BALNEO RESEARCH JOURNAL
English Edition
eISSN 2069-7619 pISSN 2069-7597 ROMANIAN ASSOCIATION OF BALNEOLOGY

Therapeutic difficulties in recurrent, multidrug-resistant epilepsy and vagal nerve stimulation, with recent traumatic brain complications needing iterative neurosurgical interventions

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Balneo Research Journal DOI: http://dx.doi.org/10.12680/balneo.2019.294 Vol.10, No.4, December 2019 p: 530–534

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Abstract

Introduction: Focal epilepsy (possible with secondary generalization) may be a secondary complication to any brain damage (traumatic, vascular, infectious), and is characterized by abnormal excessive neuronal activity with motor, cognitive and psychosocial manifestations. About one third of the patients who suffer from epilepsy have a refractory, multidrug clinical form. Falls are one of the most common medical complications in neurologic patients, occurring during paroxysmal epileptic attacks, or due to sequelary gait limitations. Physical injuries are common, and about 47% patients with epilepsy report at least one injury in the past 12 months.

Case presentation: We present a 36-years-old male patient with a medical history of right frontal congenital arteriovenous malformation, ruptured and operated at the age of eight, complicated with left spastic hemiplegia and refractory epilepsy, needing three antiepileptic drugs (AED) and vagus nerve-stimulation (VNS).This presentation was approved by THEBA Bioethics Committee (No.17464/14.06.2019). During a recent epileptic seizure he suffered a severe traumatic brain injury with coma (GCS 5), needing iterative neurosurgical interventions, intensive care supervision, and orotracheal intubation. CT cerebral scan revealed right hemispheric subdural hematoma, operated (on the 2nd May 2019). Rebleeding occurred seven days later, due to an extradural hematoma, and neurosurgical intervention was performed again. The patient was transferred in our neurorehabilitation clinic with left spastic hemiplegia (global motor score was 65/100, and functional independence measure (FIM) 24/91. Neuropsychological assessment revealed an obtunded level of consciousness, depression and dysmnesia for recent events, MMSE 9/30.
During hospitalization the patient has continued his previous daily AED treatment with: levetiracetamum 2000 mg + clonazepamum 1mg + carbamazepinum retard 600 mg, associated with VNS. During hospitalization emerged three new short jacksonian seizures, who gave up spontaneously. The overall evolution was favorable with rehabilitation program and psychological support, with improvement of the global motor score, FIM (44/91), and partial restoration of walking ability, but still needing human help.

Discussion: The pathophysiological mechanism of relapsed seizures has complex, multiple causes: imbalance of the local brain metabolism and /or a dysfunctional VNS procedure (a possible technical issue due to an impaired electronic device or a bioelectrical one, due to local fibrosis and increased impedance at the contact level between the electrode and the vagal nerve). Specialized technical control disclosed normal electric parameters provided by the electronic device. Other neuromodulatory devices and related technologies, such as deep brain stimulation (DBS) immediately demonstrate their effect control (motor correction) of Parkinson's or dystonic movements. Unfortunately VNS has not the possibility of immediate clinical feed-back control.
The AED schedule was modified, by increasing clonazepamum to 2 mg daily. Video-EEG monitoring was recommended. The *quod ad vitam* prognosis might be unfavorable, because seizures can relapse anytime and evolution is uncontrolled. Furthermore, new brain injures may exacerbate the severity of the epilepsy, any new seizure may worsen the neurologic evolution. The *quod ad functionem* rehabilitation outcome might be precarious. The family support is essential in the therapeutic efforts. This clinical case underlines the necessity to implement a fall prevention program in patients with epilepsy, the importance of therapeutically tailoring AED for different pathophysiological stages of the disease, and emphasizes the limits of the modern techniques for seizures control. A multi-/ interdisciplinary team management of a such complex clinical case is mandatory.

Key words: *cerebral arteriovenous malformation, multidrug-resistant (refractory) epilepsy, vagal nerve electrostimulation (VNS), falls, traumatic brain injury,*

Introduction

Focal epilepsy (possible with secondary generalization) may be a complication of any brain damage: traumatic, vascular, infectious, tumoral, or degenerative (1). It is characterized by abnormal, excessive neuronal activity, with motor, cognitive and psychosocial manifestations (2).

Patients are considered to have uncontrolled or refractory epilepsy if disabling seizures continue, despite appropriate trials of two antiepileptic drugs (AEDs), either alone or in combination. It is estimated that 30 - 40% of people with epilepsy have seizures that are not controlled by medication (3). Vagal nerve electrical stimulation therapy (VNS) is used for patients who have multidrug resistant epilepsy, as an adjunctive therapy to medication management, surgical resection, and other epileptic therapies (4).

Falls are one of the most common medical complications in neurologic patients, occurring during paroxysmal epileptic seizures, or due to sequelae of gait impairments (5),(6).

Physical injuries are common at patients with epilepsy; about 47% have reported at least one injury in the past 12 months. Most of the injuries were mild and only 14% of patients reported severe injuries (6).

The risk factors are: neurodevelopmental abnormalities, seizures type and frequency, uncontrolled epilepsy, comorbidities and co-medication related adverse effects (7).

Case report: This is a retrospective case study of a 36-years-old male patient with residual neurological impairments after right frontal cerebral arterio-venous malformation, operated at the age of eight: left spastic hemiplegia and refractory epilepsy, needing 3 AEDs and left VNS.

The paper was approved by our Hospital Bioethics Committee, no.17464/14.06.2019.

Medical history of the chronological neurologic evolution is presented below:

- the first seizure has occurred at the age of nine, and was controlled with 1 AED (phenobarbital);
- seizures had a secondary "pick", being aggravated at the age of 33 y.o. Their daily frequency gradually increased (from 2-3, up to 10 crises / daily, occurring at one week interval between them). Convulsions were poorly controlled with 3 associated AED (carbamazepinum retard, clonazepamum, levetiracetamum), and were probably related to emotional distress (divorce).
- on May 2017, at the age of 34 y.o. treatment was supplemented by adding left vagus nerve electrical modulation.
- Subsequent evolution and outcome were favorable, with this complex therapeutic approach: 3 associated AEDs (levetiracetamum 2000 mg + clonazepamum 1mg + carbamazepinum retard 600 mg) and VNS.
- during 2018 (at the age of 36 y.o.) seizures occurred at 1.5-month intervals, with an average frequency of 5-6 crisis daily.

On 02.05.2019 after a severe seizure occurred at home, the subject suffered a severe traumatic brain injury (TBI) with left subdural hematoma. He was admitted in the neurosurgical department with severe coma (GCS 5) needing tracheal intubation, and emergent surgical intervention. Seven days later (on 09.05.2019) bleeding has relapsed (extradural hematoma in the left cerebral hemisphere) needing an iterative neurosurgical intervention. The subject was supervised in the intensive care unit since 02.05.2019 until 15.05.2019. The tracheal intubation was discontinued on 09.05.2019.

Post surgery cerebral CT scan control is depicted in fig.1

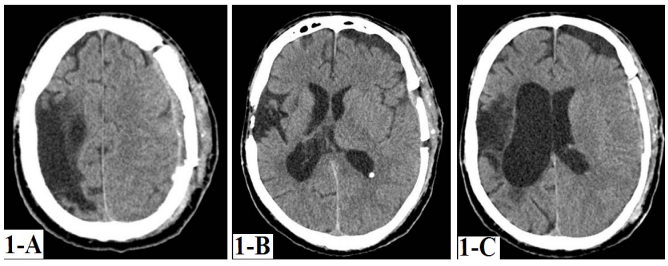

Fig.1 CT cerebral scan control (on 20.05.2019, after two consecutive neurosurgical interventions).
(1-A) right hemisphere hypodense sequelae, after neurosurgical intervention for arteriovenous malformation.
(1-B) Increased intracranial pressure and subfalcine herniation. **(1-C)** Residual, asymmetric, frontal subdural hygroma.

He was admitted in our neurorehabilitation clinic during 29.05.2019 - 13.06.2019.
The clinical examination has revealed: left spastic hemiplegia, obtunded level of consciousness, depression and dysmnesia for recent events.
Global motor score at admission was 65/100. Left upper limb motor score was: proximally (biceps) 2/5, triceps 3/5; distally 0/5. Assessment of the left lower limb: proximally (3/5), quadriceps 3/5, distally 2/5.
FIM (subtotal motor) score at admission was 24/91.
Spasticity: 1+ for the left upper extremity and 2 for the left lower limb (assessed with Asworth scale).
Respiratory rate was 22/min, heart rate 74/min, blood pressure 110/70 mmHg.
Usual blood tests. Before surgery (on 02.08.2019) slight anemia (10.82 g/dL) and leukocytosis (WBC 15.03 x $10^3/\mu L$), were present, subsequently were normalized (during admission in the rehabilitation clinic, on 29.05.2019)
Cerebral CT scan control performed in the Neurorehabilitation clinic (on 11.06.2019) is depicted in fig 2.

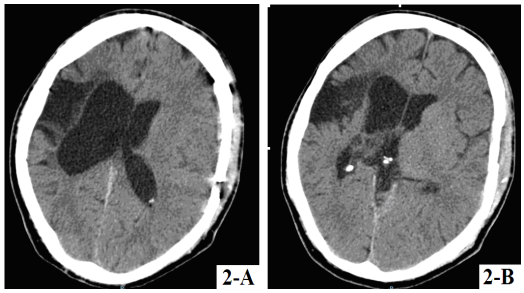

Fig 2. Cerebral CT scan control (11.06.2019):
(**2-A**) Hypodense sequelae in the right hemisphere (since childhood). Resolution of the left hemisphere hygroma.
(**2-B**) A slight modification of the intracranial pressure has still persisted (insignificant subfalcine herniation and offset of the midline).

Psychological examination identified: severe auto-/ and allopsychic temporal-spatial disorientation, severe attention deficit, accentuated fatigue, massive concentration efforts, major latencies. Memory had conserved its immediate "recording" capacity, with antero-retrograde amnesia of the trauma.
Cognitive processes were impaired, operating at a low level, with loss and degradation, QD = 0.4 (44%) MMSE = 9p/30. Severe anxiety and masked depression (due to dissimulation and denial) were evaluated with a HARD score of 23p.
Bach floral therapy was initiated. Psychotherapy for cognitive support and reorganization was initiated. Counseling identified a post-divorce depression and a recent psycho-trauma (his father's death).
Pharmacological therapy during admission in our department consisted in 3 antiepileptic drugs (AED): levetiracetamum 2000 mg + clonazepamum 1mg + carbamazepinum retard 600 mg.
Furthermore the patient has benefited from synergic association of neurotrophic drugs, anxiolytic therapy (flurazepamum), and gastric protection.
During hospitalization two new tonic-clonic seizures have occurred lasting few seconds, giving up spontaneously. The first one was in the gym room (during subliminal effort) and the last one on the stretcher, in the elevator, returning from CT native brain control.
The patient's overall evolution was favorable after the complex neurorehabilitation program and psychological support, with improvement of the global motor score and FIM 44/91. The subject acquired partial restoration of walking ability, on small distances, still needing human support. At discharge Barthel score was 60%, ADL was 3/10 (assisted independency), and I-ADL score 2/8.

Discussion:
Relapse of convulsions imposed a careful pathophysiological analysis: imbalance of the local brain metabolism (after the severe, recent TBI and neurosurgical interventions (7) and/or a dysfunctional VNS procedure (due to either an impaired electronic device, or a biological issue - local fibrosis and increased impedance at the contact level between the electrode and the vagal nerve) (8).
The electronic device was assessed on 13.06.2019, and its electrical parameters were within normal limits (output 1.75 mA, signal frequency 30Hz, pulse width 250 µsec, signal off time 5.0 min, Mag current 2.00 mA, Mag on time 60 sec, Mag pulse width 500 µsec). When the stimulator was turned on the patient felt hoarseness.
At discharge the daily dose of Clonazepamum was raised to 2 mg, with a further progressive increase by 0.5 mg weekly. He was recommended video EEG monitoring.
Rehabilitation targets and objectives aimed at: improvement of basic activities of daily living (B-ADL), familial reintegration and (eventually) socio-professional independence, enhancement of the quality of life, and identification of the risk factors, to prevent further seizures and injuries.

The immediate *quod ad vitam* outcome might be unfavorable, because epileptic seizures could relapse anytime and evolution is uncontrolled. Any new brain injury may exacerbate the severity of the epilepsy, and any relapsed seizure may worsen the neurologic evolution.

The rehabilitation *quod ad functionem* prognosis might be precarious. The family support is essential in the therapeutic efforts.

Vagus nerve stimulation (VNS) is an invasive procedure approved by FDA in 1997, and has become an integral part of epilepsy therapy, indicated in individuals with refractory disease who are not candidate for epilepsy neurosurgery (9).

In 2005, VNS has received FDA approval for the treatment of resistant depression.

The VNS device for epilepsy and depression is manufactured by Cyberonics (Houston, Texas).

In 2013, the FDA approved the RNS® Neurostimulator by NeuroPace RNS System (Mountain View, California) for treatment-resistant epilepsy.

In January, 2015, the FDA approved another implantable VNS device, the vBloc® Maestro® system manufactured by Entero Medics (St Paul, Minnesota) as a hunger suppressant, to treat refractory obesity in patients with a body mass index (BMI) of 35-45 kg/m2.

The vagus nerve contains myelinated A and B fibers, as well as unmyelinated C fibers. Chronic VNS stimulation appears to primarily engage afferent A fibers (10),(11). Afferent signals target the brainstem and, ultimately, the limbic, reticular, and autonomic centers of both hemispheres (10). The device provides an electrical pulse that stimulates the nerve in an afferent direction, up into the brainstem, thereby up regulating the neurotransmitters GABA, norepinephrine and serotonin. These are thought to balance out the excitatory neurotransmitters, like glutamate. Potential mechanisms of action include a desynchronizing effect, changes in neurotransmitters and neuronal metabolism, and an increase in Fos expression (10).

Neuroimaging has revealed VNS-induced changes in the cerebellum, limbic system, and thalamus (11). However, the exact anticonvulsant and antidepressant mechanisms of VNS are unknown (9-11).

To date, more than 70000 patients worldwide have received a VNS implant (8, 9). Adverse events of VNS include: chest pain, bradycardia, dyspnea, paresthesia, nausea, coughing, throat pain and voice alteration (hoarseness) (12). Surgical side effects are rare, but might occur: significant bleeding, infection and permanent vocal cord paralysis.

A $\geq$ 50% reduction in seizure frequency is often used as outcome measure to assess efficacy in epilepsy drug trials (13). In a multicenter, double-blind, 3-month, randomized study (14) of 191 patients with AED refractory partial-onset seizures, emphasized that when device was turned on, the seizure were reduced in more than twice of the cases, compared with those with the device turned off (38% vs 17%, respectively). Unlike the situation with many AED, seizure control improved over time. Cognition and mood were not adversely affected (14).

Even though seizure freedom is rarely achieved, patients who have undergone VNS have generally experienced fewer and less severe seizures, fewer consultations to the emergency room, and less admissions for hospital care (15,16,17,18).

Conclusions:

The multi- / interdisciplinary team management of such a complex clinical case is mandatory.

This case report underlines the importance of falls prophylaxis in patients with epilepsy, and the significance of individualized / tailored therapeutic program, for each different pathophysiological stages of the disease. It also emphasizes the limits of the modern neuromodulation techniques to control seizures.

Conflict of interest: Authors have no conflicts of interest to declare.

Written informed consent for publication was obtained from the next of kin (the patient`s mother).

Author contributions:

Anghelescu Aurelian has designed the study, was involved in writing, analyzing and reviewing the manuscript.

Deaconu Valentin and Axente Catalina were involved in drafting the figures, and writing of the manuscript.

Onose Gelu was involved in supervision of the work, reviewing and approving of the final paper.

Acknowledgements

Rotarescu Virginia, PhD Psychologist, Teaching Emergency Hospital "Bagdasar-Arseni"

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