Combining perampanel and ketamine in super refractory post-traumatic status epilepticus: A case report

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Status Epilepticus (SE) is a condition resulting either from the failure of seizure termination mechanisms or from the abnormal activation of prolonged seizure mechanisms. It represents a life-threatening medical emergency associated with high morbidity and mortality that requires prompt diagnosis and treatment. SE treatment begins with a quick-acting benzodiazepine, followed by intravenous (IV) loading and a continuous infusion of antiseizure medications (ASMs). The failure of first- and second-line treatments is defined as "refractory SE" (RSE) and requires infusion of IV anaesthetics. If anaesthetics fail or SE recurs after 24 hours, SE is defined as "super refractory status epilepticus" (SRSE). There is no compelling evidence regarding SRSE best treatment. However, ketamine has a peculiar role in SRSE, due to its antagonism on NMDA receptors and glutamatergic transmission inhibition [1]. Recently, a possible role in treating RSE and SRSE for perampenel was described [2]. In this article we report the case of a young man who developed a post-traumatic SRSE and was successfully treated after weeks of SE, showing also a brilliant recovery, with a combination of ketamine and high perampanel doses.

A 23-year-old male, with an unremarkable medical history, was admitted to the Intensive Care Unit (ICU) after being involved in a motor accident. He was found unresponsive on the scene, and promptly taken to the Emergency Department where he was intubated and sedated with IV propofol. He performed a brain CT scan that resulted unremarkable.

The next day, propofol was progressively reduced, but the patient developed generalized myoclonic jerks of axial muscles and face. Therefore, propofol infusion was restored and a spot electroencephalogram (EEG) showed generalized delta slowing. The patient was then treated with IV levetiracetam (2000 mg ev followed by 3000 mg/24h). EEG was performed again on the next day and revealed generalized SE (Fig. 1a): a continuous infusion of midazolam, along with propofol, was administrated to achieve burst suppression. A loading dose of valproic acid was administered (maintenance dose of 2 mg/kg/h), but the patient continued to experience breakthrough myoclonus, which ceased only after thiopentone infusion. The medical team subsequently introduced phenytoin (18 mg/kg IV) and consequently the myoclonic jerks disappeared. However, continuous EEG monitoring showed persistent generalized epileptiform discharges compatible with non-convulsive status epilepticus (NCSE) at the weaning of anaesthetic treatments (according to Salzburg criteria). Given the lack of response to multiple ASMs and to third line anaesthetic drugs, SRSE was diagnosed. The patient was then treated with high doses of intravenous steroids (Methylprednisolone 1000mg for 5 days). Meanwhile, an MRI brain scan was performed and showed microhaemorragic diffuse axonal injury (moderate grade according to Adams DAI Classification), represented by T2 and FLAIR hyperintense lesions of the corpus callosum and basal ganglia and fronto-parietal T1 hyperintense and FFET2 hypointense alterations consisting of punctate petechial haemorrhages (Fig. 1d-f). After thirteen days of hospitalization, the patient developed increased

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levels of transaminases and signs of hepatic dysfunction, valproic acid was thus discontinued and intravenous lacosamide was started (400 mg ev in 24h, increased to 600 mg in 24h), without significant improvement. Indeed, EEG monitoring showed a continuous slow activity rhythm that evolved in spikes with concomitant clinical facial jerks, as the medical team lightened the anaesthetic drugs. To break his continuous epileptic activity, treatment with 16 mg of oral perampanel through a nasogastric tube and intravenous ketamine was initiated. Midazolam was progressively reduced, meanwhile a loading dose of ketamine (1,5-3 mg/kg) was administered before a continuous infusion (range of maximum dose between 2 and 10 mg/kg/h). A complete burst-suppression EEG (Fig. 1b), with no clinical or electrographic evidence of seizures, was achieved. After 48h of ketamine administration, EEG showed a marked reduction in the epileptiform discharges with no evidence of SE recurrence. After 72h, ketamine infusion was progressively reduced and thus stopped, while perampanel was maintained at the dose of 16 mg. Four days after the perampanel and ketamine introduction, the patient was seizure-free and EEG did not show any ictal activity marking the resolution of SRSE after 39 days from ICU admission (Fig. 1c). Subsequent serial EEGs showed focal frontal epileptiform discharges, IV levetiracetam and phenytoin were slowly tapered and replaced with oxcarbazepine. The patient was then discharged from ICU and admitted to our clinic: his neurological examination showed only a mild left hemiparesis. After one month, he was transferred to a neurological rehabilitation unit where he was given a maintenance treatment with perampanel 6mg, lacosamide 400mg and oxcarbazepine 600mg. His neurological and neuropsychological examination was unremarkable, and after 5 months, the patient was

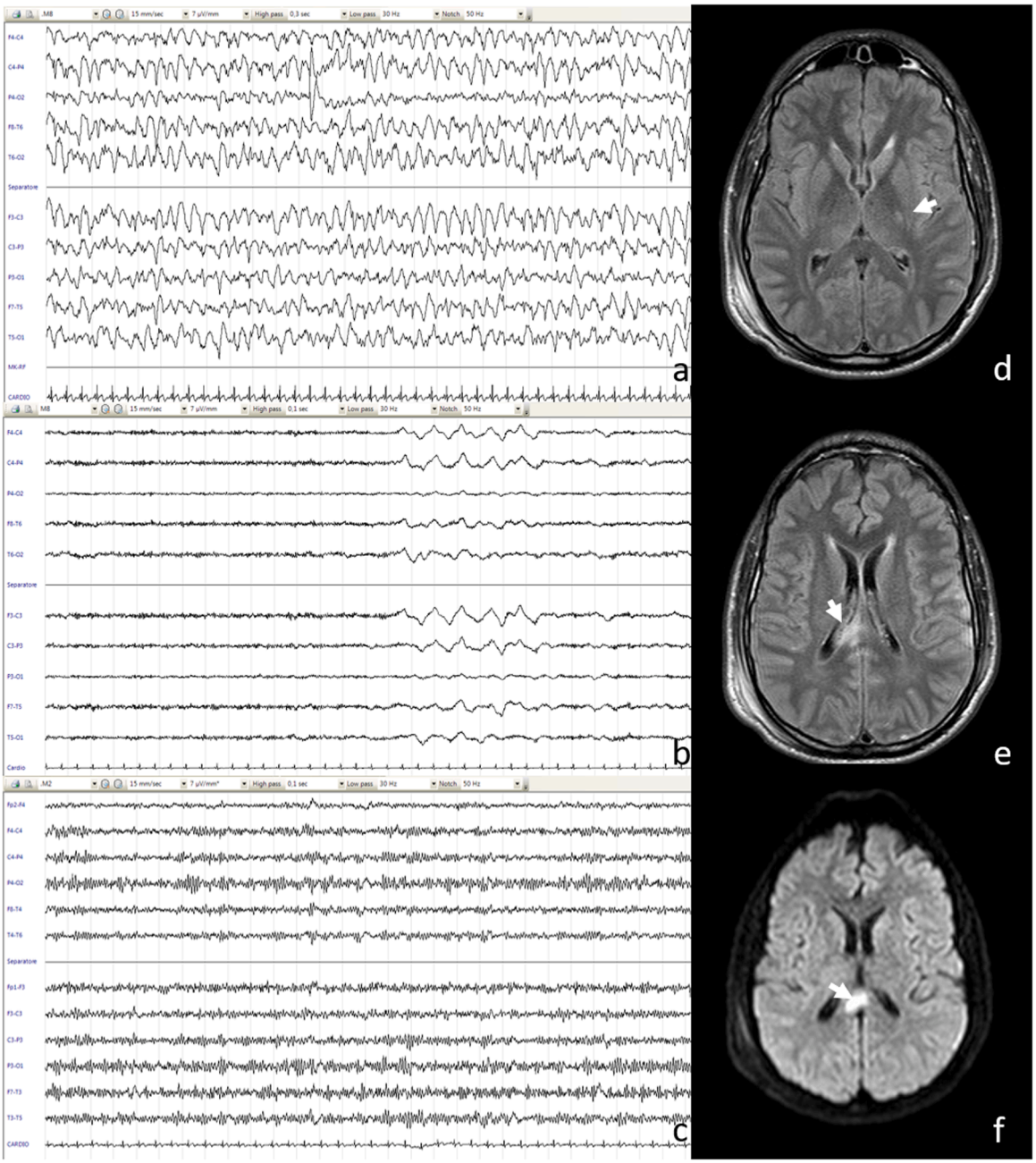

Fig. 1. a: EEG showing generalized continuos epileptic discharges. b: EEG after treatment with ketamine, alpha rythm with sporadic delta activity. c: EEG after discharge, without epileptic activity. d: FLAIR hyperintense lesion of basal ganglia. e: FLAIR hyperintense lesion of corpus callosum, showing restricted diffusion in DWI (f).

discharged home with no cognitive or physical deficit. At 6 months outpatient evaluation, the patient did not report any further seizure.

Our case highlights that the use of new ASMs and their combination is a valid, safe, and effective SRSE treatment strategy. Our patient experienced a full recovery after 39 days of SE with no physical or cognitive deficit, after the introduction of ketamine and perampanel. Our patient is a young man, with no previous disease, and who experienced a moderate grade diffuse axonal injury with no further complications. Ketamine and perampanel showed efficacy in SRSE when administered alone, while their co-administration has not been reported yet [3, 4]. Interestingly, the two drugs may have a synergic role in inhibiting glutamatergic transmissions with different mechanisms (Supplementary materials). Our report has some limitations: the first one is obviously related to its single case report nature; the second one regards the pharmacokinetics of ketamine and perampanel. Indeed, it may be difficult to judge the individual efficacy of each of the two ASMs: we cannot exclude that ketamine could have a prominent role in SRSE cessation, given the slow pharmacokinetic proprieties of perampanel. Further studies with a higher number of patients and with a focus on ASMs pharmacokinetics could address this issue and confirm the synergic effect between these two drugs.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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