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Intraparenchymal cerebral hemorrhage in a patient undergoing treatment with galcanezumab: the importance of adequate blood pressure control

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ABSTRACT
Background: Calcitonin gene-related peptide (CGRP) is a neuropeptide involved in pain transmission and modulation, and implicated in migraine pathophysiology. Due to the vasodilatory action of CGRP, anti-CGRP drugs, while ameliorating migraine, may increase hypertension, a major risk factor for cerebrovascular diseases. Although most studies support the safety of this class of drugs, the use of anti-CGRP drugs in some individuals has been associated with elevated blood pressure.
Case Presentation: We report a case of a cerebral hemorrhage in a patient treated with an anti-CGRP monoclonal antibody and a poorly controlled blood pressure.
Discussion: Migraine is associated with increased cerebrovascular risk and hypertension, and anti-CGRP therapies could potentially contribute to acute hypertensive episodes, possibly increasing the risk of complications, including cerebral hemorrhage, in vulnerable individuals.
Conclusions: Limited evidence links anti-CGRP therapies to hypertension. Pending additional data, caution is recommended when prescribing these drugs, especially in patients with cardiovascular risk factors.

Key words: intraparenchymal cerebral hemorrhage, galcanezumab, anti-CGRP monoclonal antibody, blood pressure hypertension.

Introduction

Involved in nociceptive transmission and modulation, the neuropeptide, calcitonin gene-related peptide (CGRP), has been implicated in the pathophysiology of migraine and has emerged as a valuable therapeutic target for both the acute treatment and prophylaxis of migraine. CGRP, released from terminals of primary sensory neurons, also exerts a potent vasodilatory action. (1) Additionally, CGRP may influence heart rate and myocardial contractility. (2) These findings suggest that antagonism of the CGRP pathway, either by blocking the neuropeptide or its receptors, could potentially increase cardiovascular and cerebrovascular risk. (2) However, both clinical trials on CGRP-related vascular function and real-world data have not revealed any significant safety concerns associated with anti-CGRP therapies (3). Notably, to date, no cases of cerebral hemorrhage have been reported in patients undergoing treatment with monoclonal antibodies targeting CGRP. Here, we report a case of cerebral hemorrhage in a migraine patient treated with an anti-CGRP monoclonal antibody.

Case Report

A 55-year-old male presented to the Emergency Department of our hospital on March 14, 2025, with scintillating visual symptoms in the upper portion of the visual field bilaterally, occurring alongside his typical pulsating frontal headache on the left side. High blood pressure was notably high (systolic blood pressure [SBP]/diastolic blood pressure [DBP] 244/160 mmHg). The patient had a history of mild, untreated hypertension, with recent measurements around 145/95 mmHg. He did not smoke or consume alcohol. His body mass index (BMI) was 27.7 kg/m^2, indicating that he was slightly overweight. Regarding his family's history, his father experienced an ischemic stroke. There is no known family history of headaches, and no other cardiovascular risk factors, such as diabetes or dyslipidemia, were present. The patient was not taking any other chronic medications apart from galcanezumab. Regarding arterial hypertension, he had previously started treatment with amlodipine and olmesartan, which were discontinued due to the onset of side effects. He also reported poor tolerance to angiotensin-converting enzyme (ACE) inhibitors. Therefore, he had initiated relaxation techniques, with moderate benefit, considering that the elevated hypertension values were mainly related to states of strong emotional stress. During treatment with galcanezumab, according to the Italian Medicines Agency (AIFA) monitoring forms, the recorded blood pressure was in good control (SBP/DBP 130/80 mmHg).

Headache history. The patient has experienced headaches since childhood. The pain, initially frontal-periorbital, has become lateralized to the right in recent years. Each episode lasts about 12 hours, is severe in intensity, and is associated with nausea, photophobia, phonophobia, and osmophobia.

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During attacks, the patient reports mild conjunctival hyperemia and tearing.

Previous acute treatments have been paracetamol/codeine with partial benefit, ketorolac that was effective, oxycodone/naloxone, which were not tolerated, and some triptans that were characterized by poor efficacy. The patient was treated with preventatives, including propranolol (40mg 2/day), which was not tolerated due to abdominal tension, ankle swelling, asthenia, and erectile dysfunction, and amitriptyline, flunarizine, and dihydroergotamine, which were ineffective. Topiramate therapy was not initiated due to a positive history of kidney stones. In December 2021, he started the treatment with galcanezumab, with good efficacy for the first 25 days, followed by a relapse in the last 5 days. Since the beginning of the therapy, the episodes had decreased from daily occurrences to about 8 times per month, with a moderate intensity (Numeric Rating Scale [NRS] 7/10). During the drug suspension period (March 2024), headache episodes increased to 23 episodes per month. Due to partial efficacy and high symptomatic drug intake (>10 doses/month), discontinuation of galcanezumab and initiation of intravenous eptinezumab were proposed in April 2024, but the patient declined for personal reasons. He therefore continued therapy with galcanezumab, reporting an average of 15 episodes per month of mild intensity.

In the Emergency Unit, the hypertensive peak was initially treated with diazepam 5 mg/mL (20 drops) and amlodipine 5 mg, which resulted in moderate improvement, reducing blood pressure to SBP/DBP 180/110 mmHg. Given the new onset of visual symptoms, an urgent ophthalmologic consultation was requested. Findings included: visual acuity: OD 10/10; OS 10/10; intraocular pressure: OD 15 mmHg; OS 13 mmHg; presence of direct and consensual pupillary reflexes; normal extraocular motility; and normal anterior and posterior segment examination. On neurological examination, no other focal neurological deficits were observed aside from those previously described. An urgent head CT scan was performed (**Figure 1**), which revealed a hyperintense lesion in the deep right temporal region, likely representing a hemorrhagic lesion.

The patient was admitted to the Stroke Unit. During hospitalization, blood pressure progressively improved with intravenous labetalol therapy (5 mg/mL, 35 mg in total in the first hour), reaching a value of SBP/DBP 158/102 mmHg. In the subsequent days, blood pressure monitoring was maintained using oral therapy as outlined in **Figure 2**.

Blood pressure progressively decreased (**Figure 3**), reaching a value of SBP/DBP 135/95 mmHg on the sixth day of hospitalization. The visual disturbances had been resolved by the third day.

Subsequently (20 March 2025), an MRI of the brain with contrast was performed for further diagnostic evaluation (**Figure 4**). The patient was discharged from the Stroke Unit with the diagnosis of right deep temporal cerebral hemorrhage and microlesions with diffusion restriction on MRI. Given the current clinical picture, it was deemed appropriate to discontinue migraine prophylaxis with galcanezumab and initiate combination therapy for blood pressure control. Due to the finding of

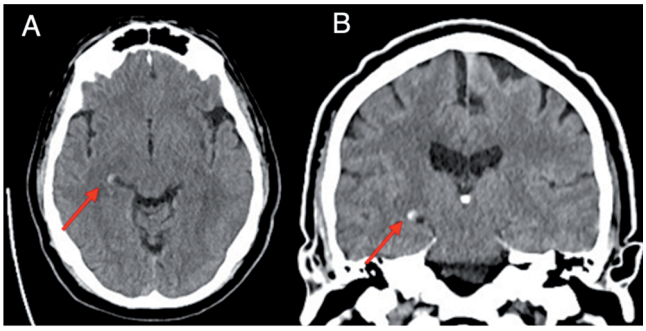

Figure 1. Head CT scan: a small hyperdensity (approximately 7 mm) was observed in the deep right temporal region, likely of hemorrhagic nature, though its precise location (intraparenchymal vs. choroidal fissure) was uncertain. The lesion can be observed both in the axial plane (A) and the coronal plane (B). Evident signs of leukoencephalopathy were noted in the bilateral frontoparietal region, possibly due to chronic vascular pathology. No midline shift was observed.

	DAY 1		DAY 2		DAY 3		DAY 4		DAY 5			DAY 6			DAY 7		
	8.00 a.m	8.00 p.m	8.00 a.m	8.00 p.m	8.00 a.m	8.00 p.m	8.00 a.m	8.00 p.m	8.00 a.m	4.00 p.m	8.00 p.m	8.00 a.m	4.00 p.m	8.00 p.m	8.00 a.m	4.00 p.m	8.00 p.m
Labetalol IV (mg)		35	200 mg CIV		200 mg CIV												
Ramipril (mg)			5		10		10		10			10			10		
Amlodipine (mg)				10		10		10			10			10			10
Doxazosin (mg)			2	2	2	2	2	2	2								
Hydrochlorothiazide (mg)					25		25		25			25			25		
Spironolactone (mg)										25			25			25	
SBP mmHg		158	160	160	150	160	120	155	153		135	135		144	145		
DBP mmHg		102	100	100	90	100	90	100	98		95	95		104	100		

Figure 2. Oral therapy: We started ramipril 5-10 mg in the morning, Amlodipine 10 mg in the evening, doxazosin 2 mg in the morning and evening, hydrochlorothiazide 25 mg in the morning, and spironolactone 25 mg at 4:00 PM in place of doxazosin (even considering a slight hypokalemia found in the blood tests). We can notice a slow and gradual decrease in SBP and DBP.

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microlesions with diffusion restrictions, a follow-up brain MRI was scheduled, which did not reveal any possible vascular malformations but only showed the outcomes of the previous hemorrhage and microhemorrhages in both supra- and infratentorial regions. An angiographic study was scheduled to rule out other possible causes of bleeding. During the cardiology follow-up visit, performed one month after the acute cerebrovascular event, elevated blood pressure was still noted (SBP/DBP 170/100 mmHg). Therefore, the antihypertensive therapy was adjusted by adding hydrochlorothiazide 25 mg, one tablet daily, and doxazosin 2 mg as needed. To rule out causes of secondary hypertension, a contrast-enhanced CT scan of the upper abdomen was scheduled. It was not possible at that time to perform laboratory tests (such as aldosterone, plasma renin activity, and aldosterone/renin ratio) due to the inability to discontinue interfering antihypertensive medications.

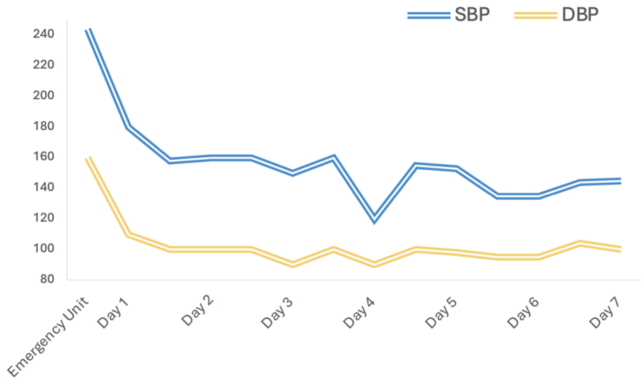

Figure 3. Trend of blood pressure during hospitalization (SBP, systolic blood pressure; DBP, diastolic blood pressure).

Discussion

CGRP, which is involved in the pathophysiological mechanism of migraine, has proven to be an important target in the treatment of this disease. In recent years, several monoclonal antibodies targeting CGRP and its receptor and small molecule receptor antagonists have been developed, demonstrating excellent efficacy in reducing the disease burden in migraine patients. Despite the overall good safety profile of the anti-CGRP drugs, concerns have arisen regarding the possible emergence of rare but severe side effects.

Since CGRP has a vasodilatory function, the anti-CGRP drugs might theoretically increase blood pressure. However, monoclonal antibodies directed against CGRP, including galcanezumab, have been well tolerated in adult patients during clinical trials. (4) The main reported side effects were injection site reactions (erythema, itching). Still, no significant differences were observed between patients treated with galcanezumab and those receiving a placebo regarding vital parameters or electrocardiogram alterations. (5) Although several studies have shown no increased risk of hypertension or other cardiovascular diseases has been demonstrated, (6,7) there have been reports of individual cases of increased blood pressure in patients treated with erenumab, a monoclonal antibody targeting the CGRP receptor. (7,8)

CGRP released from terminals of dorsal root and trigeminal ganglion neurons elicits vasodilatory effects in arterioles and pain. However, CGRP does not appear to elicit acute nociceptive responses in rodents (9) or acute pain in humans, (10) suggesting the absence of a CGRP receptor in nociceptors. The analgesic response to CGRP is confined to the development of mechanical hypersensitivity, an effect that is mediated by the CGRP receptor in Schwann cells. (11) Due to its short half-life in plasma, vasodilatory response to CGRP is a localized phenomenon that is not associated with a significant regulation of systemic blood pressure. (2,12,13)

CGRP receptors have been documented in vascular smooth muscle cells (14) that can be stimulated by the neuropeptide released from nerve terminals in the arterial adventi-

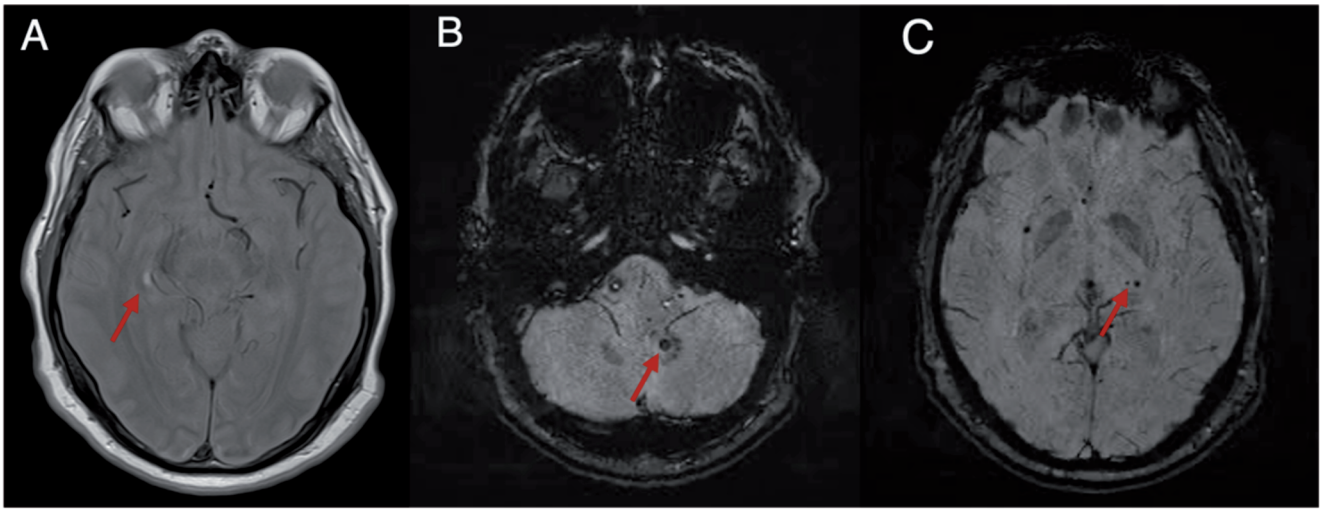

Figure 4. In the deep right temporal region, medially to the temporal horn of the right lateral ventricle and laterally to the right ambient cistern, an area of T2/FLAIR (A) and T1 hyperintensity with diffusion restriction and signal dropout on susceptibility-weighted imaging (SWI) was noted, consistent with a late subacute hemorrhagic lesion. Another small focal area of hyperintensity was observed in the right temporal region, with diffusion restriction; a similar but less pronounced alteration was noted in the ipsilateral putamen. SWI sequences revealed multiple focal signal dropouts, located in the left dentate nucleus (B), left temporal region, right putamen, and two in the left thalamus (C), likely hemosiderin deposits.

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tia. (15) CGRP, released from nerve terminals, binds to its receptor on vascular smooth muscle cells, leading to the activation of protein kinase A, which phosphorylates multiple downstream targets, including adenosine triphosphate (ATP)-sensitive potassium channels (KATP), (16) resulting in cellular hyperpolarization. Additionally, the phosphorylation of cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB) reduces cytosolic Ca^{2+} concentration, ultimately causing smooth muscle cell relaxation and subsequent vasodilation (17).

The fraction of CGRP inhibited by monoclonal antibodies is the circulating fraction, which has been extensively studied but with conflicting results. A study found differences in circulating CGRP immunoreactivity in hypertensive patients compared to normotensive controls. (18) Other studies observed no differences in vascular CGRP concentration in hypertensive patients compared to controls but identified a relationship between circulating plasma CGRP levels and blood pressure (19) or reported lower CGRP levels in hypertensive patients while maintaining their circadian rhythm. (20) Conversely, higher CGRP levels have been measured in patients with acute hypertension compared to healthy controls. (21)

These findings have led to the hypothesis that CGRP may act as an acute rather than a tonic regulator of blood pressure, as suggested by the increase in CGRP during acute physical exercise as a compensatory mechanism against sympathetic system-mediated vasoconstriction (22) and in hypertensive rats following angiotensin-2 administration. (23) Although these data suggest a potential compensatory role of CGRP in acute hypertension conditions, evidence supporting its involvement in essential hypertension is limited. Further research is needed to clarify the hypertensive risk associated with anti-CGRP treatment, particularly in subgroups of patients who may be more susceptible due to the presence of predisposing conditions. In the present case, it cannot be ruled out that other risk factors – such as being overweight, albeit mildly – may have contributed to the onset of the cerebrovascular event. Moreover, controlling blood pressure through just relaxation techniques may not have ensured consistently stable levels. It remains necessary to exclude secondary causes of hypertension as well as other potential causes of cerebral hemorrhage.

Conclusions

Although most studies do not definitively demonstrate a correlation between anti-CGRP treatments and increased blood pressure, it is advisable to carefully evaluate the cardiovascular and cerebrovascular risk profiles when patients are treated with anti-CGRP drugs, including monoclonal antibodies. This is particularly important given that migraine itself is a cerebrovascular risk factor (24) and is associated with hypertension. Therefore, while the chronic use of anti-CGRP drugs may not be directly linked to poor blood pressure control, it cannot be excluded that, in this patient, the treatment with the anti-CGRP monoclonal antibody has contributed to the inadequate management of an acute hypertensive episode, thereby increasing the risk factor of cerebral hemorrhage.

References

1. Monteith D, Collins EC, Vandermeulen C, Van Hecken A, Raddad E, Scherer JC, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the CGRP Binding Monoclonal Antibody LY2951742 (Galcanezumab) in Healthy Volunteers. Front Pharmacol 2017;8:740.
2. MaassenVanDenBrink A, Meijer J, Villalón CM, Ferrari MD. Wiping Out CGRP: Potential Cardiovascular Risks. Trends Pharmacol Sci 2016;37:779–88.
3. Messina R, Huessler EM, Puledda F, Haghdoost F, Lebedeva ER, Diener HC. Safety and tolerability of monoclonal antibodies targeting the CGRP pathway and gepants in migraine prevention: A systematic review and network meta-analysis. Cephalalgia Int J Headache 2023;43: 3331024231152169.
4. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia Int J Headache 2018;38:1442–54.
5. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e2211–21.
6. Mascarella D, Andrini G, Baraldi C, Altamura C, Favoni V, Lo Castro F, et al. Blood pressure monitoring in elderly migraineurs starting an anti-CGRP monoclonal antibody: a real-world prospective study. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 2024;45:5365–73.
7. Dodick DW, Tepper SJ, Ailani J, Pannacciulli N, Navetta MS, Loop B, et al. Risk of hypertension in erenumab-treated patients with migraine: Analyses of clinical trial and postmarketing data. Headache 2021;61:1411–20.
8. Kudrow D, Pascual J, Winner PK, Dodick DW, Tepper SJ, Reuter U, et al. Vascular safety of erenumab for migraine prevention. Neurology 2020;94:e497–510.
9. De Logu F, Landini L, Janal MN, Li Puma S, De Cesaris F, Geppetti P, et al. Migraine-provoking substances evoke periorbital allodynia in mice. J Headache Pain 2019;20:18.
10. Weidner C, Klede M, Rukwied R, Lischetzki G, Neisius U, Skov PS, et al. Acute effects of substance P and calcitonin gene-related peptide in human skin—a microdialysis study. J Invest Dermatol 2000;115:1015–20.
11. De Logu F, Nassini R, Hegron A, Landini L, Jensen DD, Latorre R, et al. Schwann cell endosome CGRP signals elicit periorbital mechanical allodynia in mice. Nat Commun 2022;13:646.
12. Smillie SJ, King R, Kodji X, Outzen E, Pozsgai G, Fernandes E, et al. An ongoing role of α-calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress. Hypertens Dallas Tex 1979 2014;63:1056–62.
13. McCulloch J, Uddman R, Kingman TA, Edvinsson L. Calcitonin gene-related peptide: functional role in cerebrovascular regulation. Proc Natl Acad Sci USA 1986;83: 5731–5.
14. Jansen-Olesen I, Jørgensen L, Engel U, Edvinsson L. In-depth characterization of CGRP receptors in human intracranial arteries. Eur J Pharmacol 2003;481:207–16.
15. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J Pain 2013;14:1289–303.
16. Wellman GC, Quayle JM, Standen NB. ATP-sensitive K+ channel activation by calcitonin gene-related peptide and protein kinase A in pig coronary arterial smooth muscle. J Physiol 1998;507:117–29.
17. Brain SD, Grant AD. Vascular actions of calcitonin gene-related peptide and adrenomedullin. Physiol Rev 2004;84: 903–34.
18. Edvinsson L, Ekman R, Thulin T. Circulating perivascular dilatory neuropeptides in hypertension. J Hypertens 1989;7:S194.
19. Schifter S, Krusell LR, Sehested J. Normal serum levels of

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calcitonin gene-related peptide (CGRP) in mild to moderate essential hypertension. Am J Hypertens 1991;4:565–9.
20. Portaluppi F, Trasforini G, Margutti A, Vergnani L, Ambrosio MR, Rossi R, et al. Circadian rhythm of calcitonin gene-related peptide in uncomplicated essential hypertension. J Hypertens 1992;10:1227.
21. Edvinsson L, Erlinge D, Ekman R, Thulin T. Sensory nerve terminal activity in severe hypertension as reflected by circulating calcitonin gene-related peptide (CGRP) and substance P. Blood Press 1992;1:223–9.
22. Lind H, Brudin L, Lindholm L, Edvinsson L. Different levels of sensory neuropeptides (calcitonin gene-related peptide and substance P) during and after exercise in man. Clin Physiol Oxf Engl 1996;16:73–82.
23. Li J, Wang DH. Development of angiotensin II-induced hypertension: role of CGRP and its receptor. J Hypertens 2005;23:113.
24. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 2010;123:612–24.

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Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

Consent for publication: written informed consent was obtained from the patient for publication of this case report and accompanying images.
Availability of data and materials: all data underlying the findings are fully available.

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