



# Adverse effects of erenumab on cerebral proliferative angiopathy: A case report

Laura L Lehman<sup>1,2</sup>, Rebecca Bruccoleri<sup>3,4</sup>, Amy Danehy<sup>2,5</sup>, Julie Swanson<sup>1</sup>, Christine Mrakotsky<sup>1,2,6</sup>, Edward Smith<sup>2,7</sup>, Darren B Orbach<sup>2,5</sup> and Rami Burstein<sup>2,8</sup>

Cephalalgia

0(0) 1–5

© International Headache Society 2020

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/0333102420950484

journals.sagepub.com/home/cep



## Abstract

**Background:** Cerebral proliferative angiopathy is a vascular malformation associated with compromised blood-brain barrier and with migraine-like headache. Treating blood-brain barrier-compromised patients with erenumab, an anti-calcitonin gene-related peptide receptor monoclonal antibody, may be risky.

**Case:** We describe a case of a 22-year-old chronic migraine patient with cerebral proliferative angiopathy who presented to our hospital in status epilepticus 2 d after his first dose of erenumab. Serial magnetic resonance imaging (MRI) studies demonstrated progressive areas of diffusion restriction including the brain tissue adjacent to the cerebral proliferative angiopathy, bilateral white matter and hippocampi. His 6-month post-presentation magnetic resonance imaging was notable for white matter injury, encephalomalacia surrounding cerebral proliferative angiopathy and bilateral hippocampal sclerosis. He remains clinically affected with residual symptoms, including refractory epilepsy and cognitive deficits.

**Conclusion:** The evidence presented in this case supports further investigation into potential deleterious side effects of erenumab in patients with compromised blood-brain barrier, such as individuals with intracranial vascular malformations.

## Keywords

Cerebral proliferative angiopathy, CGRP receptor monoclonal antibody, migraine, headache

Date received: 16 April 2020; revised: 22 June 2020; 13 July 2020; accepted: 21 July 2020

## Introduction

Previously categorized as an arteriovenous malformation (AVM), cerebral proliferative angiopathy (CPA) is now recognized as a distinct entity, defined as a cerebral vascular malformation characterized by appearance of diffuse vascular spaces in multiple lobes of the brain intermingling with normal parenchyma. This is unlike brain AVMs, which are characterized by higher flow than CPA, with more brisk arteriovenous shunting, and which do not demonstrate intervening brain parenchyma within their boundaries (1). Evidence suggests that endothelial cell function and the normal blood brain barrier (BBB) may be dysregulated in these dynamic, congenital vascular lesions (2,3). These data have led to the exclusion of patients with suspicion of cerebral vascular malformation from the Phase 2 and 3 studies of erenumab, a new anti-calcitonin gene related protein (CGRP) receptor monoclonal antibody (anti-CGRP-mAbs) approved by the

FDA for the treatment of chronic migraine. This exclusion was adopted to lower the risk of cerebral ischemia induced by blockade of CGRP-mediated dilatation of

<sup>1</sup>Department of Neurology, Boston Children's Hospital, Boston, MA, USA

<sup>2</sup>Harvard Medical School, Boston, MA, USA

<sup>3</sup>Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA

<sup>4</sup>Department of Medicine, Vanderbilt University, Nashville, TN, USA

<sup>5</sup>Department of Radiology, Boston Children's Hospital, Boston, MA, USA

<sup>6</sup>Department of Psychiatry, Boston Children's Hospital, Boston, MA, USA

<sup>7</sup>Department of Neurosurgery, Boston Children's Hospital, Boston, MA, USA

<sup>8</sup>Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Hospital, Boston, MA, USA

## Corresponding author:

Laura Lehman, Department of Neurology, Boston Children's Hospital, 300 Longwood Avenue Fegan 11, Boston, MA 02115, USA.

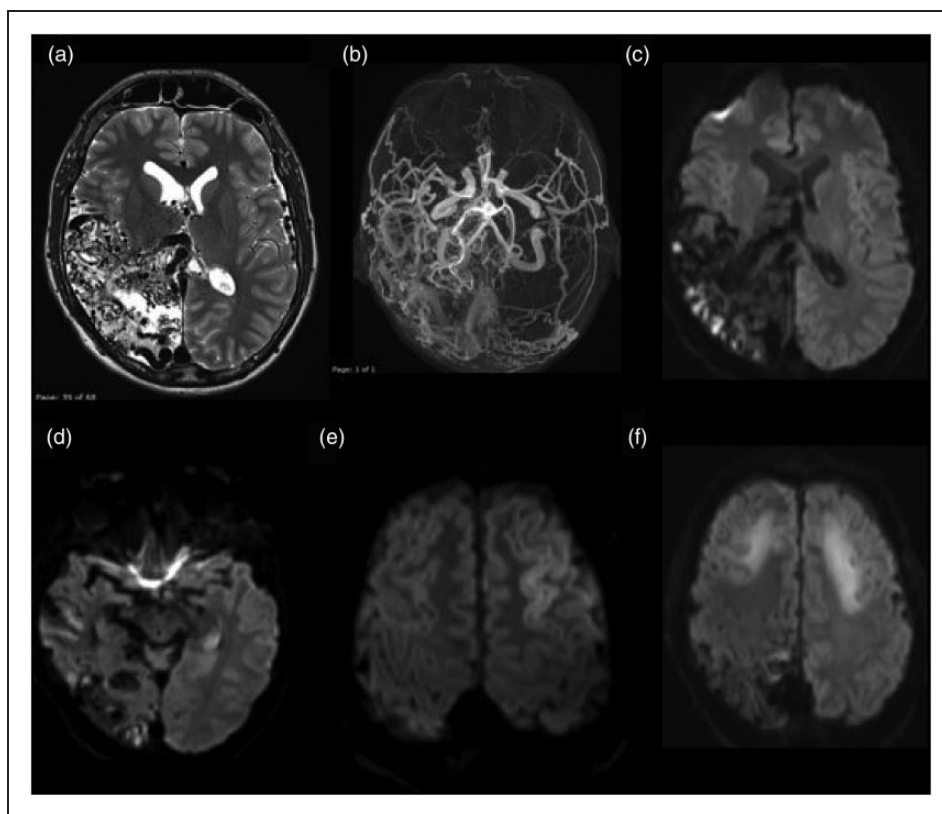
Email: Laura.Lehman@childrens.harvard.edu

cerebral arteries; specifically, it was posited that anti-CGRPr-mAb might reach appreciable concentrations in brain areas where the BBB is compromised. To our knowledge, patients with known CPA treated with an anti-CGRPr-mAb have not been previously reported. We describe the significant sequelae after a 22-year-old male with known CPA and migraines was treated with erenumab.

## Case

A 22-year-old male with known right parietal, occipital and temporal CPA (Figure 1(a) and (b)) and chronic right-sided migraines refractory to treatment presented 2 d after his first subcutaneous injection of erenumab, 70 mg, in status epilepticus. His past medical history was significant for a single seizure in 2015, but he was not prescribed any antiepileptic medication at the time of the current presentation. On the day of presentation, he was found at home having a generalized tonic-clonic seizure of unknown duration, having last been seen well 5 h prior. At an outside hospital, he received lorazepam and leviteracetam and was intubated for

airway protection. Computed tomography (CT) of the brain did not reveal any acute hemorrhage. Upon transfer to our institution he was febrile to 105°F and was placed on electroencephalogram (EEG) monitoring, which was significant for periodic lateralizing epileptiform discharges (PLEDS). Magnetic resonance imaging (MRI) of his brain was significant for diffusion restriction in the parenchyma surrounding and between the vessels of his known CPA (Figure 1(c)). Serum laboratory investigation at presentation demonstrated multi-organ dysfunction. His liver was affected, with elevated liver function tests (LFTs) with aspartate aminotransferase test (AST) of 120 unit/L and alanine aminotransferase test (ALT) 37 unit/L. Muscle enzyme creatine kinase was elevated at 3565 unit/L and he had an elevated lactate (2.5 mmol/L). His renal function was affected, with creatinine elevated at 1.89 mg/dL and blood urea nitrogen (BUN) normal at 18 mg/dL. Cardiac enzymes were also elevated, with his troponin at 0.53 ng/mL. He had a thorough toxicology screen including novel psychoactive substances, which was positive for lorazepam, alphahydroxymidazolam, cotinine, 9-carboxy THC, and



**Figure 1.** (a) T2 weighted axial image demonstrating right parietal occipital CPA. (b) MRA demonstrating CPA. (c) Trace diffusion-weighted axial image demonstrating restricted diffusion in the parenchyma between the vessels of the CPA. (d) Trace diffusion-weighted axial image demonstrating restricted diffusion in the left hippocampus. (e) Trace diffusion-weighted axial image demonstrating restricted diffusion in bilateral frontal lobes. (f) Trace diffusion-weighted axial image demonstrating restricted diffusion in bilateral white matter.

leviteracetam. He had received lorazepam, midazolam, and leviteracetam as part of his medical treatment. He had a history of marijuana and cigarette use, which explained the 9-carboxy THC and cotinine respectively in his toxicology screen. He was started on acyclovir and antibiotics at meningitic doses, but due to an international normalized ratio (INR) of 5.78 he did not have a lumbar puncture at time of presentation.

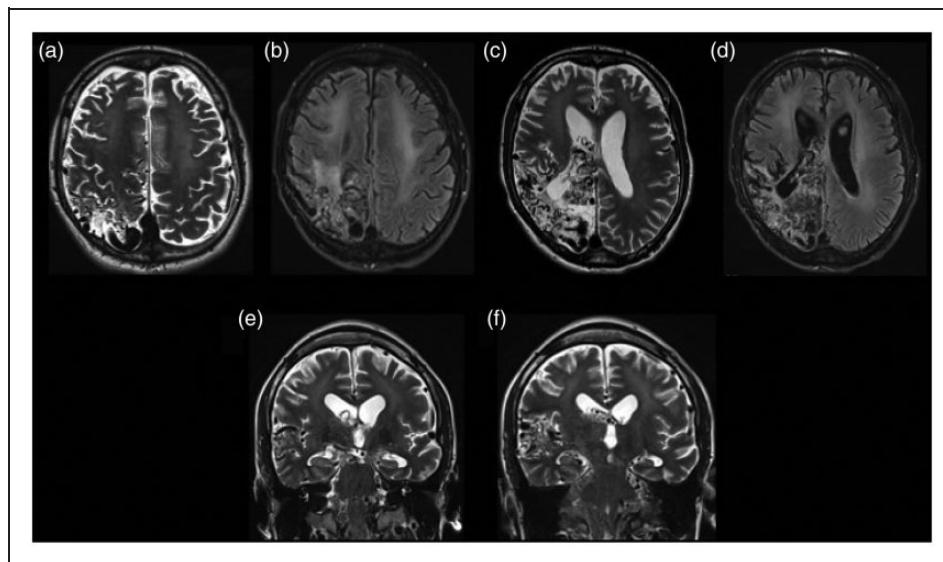
On Day 2, a repeat MRI of the brain was stable. On Day 4, he continued to have PLEDS on EEG, and had a repeat MRI that was significant for new areas of diffusion restriction in the left hippocampus concerning for seizure edema (Figure 1(d)). He was placed in a pentobarbital coma, which was lifted on Day 6. On Day 7, he had repeat MRI significant for new areas of restricted diffusion in the right thalamus, temporal lobe and frontal lobe as well as concern for cerebellar swelling (Figure 1(e)). He had a lumbar puncture on Day 8, which was negative for HSV, with 11/mm<sup>3</sup> WBC, 81.3 mg/dL protein and 75 mg/dL glucose. On Day 10, his MRI showed both cortical and more prominent white matter restricted diffusion in both frontal lobes and the left parietal lobe (Figure 1(f)). He had a second lumbar puncture that resulted in a negative autoimmune encephalitis panel and no oligoclonal bands. As diagnostic evaluations progressively excluded common causes for his clinical decline, multidisciplinary team consultants began to consider aimovig as a potential causative agent. Consequently, plasmapheresis to remove the agent was proposed. With a molecular weight of 150 kilodaltons, this was deemed feasible,

and he began plasmapheresis on Day 11. He had plasmapheresis three times over the course of 5 d, which is standard at our institution for removing toxic substances. He was also extubated on Day 11. Soon after plasmapheresis was completed he was able to state his name and follow simple commands. Over the next few weeks he continued to improve and was eventually discharged to an inpatient rehabilitation facility 2 month after his initial presentation.

Follow up MRI 6 months after presentation was significant for encephalomalacia within the parenchyma between the vessels of the CPA, bilateral hippocampal sclerosis, and global white matter loss (Figure 2). Now 1.5 years later, he has refractory epilepsy despite treatment with multiple anti-epileptic medications. On neurologic exam, he has a mild left-sided weakness. He underwent neuropsychological evaluation showing significant deficits in visual-spatial skills, working memory and processing speed. Of note, he had a previous neuropsychological evaluation 7 years prior to his presentation that was significant for deficits in visual-spatial skills consistent with known right posterior CPA.

## Discussion

The short but substantial clinical experience with the anti-CGRP-mAbs suggests that they are very safe to use in chronic migraine patients whose BBB is uncompromised. The current case report raises the possibility that this class of drugs may not be safe and should not be used in patients with compromised BBB, as it may



**Figure 2.** (a) T2 weighted axial image demonstrating encephalomalacia in the parenchyma around the vessels of the CPA. (b) FLAIR axial image demonstrating encephalomalacia in the parenchyma around CPA as well as white matter hyperintensity bilaterally. (c) T2 weighted axial image demonstrating encephalomalacia in the parenchyma around the vessels of the CPA. (d) FLAIR axial image demonstrating encephalomalacia in the parenchyma around CPA as well as white matter hyperintensity bilaterally. (e) T2 weighted imaging demonstrating bilateral temporal mesial sclerosis. (f) T2 weighted imaging demonstrating bilateral temporal mesial sclerosis.

lead to progressive and severe brain injury. Our suspicion that erenumab's action inside the BBB caused the brain injury is supported by a) the MRI findings, b) the neurological presentation, c) the effects of the plasmapheresis, d) our judgment that neither his imaging nor the time frame of evolution are consistent with other processes we have considered, including hypoxic ischemic injury, herpes simplex virus or other infectious etiologies, other toxic agents that could explain his presentation, or autoimmune encephalitis. Seizure edema is also unlikely due to the extended time in which we saw diffusion restriction on MRI. Also, while he was in a pentobarbital coma, the diffusion restriction continued to occur in new territories, which is more suggestive of an alternative source or cause for the continued restricted diffusion. Seizure edema should also resolve once the seizures are managed.

Recent studies showing insignificant or no BBB penetration of anti-CGRP-mAbs in animals in which the BBB is intact, versus transient binding in brain parenchyma of animals with compromised BBB, and prolonged binding in brain parenchyma surrounding a stroke site, further support our conclusion (4,5). Difficulty with speculating on how a compromised BBB may explain the outcome seen in this patient after treatment with erenumab stems from the fact that CGRP knockout mice lacking  $\alpha$ -CGRP, which is the most dominant CGRP in the cortex, behave normally and show no signs of impairment in cognitive, motor or any other high-order cortical functions (6–12). Nevertheless, evidence for CGRP's ability to facilitate and inhibit synaptic transmission in different cortical and subcortical regions raises the possibility that accidental introduction of an anti-CGRP-mAb into a small and well-localized area of the cortex can interfere with proper regulation of (cortical) neuronal firing through two possible mechanisms: The first may be the disruption of facilitation of synaptic transmission that regulates proper firing of inhibitory cortical neurons and the second may be disruption of  $\alpha$ -CGRP's ability to reduce firing (reduce evoked EPSPs) in neurons that facilitate cortical excitability (13–16). Induction of long-term potentiation, and increased excitatory postsynaptic current and amplitude (but

not frequency) by CGRP, support the view that it enhances excitability of post-synaptic neurons, likely through PKA- and NMDA-dependent mechanisms (13,14). On the other hand, CGRP's ability to reduce glutamate-mediated EPSPs amplitude without altering input resistance or inward current in lateral parabrachial neurons suggest that the inhibitory effect of CGRP is pre- but not post- or poly-synaptic, a concept supported by another study showing that local administration of CGRP in certain areas of the hypothalamus, thalamus, cortex, preoptic area, septum and the premamillary nucleus inhibits spontaneous firing of neurons in the immediate vicinity of the applied CGRP (16,17). Theoretically, either one of these scenarios can lead to abnormal synchronized and unsynchronized firing within the affected cortical area. Another possible explanation for the outcome seen in this patient after treatment with erenumab is that the accidental presence of this anti-CGRP-mAb outside, rather than inside, the anatomically abnormal cerebral blood vessels within the AVM area allowed erenumab to bind to the ab-luminal CGRP receptors and prevented dilatation/facilitated constriction, which eventually led to the neuronal outcome we report. In considering this possibility, one must take into consideration two points. The first is that only ab-luminal (but not luminal) CGRP can prevent dilatation of cerebral blood vessels, and the second is the possibility that the concentration of ab-luminal CGRP receptors along the walls of the chronically abnormally-formed blood vessels within the AVM is putatively elevated as an adjustment to allow the blood vessel to remain open enough to supply oxygen within its territory (18). In perspective, though, we must reiterate the need to evaluate these possibility with great caution as they are purely speculative and lack supporting data. In conclusion, we recommend using caution when considering the use of CGRP-targeting therapy in patients with potentially compromised BBB, including patients with epilepsy and/or traumatic brain injury as well as patients with CPA or AVM.

Consent to submit this case report was given by parents of the patient, who are his legal guardians.

### Clinical implications

- Case report of 22-year-old male with cerebral proliferative angiopathy (CPA) and chronic migraines had possible adverse reaction to erenumab.
- CPA is thought to have a disrupted blood brain barrier (BBB) and erenumab, an anti-CGRP receptor monoclonal antibody, can cross a disrupted BBB.
- Caution is advised for treating patients with cerebral vascular malformations with an anti-CGRP receptor monoclonal antibody.

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## References

1. Lasjaunias PL, Landrieu P, Rodesch G, et al. Cerebral proliferative angiopathy: Clinical and angiographic description of an entity different from cerebral AVMs. *Stroke* 2008; 39: 878–885.
2. Fehnel K, Penn D, Duggins-Warf M, et al. Dysregulated EphrinB2-EphB4 ratio in pediatric cerebral arteriovenous malformations is associated with endothelial cell dysfunction *in vitro* and functions as a novel non-invasive biomarker in patients. *Expim Mol Med* 2020; 52: 658–671.
3. Winkler EA, Birk H, Burkhardt JK, et al. Reductions in brain pericytes are associated with arteriovenous malformation vascular instability. *J Neurosurg* 2018; 129: 1464–1474.
4. Johnson KW, Morin SM, Wroblewski VJ, et al. Peripheral and central nervous system distribution of the CGRP neutralizing antibody [(125)I] galcanezumab in male rats. *Cephalalgia* 2019; 39: 1241–1248.
5. Nosedá R, Schain AJ, Melo-Carrillo A, et al. Fluorescently-labeled fremanezumab is distributed to sensory and autonomic ganglia and the dura but not to the brain of rats with uncompromised blood brain barrier. *Cephalalgia* 2020; 40: 229–240.
6. Amara SG, Arriza JL, Leff SE, et al. Expression in brain of a messenger RNA encoding a novel neuropeptide homologous to calcitonin gene-related peptide. *Science* 1985; 229: 1094–1097.
7. Lu JT, Son YJ, Lee J, et al. Mice lacking alpha-calcitonin gene-related peptide exhibit normal cardiovascular regulation and neuromuscular development. *Mol Cell Neurosci* 1999; 14: 99–120.
8. Ogoshi M. Calcitonin gene-related peptide. In: Takei Y, Ando H and Tsutsui K (eds) *Handbook of hormones: Comparative endocrinology for basic and clinical research*. London: Elsevier, 2015, pp.235–237.
9. Oh-hashí Y, Shindo T, Kurihara Y, et al. Elevated sympathetic nervous activity in mice deficient in alphaCGRP. *Circ Res* 2001; 89: 983–990.
10. Salmon AM, Damaj MI, Marubio LM, et al. Altered neuroadaptation in opiate dependence and neurogenic inflammatory nociception in alpha CGRP-deficient mice. *Nat Neurosci* 2001; 4: 357–358.
11. Wattiez AS, Wang M and Russo AF. CGRP in animal models of migraine. *Handb Experim Pharmacol* 2019; 255: 85–107.
12. Zhang L, Hoff AO, Wimalawansa SJ, et al. Arthritic calcitonin/alpha calcitonin gene-related peptide knockout mice have reduced nociceptive hypersensitivity. *Pain* 2001; 89: 265–273.
13. Han JS, Adwanikar H, Li Z, et al. Facilitation of synaptic transmission and pain responses by CGRP in the amygdala of normal rats. *Mol Pain* 2010; 6: 10.
14. Han JS, Li W and Neugebauer V. Critical role of calcitonin gene-related peptide 1 receptors in the amygdala in synaptic plasticity and pain behavior. *J Neurosci* 2005; 25: 10717–10728.
15. Saleh TM and Cechetto DF. Peptides in the parabrachial nucleus modulate visceral input to the thalamus. *Am J Physiology* 1993; 264: R668–R675.
16. Saleh TM, Kombian SB, Zidichouski JA, et al. Peptidergic modulation of synaptic transmission in the parabrachial nucleus in vitro: Importance of degradative enzymes in regulating synaptic efficacy. *J Neurosci* 1996; 16: 6046–6055.
17. Twery MJ and Moss RL. Calcitonin and calcitonin gene-related peptide alter the excitability of neurons in rat forebrain. *Peptides* 1985; 6: 373–378.
18. Desai M, Slusarczyk AL, Chapin A, et al. Molecular imaging with engineered physiology. *Nat Commun* 2016; 7: 13607.