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SCIENTIFIC LETTER

Cerebral venous sinus thrombosis after Russell's viper (*Daboia russelii*) envenomation: A case report

Trombosis venosa cerebral tras mordedura por víbora de Russell (*Daboia russelii*): Descripción de un caso

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Dear Editor,

Cerebral venous sinus thrombosis (CVST) is one of the most recognized causes of stroke among young adults.[1–3] Clinical manifestation at onset is highly variable, including headache, behavioral abnormalities, seizures, altered consciousness, and motor paresis.[1–5]

In India, common venomous snakes include the common krait (*Bungarus caeruleus*), the Indian cobra (*Naja naja*), Russell's viper (*Daboia russelii*), and *Echis carinatus*. Except for the common krait, these snakes typically bite during the day or early evening; their bites are associated with severe and rapidly progressing local edema, pain, regional lymphadenopathy, and visible fang marks.[6]

Snakebite envenomation is a life-threatening and often neglected public health nodus. Local envenomation effects (swelling, pain, soft-tissue necrosis, and regional lymphadenopathy) and systemic toxicity (including vasculotoxicity, coagulopathy, nephrotoxicity, and myotoxicity or paralysis or, less commonly, a combination of paralysis with other systemic effects) can occur depending on the venomous snake species.[1,7–9] A nationwide study estimated that 43% of reported bites in India are likely due to Russell's viper envenoming.[10]

CVST following Russell's viper bite is exceptional.[1,11–13] We herein report another case.

A previously healthy 37-year-old woman from rural West Bengal (India) was brought to the emergency department after sustaining a Russell's viper bite. She presented with gum bleeding, bilaterally symmetrical ptosis, and unremitting bleeding from the wound site. No other neurological or neuro-ophthalmologic deficits were noted. The snake was caught and identified by a snake expert. The initial emergency room 20-min whole blood clotting test (WBCT) was positive,[14] and single breath count (SBC) was 12.[15] Intramuscular tetanus toxoid was administered as the vaccination status was unknown. The patient was immediately administered 10 vials of polyvalent anti-snake venom (F(ab')2; VINS Bioproducts Ltd., Telangana, India), which were diluted in 400 mL of normal saline and infused over 60 minutes. Neostigmine and atropine were given for the neurotoxic

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symptoms. Intravenous fluids with 0.9% normal saline (500 mL every 8 hours) were prescribed, along with intravenous pantoprazole (40 mg/day) to prevent stress ulcers. Oral cefuroxime axetil (1000 mg/day) was also prescribed as prophylaxis, and also, as the bleeding was profuse, she received 8 units of fresh frozen plasma. A complete blood cell count revealed mild anemia (hemoglobin 9.6 g/dL), neutrophilic leukocytosis (total leukocyte count was 18 300, 84% neutrophils), and thrombocytopenia (platelet count was 52 000/μL). Bleeding time (BT), prothrombin time (PT), and activated partial thromboplastin times (APTT) were prolonged. Urinalysis revealed hematuria and proteinuria. Liver and renal function tests, arterial blood gas analysis, fibrinogen, and D-dimer levels were normal. The patient was reassessed after 8 h. Spontaneous bleeding abated, and the ptosis got improved. However, the WBCT was still prolonged, and the SBC was 16. We continued the neostigmine and atropine and gave another 10 vials of polyvalent anti-snake venom. On day 2, the patient was again given another 10 vials of polyvalent anti-snake venom as the WBCT remained prolonged; we started tapering the dose of neostigmine–atropine. Neurological manifestations had significantly improved, and the SBC was greater than 20. Within the next 24 hours, her 20-minute WBCT clotted within 15 minutes, and relevant laboratory investigations on day 4 showed normalization of urinalysis, BT, PT, and APTT. She remained stable, and no new danger signs were reported in the following days.

On day 7, the patient developed acute onset hiccoughs, dizziness, gait unsteadiness, vomiting, slurring of speech, dysphagia, and non-localized thunderclap headache. The patient was otherwise hemodynamically stable with no further bleeding, and the WBCT was corrected. Neurological examination was remarkable for bilateral grade 2 papilledema, bilateral symmetrical lateral gaze restriction and nystagmus, severe cerebellar-type ataxia, ataxic dysarthria, and palatal clonus with brisk deep tendon reflexes. Clinical phenomenology suggested an acute dysfunction of brainstem–cerebellum connections, possibly of vascular etiology. Magnetic resonance imaging of the brain revealed hyperintense lesions on T1-weighted, T2-weighted, and T2-FLAIR imaging, with signal blooming on the gradient echo sequence, involving the right cerebellar hemisphere. These findings were suggestive of thrombosis with hemorrhage involving the right transverse venous sinus and the Torcular Herophili (Fig. 1). Magnetic resonance angiography of the brain failed to show any definite occlusive lesion over posterior circulation. However, magnetic resonance venography revealed thrombosis at the right transverse sinus and partial thrombosis of the superior sagittal sinus (Fig. 2). Relevant history, clinical examinations, and tests for inherited and acquired thrombophilias and secondary hypercoagulable states were negative. She was started on anticoagulation therapy with low-molecular-weight heparin, bridged with warfarin, with close monitoring of aPTT and PT-INR. After another 7 days of therapy, her clinical condition improved remarkably. The headache, blurred vision, nystagmus, hiccups, and vomiting completely subsided. There was partial recovery of ataxia and speech.

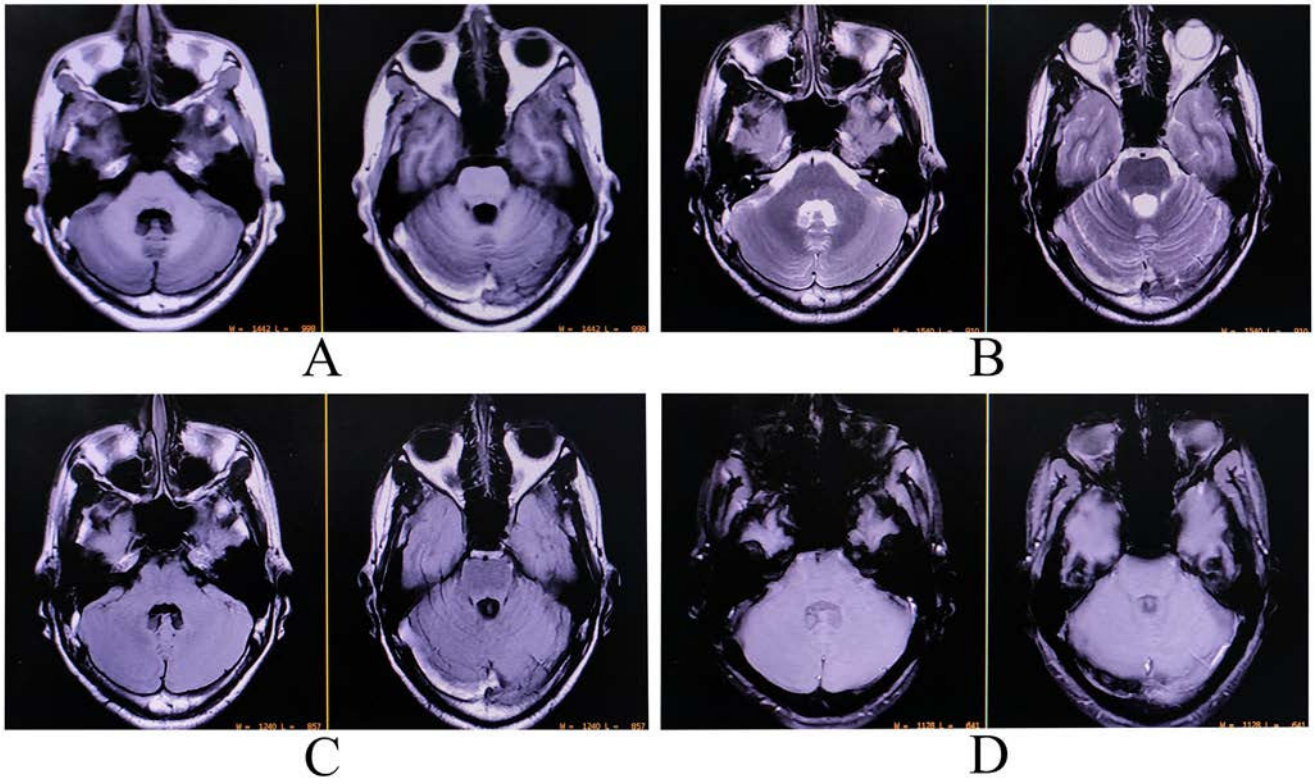

Fig. 1 Magnetic resonance imaging of the brain reveals hyperintense lesions on axial T1-weighted (A), axial T2-weighted (B), and axial T2-FLAIR (C) imaging, with signal blooming on the axial gradient echo sequence (D), involving the right cerebellar hemisphere. These findings are suggestive of thrombosis with hemorrhage involving the right transverse venous sinus and the Torcular Herophili.

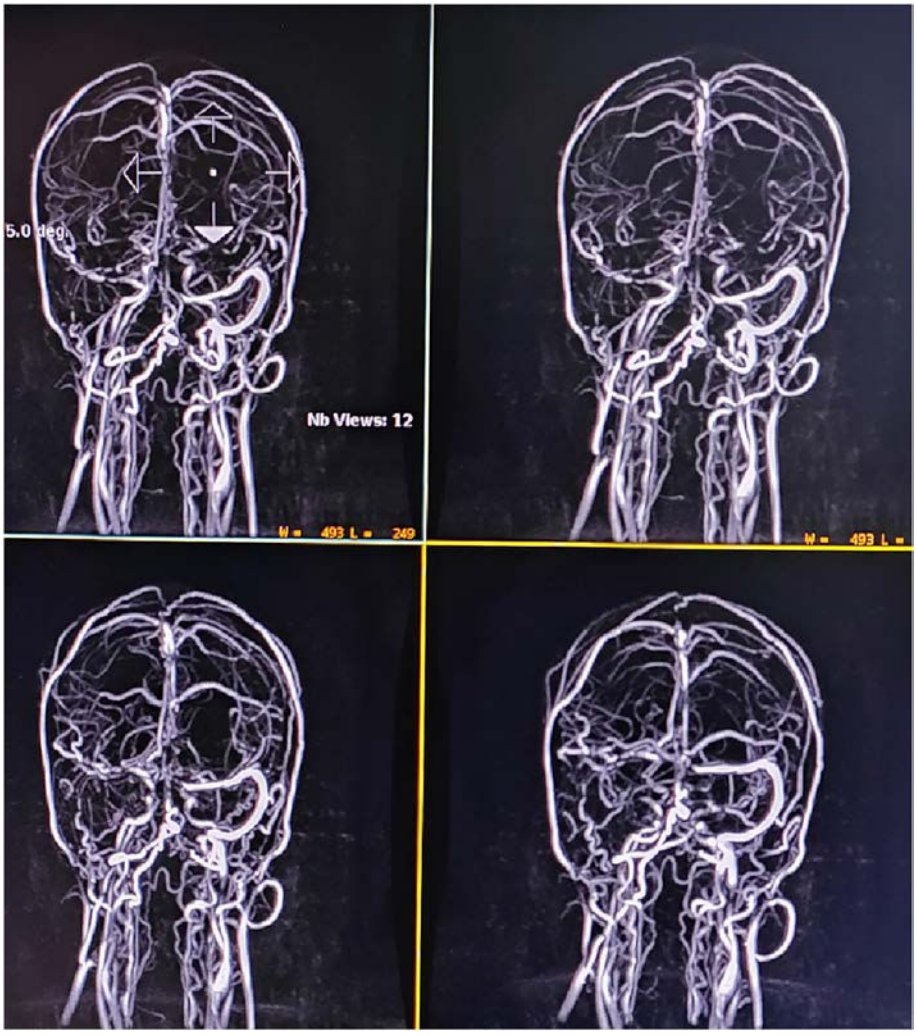

Fig. 2 Magnetic resonance venography reveals filling defects with the development of extensive collateral vessels, suggestive of acute thrombosis in the right transverse sinus and partial thrombosis of the superior sagittal sinus.

She was clinically stable at 3 months of follow-up, and at this time, repeat imaging was considered. However, the patient did not turn up for further follow-ups.

Cerebral complications following snakebites are rare, and cerebral vascular complications can be considered exceptional. Occurrence of vascular thrombosis instead of bleeding and cortical venous thrombosis (posterior superior sagittal and transverse sinus occlusion) are sporadic presentations of *D. russelii* envenoming, exemplifying involvement of remote areas from the envenomation site.[1,11–13] All those cases resulted in an unusual and challenging clinical, neuroradiological, and therapeutic management scenario.[1,11–13] Of note was the case of Ghosh et al.,[1] who developed CVST involving the right transverse sinus extending to the internal jugular vein and Torcular Herophili following disseminated bleeding diathesis, highlighting the pro-coagulant effects of *D. russelii* envenomation similar to this case. Similarly, Yousaf et al.,[13] reported a similar case of CVST following a viper bite in a young adult non-comorbid man from Pakistan, who presented with headache and seizures and responded readily to treatment with anti-coagulant (rivaroxaban), anti-snake venom, and anti-epileptic. Das et al.[11] reported a case of cortical CVST following a viper bite who presented with combined hemotoxic and neurotoxic features and later, during the hospital stay, developed Gerstmann syndrome due to the inciting event.

The exact pathophysiology of CVST following *D. russelii* envenomation remains obscure. Snake venoms can impair hemostasis, triggering coagulation and anticoagulation effects.[16] Many viperid venoms and elapid and non-front-fanged colubrid venoms contain pro-coagulant enzymes.[16] Some medically significant non-front-fanged snakes that cause defibrinating coagulopathy belong to families other than Colubridae.[16] These enzymes are snake venom metalloproteinases (SVMPs) or snake venom serine proteinases that cause ischemia, stroke, CVST, and neurological sequelae by affecting the coagulation cascade and endothelial function.[16] The endothelial injury releases vascular endothelial growth factor and von Willebrand factor, which generate toxic vasculitis.[16] SVMPs act synergistically to degrade the extracellular matrix of blood vessels,

compromising the integrity of the vessel wall and inducing thrombus formation.[1,17] SVMPs may trigger a consumption coagulopathy, leading to defibrinogenation and abnormal bleeding, as detected in blood clotting assays. This contributes to systemic bleeding, often associated with thrombocytopenia, particularly in venoms containing hemorrhagic toxins that disrupt the integrity of blood vessels.[18] Besides, the serine proteases increase vascular permeability and systemic plasma leakage, causing hypovolemia.[18] On the other hand, these enzymes, combined with disintegrins and C-type lectin-like proteins, impair platelet aggregation by blocking platelet receptors or interacting with the von Willebrand factor.[1]

This case highlights the importance of early diagnosis and prompt treatment of this challenging, life-threatening condition. A high index of suspicion is crucial in diagnosing CVST. These cerebrovascular diseases are usually diagnosed on clinical grounds and confirmed by neuroimaging. Clinicians should consider this possibility when managing prothrombotic complications alongside more common manifestations of disseminated coagulopathy, as timely intervention can reduce disability and mortality. The risks of using heparin and dabigatran should also be carefully considered, and caution must be exercised in cases of severe coagulopathy to ensure prompt and accurate identification, diagnosis, and treatment of these patients.

Informed consent

Written informed consent was obtained from the patient participating in the study (consent for research).

Ethical considerations

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Author contributions

All authors contributed significantly to the creation of this manuscript; each fulfilled the criterion established by the ICMJE.

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Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that all have approved the order of authors listed in the manuscript of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication concerning intellectual property, including the timing of publication. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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References

1. Ghosh R, León-Ruiz M, Roy D, Naga D, Sardar SS, Benito-León J. Cerebral venous sinus thrombosis following Russell's viper (*Daboia russelii*) envenomation: a case report and review of the literature. Toxicon. 2022;218:8–12. https://doi.org/10.1016/j.toxicon.2022.08.014.
2. Ghosh R, Roy D, Mandal A, Pal SK, Chandra Swaika B, Naga D, et al. Cerebral venous thrombosis in COVID-19. Diab. Metab. Syndr. 2021;15:1039–45. https://doi.org/10.1016/j.dsx.2021.04.026.
3. Dutta A, Ghosh R, Bhattacharya D, Bhat S, Ray A, Pandit A, Das S, Dubey S. Anti-PF4 antibody negative cerebral venous sinus thrombosis without thrombocytopenia following immunization with COVID-19 vaccine in an elderly non-comorbid Indian male, managed with conventional heparin-warfarin based anticoagulation. Diab. Metab. Syndr. 2021 Jul-Aug;15(4), 102184. https://doi.org/10.1016/j.dsx.2021.06.021 Epub 2021 Jun 24. PMID: 34186376; PMCID: PMC8223002.

4. Biswas U, Ghosh R, Chakraborty A, Mondal SR, Roy D, Bhattacharjee A, Roy D, Benito-León J. Cerebral venous sinus thrombosis following scrub typhus infection: a case report and a review of the literature. Med. Res. Arch. 2022 Oct;10(10). https://doi.org/10.18103/mra.v10i10.3196 Epub 2022 Oct 31. PMID: 36382204; PMCID: PMC9648351.
5. Silvis SM, de Sousa DA, Ferro JM, Coutinho JM. Cerebral venous thrombosis. Nat. Rev. Neurol. 2017;13:555–65. https://doi.org/10.1038/nrneurol.2017.104.
6. Bawaskar HS, Bawaskar PH, Bawaskar PH. Snake bite in India: a neglected disease of poverty. Lancet. 2017;390:1947–8. https://doi.org/10.1016/S0140-6736(17)32175-X.
7. Ghosh R, Maity A, Biswas U, Das S, Benito-León J. Lance-Adams syndrome: an unusual complication of snakebite envenomation. Toxicon. 2022;209:50–5. https://doi.org/10.1016/j.toxicon.2022.02.008.
8. Kumar KS, Narayanan S, Udayabhaskaran V, Thulaseedharan NK. Clinical and epidemiologic profile and predictors of outcome of poisonous snake bites - an analysis of 1,500 cases from a tertiary care center in Malabar, North Kerala, India. Int. J. Gen. Med. 2018;11:209–16. https://doi.org/10.2147/IJGM.S136153.
9. Seneviratne U, Dissanayake S. Neurological manifestations of snake bite in Sri Lanka. J. Postgrad. Med. 2002;48:275–8 discussion 278–9. PMID: 12571382.
10. Suraweera W, Warrell D, Whitaker R, Menon G, Rodrigues R, Fu SH, et al. Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. Elife. 2020;9, e54076. https://doi.org/10.7554/eLife.54076.
11. Das SK, Khaskil S, Mukhopadhyay S, Chakrabarti S. A patient of Russell's viper envenomation presenting with cortical venous thrombosis: an extremely uncommon presentation. J. Postgrad. Med. 2013;59:235–6. https://doi.org/10.4103/0022-3859.118051.
12. Senthilkumaran S, Balamurugan N, Thirumalaikolandusubramanian P. Viper envenomation and cerebral venous thrombosis. J. Postgrad. Med. 2013;59:171–2. https://doi.org/10.4103/0022-3859.118030.
13. Yousaf M, Khan QA, Anthony MR, Badshah A, Abdi P, Farkouh C, Hadi FA, Jan R, Khan A, Iram S. Snakebite induced cerebral venous sinus thrombosis: a case report. Clin. Med. Insights Case Rep. 2023 Apr 3(16) https://doi.org/10.1177/11795476231165750 11795476231165750. PMID: 37033678; PMCID: PMC10074634.
14. Lamb T, Abouyannis M, de Oliveira SS, Shenoy KR, Geevar T, Zachariah A, et al. The 20-minute whole blood clotting test (20WBCT) for snakebite coagulopathy-A systematic review and meta-analysis of diagnostic test accuracy. PLoS Negl. Trop. Dis. 2021;15, e0009657. https://doi.org/10.1371/journal.pntd.0009657 Erratum in: PLoSNegl Trop Dis 2023;17(1): e0011080.
15. Doran CM, Woolley T, Midwinter MJ. Feasibility of using rotational thromboelastometry to assess coagulation status of combat casualties in a deployed setting. J. Trauma. 2010;69: S40–8. https://doi.org/10.1097/TA.0b013e3181e4257b.
16. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat. Rev. Dis. Primers. 2017;3, 17079. https://doi.org/10.1038/nrdp.2017.79 Erratum for: Nat Rev Dis Primers. 2017;**3**:17063.
17. Patil VC, Patil HV, Patil A, Agrawal V. Clinical profile and outcome of envenomous snakebite at tertiary care centre in western Maharashtra. Int. J. Med. Publ. Health. 2011;1:28–38.
18. Prasad UDN, Bandara JMRP, Senanayake HMS. Multiple cerebral and cerebellar infarctions following Russell's viper (*Daboia russelii*) envenomation - a case report. Clin. Med. Rev. Case Rep. 2020;7:313.