

C A S E R E P O R T

An uncommon case of nonconvulsive status epilepticus successfully treated with enteral brivaracetam

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Abstract. *Background and aim of the work:* We present a case of a woman affected by nonconvulsive status epilepticus (NCSE) caused by cerebral hyperperfusion syndrome (CHS) after carotid endarterectomy (CEA) who was successfully treated with Brivaracetam (BRV) administered via nasogastric tube (NGT). *Case Presentation:* An 82-years old woman was referred for increasing blood pressure, severe headache and two focal motor seizures on postoperative day four after right CEA. CT scan showed edema of the right hemisphere with a midline shift of 5 mm. The patient underwent daily Electroencephalography (EEG) monitoring which showed continuous epileptiform discharges over the right hemisphere, compatible with a diagnosis of status epilepticus. She was treated with standard antiepileptic drugs (Phenytoin, Lacosamide and Levetiracetam iv) without clinical response. A therapeutic trial with BRV 200mg administered via nasogastric tube (NGT) was tried which resulted in substantial clinical benefit. *Conclusions:* The administration of new antiepileptic drugs (AEDs) such as BRV may result in significant clinical improvement in refractory cases of status epilepticus. The enteral administration of AEDs via NGT should always be considered for refractory cases of status epilepticus when standard iv treatment has failed or is not possible.

Key words: Brivaracetam, nonconvulsive status epilepticus, status epilepticus, carotid endarterectomy, cerebral hyperperfusion syndrome.

Introduction

Cerebral hyperperfusion syndrome (CHS) is an uncommon complication of carotid endarterectomy (CEA) related to sudden changes in arterial blood flows after revascularization of carotid stenosis. CHS is more likely with recanalization of subocclusive carotid stenosis ($\geq 80\%$) and when CEA is performed after recent ischaemic stroke (1-3). Clinical features of CHS can vary from mild headache to focal motor seizures but severe and life-threatening complications (i.e. massive cerebral hemorrhage) may also occur (4). We present case of a patient with non-convulsive status epilepticus (NCSE) secondary to CHS who showed a

significant clinical improvement after treatment with BRV administered via NGT.

Case Presentation

An 82-year-old woman, affected by hypertension and with a history of previous right occipital ischaemic stroke, developed acute left-leg mild weakness starting 24 hours before the admission to the emergency ward. CT-Angiography (CTA) of intra- and extracranial cerebral arteries showed subocclusive stenosis (99%) of the right internal carotid artery (ICA) (Fig.1). Brain MRI showed rosary-like watershed infarcts involving

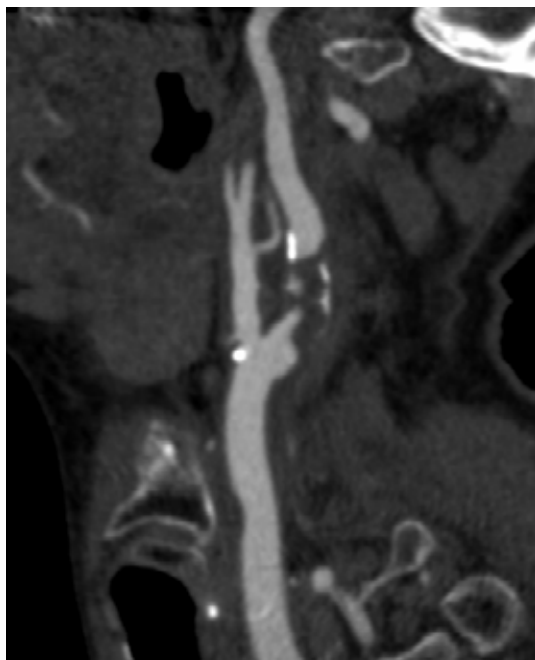


Figure 1. CT-Angiogram of the neck showing right internal carotid artery (ICA) subocclusion ($\geq 99\%$).

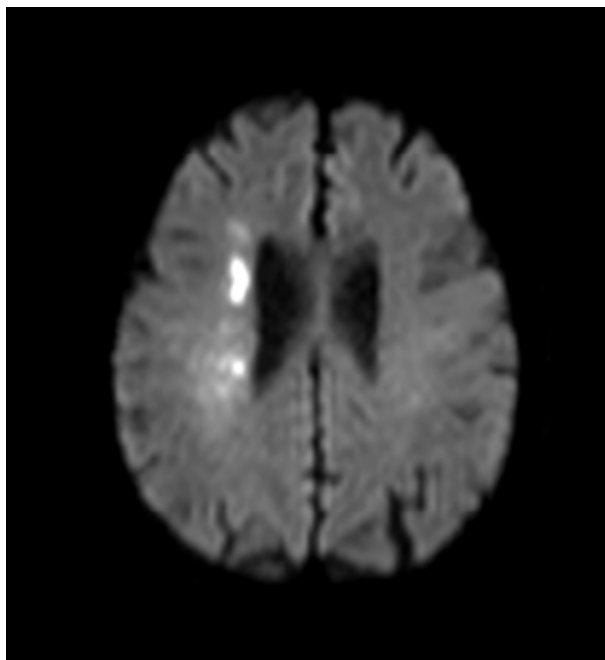


Figure 2. MRI showing rosary-like watershed infarcts in the right hemisphere involving the junction between middle cerebral artery (MCA) and anterior cerebral artery (ACA) cortical territories.

the junction between middle cerebral artery (MCA) and anterior cerebral artery (ACA) cortical territories (Fig. 2). The patient was referred for right CEA within two weeks after the event (5). Neurological examination performed the day before surgery was normal. Right CEA was performed without recognized complications. On postoperative day four, she developed severe headache non-responsive to intravenous Paracetamol. On examination, she presented elevated blood pressure (200/100 mmHg) which required treatment with Furosemide iv.

Afterward, she presented clonic jerks of her left arm and leg followed by focal to bilateral tonic-clonic seizures (6). Lorazepam 4 mg iv was administered which successfully terminated the seizures. The following day, she was found non-responsive, with impaired awareness and inability to perform simple motor tasks. On neurological examination, complete left hemiplegia was noted. A CT scan of the head revealed massive cerebral edema of the right hemisphere with a 5 mm midline shift (Fig. 3). The EEG showed diffuse background slowing and subcontinuous, periodic lateralized epileptiform discharges (PLDs), with a

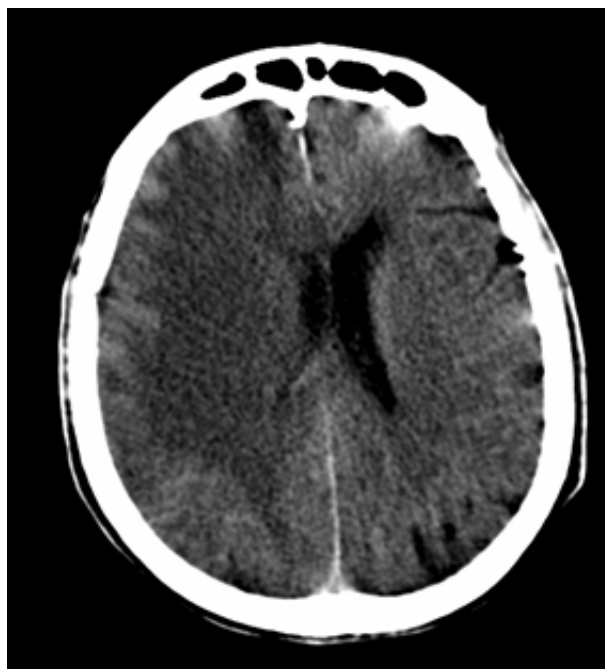


Figure 3. CT scan of the head showing cerebral edema of the right hemisphere with a 5 mm midline shift.

frequency >3,5 Hz, over the right hemisphere, configuring an electroclinical diagnosis of NCSE (7). Despite intravenous treatment with Phenytoin 300mg/day, Lacosamide 400mg/day, Levetiracetam 2000mg/day and antiedemigen therapy with Mannitol, NCSE persistent for over 24h configuring a state of refractory status epilepticus. A therapeutic switch from Levetiracetam to BRV 200mg/day administered via NGT was tried, which ultimately resulted in the resolution of the NCSE and improved neurological status over the next 5 days.

Discussion

CHS is a known complication of carotid angioplasty and carotid endarterectomy, and focal motor seizures represent a frequent clinical manifestation of this condition (4). The pathophysiology of CHS may be explained by a state of cerebral oligemia caused by carotid stenosis which is reflected by maximal vasodilatation of vessels distal to the stenosis. After recanalization, subsequent reperfusion of vessels with defective autoregulation and inability to readily constrict to sudden changes in blood flows produces a breakthrough, resulting in transudation of fluid into the pericapillary astrocytes and interstitium, potential endothelial damage, vessel disruption, edema and eventually cerebral hemorrhage (4,8).

The majority of patients with CHS may present mild symptoms and signs at onset, but progression to severe and life-threatening complications can occur if CHS is not recognized or misdiagnosed with other better-known causes of perioperative complications, like thromboembolism (4). Intracerebral or subarachnoid hemorrhage complicating CHS presents an incidence of 0.4-1.0% following CEA, they are associated with a high mortality (36 – 60 %) and disability (80%) rate (9-11) and are usually associated with seizures (12).

Seizures complicate CEA in approximately 3% of patients (13) and studies of post-endarterectomy seizures suggest that they exclusively occur in patients with CHS (14). EEG patterns in patients presenting seizures after CEA have been described displaying

either diffuse slowing or periodic lateralized epileptiform discharges (PLDs) even in the absence of seizures (4). Interestingly, our patient developed seizures even before the appearance of cerebral edema on CT scan of the head and the EEG features, characterized by continuous PLDs, also anticipated neuroradiological worsening. We may speculate that in our patient the development of cerebral edema was coupled with the EEG evolution and worsening which was also suggestive of NCSE and advocated for urgent AED treatment.

An altered mental status was the only clinical manifestation of SE in our patient, which persisted despite aggressive therapy with standard AEDs commonly used for the treatment of SE, configuring a refractory NCSE (15). Although constituting a minority of cases of status epilepticus (15) the appropriate therapy for refractory and super-refractory SE is still poorly known. Anesthesia is not often required in primarily non-convulsive cases, it certainly should not be given early, and it was in fact delayed also in our case. Several therapies have been tried in refractory NCSE cases, and new well-tolerated AED are needed for these particular cases. BRV is one of the newest AEDs on the market and it is currently indicated as add-on therapy for focal onset seizures with or without secondary generalization.

Brivaracetam has already been used in several case reports for the acute treatment of status epilepticus with encouraging results (16). However, to our best knowledge, the enteral administration of BRV for treatment of SE has never been reported.

Enteral administration of AEDs is a safe and effective strategy to treat refractory and super refractory cases of SE when intravenous administration of standard AEDs is not feasible because of pharmacokinetic parameters. Oral absorption of BRV is complete and rapid; therefore, oral and injectable formulations can be used interchangeably (16). Our own experience with enteral administration of BRV via NGT showed excellent results: with complete resolution of NCSE after approximately 5 days from the beginning of the therapy. Interestingly, our own experience challenges findings from other case reports suggesting discouraging results of BRV in patients who already failed

a therapeutic trial with Levetiracetam, which is supposed to present the same mechanism of action of BRV. We may speculate that in our patient the higher affinity of BRV for SV2 compared to Levetiracetam appeared to be a key element in determining the clinical response and the resolution of NCSE (16).

In conclusion, CHS is a challenging diagnosis that should always be considered in patients presenting an acute worsening of the neurological status following carotid stenosis interventions. SE is not uncommon as a complication of CHS and refractory and super refractory cases are possible. The administration of new AEDs such as BRV may result in significant clinical improvement of seizures and the enteral administration of AEDs via NGT should always be considered an effective therapeutic strategy when standard iv treatment has failed or is not feasible.

Conflicts of interest: Authors have no conflicts of interest or funding to declare.

References

- Galyfos G, Sianou A, Filis K. Cerebral hyperperfusion syndrome and intracranial hemorrhage after carotid endarterectomy or carotid stenting: a meta-analysis. *J Neurol Sci* 2017; 381:74–82.
- Lieb M, Shah U, Hines GL. Cerebral hyperperfusion syndrome after carotid intervention: a review. *Cardiol Rev* 2012; 20(2):84–9.
- Kirchoff-Torres KF, Bakradze E. Cerebral hyperperfusion syndrome after carotid revascularization and acute ischemic stroke. *Curr Pain Headache Rep* 2018; 22(4):24.
- van Mook WNKA, Rennenberg RJMW, Schurink GW, et al. Cerebral hyperperfusion syndrome. *Lancet Neurol* 2005; 4(12):877–88.
- Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke* 2009; 40(10):e564–72.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58(4):522–30.
- Leitinger M, Trinkka E, Gardella E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. *Lancet Neurol* 2016; 15(10):1054–62.
- Ho DSW, Wang Y, Chui M, et al. Epileptic seizures attributed to cerebral hyperperfusion after percutaneous transluminal angioplasty and stenting of the internal carotid artery. *Cerebrovasc Dis* 2000; 10(5):374–9.
- Naylor AR, Ruckley C V. The post-carotid endarterectomy hyperperfusion syndrome. *Eur J Vasc Endovasc Surg* 1995; 9(4):365–7.
- Jorgensen LG, Schroeder T V. Defective cerebrovascular autoregulation after carotid endarterectomy. *Eur J Vasc Surg* 1993; 7(4):370–9.
- Jansen C, Sprengers AM, Moll FL, et al. Prediction of intracerebral haemorrhage after carotid endarterectomy by clinical criteria and intraoperative transcranial Doppler monitoring: results of 233 operations *Eur J Vasc Surg*. 1994; 8(2):220–5.
- Naylor AR, Evans J, Thompson MM, et al. Seizures after carotid endarterectomy: hyperperfusion, dysautoregulation or hypertensive encephalopathy? *Eur J Vasc Endovasc Surg* 2003; 26(1):39–44.
- Penn AA, Schomer DF, Steinberg GK. Imaging studies of cerebral hyperperfusion after carotid endarterectomy: case report. *J Neurosurg* 1995; 83(1):133–7.
- Nielsen TG, Sillesen H, Schroeder T V. Seizures following carotid endarterectomy in patients with severely compromised cerebral circulation. *Eur J Vasc Endovasc Surg* 1995; 9(1):53–7.
- Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* [Internet] 2011; 134(10):2802–18. Available from: <https://doi.org/10.1093/brain/awr215>
- Farrokh S, Bon J, Erdman M, et al. Use of newer anticonvulsants for the treatment of status epilepticus. *Pharmacother J Hum Pharmacol Drug Ther* 2019; 39(3):297–316.

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Arrived: 29 April 2020

Accepted: 30 April 2020

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