Double antigitamatergic therapy in a case of postanoxic super-refractory status epilepticus

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Neurology: Clinical Practice October 2020 vol. 10 no. 5 e44-e46 doi:10.1212/CPJ.0000000000000740

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Postanoxic status epilepticus (SE) is considered a strong predictor of poor outcome. Nevertheless, rare cases of refractory SE with a combination of good prognosticators are associated with a neurologic recovery.¹ We report a case of a postanoxic patient with super-refractory nonconvulsive SE (NCSE) successfully treated with a double antigitamatergic therapy. NCSE was assigned according to the Salzburg EEG criteria² and the International League Against Epilepsy classification³; refractory and super-refractory SE were defined after the failure of antiepileptic drugs and anesthetics, respectively.⁴

PRACTICAL IMPLICATIONS

Double antigitamatergic therapy may be a promising option for super-refractory postanoxic status epilepticus.

Case

A 26-year-old woman, on oral contraceptives, reached the emergency department presenting with dyspnea, sweating, and leg pain. In hospital, she had a cardiac arrest (CA) due to a massive pulmonary embolism requiring urgent cardiopulmonary resuscitation (no-flow time 0 minutes and low-flow time 35 minutes), systemic fibrinolysis, and admission to our intensive care unit (ICU). According to the local standardized protocol for the treatment of hypoxic-ischemic encephalopathy in the ICU, a 24-hour hypothermia up to 34°C and an anesthetic coma were induced. After rewarming and weaning of neuroanesthesia under continuous EEG monitoring, our patient remained in an unresponsive state, and the EEG disclosed an NCSE (figure, A). In line with our institutional protocol, an aggressive standardized treatment of the postanoxic SE was applied.⁵ Because IV administration of benzodiazepines, valproate (30 mg/kg bolus + 1.5 mg/kg/h infusion), and levetiracetam (40 mg/kg bolus + 3.5 mg/kg/h infusion) did not modify the epileptic activity, a first 48-hour propofol-midazolam coma up to burst-suppression state was induced under continuous EEG monitoring. After weaning of anesthetics on day 4 of admission, continuous ictal activity without periodic discharges still emerged on EEG configuring a super-refractory NCSE. Predictors of a potential favorable neurologic outcome were detected: (1) 24 hours after CA, both pupillary light and corneal reflexes were elicited during neurologic examination; (2) serum neuron-specific enolase (NSE) was 39 µg/L; and (3) 72 hours after CA, somatosensory evoked potentials (SSEP) recording documented the presence of an N20 response bilaterally. These data prompted us to continue life support and the antiepileptic and anesthetic therapy. Sequential add-on antiepileptic drugs, i.e., lacosamide (400 mg IV bolus + 400 mg/d infusion), topiramate (400 mg oral bolus + 400 mg/d oral administration), phenytoin (20 mg/kg IV bolus + 400 mg/d oral administration), and 2 further propofol-midazolam coma, failed to resolve the NCSE. On day 9, we started a further add-on therapy, based on ketamine (3 mg/kg IV bolus + 3 mg/kg/h infusion) associated with perampanel (6 mg oral bolus + 6 mg/d oral administration). Seventy-two hours after ketamine-perampanel administration, super-refractory SE resolved, and then, the complex pharmacologic regimen was slowly reduced. On day 18, our patient became able to open her eyes after stimulation and, after a few days, to obey examiner commands. A brain MRI, performed on day 17, revealed a mild basal ganglia T2 hyperintensity due to anoxic cerebral damage. After 28-day ICU stay, she was moved to the rehabilitation unit. Three months later, her neuropsychological tests were normal, and 6 months later, she returned to work and her previous social life (figure, B).

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Figure Representative EEG epochs recorded 3 days and 3 months after cardiac arrest (CA)

(A) Three days after CA, a simplified 8-channel EEG showed continuous epileptiform discharges with a frequency of >2.5 Hz, indicating a diagnosis of nonconvulsive status epilepticus according to the Salzburg criteria. (B) Three months after CA, an outpatient 18-channel EEG showed a well-organized alpha rhythm without epileptiform discharges.

Discussion

A stepwise multimodal assessment, based on neurologic examination, biomarkers of cerebral injury (NSE), electrophysiologic investigations (EEG and SSEP), and brain imaging (brain CT/MRI), is recommended for the management of comatose survivors of CA to choose an appropriate strategy of care and to avoid overtreatment.¹ In our patient, several features suggested a good prognosis: (1) the presence of bilateral pupillary light and corneal reflexes, (2) a mild increase in serum NSE 48 hours after CA, (3) the N20 responses preserved bilaterally 72 hours after

CA, and (4) a mild basal ganglia T2 hyperintensity at brain MRI on day 17 of hospitalization. The presence of good prognostic indicators prompted us to try several pharmacologic strategies, including a double antiepileptic therapy combining ketamine with perampanel. This treatment finds its rationale in hampering the synaptic maladaptive receptors trafficking. Indeed, leading to a progressive gamma-aminobutyric acid A receptor internalization and a glutamatergic receptor overexpression, it is supposed to underlie the pathophysiology of drug-resistant SE.⁶ In our case, ketamine, a NMDA receptor antagonist, was combined with perampanel, a negative allosteric

modulator of amino-hydroxy-methyl-isoxazole-propionic acid receptors, and obtained a curative effect 72 hours after administration. The efficacy of perampanel in refractory SE is still an unsettled issue, even if a significant favorable effect was reported when used in association with a variety of anesthetic medications in case of postanoxic super-refractory SE.⁷ Further multicentric studies are needed to confirm the efficacy and tolerability of the double antiepileptogenic therapy in patients with postanoxic super-refractory SE.

Acknowledgments

The authors thank the medical and nursing staff of the ICU at San Gerardo Hospital ASST Monza for their support and collaboration and Francesco Deleo, MD, for discussion.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication history

Received by *Neurology: Clinical Practice* May 17, 2019. Accepted in final form August 5, 2019.

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Andrea Stabile, MD	Department of Neurology, San Gerardo Hospital ASST Monza, University of Milano Bicocca, Monza, Italy	Conceptualization of the study, acquisition data, analysis and interpretation of data, and drafted the manuscript for intellectual content
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Appendix (continued)

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Graziella Bogliun, MD	Department of Neurology, San Gerardo Hospital ASST Monza, University of Milano Bicocca, Monza, Italy	Revision of the manuscript for intellectual content
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