seizure frequency (90%). The girl, now, is affected by 1–2 partial complex secondarily generalized seizures/month. Sometimes she needs medical assistance and admission at Hospital. Severe motor hyperactivity and aggressive behavior coexist.

In Case 3, (14.3 months FU) an early 40% reduction in seizure frequency and improvement in alertness and social interaction were observed. Now, the girl is seizure-free since 4 months.

In Case 4, VNS implant has been performed while the child was in barbiturate coma for status epilepticus. The VNS was activated 3 days after implant (intensity 0.25 mA. OFF time 5 min and ON time 30 s) with increases every 3 days. At 1 mA level of stimulation intensity, the seizures reduced in intensity and frequency; at day 15 after implant, the child has been discharged from ICU. In the early follow-up, seizure clusters persisted but without severe apnoeas. The child has been discharged 46 days after VNS implant with AED polytherapy (Sodium Valproate 25 mg/kg/die, Oxcarbazepine 30 mg/kg/die, Levetiracetam 60 mg/kg/die) and VNS parameters were: amplitude 1.50 mA, OFF time 5 min and ON time 30 s. Subsequently, patient had to be admitted in Hospital for a clusters of seizures. AED therapy and VNS stimulation paradigms have been further modified. VNS parameters reached 2 mA amplitude and 3 min OFF time. At last evaluation, 3 years and 1 months of follow-up, a 40% seizure reduction and mild progressive improvement in psychomotor functions have been achieved. Mild parental and caregivers' satisfaction has been observed.

In Case 5, VNS implant has been performed while the child was admitted to ICU since 10 days for status epilepticus. His therapy was Phenobarbital 5 mg/kg/die, Nitrazepam 0,1 mg/kg/die, Diphenilhidantoine 10 mg/kg/die and Midazolam 3 mg/kg/die. The Vagal stimulator has been activated 7 days after implant with the following paradigms: amplitude 0.25 mA, 5 min OFF time, 30 s ON time. Subsequently, stimulation intensity rises have been performed every 3 days. Child has been discharged from ICU 20 days after implant. He presented few seizures/day without apnoea and he showed better post ictal recovery. Child has been discharged from Hospital 45 days after implant and

Table 2 Vineland standard scores at baseline and at follow-up (FU) express in standard deviation units the extent to which the individual's score exceeds or falls below the mean score of persons the same age with whom the instrument was standardized

Case	Vineland scores									
	Adaptive behavior		Communication		Daily living skills		Socialization		Motor skills	
	Baseline	FU	Baseline	FU	Baseline	FU	Baseline	FU	Baseline	FU
1 (CC)	89	56	71	62	67	58	79	73	59	51
2 (MF)	54	25	62	27	61	19	55	37	58	38
3 (PA)	73	68	72	69	84	79	80	67	81	81
4 (AC)	53	41	59	47	61	47	54	50	56	34
5 ML)	69	52	73	60	95	61	64	54	68	51
6 (GN)	57	60	73	64	82	72	67	59	72	64

The Vineland standard scores have a mean of 100 and a standard deviation of 15. Broad ranges of standard scores may be described using the adaptive levels of Adequate (85 to 115), Moderately Low (70 to 84) and Low (below 20 to 69)

with VNS parameters as the following: 1.75 mA, OFF time 5 min, ON time 30 s. At last follow-up evaluation (1 years and 9 months) a 60% seizure reduction has been observed with the same therapy than before VNS implant. Severe cognitive and neurological impairment persist.

In Case 6, VNS implant has been performed while child was admitted in ICU since 15 days because of status epilepticus. His therapy was Phenobarbital 5 mg/kg/die, Vigabatrin 30 mg/kg/die, Levetiracetam 30 mg/kg/die, Lamotrigine 5 mg/kg/die, Midazolam 3 mg/kg/die. VNS stimulation has been activated 3 days after implant with 0.25 mA of intensity, OFF time 5 min, ON time 30 s and subsequently increased in amplitude every 2 days until 2 mA. Twenty days after VNS activation, seizure intensity has been relatively reduced and the child has been discharged from ICU. At follow-up, poor seizures control has been achieved in spite of several AED changes. At last follow-up, 1 year and 5 months post VNS, no significant seizure reduction has been observed and severe neurological and general conditions persist.

Table 3 Analogical scale scores at baseline (B) and at follow-up (FU) (minimum, 0; maximum, 100)

Case	Child's QOL		Parental satisfaction	
	B	FU	B	FU
1 (CC)	1	99	20	88
2 (MF)	20	70	30	100
3 (PA)	65	86	94	100
4 (AC)	20	80	15	90
5 (ML)	42	97	96	87
6 (GN)	12	76	49	100

QOL and parental satisfaction

As shown in Table 2, Vineland Adaptive Behavior Scales scores showed no significant improvement at last clinical visit neither regarding total VABS score nor VABS sub-domain scores, showing that none of the clinical variables evaluated with the scales had a great improvement after VNS therapy, even though in every single patient some variable stayed relatively permanent, showing no significant decline with the time. On the other hand, as shown in Table 3, quality of life and parental satisfaction greatly improved for all the patients.

Discussion

Very young children often face severe neurodevelopmental consequences due to early onset epilepsy.

An effective therapy for these children would have a major impact in reducing morbidity and potentially improving psychomotor development but often they are resistant to existing therapies.

Initial treatment consists of AED, often with multiple drug regimens, but nonpharmacological interventions (surgery, ketogenic diet, and VNS) are important aspects of a comprehensive treatment plan [21].

Since 1994, the VNS therapy system has been available in Europe, without any age-related restriction, to patients with pharmacoresistant partial or generalized epilepsy.

More than one-third of patients currently treated with VNS are under the age of 18 years, but limited experience is available on its use in very young children, specifically those younger than 3 years [4, 19].

Based on implant registration cards returned to Cyberonics, approximately 450 devices have been implanted in patients up to 3 years of age and approximately 1,000 implanted in patients between 3 and 5 years of age.

No significant surgical or postoperative complications have been reported in this group of patients.

Vitale and co-workers [19] reported two toddlers treated by VNS. The procedure was well tolerated and the frequency of seizures dramatically improved. They concluded VNS is a successful treatment option in disabled children younger than 3 years.

Blount et al. [4] reviewed retrospectively their experience with VNS in very young children below 5 years old). Of the six patients (three males and three females) with long-term follow-up, 83% had a significant decrease in the frequency of their seizures. Of these, two were seizure-free (33%), three have improved (50%), and one (17%) had no change in seizure status, at their most recent clinical examination.

Our case series includes very young children less than 3 years old at implant. Most of them showed good clinical recovery, without any significant side effects and surgical complications. Three of our patients had VNS implant as a "last resort" procedure because of drug refractory epilepticus status. The role of VNS in the treatment of status epilepticus is unknown. Only a few studies describe single cases in both adults and children. In these patients, insertion of the vagal nerve stimulator allowed early cessation of status and good neurological outcome [11, 20].

In our cohort, five children had status epilepticus that complicated the course of epileptic syndrome requiring several ICU admissions. One of them had hypoxic-ischemic encephalopathy, one of them had hemimegalencephaly and three of them had migrating partial seizures of infancy which is an epileptic syndrome. This last syndrome is characterized by severe drug resistance, subcontinous partial seizures, and poor neurological outcome with high mortality rate during the course of status epilepticus.

In our patients it is likely that status epilepticus interruption and early clinical response could be related to the VNS action alone, because the AED were not changed in the first period post-VNS implant. On the contrary, the long term clinical response could be associated to modifications both in AED and VNS stimulation parameters.

The results of QOL evaluation, showed no significant improvement in adaptive behavior scores but a great improvement in both child's QOL and parental satisfaction, suggesting that for parents some variable might have had an impact on the relative changes in child's QOL and their own satisfaction. These results seem to suggest that in these very difficult cases, even a slight improvement of child's vigilance or temperament, that can be perceived by the parent, leads to a positive statement for them. In addition, most of these cases were hospitalized from the beginning of their life because of their difficult breathing or feeding conditions and status epilepticus or nontractable seizures. The VNS therapy give parents and children the opportunity to change their life conditions with seizure decrease or total control. This change was apparently enough to give them the feeling of a great satisfaction and effectively changed their quality of life even though the children could not achieve great improvement in development.

Conclusions

Catastrophic epilepsy in infancy can be devastating and difficult to treat with drugs and resective surgery. If surgery is inappropriate or refused, VNS can be considered.

Currently, VNS is used as a last-resort treatment, but many VNS advocates hope the treatment will become more widespread, as there are much fewer related risks than that in brain surgery. Early treatment at a very young age can be successful because of a remarkable amount of plasticity that gives children the potential for recovering significant motor functions with often an improvement in their cognitive function. This is likely due to the lessened impact of intractable seizures on their cognitive and neurological development [8, 12, 20].

We believe that VNS is a feasible, well-tolerated, and effective procedure even in toddlers affected by severe epilepsy and multiple developmental disabilities.

Controlled trials, larger groups of patients and more prolonged follow-ups are needed to verify our clinical observations.

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Comments

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Vagus nerve stimulation (VNS) was the first adjunctive treatment for epilepsy using electrical stimulation that has been approved by the FDA in 1997 for the treatment of medically intractable epilepsy in patients over age 12. The VNS device provides chronic intermittent stimulation to the left vagus nerve through a surgically implanted circumneural bipolar cuff electrode. Premarketing trials have shown that 30 to 40% of individuals with medically intractable partial seizures had a significant improvement, defined as a seizure reduction of ≥50% [1]. Postmarketing experience suggested that the device may also be effective in the treatment of generalized seizures [2]. The initiation of extra cycles by the patient by placing a magnet over the device has been shown to abort or ameliorate seizures in about a third [3].

However, with a decade experience in VNS, we know that the level of effectiveness is moderate, leaving many patients with frequent seizures: The device generally reduces rather than eliminates seizures. The experience with VNS in very young children, particularly in children younger than 5 years, is limited. There are only a few uncontrolled studies based on small cohorts, suggesting that VNS may also be safe and moderately effective in the very young [4, 5]. In this article, Zamponi et al. again report on the safety and efficacy of VNS in a small cohort of very young children suffering from catastrophic epilepsy with frequent seizures and severe psychomotor retardation. There were no surgery-related complications. The authors found a 60 to 90% seizure reduction in four of six patients, and a 4-month seizure-free period in a 2.7-year-old girl, subsequent to a 40% seizure reduction during the early course of treatment (however, it is pertinent to note that some of these effects may also have been related to modifications of antiepileptic drug treatment during the study period). Quality of life and parental satisfaction is said to have improved (as assessed by an analog scale), but this improvement was not significant when using the standardized Vineland Adaptive Behavior Scale for quality of life evaluation. Considering that complete seizure control is a key predictor of improved quality of life, the reductions in seizure frequency may not have been great enough to affect quality of life.

Now, does a moderate level of VNS effectiveness affect quality of life in a way that would justify the surgical procedure in toddlers? Would it be good enough for you, if you had seizures? Shouldn't improvement with VNS be much better than that found with medications to justify the increased risk (and costs) of an invasive procedure? There may be no definite general answers to these questions. What we do know is that VNS in patients with epilepsy, irrespective of age, appears to be less efficacious than had been hoped. Moreover, it is important to bear in mind that surgical sham control in VNS studies is a priori precluded due to unavoidable though usually mild to moderate side effects with VNS, such as hoarseness, discomfort in the throat, cough or swallowing difficulties. In that sense, the investigation of VNS in toddlers is interesting, considering that there is hardly any placebo effect to be expected in very young children. Nevertheless, to truly ascertain how much of any benefit is related to VNS, it would be very informative to know the actual effectiveness of VNS in those 1,450 patients aged 0 to 5 years implanted with the device (the number 1,450 is based on the implant registration cards returned to Cyberonics, mentioned by the authors in this issue). There is not much hope considering the publication bias (that is, the phenomenon that studies with positive results are more likely to be published than studies with negative results).

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