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Does emergent implantation of a vagal nerve stimulator stop refractory status epilepticus in children?

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ABSTRACT

Purpose: Status Epilepticus can be a serious life threatening event in epileptic patients. The definition of refractory or super-refractory Status Epilepticus was based on the therapeutic response to anti-epileptic and anesthetic drugs. Vagal Nerve Stimulation showed efficacy in treating drug-resistant epilepsy but there are only few reports on emergentplacement of Vagal Nerve Stimulator for refractory or super-refractory Status Epilepticus.
Methods: Among 49 children implanted at our Institution with Vagal Nerve Stimulation for drug-resistant epilepsy, the authors retrospectively identified those implanted for refractory or super-refractory Status Epilepticus, according with the current definitions.
Results: 4 patients were operated upon at ages ranging 7 to 17 months and reached the programmed output current of 1 mA over a time ranging from 24 to 36 h (fast ramping-up).

In 3 out of 4 patient we observed the abrupt of Status Epilepticus; one patient was refractory both to drugs and Vagal Nerve Stimulation and later died, without recovering from SE. At follow up, ranging from 24 to 45 months, the remaining 3 patients showed a decrease of the seizures frequency > 80% without relapse of Status Epilepticus; in all the patients, output current and/or Duty Cycle were increased later.
Conclusion: VNS can be effective in treating refractory or super-refractory Status Epilepticus.

1. Introduction

Status Epilepticus (SE) can be a life threatening event in an epileptic population. Accurate definition of SE was necessary for clinical and therapeutic purposes. The definition of SE changed over the years: in the revision (1981) by ILAE [1] SE is “a seizure” that “persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur”. The treatment of SE needs adequate and shared timing-measurements to plan therapeutic decisions. Four phases were currently proposed [2], for practical purposes: I) early phase, until the first 5–10 minutes; II) established SE, until 30 min; III) refractory SE (R-SE), if it does not stop despite stage I/II treatment with benzodiazepines plus one antiepileptic drug; IV) super-refractory SE (SR-SE), if it endures longer than 24 h, despite treatment with anesthetics. The terms R-SE or SR-SE concern drug responsiveness only. Few papers [3] reported the outcomes of R-SE and SR-SE treated with non pharmacological therapies, like Vagal Nerve Stimulation (VNS). Concerning *the mechanism of action of chronic VNS, experimental data demonstrate that* the electrical stimulation [4] of the left Vagus Nerve causes, via the Nucleus of Tractus Solitarius (NTS), the release of Norepinephrine from the Locus Cerouleus (LC) and of Serotonin from Raphe Nuclei (RN). These neuromodulators have an anticonvulsant effect, reproducing the mechanisms of action of some anticonvulsant drugs like valproate, phenytoin and carbamazepine [5]. *In humans*, Vonck K [6] also reported, by single-photon emission computed tomography (SPECT), changes in regional cerebral blood flow (rCBF) in the thalamus (chronic thalamic hypo-perfusion) and limbic system (acute limbic hyper-perfusion) after *chronic* VNS stimulation. At the best of our knowledge, there are currently insufficient data to recommend emergent VNS as routine management of R-SE or SR-SE; moreover, notwithstanding the small number of patients reported in the literature, there are intriguing clinical observations, which could suggest new strategies to treat R-SE and SR-SE. The authors report their experience in the treatment of a small cohort of children presenting with SE, with the aim to explore and share the efficacy of VNS in this emergent and life threatening condition.

2. Methods

According to the definitions reported above, among 49 children

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treated at San Gerardo Hospital by means of VNS for drug resistant epilepsy between 2007 and 2017, we retrospectively analyzed those implanted during R-SE or SR-SE. Clinical and neurophysiological data were collected through with clinical reports and database of Electroencephalogram (EEG) recordings. All the patients were operated for VNS with standard technique: under general anesthesia, the left vagal nerve was approached with a linear transverse skin incision at the neck, running from midline to medial margin of SCM muscle; after careful preparation of the platisma, the nerve was reached with blunt dissection of SCM and homoyoideus muscles, exposing the carotid artery and the giugular vein: possibly, the vagus nerve lays deeply between the vessels; the nerve was gently dissected for two centimeters length, sparing the perinevrium; the spiral electrodes were finally wrapped around the nerve trunk, taking care to obtain a satisfactory contact between the nerve and the electrodes; repeated impedance measurements assured for an effective stimulation (accepted values < 1.2 KOhms); finally a subclavear pouch was obtained to place the stimulator in, and the connecting cable was passed under the skin and fixed at the superficial cervical fascia, to prevent dislocation. Immediately before surgery, antibiotics were administered by the anesthetist, as usual done in prosthetic neurosurgery in our Institution. All the families signed informed consensus for surgery. In case of children under 12 years, a local ethic Committee consensus was obtained. Four patients were implanted for R-SE or SR-SE with VNS between May 2012 and July 2017. All the patients received a diagnosis of drug-resistant epilepsy and were implanted during R-SE or SR-SE according to the ILAE definition [7,2]. Before surgery, the frequency and severity of the seizures (evaluated according to McHugh score [8]) and the drug regimen were gathered in each patient; after surgery the same data were collected, in addition to stimulation parameters (output current, frequency, pulse width, duty cycle, impedance, total delivered charge). All the patients were implanted with 103 IPG device (Cyberonics/Livanova MN US).

3. Results

Patient 1. Female, aging 16 months at implant. Diagnosis: Left Hemimegalencephaly. The child presented with motor milestones and psycho-motor delay together with early onset of focal seizures from the age of 4 months. The seizures increased in frequency and severity despite several anti-epileptic drugs (AED), alone on in combination [Carbamazepine (CBZ), Levetiracetam (LEV), Vigabatrin (GVG), Valproic Acid (VPA), Phenobarbitale (PB)], until a focal refractory SE arose, requiring admission to pediatric intensive care unit (PICU); the baby was mechanically ventilated and Midazolam i.v. and Propofol i.v. were administered. After the discharge from PICU the child was anyway stuporous and the frequency of the seizures remained about 90 seizures per day. We performed an urgent left VNS surgery; fast increase of stimulus intensity was performed, reaching 1 mA, Duty Cycle (DC) of 10% and PW 500 usec (Total Charge 129.6 mC/24 h) in 36 h in steps of 0.25 mA, obtaining a decrease of the seizures from 90/day to 4/day over 4 days. At the current follow-up (45 months) the child never developed novel SE and the frequency of the seizures was stable about 5/7 brief focal seizures per day. The stimulation parameters were: intensity 2 mA, frequency 30 Hz, PW 250 usec, ON Time 30 s, OFF Time 3 min, magnetic current 2.25 mA, impedance 1869 Ohms (Total Charge 207.36 mC/24 h). No adverse effects were observed during the follow-up. Patient 2. Male, aging 16 months at surgery. Diagnosis: Non Ketotic Hyperglicinemia (NKH). The child presented with neonatal onset of drug resistant seizures (spasms and tonic seizures, Bursts Suppression Tracing on the EEG). The seizures became drug-resistant and, at the age of 3 months, the child experienced a first R-SE, requiring admission to PICU; after discharge, the frequency of the seizures was stable over 6 months; at the age of 16 months, after a progressive worsening of the seizures and of neurological picture, the patient developed a new R-SE for repeated focal tonic asymmetric seizures, lasting until 2 min, every 10 min. The seizures were refractory to Benzodiazepines (BDZ) i.v., PB i.v. and LEV i.v. administered at the maximum dosage allowed. After 5 days of R-SE, left VNS surgery was performed. Current was increased from 0.25 until 1 mA over 36 h, Duty Cycle (DC) was 10%, PW 500 usec (total charge 1296 mC/24 h). Five days after the implant, the seizures decreased to 6 brief seizures a day. No recurrence of SE was observed during follow-up. At the last control (40 months) the child presented with brief seizures occurring occasionally in case of fever or infections; the AED decreased from two (PB and LEV) to one (LEV). The stimulation parameters at the last control were: intensity 1.25 mA, frequency 30 Hz, PW 250 usec, ON Time 30 s, OFF Time 5 min, magnetic current 1.5 mA, impedance 2718 Ohms (Total Charge 81 mC/24 h). No adverse effects were observed during the follow-up. Patient 3. Female, aging 17 months at implant. The Array-CGH showed a microdeletion of 1q43q44 [9] causing microcephalia, corpus callosum agenesia and epilepsy. First focal SE occurred at the age of 8 month; at the age of 16 months the child presented a relapse of a cluster of focal secondary generalized seizures treated with VPA i.v. in add-on to PB. The child developed metabolic acidosis and progressive liver failure (AST 12454 U/L, ALT 7.068 U/L, blood ammonia 56 mcg/ml) accompanying with worsening

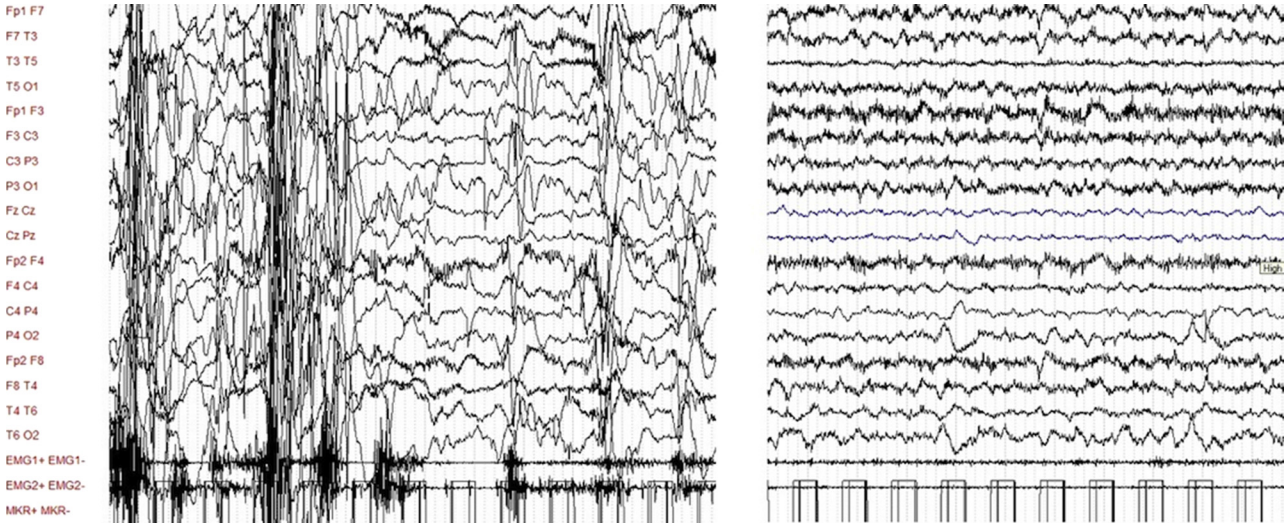

Fig. 1. On left: EEG recording before VNS implant showing periodic spasms (EMG) concomitant with slow vawes (EEG). On right: EEG recording after VNS implant showing the disappearance of all spasms.

of the frequency and severity of the seizures and requiring admission in PICU and deep sedation (continuous Midazolam i.v at appropriate dosage). After discharge, the child developed bilateral asymmetrical spasms (Fig. 1) every 2 min, unresponsive to GVG in add-on to LEV and PB. The child underwent an urgent left VNS implant; the device was switched immediately on with a current of 0.25 mA, reaching the maximum amperage (1 mA, Duty Cycle 10%, PW 250 usec, total charge 64.8 mC/24 h) over 36 h and reducing the number of AED from 3 to 1 (PB). After the VNS implant, spasms stopped at 1 mA of current (Fig. 1). At the follow up (24 months) the child never developed further SE, presenting only few brief spasms a day and stopped all AED. The stimulation parameters at the last check (24 months after the implant) were: intensity 1.75 mA, frequency 30 Hz, PW 500 usec, ON Time 30 s, OFF Time 3 min, magnetic current 2 mA, impedance 2177 Ohms (Total Charge 362 mC/24 h). No adverse effects were observed during the follow-up. Patient 4. Male, aging 7 months at implant. Malignant migrating partial seizures in infancy [10]. The child was born after sperm and ovule donation. He presented with early onset of partial motor seizures, starting from the age of three months, increasing in frequency and severity over three months, finally suffering from a partial motor migrating SE (stormy phase). MRI, performed at the age of three months, and metabolic and genetic tests (Ion Torrent Platform) were normal. The seizures were resistant to several AEDs administered alone or in add-on; the child developed repeated R-SE treated with Midazolam, Propofol and Thiopentone. At the age of 7 months, during a relapse of a focal R-SE, left VNS was implanted with poor results (only four days of seizures freedom); the device was switched on to 1 mA in steps of 0.25 mA, 30 s ON 5 min OFF and PW 250 usec (Total Charge 64.8 mC/24 h) over 24 h. The SE became super-refractory despite the increase of current and Duty Cycle and the child died at the age of 8 months under palliative care.

4. Discussion

Few reports concern with treatment of SE with vagal nerve stimulation. Zeiler [3] reported only 8 studies for a total of 18 patients undergoing urgent VNS during SE in paediatric age. Three of these studies are meeting abstracts. The remaining 5 studies reported 6 cases of VNS placement during SE and one paper [11] reported cases of Epilepsia Partialis Continua (EPC) due to various heterogenous underlying pathologies (chronic inflammatory encephalopathy and Rasmussen encephalitis) treated with both resective surgery and VNS. The meeting abstracts reported incomplete data (Donahue 2013, Malik and Hernadez 2004, Soto 2009). As a consequence, the effectively addressable literature (Table 1) documents only 6 paediatric cases implanted for R- or SR−SE between 2001 and 2016 : 1 case by Winston [12], three cases by Zamponi [13], 1 case by De Herdt [14] and 1 case by Howell [15]. In our experience, R-SE or SR-SE stopped after VNS in 3 out of 4 cases. The ramping-up time frame was around 36 h in all cases, achieving the current intensity of 1 mA; the DC was of default (30 s ON 5 min OFF). The SE stopped in 36–120 hours after the implant; at the last follow-up we observed enduring efficacy of VNS (all responding patients were in 1 A score and *presented no relapse of SE*) and reduction of the number of antiepileptic drugs. Output current was increased during the follow up in all 3 cases responder to VNS (1.25, 1.75, 2 mA respectively) even if the total charge was increased only in case 2 and 3. *Winston described the efficacy of VNS in a 13-year-old boy who underwent emergent implant of VNS during generalized convulsive SE; the patient has previously undergone 90% anterior corpus-callosotomy. SE stopped with a total charge of 86.4 mC/24 h and after 18 months the seizures rate decreased until 1–2 monthly clusters of 3–5 brief generalized seizures. Zamponi N. reported 3 cases affected by Migrating Epilepsy of Infancy implanted during profound sedation. The ramping-up ranged between 16 and 21 days and in all the cases the SE ended after switching VNS on, moreover, the long-term follow up was unsatisfactory, due to recurrence. De Herdt V. reported the case of a 7-years old epileptic girl, who presented with a refractory non convulsive SE at the age of six years. The SE ceased and the EEG showed normalization one week after the start of VNS. Howell reported an emergent VNS in a 14 years old child presenting with refractory SE during FIRES with no improvement over 15 days after VNS implantation (the patient died on day 29). A recent report by Carosella* [16] *reported the successful VNS in a young child aging 12 years, presenting with continuous spike and waves during slow-waves sleep (CSWSS). The VNS resolved the CSWSS, remaining the child seizures free for more than one year and improving his intellectual skills.* Concerning the etiology of SE, actually we cannot define a possible strong indication to emergent VNS versus conventional intensive AED treatment; in detail, VNS usually stopped R-SE or RS-SE in case of *structural, genetic and metabolic pathologies, without any prevalence of clinical efficacy. Particularly, our data confirm* the observation of Tsao [17] who reported two cases of NKH patients treated with left VNS with good results: the first reduced seizure frequency up to 75% and the later became seizures free. Although Zeiler F.A. et al suggested that the use of VNS cannot be recommended in R-SE or SR-SE, our observations, according to other reports, seem to suggest satisfactory clinical results after VNS, also reporting early termination of R-SE in some cases.The planning of ramping-up and the current and cycle values were different in the literature, ranging from fast to slow ramping up (from 36 h to several days), standard or rapid cycles and low or high current intensity or delivered total charge. We observed the efficacy of VNS in interrupting R-SE at low values of current (1 mA over 24–36 hours or Total Charge between 64.8 and 129.6 mC/24 h) but its mechanism is still unknown. The delivering of a small amount of current in a very short time could explain the early efficacy of VNS, although all the patients needed to increase the current and/or DC later. Our data, regarding the total charge delivered pro die, accord with Winston, Carosella, De Herdt and Howell findings. Ghani [18] reviewed the literature to investigate the

Table 1
Patients demographics and VNS parameters. Legenda. Febrile Infection Related Epilepsy Syndrome (FIRES); Continuous Spike and Waves during Slow-Waves Sleep (CSWSS); Non Ketotic Hyperglicinemia (NKH); milliAmpere mA; milliCoulomb mC.

Author	Diagnosis	Age at implant (years)	Current (mA)	Total charge mC/24 h	Ramping up (days)	Follow-up (months)	Final Current (mA)	Final total charge (mC/24 h)
Winston	Generalized Convulsive SE	13	1	86.4	2	2	1.25	
Zamponi	Migrating Epilepsy	1.4	1.5	194.4	21	37	2	414.72
Zamponi	Migrating Epilepsy	0.9	1.75	226,8	30	21	1.75	414.72
Zamponi	Migrating Epilepsy	0.7	2	259.2	19	17	N/A	N/A
De Herdt	Generalized Non Convulsive SE	7	1.5	194.4	2	4	1.75	226,8
Howell	FIRES	14	1.75	362.88–997.92	1.5	died		
Carosella	CSWSS	12	1	103,68		8	1	103,68
Present Study	NKH	1.2	1	129,6	1.5	40	1.25	81
Present Study	Microdeletion 1q43q44	1.5	1	64,8	1.5	24	1.75	362
Present Study	Hemimegalencephaly	1.5	1	129.6	1.5	45	2	207.36
Present Study	Migrating Epilepsy	0.5	1	64.8	1	died		

efficacy of low versus high stimulation intensity, suggesting that high stimulation parameters are more effective than low stimulation parameters to obtain reduction in seizures frequency and that the efficacy of VNS improves over time for its cumulative effect. Moreover, the conclusion of the review by Ghani seems to confirm our experience concerning the long-term efficacy of VNS; VNS efficacy seems to be due to a somewhat cumulative effect of high stimulation parameters; moreover, this effect cannot explain the precocious termination of R-SE after VNS. Alexander G.M. [19] demonstrated in amigdala-kindled rats a significant reduction of electrografic seizures threshold (EST) at the time points of 60 min and 1 weeks after kindling in non-stimulated group but the stimulation at 0.5 mA prevented it: these findings elucidated the anticonvulsant effects of VNS in an experimental preparation and could explain the early anticonvulsant action of VNS in humans. The same authors demonstrate also the progressive loss of power of VNS stimulation requiring an increase of current to obtain the same effects on compound action potential. In our clinical experience, we also observed an early clinical response at 1 mA and, similarly, the need to increase over the time the current to maintain the clinical anticonvulsant effects. *Beyond the clinical findings and the theoretical speculations, the limits of the present study are the small series and the great heterogeneity with respect to seizures types, etiology and stimulation parameters.*

5. Conclusion

In our experience, despite the different etiologies and clinical form of epilepsy, VNS was efficacious in treating R-SE or SR-SE. Moreover, the Authors suggest careful discernment with the use of VNS in SE. More clinical experience is mandatory to asses the real efficacy of this technology in clinical practice. In addition, some questions urge to be answered by means of wider, shared, detailed and standardized clinical observations: for instance, it is not yet clear if etiology or clinical type of seizure are more important to determine the outcome after VNS. Another question concerns the effective dosage of the total charge over time (rapid ramping-up). A method to enlighten these, and other unexplained items, should be the founding of an European Register to collect and to evaluate the outcomes in all the paediatric cases of R-SE or SR-SE treated with VNS. comparing seizure type, etiology and total charge over time.

Conflict of interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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