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Clinical course of young patients with Dravet syndrome after vagal nerve stimulation

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ABSTRACT

Medical treatment of Dravet syndrome is disappointing. Ketogenic Diet and neurostimulation procedures as Vagus Nerve Stimulation (VNS) and Deep Brain Stimulation are in ongoing evaluation. In the present study, the long-term effectiveness of VNS on seizures, cognition and behavior was retrospectively evaluated in eight young patients with DS and medically refractory epilepsy (mean age at VNS implant: 10.28 years, range: 5–25). The average duration of treatment was 54 months (range: 12–120). Compared to baseline (mean: 55; standard deviation: 83, range: 4–200), the mean number of monthly seizures after VNS implantation was 39 ± 67 at 3 months, 42 ± 67 at 6 months and 38 ± 69 at twelve months (not significant comparisons). In particular, VNS produced a mean seizure rate reduction of 12% at three months, 6% at six months, and 31% at twelve months. All patients but three experienced some reduction in seizure burden (range: 33–61%) at twelve months. Seizure outcome after one year of stimulation was rated as Mc Hugh class II (50–79% reduction in seizure frequency) in four patients, class III (<50% reduction) in one patient and class V (no improvement) in three patients. In this small case series of patients with DS, VNS therapy had a clinically significant effect in reducing seizures at twelve months in four of the eight patients. Even in patients in whom seizure reduction was not dramatic, a slight improvement in alertness and communicative skills was seen. The long-term clinical course of two selected cases is discussed.

1. Introduction

Severe myoclonic epilepsy in infancy (SMEI), or Dravet syndrome (DS), is a rare and distinct malignant epileptic encephalopathy, which appears during the first year of life in previously healthy children.[1] In up to 80% of cases, DS is caused by a mutation in the SCN1A gene, which codes for the neuronal voltage-gated sodium ion channel.[2] The first seizure episode is often seen as generalized or unilateral tonic–clonic or clonic seizure induced by fever, and tends to be prolonged, advancing to status epilepticus. As these children grow, the clinical features evolve into a variety of afebrile or fever-induced seizure types, including myoclonic seizures, partial seizures and atypical absences, which are generally refractory. Psychomotor development is delayed from the second year and almost all patients with DS show from severe to moderate mental retardation. Patients with developmental deterioration have severe epilepsy with persistence of frequent seizures and slow EEG backgroundat follow-up.[1–4]

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Medical treatment is disappointing. Valproate and benzodiazepines (clonazepam, lorazepam) are the most useful drugs.[5] Stiripentol in combination with valproate and clobazam was effective in a randomized placebo-controlled study.[6] Topiramate has been shown to be effective against the convulsive seizures and the status epilepticus.[7,8]

Ketogenic Diet (KD) and neurostimulation procedures as Vagus Nerve Stimulation (VNS) and Deep brain Stimulation (DBS) are in ongoing evaluation. VNS has been used in cases of severe epilepsy not eligible for surgery.[9–11] This is the case in most of patients with DS. Furthermore, mental retardation and behavioral disturbance characterized by hyperactivity and autistic traits can be observed in DS.[12,13] These symptoms may deteriorate even further due to the common side effects of antiepileptic drugs, such as somnolence, disturbed concentration, agitation, and ataxia. It is well documented that VNS therapy may have a positive effect on mood and behavior, often regardless of seizure reduction.[14] Finally, the lack of clinically relevant side effects with VNS may further encourage the use of this treatment modality.

To our knowledge, there are very few studies which have addressed the effects of VNS in DS patients. Some anecdotal reports and single cases from published clinical series suggest that VNS could be useful in treatment of refractory partial and generalized seizures in this syndrome.[15] Thus, the main purpose of this study was to retrospectively explore the effectiveness of VNS on seizure, cognition and behavior in a case series of young patients with DS.

2. Material and methods

2.1. Patients

Medical reports from all patients who underwent VNS for the treatment of drug-resistant epilepsy at "G. Salesi" Children's Hospital in Ancona were retrospectively reviewed (105 patients from 2000 to 2009) after the approval by the local Ethic Committee. Eight of these patients were affected by Dravet Syndrome, according to the diagnostic criteria established by the International League Against Epilepsy (ILAE): normal development before seizure onset; occurrence of either generalized, unilateral, or partial seizures during the first year of life; seizures that were frequently provoked by fever; presence of myoclonic seizures with spike and wave-complex or segmental myoclonus, diffuse spike-waves or focal spikes on EEG during the clinical course; intractable epilepsy; gradual evidence of psychomotor delay after two years of age.[16] For each patient the following clinical features were considered: age at onset of first febrile seizure, family history in first and second degree relatives, number of seizures before one year of age, seizure types, epilepsy duration (until VNS implant), age at implant, duration of VNS stimulation. In addition, the time between the first seizure's onset and previous vaccination was considered. This relation was classified as "proximate", if first seizure occurred within two/three days from the previous vaccination, "distant", if within 90 days, or no relation, if time window was larger than 90 days.[17] Moreover, a genetic analysis using dHPLC (i.e., denaturing High-Performance Liquid Chromatography), gene sequencing and MPLA (i.e., Multiple Ligation Probe Amplification) was available for all patients.

2.2. Surgical procedure

VNS was implanted according to standard techniques.[18] Children were discharged 72 h after surgery with neurostimulator switched ON and thereafter re-evaluated as outpatients every week for 1 month for the ramp-up. The VNS generator has been non-invasively programmed via an externally placed programming wand and software on a standard personal computer. The intensity of stimulation was increased step by step by 0.50 mA until the stimulation parameters reached 2 mA, at a frequency of 30 c/s, with OFF-period of 5 min alternating with ON-period of 30 s (standard stimulation setting). During this adjustment period, 1-h polygraphic recordings (i.e., electroencephalogram, left deltoid muscle, right hand extensor, electrocardiogram and pneumogram) were systematically performed at the beginning of the activation, while the intensity of stimulation reached 1 mA and 2 mA. The patient was encouraged to swipe the hand held magnet over the generator at the onset of the epileptic aura. This triggers the release of a train of stimuli superimposed on the baseline discharge of the generator. This may abort the seizure or prevent it from getting secondarily generalized.

2.3. Clinical evaluation measures

Seizure frequencies at baseline were determined by asking parents to record the number of monthly seizures on a clinical diary, and then averaging the number of monthly seizures relative to the last three months before the implant. Clinical outcome was determined by comparing the frequency of monthly seizure after VNS (i.e., at 3, 6, 12, 24 and 36 months) with seizure frequency during the three months pre-implantation period (baseline), by using the following formula: (seizures/month on VNS − baseline seizures/month)/(baseline seizures/month) × 100. Patients were defined as "responders" when experienced a reduction in seizure frequency of 50% or more compared to baseline. Seizure outcome was expressed also with a VNS-specific outcome scale proposed by McHugh et al.[19] This novel classification system for VNS outcome includes assessment of both seizure frequency and severity. Patients are divided in five classes (class I–V) according to the percentage of change in seizure frequency. The first three classes are further subdivided into two distinct sub-groups (A–B) in relation to the reduction in the intensity and duration of seizures (improvement in ictal or postictal activity) (see Table 1). Paired sample Wilcoxon signed rank tests were used to compare seizure frequency between the baseline and the follow-up sessions (non parametric data). A P value <0.05 was considered statistically significant.

2.4. Cognitive and behavioral measures

A formal psychological assessment including Developmental Quotient (DQ) and adaptive behavior was performed in two sessions: at the time of VNS implant (i.e., baseline) and one year after the implant (i.e., 1 year follow-up). Cognitive functioning was evaluated using the Italian version of Stanford–Binet Scale for patients from 2 to 6 years old, and the Weschler scales for patients from 6 to 16 years (WISC-R), and above 16 years (WAIS).[20,21] Mental retardation was classified as "severe",

Table 1 – McHugh's classification of VNS outcome.

Class I	80–100% reduction in seizure frequency
IA	Improved ictal or postictal activity
IB	No improvement in ictal or postictal activity
Class II	50–79% reduction in seizure frequency
IA	Improved ictal or postictal activity
IB	No improvement in ictal or postictal activity
Class III	<50% reduction in seizure frequency
IA	Improved ictal or postictal activity
IB	No improvement in ictal or postictal activity
Class IV	Magnet benefit only
Class V	No improvement

"moderate" or "mild", when the DQ was below 40, between 40 and 55, and between 55 and 70, respectively. Adaptive behaviour, including four domains (communication, daily living skills, socialization, and motor skills) was measured using the Italian version of Vineland Adaptive Behavior Scales (VABS).[22] This instrument is a semi-structured interview addressed to parents, which provides normative scores for children from 0 to 18 years of age. It was selected because it measures personal and social sufficiency and it is particularly well indicated for evaluation and diagnosis of mentally retarded patients or patients with other handicaps. The VABS provides standard scores (mean = 100, standard deviation = 15) and higher scores indicate better functioning.

Two experienced psychologists carried out all test and interviews, in a single blind design (i.e., assessment at one year was carried out by a different investigator, who was not aware of the outcomes recorded at baseline). Paired sample Wilcoxon signed rank tests were used to compare scores at baseline and 12 months after VNS implantation.

3. Results

3.1. *Patient demographics*

Clinical and demographic data from the eight patients who were submitted to VNS implant are summarized in Table 2 and Table 3. There were five females and three males who ranged in age from 5 to 25 years when the VNS was implanted (mean age: 10.28 years; st.dev: 6.58). The age at seizure onset ranged from 2 months to 12 months (mean age: 6.03; st.dev: 3.35 months). Six patients had a number of seizure >5 during the first year of life. As a group, the number of monthly seizure occurred before one year of life was 8.50 ± 5.42 (range:4–15). Three patients had a positive family history for convulsions. The average time between the last vaccination and seizure onset was 40 days (dev.st: 38, range: 1–100). Only in one patient (P2) the first seizure appeared one day after the vaccination. A distant relation was identified in five patients, while no relation was found in two patients. Epilepsy duration until VNS implant range from 4 to 25 years (mean: 9.64; st.dev: 6.87). Before implantation, patients had a mean of 55 monthly seizures (range: 4–200). Seven patients (87%) presented generalized tonic–clonic seizures; four out of these patients also showed myoclonic seizures with hemisomic prevalence. Two patients presented complex partial seizures. All patients were SCN1A mutation positive with a missense mutation. All patients were taking at least three different AEDs, with two subjects taking four AEDs. The mean number of failed AEDs for the entire cohort prior to VNS insertion was 3.2. Three patients had been unsuccessfully treated with a ketogenic diet before VNS implantation.

3.2. *Clinical outcomes*

Seizure outcomes are summarized in Table 3, Figs. 1 and 2. All patients completed the 12 months follow-up, four out of them the 24 months follow-up, and three the 36 months follow-up. One patient (P1) had a follow-up ten years after the implantation. Only data collected at 1 year follow-up was considered for statistical analysis. Among the eight patients who underwent implantation, the duration of treatment ranged from 12 to 120 months (mean: 54 ± 38 months). Compared to baseline (mean: 55; standard deviation: 83, range: 4–200), mean number of monthly seizures after VNS implantation was 39 ± 67 at 3 months, 42 ± 67 at 6 months and 38 ± 69 at 12 months ($p > .4$ in all comparisons). In particular, VNS produced a mean seizure rate reduction of 12% at 3 months, 6% at 6 months, and 31% at 12 months. All patients but three (P3, P4, P7) experienced some reduction in seizure burden (range: 33–61%) at 12 months. Seizure outcome after one year of stimulation was rated as class II (50–79% reduction in

Table 2 – Clinical and demographic data at seizure onset.

Patients	Sex	Febrile seizure onset (months)	Time window between seizure onset and previous vaccination	Epilepsy duration before VNS (years)	Family History	Presence of Status Epilepticus at seizure onset
1	M	9	Distant	9	+	–
2	F	2	Proximate	25	–	+
3	F	4	Distant	4	+	+
4	M	5	Distant	13	–	+
5	F	4	Distant	12	–	+
6	M	12	Distant	4	–	+
7	F	8	No relation	7	+	+
8	F	4	No relation	9	–	–

M: male; F: female; +: positive: –: negative; proximate: seizure onset within two/three days from previous vaccination; distant: seizure onset within 90 days; no relation: seizure onset after 90 days.

Table 3 – Clinical data at the time of VNS implantation and outcome at 12 months follow-up.

Patients	Seizure types at implant	Presence of SE at implant	Cognitive Level at implant	Age at VNS implant (years)	No of seiz./month at baseline	No of seiz./month after 12 months	Seizure reduction after 12 months	McHugh's Class
1	GTC + MS	–	MMR	10	180	70	−61%	IIB
2	GTC	–	SMR	25	15	10	−33%	III
3	GTC	+	mMR	5	6	6	0%	V
4	GTC	+	SMR	13	4	4	0%	V
5	GTC + MS	–	SMR	6	8	4	−50%	IIB
6	GTC + MS	–	SMR	5	15	7	−53%	IIB
7	GTC + CPS + MS	+	mMR	8	200	200	0%	V
8	CPS	–	MMR	9	10	5	−50%	IIB

SE: Status Epilepticus; GTC: generalized tonic–clonic seizures; MS: Myoclonic seizures; CPS: complex partial seizures; mMR: mild mental retardation; MMR: moderate mental retardation; SMR: severe mental retardation; +: positive: –: negative.

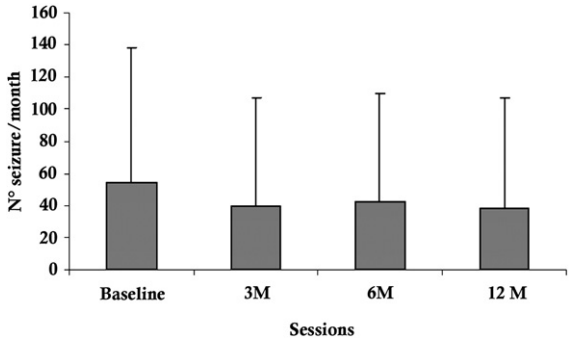

Fig. 1 – Number of monthly seizure (mean and st.dev) at baseline (i.e., before VNS), and at three (3 M), six (6 M) and twelve months (12 M) after VNS implantation.

seizure frequency) in four patients (P1, P5, P6, P8), class III (<50% reduction in seizure frequency) in one patient (P2), and class V (no improvement) in three patients (P3, P4, P7). In those patients who obtained a seizures rate reduction greater than 50% at one year, mean number of seizures per month was 21 (st.dev: 32, range: 5–70). No patient was rated as class I (>80% reduction in seizure frequency) and no one experienced benefit by manually activating the VNS with a magnet. Post-operatively, the number of AEDs was maintained stable in all patients. Seizure frequency was stable in those patients who were followed at 24 and 36 months (all patients but P7 and P8).

3.3. *Cognitive and behavioural outcome*

Different levels of cognitive impairment were reported at first assessment (i.e., at time of VNS implantation) (see Table 3). The impairment was mild in two subject (P3, P7), moderate in two (P1, P8), and severe in four (P2, P4, P5, P6). At baseline, all patients obtained scores below normal range (standard score <70) in the adaptive behaviour total score and in each sub-domain, showing a level of impairment from severe (four patients) to mild (four patients). Cognitive level was unchanged after one year of VNS in all patients. One patient (P1) reported a clinically relevant improvement in adapting behaviour after one year of VNS (+10 points in total standard score), referring special benefit in communication. It is worth noting that such a patient still had a high number of seizures

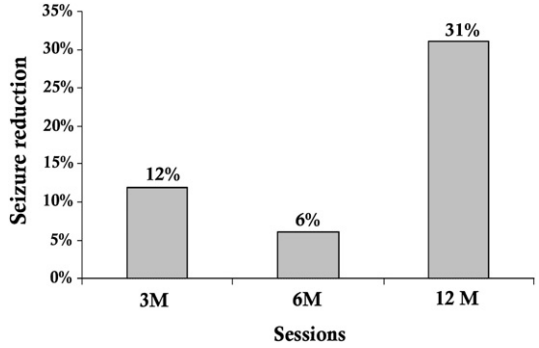

Fig. 2 – Percentage of seizure reduction after three (3 M), six (6 M) and twelve (12 M) months since VNS implantation.

per month at 1 year follow-up. However, he gained a consistent reduction (61%), leading to a significant improvement in his quality of life. All the other patients experienced a slight improvement consisting in increased alertness and communicative skills after one year of VNS. No one reported a worsening in cognition or behaviour at follow-up sessions. For those patients who were followed at 12 and 36 months the cognitive and behavioural profile remained unchanged.

4. Discussion

In 1997, the Vagal Nerve Stimulation (VNS) was approved by the Food and Drug Administration (FDA) as adjunctive therapy for adults and adolescents over 12 years of age whose partial-onset seizures were refractory to antiepileptic drugs. Case series suggest that VNS is also effective in generalized epilepsy syndromes. While some studies have found that symptomatic generalized epilepsy is more responsive to VNS than idiopathic syndromes, others have reported opposite findings or no difference.[23–25]

Data about the efficacy of VNS on Dravet Syndrome (DS) are lacking. Some anecdotal reports and single cases from published clinical series suggest that VNS could be useful in treatment of refractory partial and generalized seizures in this syndrome. Rossignol et al. describe a cohort of twenty-eight children and adolescents treated with VNS. Two out of these patients were affected by DS, and one out of them had 90% of seizure reduction.[14] Shahwan et al. reviewed twenty-six children who had VNS with a minimum follow-up period of 18 months. Two patients were affected by DS; one out of them showed a seizure reduction >50%.[15]

To our knowledge the present study is the first report of VNS efficacy in a case series of patients affected by DS. This is a retrospective and open label study, which includes only eight patients with various age groups at the time of VNS implantation. Despite these limitations, some helpful considerations can be drawn on the basis of the present findings.

In our case series, no intra-surgical or post-surgical complications were observed, neither long-term side effects. Overall, mean reduction of monthly seizure at 12 months (31%) was smaller than the mean reduction (42%) observed in the entire population of patients who received VNS in our Hospital.[26] However, after one year of stimulation, four out of the eight patients (50%) gained a seizure reduction between 50 and 79% (McHugh's Class II) and one patient gained a reduction <50%, without any change of AED therapy. More than one third of the present sample did not obtain any modification in seizure frequency, but did experience a slight improvement in behavior. As for seizure types, no confident conclusion can be drawn. However, it is worth noting that no improvement was obtained in those patients who presented status epilepticus at the time of VNS implantation.

Clinical effectiveness was found to be stable in time, even after the end of service of VNS generator, as suggested by one patient (P1) of our series. Patient 1 was implanted at 9 years of age and assessed in periodical follow-up for 10 years. He gained a consistent seizure reduction (60%) within the first six months after the implant, which maintained stable without any change in AED until the time of the present study. The greatest improvement was obtained in generalized tonic–clonic seizures. The end of service of VNS generator occurred nine years after the implant. A stable, positive effect of VNS on neural mechanisms subserving seizures can be hypothesized in such a patient, as suggested by some authors.[15,27] However, one cannot exclude that the benefit observed is due to a spontaneous evolution of the epileptic syndrome. It is known, in fact, that DS patients with intractable seizure in first childhood can show a positive evolution in adulthood.

Patient 2 (P2) and Patient 3 (P3) showed the typical outcome associated to the end of service of generator, i.e., an increase of seizure frequency and a reduction of alertness, social reciprocity and daily life abilities, with a subsequent worseness of quality of life. This profile was especially evident in P2, who was the only patient implanted in adulthood. Since the third year of life this patient showed the electro clinical pattern of Lennox–Gastaut (i.e., tonic and atonic drop attacks, awake slow spike-waves and sleep fast rhythms). A similar profile has been recently reported in literature, suggesting a possible shift from DS to Lennox-Gastaut Like syndrome.[28] When she was 21 years old, an anterior callosotomy was performed, which resulted in a consistent improvement in drop attacks. In contrast, generalized tonic–clonic seizures observed during the wakening were only slightly reduced. For this last reason the patient was implanted with VNS at 25 years. Despite a modest seizure reduction, and the persistence of a severe mental retardation, a significant improvement of alertness, daily life abilities and socialization was observed. At the end of service of generator, which occurred six years after the implant, a rapid decrease of motor and cognitive performances was reported. Add-on therapy with stiripentol and rufinamide did not determine a significant change in seizure frequency. Because of a further decline in cognitive and behavioural functioning, the device was replaced, leading to a significant improvement on these aspects. This finding confirms VNS efficacy in improving cognition in patients previously submitted to callosotomy.[29,30]

VNS is not the only therapeutic option for patients with DS and refractory epilepsy. Alternative therapies such the ketogenic diet (KD) have been tried, but results are still controversial.[31,32] In a recent work by Coppola et al., one of two patients who had been treated with KD showed a seizure reduction >50%, while the other patient showed no response.[33] In the present study, three patients had been treated with a ketogenic diet before VNS implantation, but no response was obtained. Similarly, literature on DS patients treated with deep brain stimulation (DBS) is scarce, but some clinical reports exist. Chabardes et al. described one patient who received sub thalamic DBS at age of 19 and gained a reduction of 50% in seizure frequency.[34] In a study of Andreade et al., one patient with partial-onset seizures showed a marked improvement in seizure control after DBS, while the other patient with generalized onset seizures did not show any immediate benefit.[35] Despite these interesting reports, a direct comparison of the effectiveness of these different treatment options is hard, due to the high heterogeneity of patients described in literature.

In conclusion, in this small case series of patients with Dravet Syndrome, VNS therapy had a clinically significant effect in reducing seizures at twelve months in four out of the eight patients, who obtained a reduction greater than 50%.

Even in patients in whom seizure reduction was not dramatic, a slight improvement in alertness and communicative skills was seen. The absence of neuro-cognitive side effects and pharmacokinetic interactions with AEDs and other drug therapies makes VNS a palliative treatment option, particularly for children and patients with additional comorbidities. VNS is a more invasive and expensive therapeutic option than KD. However, when KD is ineffective, VNS allows patients to better manage seizures at home, so reducing the frequency of hospitalizations. The cost–benefit relationship of this treatment needs to be evaluated in a wider population. Moreover, whether VNS treatment may change the clinical and neuropsychological outcome of Dravet Syndrome remains to be determined. The present findings suggest the need of prospective comparative trials including the use of the VNS in one treatment arm.

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