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Published Version

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Senthilkumaran, S., Williams, J., Almeida, J. R., Williams, H. F., Patel, K., Thirumalaikolundusubramanian, P. and Vaiyapuri, S. ORCID: <https://orcid.org/0000-0002-6006-6517> (2024) Snakebite-induced reversible cerebral vasoconstriction syndrome: report of three cases. *Toxicon*, 251. 108161. ISSN 1879-3150 doi: 10.1016/j.toxicon.2024.108161 Available at <https://centaur.reading.ac.uk/119379/>

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To link to this article DOI: <http://dx.doi.org/10.1016/j.toxicon.2024.108161>

Publisher: Elsevier

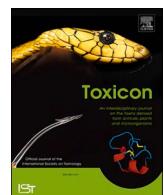
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Case report

Snakebite-induced reversible cerebral vasoconstriction syndrome: Report of three cases



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ARTICLE INFO

Handling editor: Denise Tambourgi

Keywords:

Snakebite envenoming
Reversible cerebral vasoconstriction syndrome
Nimodipine
Russell's viper
Krait
Cobra

ABSTRACT

Envenomings from Russell's viper typically result in local tissue damage and bleeding complications, but the bites from common krait and cobra primarily cause neurotoxic effects. While most symptoms can be treated with appropriate antivenom, additional support is necessary for several snakebite victims to tackle a broad range of unusual complications that they develop following bites. Reversible vasoconstriction syndrome (RCVS), characterised by the constriction of cerebral arteries, is a rare but serious issue, presenting with severe headaches and, in extreme cases, haemorrhagic/ischaemic stroke. This report presents three cases of RCVS in snakebite victims following Russell's viper, krait and cobra bites. The patients were admitted to the hospital with neurological and/or haematological complications, and they were treated with polyvalent antivenom. After two days of antivenom treatment, all the patients developed intense headaches that lasted for several hours and failed to respond to commonly used analgesics. While the physical, laboratory and computed tomography examinations were normal, the RCVS was diagnosed with multimodal magnetic resonance angiography. All patients were successfully treated with oral nimodipine, and during their follow-ups, physical and laboratory examinations were unremarkable, and the magnetic resonance imaging confirmed the reversal of RCVS. To achieve positive outcomes in patients, clinicians must swiftly identify such rare complications and make accurate diagnoses to provide prompt treatments. Overall, this report presents an unusual complication of RCVS in snakebite patients and appropriate diagnosis and treatment approaches to tackle this condition.

1. Introduction

Snakebite envenoming (SBE) is a neglected tropical disease that mostly impacts low-income communities in tropical and subtropical regions (Vaiyapuri et al., 2013; Williams et al., 2019). India has a large growing population with a significant proportion of the populace working within the agricultural industry. The daily activities of these agricultural workers put them in regular conflict with snakes and as a result, India is a hotspot for SBE (Harrison et al., 2009; Salim et al., 2023). Low-income rural communities often have little in terms of infrastructure, with poor connection to more urbanised areas and medical facilities (Patiño et al., 2023). These issues delay patients from

receiving suitable medical provisions, increasing the chances of a bite being fatal or resulting in permanent morbidities and substantial treatment costs (Schöldann et al., 2018; Williams et al., 2017). SBE can result in a plethora of clinical manifestations and complications. In addition, the inter and intraspecific variations in the composition and mechanism of action of venoms are highly variable (Casewell et al., 2020; Gutiérrez et al., 2017; Patiño et al., 2021). Therefore, medical personnel require an in-depth knowledge of the diverse range of clinical manifestations associated with SBE to ensure appropriate treatment is provided and successful patient outcomes are achieved (Michael et al., 2022; Senthilkumaran et al., 2023a,b). Hence, there is a need to report on previously undocumented or uncommon consequences of SBE,

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ensuring that clinicians can rapidly identify such manifestations following SBE and provide appropriate treatments to resolve the issue. This dissemination of knowledge is vital in saving the lives of SBE victims. Hence, we report the successful diagnosis and treatment of three SBE patients who developed reversible cerebral vasoconstriction syndrome (RCVS) following Russell's viper (*Daboia russelii*), common krait (*Bungarus caeruleus*) and cobra (*Naja naja*) envenomings.

D. russelii, *B. caeruleus* and *Naja naja* are three major species of the 'Big Four' medically significant snakes in India, however, their venom compositions and clinical manifestations are very different (Senji Laxme et al., 2019). *D. russelii* belongs to the Viperidae family, whereas *B. caeruleus* and *N. naja* belong to the Elapidae family (Gopal et al., 2023). Viper envenomations are typically haemotoxic and cytotoxic in their manifestations due to a high abundance of proteolytic and phospholipolytic enzymes within their venoms (Almeida et al., 2017). Indeed, metalloproteases, serine proteases and phospholipase A₂s are rich within the venom of *D. russelii* (Yasmin et al., 2024). These enzymes typically target the extracellular matrix, and phospholipid membranes, whilst affecting clotting factors within the blood (Slagboom et al., 2017). This results in the well-known manifestations of localised tissue damage and blood clotting disturbances resulting in bleeding due to consumption coagulopathy (Berling and Isbister, 2015). Some reports of mild to severe neurotoxicity have also been reported following Russell's viper envenomings (Silva et al., 2016a,b). *B. caeruleus* and *N. naja* as with most elapids have venoms that are predominantly consisting of low molecular weight three-finger toxins and PLA₂s (Oh et al., 2017). Elapid venoms are mainly neurotoxic, with their key toxins targeting the neuronal synapses and transmission of acetylcholine (Osipov and Utkin, 2017). Three-finger toxins such as α and β bungarotoxin are abundant in the venom of *B. caeruleus* and they act as post and pre-synaptic neurotoxins resulting in the degradation of the motor nerve terminal (Osipov and Utkin, 2023). This can manifest in the loss of motor function, ptosis, paralysis of the diaphragm and other neurological complications (Postma, 2009).

RCVS is characterised by severe headaches resulting from the constriction of cerebral arteries (Ducros, 2012; Ducros et al., 2007). This is often self-resolving, although complications can include thunderclap headaches, ischaemia, and haemorrhagic or ischaemic strokes (Ducros et al., 2010; Singhal et al., 2002). Symptoms are usually short-lived, lasting one to 3 h, and recurrence typically occurs for one to two weeks, with extreme cases lasting for up to three months (Ducros et al., 2010). RCVS may occur spontaneously, but up to 50% of cases can be associated with vasoactive medications, illicit drugs and the post-partum state (Sattar et al., 2010; Singhal et al., 2011). As far as we are aware of, there have been no reports outlining RCVS as a clinical manifestation following SBE. This report highlights the RCVS observed in SBE victims following bites from different snakes and the diagnosis and treatment approaches used to tackle this issue. We believe that the information presented in this article will aid clinicians in promptly identifying this underreported clinical manifestation and improving patient outcomes in under-resourced medical settings.

2. Case series

2.1. Patient 1

A 22-year-old female college student without any comorbidities was bitten by a snake on her right foot while walking. The offending snake was killed and brought to the hospital and identified as a common krait by a trained herpetologist. The patient developed bilateral ptosis and difficulty breathing within 90 minutes following the bite. After evaluation in a local hospital, she was treated with an intravenous infusion of 10 vials (100 mL) of polyvalent antivenom raised against the Indian 'Big Four' snakes (Bharat Serums and Vaccines Limited, India). Despite improvements, on the second day following the bite, she complained of a spontaneous severe thunderclap headache arising from the back of her

neck with nausea. Her severe headache lasted for 12 hours which was not relieved with different parental non-steroidal anti-inflammatory drugs (NSAID) (using the pain ladder approach). The computed tomography (CT) scan of her brain performed at the local hospital was normal. However, she had a persistent holocephalic headache with a dull-oppressive character and an intensity of 8/10. Hence, she was referred to the emergency department in our hospital (Manian Medical Centre, Erode, India) (around 60 hours after the bite). She denied any confusion, fever, visual symptoms, or seizures. A detailed neurological examination did not show any focal deficit. There was no neck stiffness or other signs of meningeal irritation. Her repeat brain CT scan and laboratory examination (Table 1) were unremarkable. Diffusion-weighted magnetic resonance imaging (MRI) revealed no signs of acute infarction. Susceptibility-weighted imaging, gradient echo, and T2w-fluid attenuated inversion recovery sequences did not show any evidence of subarachnoid haemorrhage, sulcal siderosis, microbleeds or cerebral venous sinus thrombosis. In addition, there was no oedema suggestive of additional posterior reversible encephalopathy syndrome and no signs raising suspicion of intracranial hypertension such as optic nerve sheath oedema or an empty Sella region. Multimodal magnetic resonance angiography (MRA) performed after around 62 hours from the bite revealed multifocal segmental cerebral artery vasoconstriction, predominantly affecting both the middle cerebral arteries and the P1-segment of the posterior cerebral artery (Fig. 1A). Additional laboratory examinations including a lipid profile, prothrombin time and activated partial thromboplastin time as well as the levels of protein C, protein S, anti-thrombin III, anti-phospholipid antibodies, complement, anti-neutrophil cytoplasm antibodies, anti-nuclear antibodies, homocysteine, HBsAg, anti-HCV, anti-HIV and VDRL were unremarkable. Based on the MRA, RCVS was diagnosed in this patient and therefore, oral nimodipine (60 mg every 6 h over three days and then reduced to 30 mg daily for up to seven days) and additional analgesics (intravenous infusion of paracetamol and ibuprofen) were started. The symptoms improved after 48 hours of administering nimodipine, and no further episodes of thunderclap headache occurred as well as no adverse effects. MRA performed on the 30th day after the bite showed complete resolution of the vasoconstriction (Fig. 1B) and there were no permanent or prolonged neurological deficits observed in this patient until they were monitored in follow-up visits up to six months.

2.2. Patient 2

A 25-year-old female patient was brought to our emergency department 2 h after being bitten on the right foot while working in a paddy field. The killed snake was brought to the hospital and identified as Russell's viper by a trained herpetologist. On arrival, she was conscious, well-oriented, afebrile, and haemodynamically stable, with adequate oxygen saturation in room air. Her 20-min whole blood clotting test was prolonged (no clot formation even after 30 minutes), and this result was confirmed by an altered coagulation profile (prolonged prothrombin time and activated partial thromboplastin time) (Table 1). She was administered 10 vials (100 mL) of polyvalent antivenom from Bharat Serums and Vaccines Limited over 6 h as per the standard protocol. She did not have any adverse reactions to antivenom. She received another 15 vials of antivenom to normalise her coagulation profile over the next 24 hours. She complained about three episodes of intense, sudden-onset headaches two days after the bite. Each headache episode started spontaneously, peaked in intensity within a minute, and lasted between five to 10 min. The headache was pulsatile starting from the occipital area and extending to the frontal region. The intensity of the headache was initially described on a numerical rating scale score of 5/10, increasing to a score of 10/10 within 30 minutes. The patient described no provoking factors preceding the sudden onset of the pain. The pain in both areas persisted for three to 4 h without fluctuations in intensity. She was alert and oriented with stable haemodynamics and adequate saturation in room air. A physical examination revealed no

Table 1

Laboratory investigation reports for all SBE patients upon admission.

Specimen	Investigation	Patient 1	Patient 2	Patient 3	Unit	Normal range
EDTA Whole Blood	Haemoglobin	11.8	13.8	13.6	gms%	13.0–16.0
EDTA Whole Blood	Total RBC count	4.28	5.10	4.33	Millions/ μ L	4.00–5.00
EDTA Whole Blood	HCT	37.7	42.4	40.0	%	41.00–50.00
EDTA Whole Blood	MCV	88.1	83.1	92.4	fL	81.10–96.00
EDTA Whole Blood	MCH	27.6	27.1	31.4	pg	27.20–33.20
EDTA Whole Blood	MCHC	31.3	32.5	34.0	%	32–36
EDTA Whole Blood	Total WBC count	7.03	26.02	16.23	$\times 10^3$ Cells/ μ L	4.00–11.00
EDTA Whole Blood	Neutrophils #	4.85	22.88	13.78	$\times 10^3$ Cells/ μ L	2.0 to 7.0
EDTA Whole Blood	Lymphocytes #	1.49	2.18	1.59	$\times 10^3$ Cells/ μ L	1.0 to 3.0
EDTA Whole Blood	Monocytes #	0.47	0.84	0.82	$\times 10^3$ Cells/ μ L	0.1 to 0.8
EDTA Whole Blood	Eosinophils #	0.20	0.07	0.02	$\times 10^3$ Cells/ μ L	0.02 to 0.5
EDTA Whole Blood	Basophils #	0.02	0.05	0.02	$\times 10^3$ Cells/ μ L	0.02 to 0.1
EDTA Whole Blood	Neutrophils	69.0	87.9	84.9	%	55–75
EDTA Whole Blood	Lymphocytes	21.2	8.4	9.8	%	15–30
EDTA Whole Blood	Eosinophils	2.8	0.3	0.1	%	1–5
EDTA Whole Blood	Monocytes	6.7	3.2	5.1	%	2–10
EDTA Whole Blood	Basophils	0.3	0.2	0.1	%	Up to 1
EDTA Whole Blood	Platelet Count	307	143	189	$\times 10^3$ Cells/ μ L	150–450
EDTA Whole Blood	MPV	8.6	9.5	9.7	fL	6.5–12.0
EDTA Whole Blood	PDW	7.7	10.1	10.7	fL	9.0–13.0
Serum	Urea	26	25	16	mg/dL	15–40
Serum	Creatinine	0.67	1.40	1.02	mg/dL	0.7–1.4
Serum	Uric acid	5.2	4.7	6.6	mg/dL	3.4–7.2
Serum	Bilirubin (total)	0.71	3.08	1.2	mg/dL	0.2–1.2
Serum	Bilirubin (direct)	0.28	0.91	0.24	mg/dL	0–0.2
Serum	Bilirubin (indirect)	0.43	2.17	0.96	mg/dL	0.2–0.9
Serum	SGOT	17	37	72	U/L	5–35
Serum	SGPT	13	29	55	U/L	5–45
Citrated plasma	Prothrombin time	12.4	13.6	15.7	Seconds	11.5–16.0
Citrated plasma	aPTT	39.9	Prolonged	31.1	Seconds	26.0–40.0
Citrated plasma	INR	0.97	1.07	1.23	Ratio	

neurological abnormalities. The pain was not positional and did not respond to any analgesics [1 g paracetamol and 40 mg piroxicam] or opioids (100 mg infusion of tramadol). The results of extensive examination for vasculitis including tests for anti-nuclear and lupus anticoagulants were negative. The levels of proteins C and S as well as cerebrospinal fluid analysis were normal. RCVS was suspected based on the sudden and severe nature of her symptoms. MRI of the brain performed after around 60 hours from the bite revealed no parenchymal abnormalities but MRA demonstrated segmental vasoconstriction in the bilateral middle and posterior cerebral arteries (Fig. 1C) with no systemic bleeding. RCVS was confirmed and therefore, treated with oral nimodipine and additional analgesics (same as in patient 1) were started. Symptoms improved after 72 hours of nimodipine administration, and no further episodes of thunderclap headache occurred. An MRA performed on the 33rd day after the bite showed complete resolution of the vasoconstriction (Fig. 1D) and there was no neurological deficit for up to six months when the patient was monitored through regular follow-up visits.

2.3. Patient 3

A 25-year-old female, without any known comorbidity, presented to our emergency department with a history of snakebite on the dorsum of her right hand, while working in her courtyard around 1 hour ago. She complained of breathlessness within 5 minutes following the bite. Her co-workers spotted the offending snake as a cobra due to its characteristic spectacle mark, killed and brought it to the hospital where the identity was further confirmed by a trained herpetologist. On examination, she was conscious and well-oriented with a heart rate of 106 beats per minute and a blood pressure of 140/100 mm Hg. Bilateral ptosis was present, and her eye movement was restricted in all directions with pupils' equal round reactive to light although no focal neurological deficit or plantar bilateral flexor response was present. There was no stiffness in her neck. The chest was clear, and the air entry was bilaterally equal with no adventitious sounds. Her clotting profile and most

of the clinical parameters were normal (Table 1). She was treated with intravenous doses of atropine (2 mg), neostigmine (0.5 mg) and 20 vials of polyvalent antivenom (Bharat Serums and Vaccines Limited) over 6 h. After 48 hours post-admission, extraocular movements were full and there was no ptosis, focal neurological deficit, plantar bilateral flexor or neck stiffness. However, on the third day, she experienced a sudden severe throbbing headache in the occipital region, with associated elevations in blood pressure up to 150/100 mm Hg. She did not have a prior history of such headaches. The headache was persistent throughout the day; however, it was not associated with nausea or vomiting. She denies visual symptoms, focal weakness, and issues with gait and balance. The headache was not relieved with paracetamol, and it became persistent with minimal improvement with rest. Her neurological examination was unremarkable and laboratory investigations including liver function and kidney function tests were normal. The analysis of her cerebrospinal fluid did not reveal any unusual values. The MRI imaging of the brain did not reveal any parenchymal abnormalities, however, an MRA performed after around 80 hours from the bite revealed segmental areas of luminal narrowing with skip areas, giving a beaded appearance in proximal segments of the bilateral anterior, middle and posterior cerebral arteries (Fig. 1E). There was no evidence of subarachnoid haemorrhage. Based on her clinical presentation of a severe acute headache, exclusion of aneurysmal subarachnoid haemorrhage and segmental cerebral arterial vasoconstriction on imaging, a probable diagnosis of RCVS was made and treated with oral nimodipine and additional analgesics as stated in case 1. The patient's symptoms improved with supportive care and she had no further thunderclap headaches. The repeat MRA 3 weeks later demonstrated complete resolution of luminal narrowing (Fig. 1F) and she did not present any further issues during follow-up visits for up to six months.

3. Discussion

D. russelii, *N. naja* and *B. caeruleus* are responsible for most of all reported SBE events in India between 2000 and 2019 (Suraweera et al.,

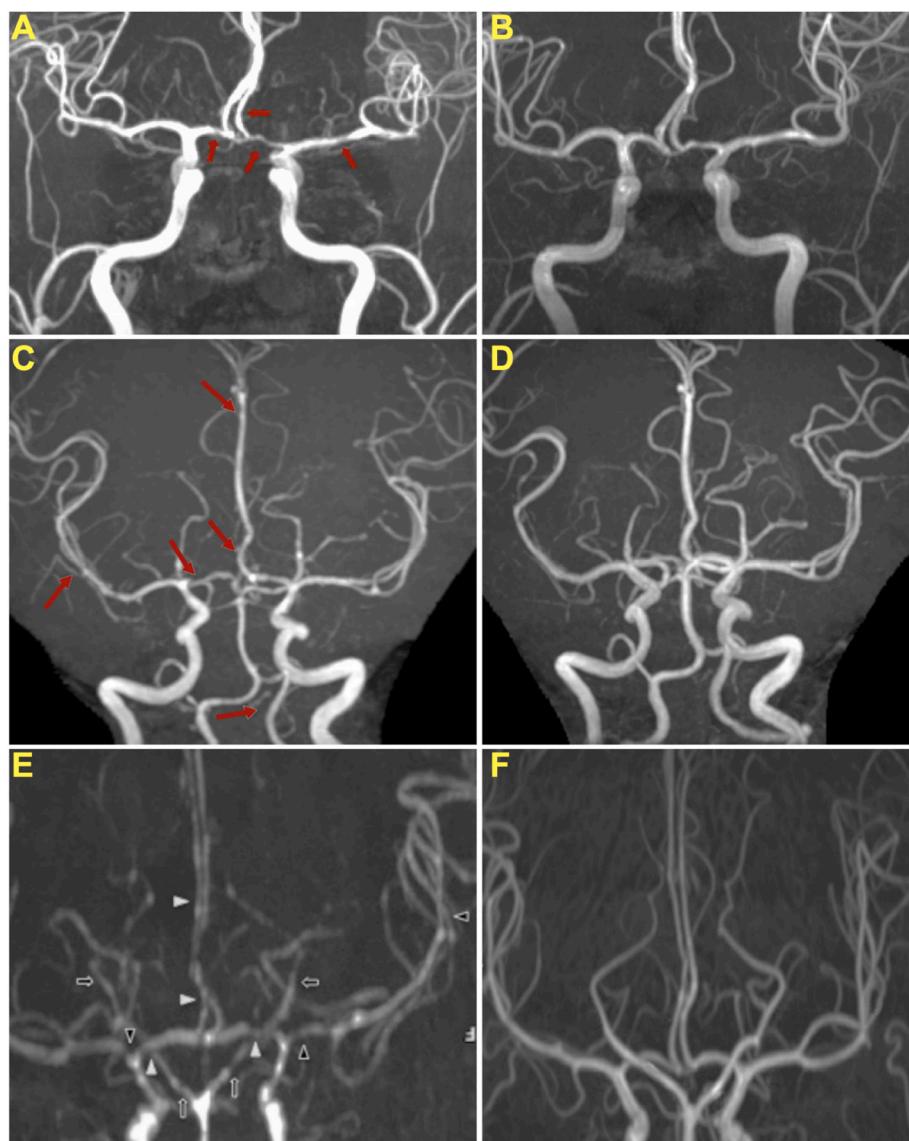


Fig. 1. Development of reversible cerebral vasoconstriction syndrome (RCVS) in patients following SBE. A) MRA of patient 1 following *B. caeruleus* envenoming. The images highlight the multifocal segmental cerebral artery vasoconstriction, predominantly affecting both the middle cerebral arteries and the P1-segment of the posterior cerebral artery (indicated with arrows). B) Following treatment with nimodipine, vasoconstriction has been reversed in cerebral arteries in patient 1. C) MRA of patient 2 following *D. russelii* envenoming evidencing the segmental vasoconstriction in the bilateral middle and posterior cerebral arteries (indicated with arrows). D) Treatment with nimodipine reversed the vasoconstriction in cerebral arteries in patient 2. E) MRA of patient 3 reveals the vasoconstriction (arrows) and bead-like structures (arrowheads) in proximal segments of anterior, middle and posterior arteries, and F) confirms the reversal of this condition in this patient.

2020). Similar statistics have been reported for SBE incidents in Tamil Nadu between 2019 and 2021 (Salim et al., 2023). Envenomings from these species require rapid administration of antivenom to normalise haemodynamics and prevent neurotoxicity (Dias da Silva et al., 2022). Most SBE events occur within rural areas where the medical infrastructure is poor. This makes accessing medical facilities challenging as patients may need to travel for several hours before they reach medical provisions with sufficient facilities and expertise to treat SBE (Werner and Soffa, 2023). As a result, a significant proportion of SBE-related fatalities occur before the victims reach medical facilities (Roberts et al., 2022). Therefore, it is critical to train and provide appropriate knowledge for rural healthcare professionals to promptly manage SBE victims without referring all of them to distant medical facilities. Hence, the broad spectrum of clinical manifestations associated with SBE should be published and disseminated to clinicians including rural healthcare professionals.

D. russelii bites are typical of most viper species, characterised by

local tissue damage and blood clotting disturbances (Bin Haidar et al., 2024). The presence of factor V and X activators within this venom results in a condition known as venom-induced consumption coagulopathy, where the coagulation cascade is rapidly activated, and clotting is induced (Berling and Isbister, 2015; Isbister et al., 2015). A secondary fibrinolytic action degrades the developing clot, resulting in the consumption of clotting factors and platelets leading to incoagulable blood. This induces systemic and local bleeding that can result in many clinical manifestations associated with coagulopathies. Recent case reports from our research team have outlined several under-reported or rare clinical manifestations following Russell's viper envenomings. These clinical manifestations can be life-threatening if left undiagnosed and untreated (Senthilkumaran et al., 2023, 2024). Similarly, clinical manifestations following *N. naja* and *B. caeruleus* bites are typical of elapid envenomings. The early symptoms may include a metallic taste in the mouth, progressive loss of strength and motor control, ptosis and difficulty breathing (Silva et al., 2016a,b). These symptoms can result in the

paralysis of muscles including the diaphragm, which can result in the cessation of breathing if left untreated. Therefore, many krait and cobra bite patients require ventilation following envenomings (Anil et al., 2010).

RCVS is the diffuse segmental constriction of the cerebral arteries, which is supposedly developing due to a transient change in the cerebrovascular tone (Calabrese et al., 2007; Ducros, 2012; Society, 2004). It is most common in postpartum but can also be a result of taking adrenergic and serotonergic drugs. Recurrent thunderclap headaches are typically the first symptom of RCVS (Dodick et al., 1999; Ducros, 2012; Ducros et al., 2007), but more severe consequences include seizure, stroke and non-aneurysmal subarachnoid haemorrhage (Ghia et al., 2011; Marder et al., 2012; Singhal et al., 2011). Diagnosis of RCVS requires direct (transfemoral) or indirect (CT or magnetic resonance) cerebral angiography, highlighting the narrowing or dilation of one or more of the arteries (Magid-Bernstein et al., 2021; Miller et al., 2015). Treatment of RCVS should be symptomatic, based on the identification and elimination of aggravating factors. Patients should rest and avoid physical exertion to tackle this condition (Ribas et al., 2023; Singhal, 2023). Similarly, vasoactive drugs should be stopped and started on analgesics and the blood pressure should be monitored. In severe cases, admission of patients to the intensive care unit is required. Benzodiazepines can be administered to reduce anxiety, which can be a contributing factor to RCVS. Drugs targeted for vasospasms such as nimodipine have been used to relieve vasoconstriction in several cases (Cho et al., 2019; Togha et al., 2021). Whilst RCVS is not a common manifestation of SBE, its importance should not be disregarded as the failure to correct the vasoconstriction of cerebral arteries can result in ischaemic or haemorrhagic stroke. These sequelae can have long-term implications for the health and general well-being of patients and their families. In patients requiring ventilation or where a loss of consciousness and responsiveness has occurred during treatment, individuals may be unable to indicate the occurrence of severe headaches. The potential for the development of RCVS in these patients should also be considered, to better mitigate any potential long-term sequelae.

The mechanisms through which the venoms of *D. russelii*, *N. naja* or *B. caeruleus* developed RCVS are unclear. Safotoxins, a peptide family known to cause vasoconstriction have been identified in the venoms of species from the *Atractaspis* genus (Kloog et al., 1988). However, these toxins have not been identified in the venoms of either *D. russelii*, *N. naja* or *B. caeruleus*. Most venom components typically induce vasodilation, enlarging the blood vessels, increasing blood flow and spreading the venom across the body (Da Silva et al., 2011; Péterfi et al., 2019). While the venom of *D. russelii* has been reported to develop thrombosis in peripheral arteries, its impact on vasoconstriction has not been studied. Similarly, the cardiovascular consequences of the venoms of *N. naja* and *B. caeruleus* have not been explored well. Hence, further investigations are needed to profile all the components of these venoms to identify any toxins with potential vasoconstrictive activity. Similarly, the indirect actions of known venom components of both venoms on vasoconstriction should be investigated. Moreover, the impact of antivenom in inducing such vasoconstriction through unknown mechanisms cannot be ruled out based on the health conditions of the patients. This case report includes only three patients who developed RCVS following bites from different snake species. Therefore, it is hard to determine the underlying cause of this manifestation, as the pathology and venom biochemistry of these venoms are hugely different. It is possible that the RCVS manifested due to the high level of anxiety and stress that the patients were likely experiencing following bites or possibly due to an adverse reaction to the administration of antivenom. Similarly, there might be a history of specific undiagnosed cardiovascular conditions in these patients that could have predisposed them to RCVS.

4. Conclusion

The clinicians working in tropical countries including in rural

regions must be aware of the diverse range of pathological events associated with SBE that may not be addressed by conventional anti-venoms. Therefore, they need to be aware of additional diagnostic and therapeutic approaches to be used in such rare cases. For instance, RCVS is an unusual complication following SBE specifically in India. The visualisation of blood vessels and identification of abnormalities through MRA is critical to aid the diagnosis and to provide prompt treatment. Nimodipine therapy resulted in positive clinical outcomes, leading to the resolution of RCVS in all SBE victims. The development, and significance of these diagnostic and therapeutic approaches for RCVS following SBE from different snake species in other countries should be investigated.

CRediT authorship contribution statement

Subramanian Senthilkumaran: Data curation, Conceptualization. **Jarred Williams:** Writing – review & editing, Writing – original draft. **José R. Almeida:** Writing – review & editing, Writing – original draft. **Harry F. Williams:** Writing – review & editing, Conceptualization. **Ketan Patel:** Data curation, Conceptualization. **Ponniah Thirumalaikolundusubramanian:** Data curation, Conceptualization. **Sakthivel Vaiyapuri:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Ethics statement

This study was performed in line with the Declaration of Helsinki, and permitted by the Institutional Ethics Committees of Toxiven Biotech Private Limited (2019-001/002 on October 11, 2019) and the University of Reading (UREC 23/05 on January 18, 2023). Written informed consent has been obtained from the patients to publish this case series.

Declaration statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of competing interest

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Acknowledgments

The authors would like to thank the Medical Research Council, UK (Reference: MR/W019353/1 & ITTP PhD studentship) for their funding support.

Data availability

Data will be made available on request.

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