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# "Adrenaline junkie": a case report of repeated use of epinephrine

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## Background

Epinephrine, the first-line treatment of anaphylaxis, is safe and effective when administered correctly [1–3]. Epinephrine acts as a non-selective agonist on α- and β-adrenergic receptors, causing vasoconstriction, increased peripheral vascular resistance, reduced mucosal oedema, increased heart rate and cardiac contractility, bronchodilation, and decreased mast cells' and basophils' degranulation [2]. Adverse events include cardiovascular, respiratory, neurologic, psychiatric, gastrointestinal, dermatologic and renal manifestations [3–5]. There is limited evidence on the safety of repeated administration of epinephrine, although around 10% of anaphylaxis reactions are treated with multiple doses of epinephrine [6–9]. Bronchodilator effect of epinephrine in severe bronchospasm has been widely investigated in the past, but no data are available on the safety of its repetitive use for an extended period of time in this setting [10–12].

## Case presentation

A 40-year-old woman was seen on a follow-up visit in mid-February 2020 for poorly controlled severe allergic asthma. While performing pulmonary function tests, she complained worsening dyspnoea, wheezing and nonproductive cough. Symptoms improved after the administration of inhaled short-acting β2-agonist (SABA) and intravenous (iv) methylprednisolone (mPDN), but in the following hours two additional exacerbations occurred with $SpO_2$ dropping to 80%. SABA and iv steroids again provided full relief of symptoms. She was admitted to our hospital for further investigations.

She had a history of several asthma exacerbations requiring hospitalization between 2009 and 2012, with last hospital admission in mid-February 2019, oral allergy syndrome with kiwi fruit, and perennial allergic rhinoconjunctivitis with sensitization to grasses, wall pellitory, cypress, *Alternaria*, house dust mite and cat dander. She had never smoked tobacco, did not drink alcohol, neither used recreational drugs. She worked as a bank employee. Her mother had asthma.

L. Salvati and C. Allegrini contributed equally to the work.

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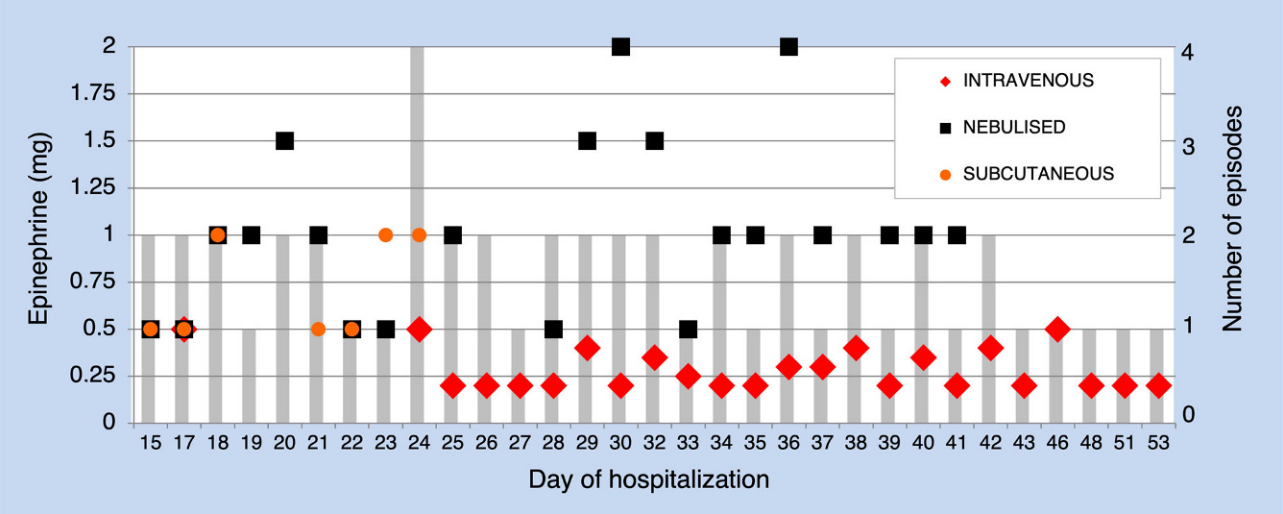


**Fig. 1** Epinephrine administration during the hospital admission. From the 15th to the 53rd day of hospitalization the patient presented 50 episodes of bronchospasm and received a total of 6.85 mg epinephrine intravenously (*red diamonds*), 5 mg subcutaneously (*orange circles*), and 21.5 mg nebulized as inhalation aerosol (*black squares*). *Grey columns* indicate the number of episodes per day

Her body mass index was 27 kg/m$^2$. Her medications included beclomethasone/formoterol 100/6 µg 2 inhalations tid, oral anti-histamine qd and omalizumab 300 mg every month since 2014.

When admitted, she was afebrile and hemodynamically stable. Lung auscultation was notable for diffuse expiratory wheezing. She reported no fever, chills, sputum production, chest pain, headache, arthralgia, myalgia, heartburn, nausea, diarrhoea or vomiting. Chest radiograph and high-resolution computed tomographic scan were normal. Besides mild neutrophilic leukocytosis and increased total IgE level, hepatorenal function, inflammatory markers, and other laboratory test results were within normal limits (Supplementary Table 1). During hospital stay, despite maximal therapy (including mPDN 1 mg/kg per day, beclomethasone/formoterol 200/6 µg 2 inhalations tid, inhaled tiotropium bromide 5 µg bid, montelukast 10 mg qd, continuously iv aminophylline, magnesium sulfate 2 g iv qd and oxygen therapy as needed), she suffered almost daily episodes of bronchospasm with hypoxemia. The episodes were usually preceded by diffuse flushing, seldom with itching and urticaria on trunk and extremities, with rapid (10 min) resolution after epinephrine administration. During 54 days of hospitalization, she complained 67 episodes of acute dyspnoea with desaturation, 50 of them treated with epinephrine (Fig. 1). Notably, in many attacks, bronchospasm resulted from direct exposure to strong irritant odours. These could have acted as triggering factors, indeed her pulmonary conditions suddenly improved once they were fully eliminated from the environment. During the 67th and last episode, after a 200 µg iv bolus of epinephrine, the patient started complaining of mild headache following a 2-day history of hypoesthesia of the left side of the body. The neurologic examination was normal. Nonetheless, magnetic resonance angiography (MRA) showed multiple irregularities in the calibre of intracranial vessels (Fig. 2a). Cranial MRI revealed hyperintensities in both cerebral hemispheres (Fig. 2b, c) and transcranial Doppler (TCD) ultrasonography evidenced increased blood flow velocity. Nimodipine was started intravenously and then shifted orally with progressive symptoms improvement and significant blood flow deceleration on TCD.

## Conclusion

This complex clinical presentation had no definite diagnosis. The scenario orientates towards difficult-to-treat asthma, exacerbated by exposure to triggering factors. During the hospital stay, the patient suffered almost daily attacks with relief only after epinephrine administration. Some episodes might indeed mimic idiopathic anaphylaxis, which is a diagnosis of exclusion [13]. Serum tryptase level was not measured after the events; however at baseline it was normal. Considering the self-limiting course of the disease, a clonal mast cell disorder or a carcinoid seemed unlikely. A psychiatric evaluation did not exclude a psychic component that could aggravate her clinical conditions; indeed, she was advised to follow psychotherapeutic treatment. Besides the respiratory manifestations, the dynamic vasospasm of cerebral vessels could have been determined by the repeated and numerous administration of epinephrine. Although the patient did not present the typical thunderclap headache, a diagnosis of reversible vasoconstriction syndrome was made [14, 15]. In fact, calcium channel blockers were resolutive and follow-up imaging studies performed 1 month (Fig. 2d–f) and 3 months

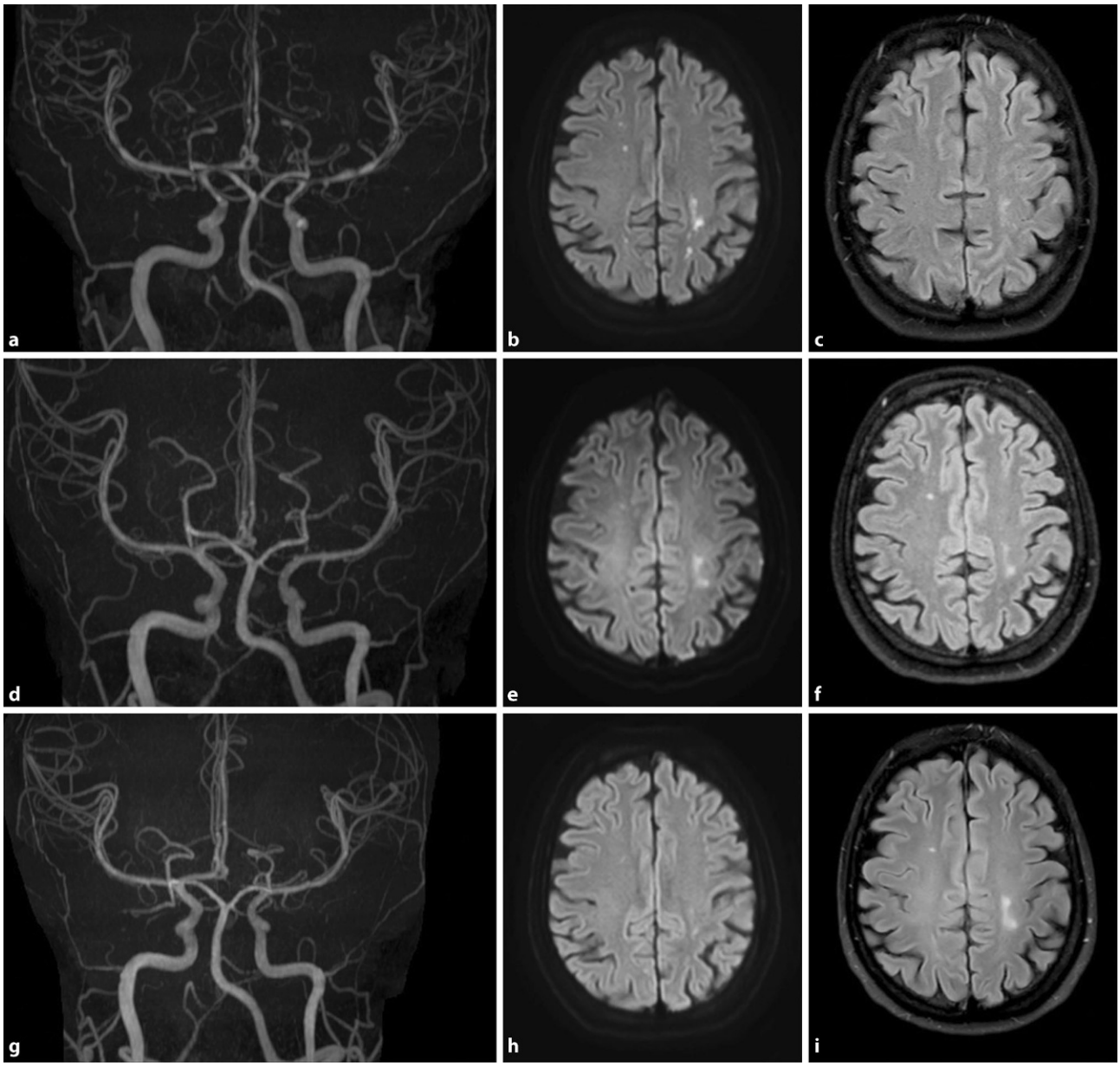


**Fig. 2** Brain imaging. Magnetic resonance angiography (**a**) shows several narrowings involving large to medium-sized arteries followed by abnormally dilated segments of second-order and third-order branches. Watershed infarcts visualized in diffusion-weighted and fluid attenuated inversion recovery (FLAIR) images (**b** and **c**, respectively). Resolution of abnormalities at 1 month (**d–f**) and 3 month (**g–i**) follow-up imaging

later (Fig. 2g–i) showed almost complete resolution of vasoconstrictions.

In this unique case, the use of epinephrine was effective in managing multiple episodes of bronchospasm in a patient under maximal asthma therapy, but eventually a temporary adverse neurologic effect developed. Our clinical observation contributes to alerting on the potentially harmful effects of epinephrine even in young adults, particularly when administered repeatedly.

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**Conflict of interest** L. Salvati, C. Allegrini, B. Piccardi, I. Lombardo, L. Ciambellotti, S. Rizzello, V. Palumbo, F. Lavorini, G. Camiciottoli and P. Parronchi declare that they have no competing interests.

**Ethical standards** All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the participant included in the study.

## References

1. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022;77:357–377. https://doi.org/10.1111/all.15032.
2. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1082–1123. https://doi.org/10.1016/j.jaci.2020.01.017
3. Brown JC, Simons E, Rudders SA. Epinephrine in the management of anaphylaxis. J Allergy Clin Immunol Pract. 2020;8:1186–1195. https://doi.org/10.1016/j.jaip.2019.12.015
4. Cohen MB, Saunders SS, Wise SK, Nassif S, Platt MP. Pitfalls in the use of epinephrine for anaphylaxis: Patient and provider opportunities for improvement. Int Forum Allergy Rhinol. 2017;7:276–286. https://doi.org/10.1002/alr.21884
5. Simons KJ, Simons FE. Epinephrine and its use in anaphylaxis: Current issues. Curr Opin Allergy Clin Immunol. 2010;10:354–361. https://doi.org/10.1097/ACI.0b013e32833bc670
6. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JTC, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. Ann Allergy Asthma Immunol. 2009;103:395–400. https://doi.org/10.1016/S1081-1206(10)60358-4
7. Carlson JN, Cook S, Djarv T, Woodin JA, Singletary E, Zideman DA. Second dose of epinephrine for anaphylaxis in the first aid setting: A scoping review. Cureus. 2020;12:e11401. https://doi.org/10.7759/cureus.11401
8. Liu X, Lee S, Lohse CM, Hardy CT, Campbell RL. Biphasic reactions in emergency department anaphylaxis patients: A prospective cohort study. J Allergy Clin Immunol Pract. 2020;8:1230–1238. https://doi.org/10.1016/j.jaip.2019.10.027
9. Patel N, Chong KW, Yip AYG, Ierodiakonou D, Bartra J, Boyle RJ, et al. Use of multiple epinephrine doses in anaphylaxis: A systematic review and meta-analysis. J Allergy Clin Immunol. 2021;148:1307–1315. https://doi.org/10.1016/j.jaci.2021.03.042
10. Melland B. The treatment of spasmodic asthma by the hypodermic injection of adrenalin. Lancet. 1910;175:1407–1411. https://doi.org/10.1016/S0140-6736(01)14446-6
11. Gotz VP, Brandstetter RD, Mar DD. Bronchodilatory effect of subcutaneous epinephrine in acute asthma. Ann Emerg Med. 1981;10:518–520. https://doi.org/10.1016/s0196-0644(81)80006-6
12. Benca J. Bronchospasm. In: Complications in Anesthesia. 2nd ed. 2007. Chapter 46. pp. 189–192. https://doi.org/10.1016/B978-1-4160-2215-2.50051-X
13. Fenny N, Grammer LC. Idiopathic anaphylaxis. Immunol Allergy Clin North Am. 2015;35:349–362. https://doi.org/10.1016/j.iac.2015.01.004
14. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol. 2012;11:906–917. https://doi.org/10.1016/S1474-4422(12)70135-7
15. Palma JA, Fontes-Villalba A, Irimia P, Garcia-Eulate R, Martinez-Vila E. Reversible cerebral vasoconstriction syndrome induced by adrenaline. Cephalalgia. 2012;32:500–504. https://doi.org/10.1177/0333102412444011