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Super refractory status epilepticus in Lafora disease interrupted by vagus nerve stimulation: A case report

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Refractory and super refractory status epilepticus (RSE/SRSE) require effective action to avoid death or serious and irreversible consequences on neurological functions. Regrettably, there is a considerable lack of evidence on the optimal treatment strategy [1]. Vagus nerve stimulation (VNS), an approved chronic therapy for pharmacoresistant epilepsy, was initiated acutely in less than 40 reported patients with RSE/SRSE, interrupting 74% of cases [2]. However, several studies failed to provide adequate information on patient clinical characteristics, concomitant and previous treatments, stimulation protocols and data on long-term prognosis [2].

In order to help overcome these limitations, we aimed at reporting the electro-clinical details, the employed protocol and the long-term outcome of a case of SRSE in a patient with Lafora disease, a severe progressive myoclonic epilepsy commonly complicated by status epilepticus (SE), interrupted with VNS.

The case at issue is a 16-year-old girl with unremarkable familial and previous medical history, who started having myoclonic seizures since 14 years of age, initially controlled with valproate monotherapy. At 16 years, myoclonic seizures recurred; moreover seizures with impaired awareness and generalized tonic-clonic seizures (GTCS), resistant to treatment with different antiepileptic drugs (AEDs) (levetiracetam, valproate, lamotrigine, topiramate and clonazepam in various combinations), appeared. Since the same period, she presented action myoclonus, ataxia and a progressive cognitive decline leading to school dropout. EEGs showed diffuse epileptiform discharges with marked photosensitivity, while magnetic resonance imaging was unremarkable.

Few months after the clinical deterioration, the patient had a convulsive SE resolved with benzodiazepines. One month later, a further convulsive SE occurred. She was admitted to her local hospital and, since there was no response to intravenous benzodiazepines and lacosamide, she was treated with continuous midazolam and propofol infusion for five days, after which the status subsided. However, two days later, a refractory convulsive SE recurred. The patient was transferred to our Hospital on the 5th day after RSE onset while on propofol and midazolam. She was admitted to the Intensive Care Unit (ICU) and underwent basic (invasive pulmonary ventilation, infection control, multimodal monitoring, artificial nutrition) and advanced (cerebral monitoring, body temperature control) intensive care treatments. Diagnostic exams were performed and multiple treatment associations were attempted (Fig. 1a), reaching a sustained burst suppression (i.e. >24 hours) on several occasions (Fig. 1b). Ketogenic diet was initiated, however, ketosis was not achieved.

When not on burst-suppression, her EEG showed a poorly organized theta-delta background activity with subcontinuous diffuse and multifocal spikes predominant over the posterior regions and, inconstantly, over the right hemisphere. Anesthetics weaning was attempted several times but either multiple-per-day prolonged GTCS requiring treatment with AED in boluses or an electroclinical status invariably recurred shortly afterwards (Fig. 1c). Consciousness never recovered.

On the 66th day after SE onset, a vagal nerve stimulator, model Aspire SR, 106, Cyberonics-Livanova, was implanted. The device was switched on immediately after returning to the ICU with the following parameters: intensity 0.125 mA, pulse width 250 mcs, frequency 30 Hz, duty cycle 30″ on- 5′ off. As no evident side effects occurred, intensity was titrated to 1.75 mA during the first 48 hours, with increases of no more than 0.125 mA per hour. On the third post-operative day we began changing the cycle (one step per day) and lastly, on the 5th post-operative day, amplitude was increased. The final parameters were: intensity 1.75 mA, 30″ on-1.8 ′ off, pulse width 500 mcs, frequency 30 Hz, magnet 2 mA. During titration no changes were made in the AED regimen and, on the third post-operative day (69 days after status onset), midazolam was withdrawn. Since then, her EEG kept on showing a slow background, but epileptiform anomalies became less frequent (Fig. 1d) and she has had only sporadic GTCS, the last of which on the 14th post-operative day, despite withdrawal of levetiracetam and decrease of phenobarbital. Since the 6th post-operative day she was on spontaneous breathing.

The final diagnosis was Lafora disease due to compound heterozygous mutations in *EPM2A*: c.491 T > G (p.Ile164Ser), c.539 T > C (p.Leu180Pro).

She was discharged with valproate 4000 mg/day (blood levels: 92 mcg/ml), phenobarbital 400 mg/day (blood levels 41.9 mcg/mL); zonisamide 400 mg/day. She was admitted to a long-term care facility where VNS was maintained with the same parameters, antiepileptic regimen was left substantially unmodified and metformin was added up to 2500 mg/die. She kept on having frequent myoclonic jerks of her right arm and hand, sometimes provoked by activating tactile stimuli and weekly/monthly clonic generalized seizures which seldom required

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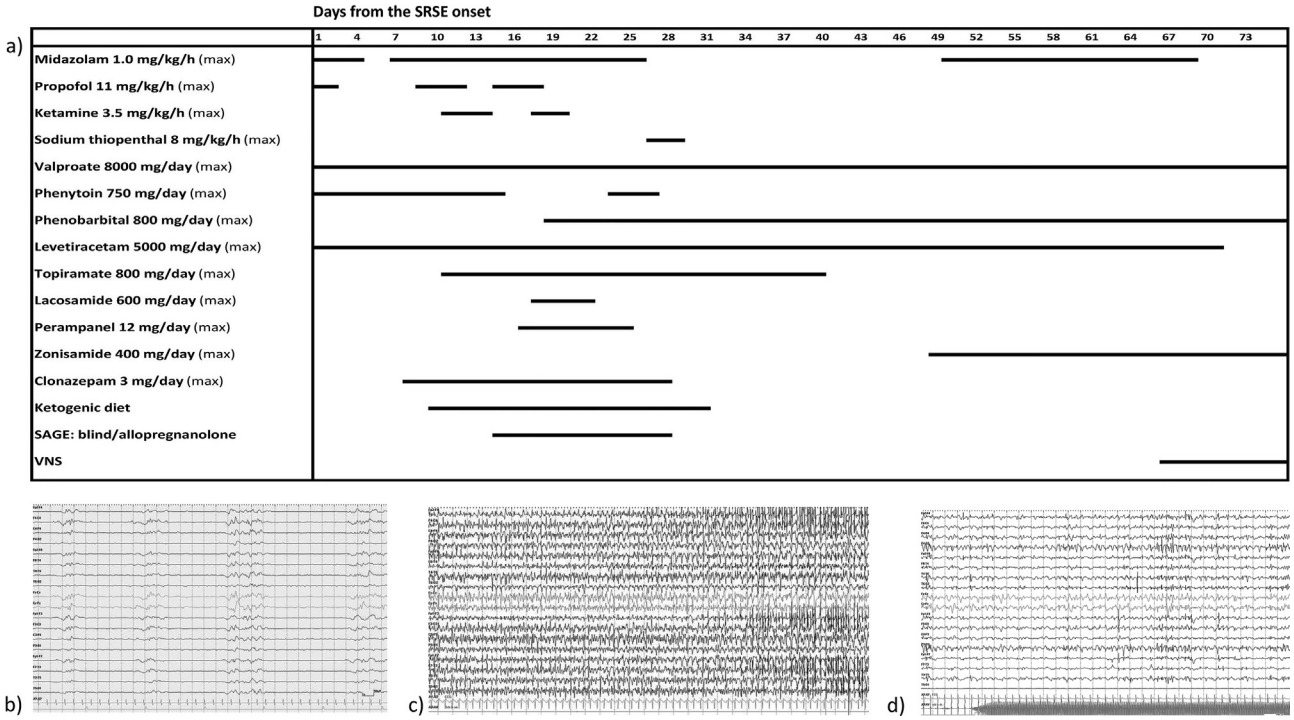

Fig. 1. a. Day by day therapies and maximal used doses; EEG (montage longitudinal bipolar, 30 seconds per page): b. day 12: burst suppression (Propofol 10 mg/kg/h, midazolam 0.65 mg/kg/h); c. day 19: attempt at weaning midazolam, immediately followed by a GTCS; d. 13th post-operative day: no anaesthetics, slow background and frequent, but not subcontinous, multifocal and diffuse epileptic abnormalities; the artifact due to VNS starting is visible on the lowest channel.

treatment with benzodiazepines. Consciousness persisted in being severely impaired: she remained in a vegetative state (Glasgow Outcome Score 2, Modified Rankin Score: 5), though with possible transient partial improvement after metformin (patient 1 in Ref. [3]), until her death, which occurred nine months after implantation, due to a tracheostomy-related late bleeding.

To our knowledge, there are only two published case reports of Lafora disease treated with VNS: both showed an improvement in different types of seizures and, in one case, in the frequency of SE episodes [4,5]; in one case, VNS also led to cerebellar symptoms improvement.

To summarize, we implanted a VNS device after more than two months from SRSE onset and multiple therapeutic attempts in a patient with Lafora disease and recurrent SE. We performed a very rapid stimulation parameter titration, without apparent side effects. We managed to withdraw anaesthetics 24 hours after reaching an assumed therapeutic setting. Therefore, according to proposed efficacy criteria in SE [6], we assumed that the VNS implant was responsible for the SRSE interruption. No further SE nor GTCS occurred over the following nine months. The outcome on consciousness, however, was dismal, probably due both to the long duration of the status and of anaesthetic treatment and to the severity of the underlying disease. This was the first and sole VNS implantation acutely performed in our Centre for a RSE. Although this is a single case, our results support considering VNS acute implantation soon in the course of this condition, with the dual purpose of interrupting the status and preventing its recurrence.

Declaration of interest

Barbara Mostacci and Paolo Tinuper have received speakers' honoraria and travel support from LivaNova.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.08.008.

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