Seizure: European Journal of Epilepsy 61 (2018) 94–97

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

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

Daniele Grioni[a,*], Andrea Landi[b], Leonardo Fiori[b], Erik Pietro Sganzerla[b]

[a] San Gerardo Hospital, University of Milan Bicocca, Child Neuropsychiatric Clinic, Via Pergolesi 33 Monza, MB, Italy
[b] San Gerardo Hospital, University of Milan Bicocca, Neurosurgery Clinic, Italy

ARTICLE INFO

Keywords:
Status epilepticus
Childhood
Vagal nerve stimulation

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

* Corresponding author.
E-mail address: neuroped@asst-monza.it (D. Grioni).

https://doi.org/10.1016/j.seizure.2018.08.008
Received 8 May 2017; Received in revised form 7 August 2018; Accepted 10 August 2018

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

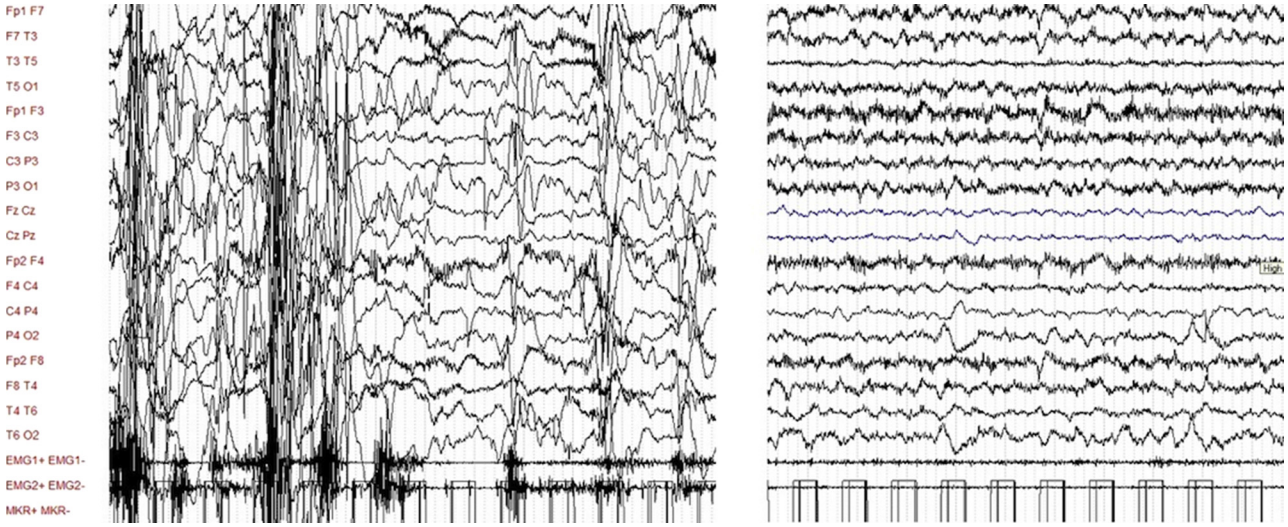

Fig. 1. On left: EEG recording before VNS implant showing periodic spasms (EMG) concomitant with slow vawes (EEG). On right: EEG recording after VNS implant showing the disappearance of all spasms.