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Review

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Hypopituitarism following envenoming by Russell's Vipers (*Daboia siamensis* and *D. russelii*) resembling Sheehan's syndrome: first case report from Sri Lanka, a review of the literature and recommendations for endocrine management

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Summary

Russell's vipers (*Daboia russelii* and *D. siamensis*) inhabit 10 South and South East Asian countries. People envenomed by these snakes suffer coagulopathy, bleeding, shock, neurotoxicity, acute kidney injury and local tissue damage leading to severe morbidity and mortality. An unusual complication of Russell's viper bite envenoming in Burma (*D. siamensis*) and southern India (*D. russelii*) is hypopituitarism but until now it has not been reported elsewhere. Here, we describe the first case of hypopituitarism following Russell's viper bite in Sri Lanka, review the literature on this subject and make recommendations for endocrine investigation and management. A 49-year-old man was bitten and seriously envenomed by *D. russelii* in 2005. He was treated with antivenom but although he recovered from the acute effects he remained feeling unwell. Hypopituitarism, with deficiencies of gonadal, steroid and thyroid axes, was diagnosed 3 years later. He showed marked improvement after replacement of anterior pituitary hormones. We attribute his hypopituitarism to *D. russelii* envenoming. Russell's viper bite is known to cause acute and chronic hypopituitarism and diabetes insipidus, perhaps through deposition of fibrin microthrombi and haemorrhage in the pituitary gland resulting from the action of venom procoagulant enzymes and haemorrhagins. Forty nine cases of hypopituitarism following Russell's viper bite have been described in the English language literature. Patients with acute hypopituitarism may present with hypoglycaemia and hypotension during the acute phase of envenoming. Those with chronic hypopituitarism seem to have recovered from envenoming but present later with features of hypopituitarism. Over 85% of these patients had suffered acute kidney injury immediately after the bite. Steroid replacement in acute hypopituitarism is life saving.

All 11 patients with chronic hypopituitarism in whom the outcome of treatment was reported, showed marked improvement with hormone replacement. Unrecognized acute hypopituitarism is potentially fatal while chronic hypopituitarism can be debilitating. Physicians should therefore be aware of this complication of severe envenoming by Russell's vipers, especially in Burma and South India, so that the diagnosis may be made without delay and replacement started with essential hormones such as hydrocortisone and thyroxine.

Introduction

Russell's vipers *(Daboia russelii* and *Daboia siamensis*) inhabit 10 South and South East Asian countries and are leading causes of fatal snake bite in India, Pakistan, Sri Lanka, Burma, Thailand and parts of Indonesia.[1] Two separate species have been identified, *D. russelii* to the West and *D. siamensis* to the East of the Bay of Bengal[2] (Figure 1). Russell's viper venoms can cause neurotoxicity, myotoxicity, haemolysis, coagulopathy and other haemostatic disturbances, shock, acute kidney injury, severe local envenoming with necrosis and death.3,4 Hypopituitarism is a relatively uncommon sequel of Russell's viper bite. To our knowledge, it has not been reported from any country other than Burma (*D. siamensis*) (Figure 2b) and South India (*D. russelii*) (Figure 2a). Here, we report the first case diagnosed in Sri Lanka and we review the literature on this subject and make recommendations for the recognition, diagnosis and endocrine management of these patients.

Case report

A 49-year-old man, a trader from Rajanganaya, near Anuradhapura, North Central Province, Sri Lanka was bitten by a snake on his left foot in 2005. The snake was neither captured nor killed but the patient and the villagers identified it as 'tit polôngā' ('spotted viper') the local Sinhala name for Russell's viper (*D. russelii*). It was much too large to be either of the other medically-important vipers (hump-nosed viper *Hypnale hypnale*; saw-scaled viper *Echis carinatus*). He bled from the site of the bite for 1 h and a tourniquet was applied. Two hours after the bite he felt faint and started vomiting. Four hours later he developed blurred vision and was taken to Rajanganaya rural hospital. There his blood was found to be incoagulable and he was given Haffkine polyvalent anti-venom, covering Indian *D. russelii*, *Echis carinatus*, *Naja naja* and *Bungarus caeruleus* venoms. He developed an early anaphylactic reaction with oedema and urticaria 1 h after the completion of anti-venom. He was transferred to the provincial hospital at Anuradhapura where he was resuscitated and discharged after 2 days. However, he remained persistently unwell over the next 3 years and, despite consulting many doctors, felt no significant improvement. His main symptoms were generalized weakness, lethargy, sleepiness and reduced libido. There was no polyuria, polydipsia, headache or visual disturbance and no history of head injury, central nervous system infection, cranial irradiation or pituitary surgery. He was afebrile and otherwise well. On examination he had a pale face; secondary sexual characteristics were preserved with secondary sexual hair and no gynaecomastia. His blood pressure was 120/80 mmHg with no postural drop. The visual fields and optic fundi were normal and there was no diplopia. The pituitary function tests revealed deficiencies of steroid, thyroid and gonadal axes (Table 1). Since the 9 am plasma cortisol concentration was very low (2.5 mcg/dl, 69 nmol/l), neither a short synacthen test (SST) nor an insulin tolerance test (ITT) was performed. The magnetic resonance imaging (MRI) revealed a normal pituitary gland (Figure 3). He was treated with hydrocortisone 10 mg twice daily (8 am and 6 pm), levothyroxine 50 mcg daily and testosterone enanthate by intramuscular (IM) injection, 250 mg every 4 weeks. When he was reviewed 1 month later, there was a marked improvement in his symptoms and general well being. This patient was not a subject of research, only standard clinical management.

Discussion

The first case of snake bite causing anterior pituitary dysfunction was described by Wolff[5] in a man who had been bitten 7 years previously by what was said to have been a jararacuçu (*Bothrops jaracussu*) in Brazil in 1958 (Figure 4). Hypopituitarism following Russell's viper bite was first reported in 1976 by Eapen *et al* [6] in three adults from Kerala in South India. Following this, there were several reports in the literature of Russell's viper envenoming causing hypopituitarism (Table 2). However, despite the wide distribution of Russell's vipers throughout South and South-east Asia, hypopituitarism following their bites has been reported from only India and Burma.

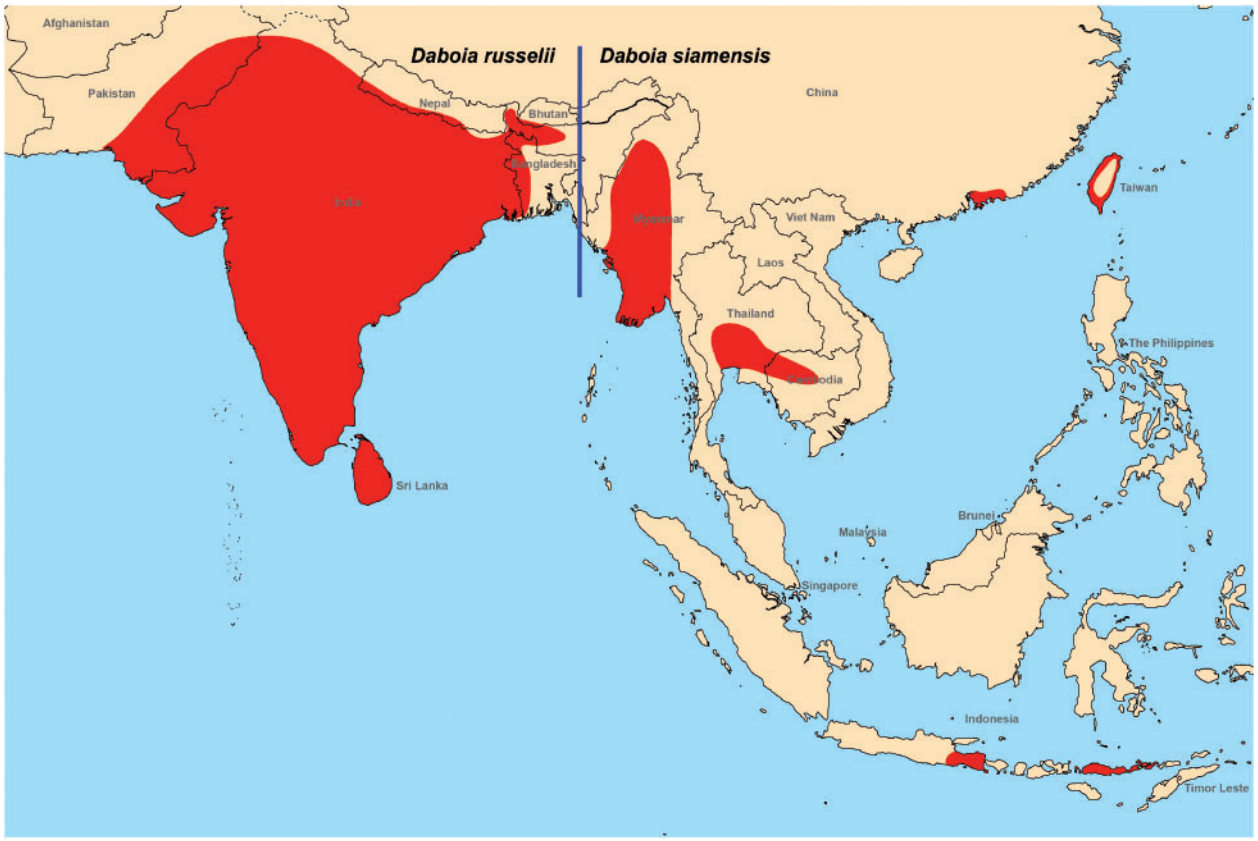

Figure 1. Distributions of the two species of Russell's vipers (Courtesy of D. J. Williams based on WHO species maps http://apps.who.int/bloodproducts/snakeantivenoms/database)

Pathogenesis

A systematic study of patients in Burma by Tun-Pe *et al.*[7] has clearly demonstrated that Russell's viper bite can lead to acute and chronic hypopituitarism. How does Russell's viper venom damage the pituitary?

Russell's viper venom is known to contain many toxins, including several different biologically active procoagulant enzymes activating factors V, X and other steps in the blood clotting cascade.[8–10] This results in the formation of cross-linked fibrin in the blood stream, most of which is immediately broken down by the body's own fibrinolytic system. Eventually, and occasionally within 30 min, the levels of clotting factors become so depleted by disseminated intravascular coagulation (DIC) that consumption coagulopathy develops.[8,11–13] Russell's viper venom also contains a metalloproteinase 'haemorrhagin' which damages vascular endothelium and toxins that impair platelet function. These venom-induced disturbances lead to the thromboses and spontaneous haemorrhages seen in victims of Russell's viper bite envenoming. Focal haemorrhage and micro vascular thrombin deposition in the pituitary may be responsible for the pathological finding

Figure 2. Russell's vipers. (**a**) Sri Lankan Russell's viper (*Daboia russelii*) 'tit polôngā' specimen 130 cm in total length from Anuradhapura. (**b**) Burmese Russell's viper (*Daboia siamensis*) specimen from Tharrawaddy

of haemorrhagic infarction of the anterior pituitary and functional consequences of acute and chronic pan-hypopituitarism.[14,15] Than-Than *et al.*[15] have reported autopsy findings in the pituitaries of

Table 1 The pituitary function tests of the patient

Test	Results	Reference range
FT4	0.87 ng/dl (11.22 pmol/l)	0.89–1.76 ng/dl (11.48–22.7 pmol/l)
TSH	1.85 mIU/ml (1.85 mU/l)	0.4–4.0 mIU/ml (0.4–4.0 mU/l)
9 am Cortisol	2.5 mcg/dl (69 nmol/l)	4.2–28.4 mcg/dl (115.92–783.84 nmol/l)
IGF1	145 ng/ml (19.33 nmol/l)	94–252 ng/ml (12.5–33.6 nmol/l)
FSH	2.6 mU/ml (2.6 U/l)	2.8–11.3 mU/ml (2.8–11.3 U/l)
LH	1.5 mU/ml (1.5 U/l)	1.1–11.6 mU/ml (1.1–11.6 U/l)
Prolactin	2.7 ng/ml (54 mU/l)	4.9–40 ng/ml (98–800 mU/l)
Testosterone	1.92 ng/ml (6.64 nmol/l)	1.95–11.38 ng/ml (6.75–39.38 nmol/l)

SI units for the results and the reference ranges are given within parenthesis. IGF1, Insulin like Growth Factor 1.

three patients who died following Russell's viper bite envenoming in Burma. They noticed focal haemorrhages (Cases 2 and 3) and small fibrin thrombi (Cases 1 and 3) (Figures 5a–c). They also showed microthrombi and histological evidence suggestive of acute tubular necrosis in the kidneys. This suggests that DIC plays a part in acute renal injury in these patients along with other causes of pre-renal renal failure such as shock. Than-Than *et al.*[15] have also reported adrenal haemorrhage but this is less common than pituitary haemorrhage (Figure 5d). Proby *et al.*[14] have referred to an unpublished work of one of their co-authors in which autopsies of five victims who survived for 8–72 h following the Russell's viper bite in Burma revealed haemorrhagic necrosis of the anterior pituitary gland with a normal posterior pituitary.

Some authors compare the pituitary lesion in survivors to classical Sheehan's syndrome.[7,14,15] Sheehan,[16] in his original article entitled 'post-partum necrosis of the anterior pituitary' published in 1937, had studied the macroscopic and microscopic appearances of the pituitary glands of 59 women who died during the puerperium. There were changes in the pituitary in 12 of them. Eleven women had died soon after delivery. Nine had postpartum haemorrhage (PPH), with retained placenta in five, and two had bronchopneumonia. All 11 showed coagulative necrosis of the anterior pituitary. This affected the antero-inferior part of the anterior lobe of the pituitary in the mid line and spread out to involve most of the rest of the lobe. The part that usually escaped was the postero-superior angle beneath and in front of the stalk and a very thin layer on the surface. Histologically, there was fibrin meshwork laid down along the walls of the sinuses interpreted by the author as *in situ* thrombosis. The 12th woman survived an episode of PPH and developed symptoms suggestive of hypopituitarism but died 18 months later following delivery at her subsequent pregnancy. The anterior lobe of her pituitary was a small shrivelled grey mass that appeared to consist of fibrous tissue. Microscopically the anterior lobe consisted merely of condensed stroma. Sheehan's conclusion was that thrombosis had occurred soon after delivery during the women's collapse usually following severe haemorrhage and often as a result of retained placenta. If the patients survived this episode, the lesion healed to a mass of condensed stroma.[16] He did not describe any haemorrhage in the pituitary.

The pathogenesis for Sheehan's syndrome is not clearly understood. The basic process is infarction secondary to arrest of blood flow to the anterior lobe of the pituitary gland. Whether this process results from vasospasm, thrombosis or vascular compression is not clear.[17] The enlargement of the pituitary gland during pregnancy might compress the blood vessels or the pituitary cells might be more susceptible to ischaemia during pregnancy. However primary thrombosis is a strong possibility.[17] The placenta is a rich source of tissue factor (F-III, 'thromboplastin'), an activator of prothrombin responsible for the defibrination and resulting hypofibrinogenaemia associated with abruptio placentae. In late pregnancy, DIC might also be activated by leakage into the maternal circulation of amniotic fluid and syncytiotrophoblastic microparticles containing functional tissue factor (P. Giangrande, P. Harrison, C. Gardner, personal communication, 2010). As a consequence of DIC, fibrin might be deposited on blood vessel walls, as observed by Sheehan in the pituitary. Other complications of pregnancy associated with DIC include intrauterine foetal death with prolonged retention of the dead foetus, massive blood transfusion, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and sepsis. Hypopituitarism associated

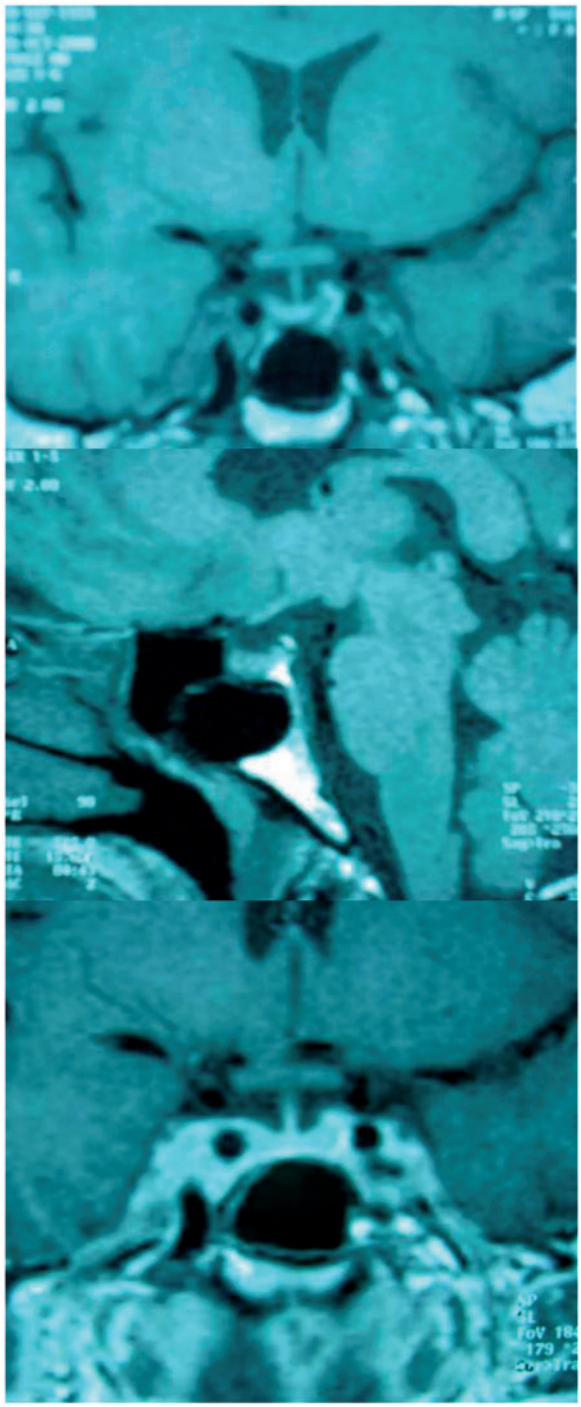

Figure 3. MRI scan of our patient showing a normal pituitary gland.

with thrombosis is also reported in pregnant women with acute fatty liver of pregnancy complicated by DIC but without significant PPH and women with sickle cell trait.[18–20] It is interesting that among the three cases of hypopituitarism after Russell's viper reported by Than-Than *et al.*[15] one did not have any haemorrhage but only microvascular thrombi (Figure 5c). A recent computed tomography (CT)

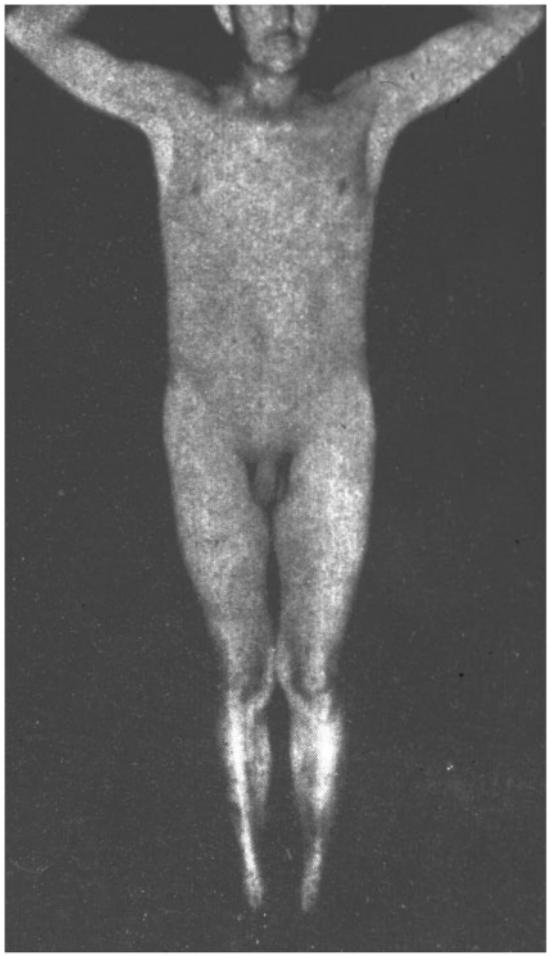

Figure 4. Patient with loss of secondary sexual hair and gynaecomastia following a bite by a *Bothrops* spp. (*B. jararacussu*) in Southern Brazil (Wolff[5]).

study of patients who developed strokes after Russell's viper bites in Sri Lanka, showed single or multiple thromboses of medium to large cerebral arteries without evidence of haemorrhage.[21]

It has been argued that Sheehan's syndrome occurs because the enlarged pituitary of normal pregnancy is more susceptible to ischaemia as a result of infarction due to hypotensive shock, DIC or haemorrhage. Is there a similar mechanism by which Russell's viper venom makes the pituitary more susceptible to the effects of DIC? A syndrome of acute generalized capillary permeability, involving lungs and glomeruli, is described after Burmese Russell's viper bites.[2] This might also result in pituitary oedema. In 1989 Hart *et al.*[22] demonstrated that *in vitro*, Burmese Russell's viper venom causes a dose-dependent release of growth hormone (GH), thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) from dispersed rat anterior pituitary cells in culture.

Table 2 Cases of Russell's Viper bite and associated hypopituitarism

Case	Snake	Age[a]	Sex	Region	Complications of envenoming	Hypopituitarism Acute/Chronic	Time to diagnose	Anterior/ Posterior Pituitary	Clinical Features at Presenation	Deficient Hormone Axes	Treatment	Outcome	Reference
1	DR	40	M	Kerala India	Coagulopathy AKI	Chronic	1 year	A	Erectile Dysfunction Loss of body hair	Steroid Thyroid Gonadal	Cortisone Thyroxine Testosterone	Well	Eapen *et al.*[6]
2	DR	38	M	Kerala India	Coagulopathy Shock	Acute	1 month	A	Unable to tail off cortisone Loss of libido Loss of body hair Hypotension	Steroid Thyroid Gonadal	Cortisone Thyroxine	Well	Eapen *et al.*[6]
3	DR	21	F	Kerala India	Coagulopathy AKI	Chronic	6 weeks	A	Amenorrhoea Loss of body hair Hypotension	Steroid Thyroid	NR	NR	Eapen *et al.*[6]
4 to 9	DR	22-42	M	Trichur India	Coagulopathy AKI	Chronic	2 months to 20 years	A	Hypocortisolism (6/6) Hypogonadism (5/6) Hypothyroidism (4/6)	Steroid (6/6) Thyroid (4/6) Gonadal (5/6)	NR	NR	Majeed *et al.*[25]
10	DR	21	F	Pune India	Coagulopathy AKI	Chronic	2.5 years	A	Amenorrhoea Weakness Reduced libido Loss of body hair Cold intolerance	Steroid Thyroid Gonadal	HRT including oestrogen	Good response	Uberoi *et al.*[28]
11	DR	15	M	Kerala India	Coagulopathy AKI	Chronic	3 years	A	Reduced energy Lethargy No body and facial hair High pitched voice	Steroid Thyroid Gonadal	Prednisolone Thyroxine	Well	Dr Joseph K Joseph
12	DR	17	M	Kerala India	Coagulopathy	Chronic	2 years	A	Weakness & lethargy High pitched voice	Steroid Thyroid Gonadal	Prednisolone Thyroxine Sustanon 250	Well	Dr Joseph K Joseph
13	DR	14	M	Jodhpur India	Coagulopathy Neurotoxicity Local	Acute	16 h	P	Polyuria	ADH	Vasopressin subcutaneous injection	Died	Gupta *et al.*[29]
14	DR	38	M	India	AKI	Chronic	7 years	A	Weakness Asthenia Postural giddiness Loss of body hair	Steroid Thyroid Gonadal	HRT	Well	Dhanwal *et al.*[27]
15	DR	23	M	Kerala India	Coagulopathy AKI Shock	Chronic	6 weeks	A & P	Fatigue Polyuria following steroids	Steroid Thyroid Gonadal GH	Prednisolone Thyroxine Testosterone DDAVP Carbamazepine	Well	Krishnan *et al.*[26]

(continued)

Table 2 Continued

Case	Snake	Age[a]	Sex	Region	Complications of envenoming	Hypopituitarism Acute/Chronic	Time to diagnose	Anterior/ Posterior Pituitary	Clinical Features at Presenation	Deficient Hormone Axes	Treatment	Outcome	Reference
16	DR	35	F	Kerala India	Coagulopathy Shock	Chronic	Few months	A	Amenorrhoea	Steroid Thyroid Gonadal	Prednisolone Thyroxine	Well	James *et al.*[23]
17	DR	38	M	Kerala India	NR	Chronic	NR	A	Oedematous state	Thyroid Other hormones were not done	Prednisolone Thyroxine	Well	James *et al.*[23]
18	DR	42	M	Kerala India	NR	Chronic	NR	A	Oedematous state	Thyroid Other hormones were not done	Prednisolone Thyroxine	Well	James *et al.*[23]
19	DR	40	M	Kerala India	NR	Chronic	18 years	A	Lack of secondary sexual characteristics	Thyroid Other hormones were not done	Prednisolone Thyroxine	Well	James *et al.*[23]
20	DS	17	M	Tharawaddy, Burma	Coagulopathy AKI Shock	Acute	During acute episode	A	Hypoglycaemia Shock	Steroid	Anti-venom Dopamine Hydrocortisone Dextrose IV	Died	Tun-Pe *et al.*[7]
21	DS	32	M	Tharawaddy, Burma	Coagulopathy AKI Shock	Acute	During acute episode	A	Hypoglycaemia	Steroid	Anti-venom Dopamine Hydrocortisone Dextrose IV	Dramatic response to Hydrocortisone	Tun-Pe *et al.*[7]
22	DS	NR	NR	Tharawaddy, Burma	Coagulopathy	Acute	During acute episode	A	Hypoglycaemia	NR	NR	Died	Tun-Pe *et al.*[7]
23-28	DS	20-49	5M 2F	Tharawaddy, Burma	NR	Chronic	6 months to 4 years	A	Weakness & lethargy (7/7) Decreased Libido (4/7) Erectile dysfunction (3/5) Menstrual irregularity (2/2) Loss of body hair (6/7)	Steroid (5/7) Thyroid (5/7) Testosterone (4/5) Oestradiol -NR GH (7/7)	NR	NR	Tun-Pe *et al.*[7]
29–48	DS	11-40	17M 3F	Rangoon Burma	Coagulopathy (20/20) AKI (20/20)	Acute	During acute episode	A	NR	Steroid (10/15) Thyroid (19/20) Testosterone (12/17) Oestradiol (1/3)	Hydrocortisone/ Prednisolone Thyroxine	12 survived 5 died 3 lost to follow up	Proby *et al.*[14]
49	DR	49	M	Rajanganaya Sri Lanka	Coagulopathy AKI	Chronic	3 years	A	Weakness Lethargy Reduced libido	Steroid Thyroid Gonadal Prolactin	Hydrocortisone Thyroxine Testosterone	Well	This study

[a]Age at diagnosis of hypopituitarism. M, male; F, female; NR, not reported, A, anterior pituitary insufficiency; P, posterior pituitary insufficiency; AKI, acute kidney injury; ADH, anti-diuretic hormone*; DR,* Daboia russelii*; DS,* Daboia siamensis.

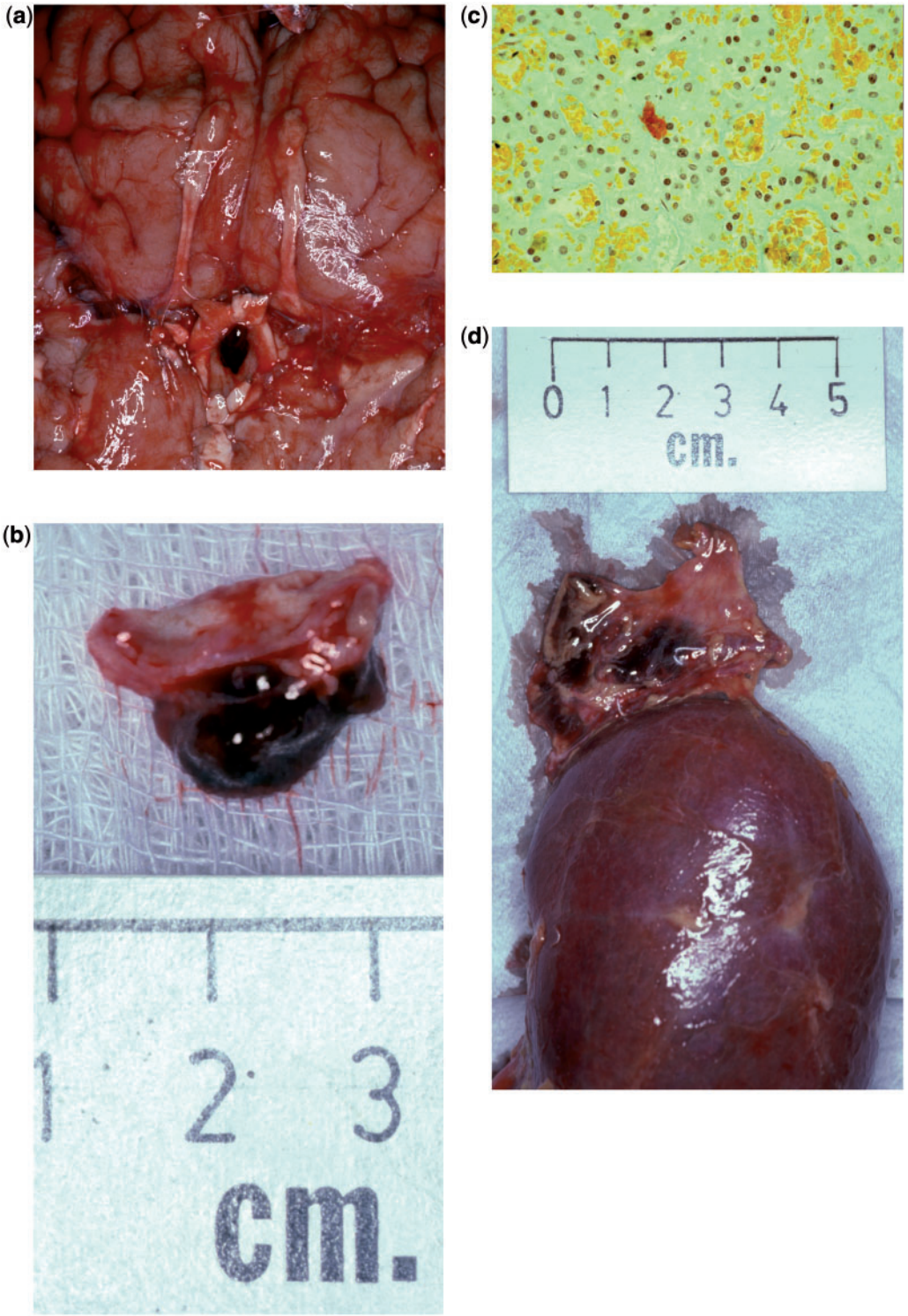

Figure 5. Seventeen-year-old Burmese rice farmer who died 36 h after being bitten by *D. siamensis*. (**a**) Showing haemorrhagic stalk of the pituitary gland. During his 15-h hospital admission, there was evidence of acute pituitary-adrenal insufficiency and acute kidney injury (Than-Than *et al.*[7]; Tun-Pe *et al.*[13]). (**b**) Pituitary gland and sella turcica (sphenoid) showing haemorrhagic infarction. (**c**) Glandular portion of the anterior pituitary gland from the same patient: showing fibrin clot, red blood corpuscles (yellow) and pituitary cells (Courtesy of Dr Nick Francis). (**d**) Left kidney and adrenal gland showing adrenal haemorrhage.

This was not due to destruction of pituitary cells as >90% of the cells were viable 4 h after exposure to venom.The clinical significance of this finding is not known although pituitary stimulation might explain the vulnerability of the pituitary to destruction by Russell's viper venom.

Thus, the pathophysiological factors shared by women at risk of developing classic Sheehan's syndrome after PPH and victims of severe Russell's viper bite envenoming include thrombotic tendency leading to DIC, deposition of fibrin in the pituitary blood vessels, and vulnerability to stagnant hypoxia/ischaemia of the pituitary secondary to an episode of profound hypotension and perhaps swelling of the pituitary gland within the confines of its indistensible pituitary fossa.

An additional explanation for the development of chronic hypopituitarism following acute pituitary damage following Russell's viper bite envenoming might be an antigen–antibody reaction similar to immune mediated glomerular damage.[23] Goswami *et al.*[24] have reported increased prevalence of pituitary antibodies in patients with Sheehan's syndrome. They believe that the occurrence of an autoimmune process after PPH and pituitary necrosis in Sheehan's syndrome might lead to added damage and progressive hypopituitarism. This possibility has not yet been explored in victims of Russell's viper envenoming.

Acute hypopituitarism

Tun-Pe *et al.*[7] studied nine patients who were brought to hospital with hypotension (systolic blood pressure < 80 mmHg), impaired levels of consciousness or other features suggestive of hypoglycaemia following Russell's viper bite in Burma. Three out of these nine patients had evidence of hypopituitarism with inappropriately low baseline serum cortisol, GH and prolactin concentrations. In these patients, collapse with hypoglycaemia occurred within 21 h and up to 9 days following the snake bite and two of these patients died, though the cause of death could not be solely attributed to hypopituitarism.[7] Proby *et al.*[14] studied 20 patients who were admitted to a renal unit with acute kidney injury following Russell's viper bite in Burma. In this study 10 out of 15 patients had inappropriately low cortisol, 19 out of 20 patients had low serum TSH and thyroxine concentrations, 12 out of 17 males had low serum testosterone with low or inappropriately normal gonadotrophins concentrations and one out of three females had low serum oestrogen concentrations. The majority of these patients were on either hydrocortisone or prednisolone which reacted with the assay used in the study. Results of the thyroid function tests might be interpreted as indicating sick euthyroid syndrome during acute illness. In 1976, in a case reported from India by Eapen *et al.*[6] the patient was given large doses of cortisone during the acute envenoming and was asked to taper it off after discharge but he could not reduce cortisone to less than one tablet a day as he felt unwell. This led to the diagnosis of hypopituitarism. He had probably developed pituitary insufficiency during the acute envenoming. Among 336 patients studied in Sri Lanka by Kularatne *et al.* no patient had clinical features suggestive of acute cortisol insufficiency (S.A.M. Kularatne, personal communication).

The acute pituitary insufficiency appears to be persistent. Proby *et al.*[14] followed up 12 patients with acute hypopituitarism for 8–156 weeks and 11 patients continued to have biochemical evidence of hypopituitarism.

Chronic hypopituitarism

In chronic hypopituitarism as opposed to the acute form, the patients apparently recover from the acute episode of envenoming with no indication of hypopituitarism at that time but present later with insidious symptoms of hypopituitarism.

Tun-Pe *et al.*[7] systematically studied 24 selected patients in Burma who had survived severe Russell's viper bite envenoming, among whom seven were found to have clinical features of hypopituitarism (Figure 6). The diagnosis was confirmed by dynamic pituitary function tests including insulin tolerance test (ITT), thyrotropin-releasing hormone (TRH) stimulation test and luteinising hormone-releasing hormone (LHRH) stimulation test. The tests revealed deficiencies of the following hormones: cortisol (5) GH (7), thyroxine (5) and testosterone (4/5 males). Among 17 with no clinical features, four had subnormal cortisol responses to ITT. These figures suggest a relatively high prevalence of hypopituitarism following severe Russell's viper bite envenoming.

The case reports give a wide range between the time of snake bite and the diagnosis of hypopituitarism. In the Burmese study the patients were bitten 6 months–4 years before the diagnosis of hypopituitarism was made. The symptoms of hypopituitarism had developed as early as 4 weeks in some patients.[7] The reports from India give a range of between a few weeks and 20 years from the time of snake bite.[23,25,26]

The presenting clinical features documented in the literature include weakness, lethargy, hoarseness of voice, swelling of the body, reduced body hair, loss of libido, erectile dysfunction and menstrual disturbance.[7,23,26–28]

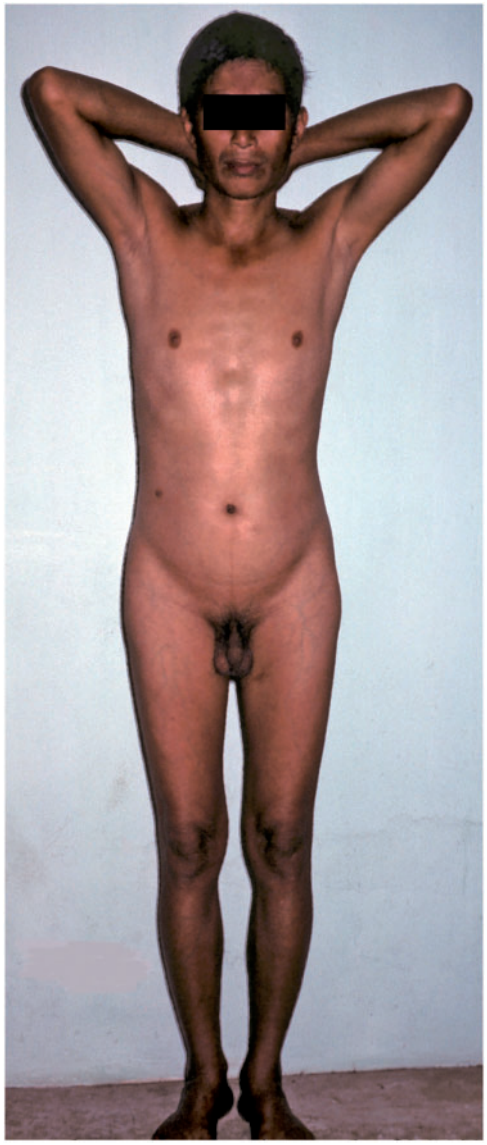

Figure 6. A 49-year-old Burmese rice farmer presented with weakness, lethargy, hoarse voice, erectile dysfunction and loss of libido 4 years after being severely envenomed by *D. siamensis*. On examination, he was clinically hypothyroid with loss of secondary sexual hair.

Pituitary imaging with CT scans in two of these cases proved to be normal.[26,27] The MRI scan of our patient also showed a normal pituitary gland (Figure 3).

Posterior pituitary insufficiency

Posterior pituitary involvement is far less common than anterior pituitary involvement after Russell's viper bite. There are only four cases of posterior pituitary insufficiency following Russell's viper envenoming reported in the literature, all from South India[26,29,30] and C.K. Eapen, unpublished data. One patient had developed coagulopathy, circulatory shock and renal failure following envenoming. He was discharged after 4 weeks in hospital. Soon after discharge, he presented with severe fatigue and was confirmed to have panhypopituitarism with a subnormal response to ITT and deficiency of thyroid and gonadal axes. He was given hydrocortisone replacement, after which he developed polyuria of 8–10 l/day with low urine specific gravity (1.000) and high serum sodium (150 mEq/l). These symptoms responded to arginine vasopressin nasal spray.[26] The second case was of a 14-year-old boy who developed coagulopathy, bilateral ptosis (neurotoxicity) and swelling of the bitten leg 1 h after the bite. Two hours later he developed polyuria and over the next 16 h his urine output was 10.7 l. He was euglycaemic. At this time his serum sodium was 166 mEq/l with a urine specific gravity of 1.000 indicating diabetes insipidus (DI). His urine output fell to 4 l over the next 24 h following treatment with vasopressin five U s.c. every six hours, but he eventually died of an intracranial haemorrhage.[29] In another study from Chennai, South India on the aetiology of spontaneous DI in 20 patients, one case was attributed to viper bite.[30] C. K. Eapen *et al.* (unpublished data) in a retrospective study of 1000 snake bite cases treated at Little Flower Hospital, Angamaly, Kerala, India have described one case of DI responding to vasopressin.

Although plasma and urine osmolalities were not measured in these cases, there is sufficient evidence to believe that they were suffering from DI. Their responses to vasopressin suggest that they had cranial DI. The pathology might be in the posterior pituitary or hypothalamus.

Predictors of hypopituitarism during acute envenoming

There were no obvious features to predict the subsequent development of hypopituitarism during the acute phase save the severity of envenoming. However, in the study done by Tun-Pe *et al.*[7] Five (71%) out of seven patients with chronic hypopituitarism had oliguric renal failure after the bite. In South India, among 16 cases whose condition in the acute phase of snake bite is described, at least 14 (88%) cases also had oliguric renal failure.[6,25–28] The prevalence of acute kidney injury following Russell's viper bite in general is between 18 and 44%.[3,4] Proby *et al.*[14] studied the pituitary function of patients with renal failure. All 20 had some abnormality of pituitary function. These observations suggest that acute renal failure might be a predictor of subsequent hypopituitarism but this requires further prospective studies.

Diagnosis

Most hormone tests are expensive and not freely available in the areas where Russell's viper bite is prevalent. Ideally, in patients suspected of having hypopituitarism, blood should be collected at the time of envenoming for, at least, free T_4, cortisol and testosterone/oestradiol prior to steroid replacement. The sample could be frozen and sent to the laboratory later. If these tests show low levels, other pituitary function tests, including TSH, follicular stimulating hormone (FSH), luteinizing hormone (LH) and a SST or an ITT, could be done at a later date to confirm the diagnosis of hypopituitarism. In the mean time treatment should be started empirically.

Management

Acute hypopituitarism

In patients with impaired consciousness and hypotension following Russell's viper bite, pituitary failure is a possibility. One patient who had persistent hypotension resistant to inotropes showed a dramatic response to intravenous (IV) hydrocortisone and saline infusion.[7] In patients with impaired consciousness, hypoglycaemia should be excluded by giving a test dose of intravenous glucose after taking a blood sample. The response may be dramatic.[2] Resuscitative measures should also include intravenous corticosteroids.[7] Some authors take a more pre-emptive approach, suggesting that the first doctor seeing the patient should give 50–100 mg hydrocortisone (IV rather than IM in view of the risk of haematoma formation). Steroid support should be continued until the patient improves. After the acute phase (3 weeks), the steroids should be withdrawn under supervision and the pituitary function checked.[31] A study from Burma has reported favourable outcomes with steroid therapy in patients with hypotension following viper bite.[32] Adrenal haemorrhage although rare could also be a cause of cortisol insufficiency in these patients but its management is the same as for secondary adrenal failure.

Steroids are not routinely used in the management of Russell's viper bite in Burma,[33] India (Dr J. Menon, personal communication) or Sri Lanka (Sri Lanka Medical Association Guidelines). However, the WHO SEARO Guidelines for management of snake-bites advocates steroid use in hypotension following Russell's viper bite in Burma and South India.[33]

Since hypopituitarism can be fatal during the acute phase of Russell's viper envenoming, we recommend that steroids be given to severely envenomed patients in geographical areas where there is a high risk of this complication.

Chronic hypopituitarism

Patients presenting with chronic hypopituitarism have shown marked improvement following replacement of their deficient hormones. Among 27 cases with chronic hypopituitarism, the treatment outcome was reported in 11 patients. All improved with hormone replacement. In patients with both steroid and thyroid axis deficiencies, care should be taken to replace the steroid axis before the thyroid axis in order to prevent an adrenal crisis. Those who develop DI can be managed with vasopressin or desmopressin.

Conclusion

Hypopituitarism is an important sequel of Russell's viper bite in countries like Burma and, less so, in South India. It can lead to severe morbidity and mortality but is often overlooked. A high degree of suspicion is needed to diagnose this condition following Russell's viper bite. As most of these bites occur in poor, remote, rural areas it may not be possible to confirm hypopituitarism with laboratory tests. Therefore, early initiation of empirical steroid therapy could be life saving especially in cases of hypotension and hypoglycaemia suggestive of hypopituitarism. Trial of steroids is recommended until formal tests for the pituitary adrenal axis can be carried out. If the patient develops polyuria, particularly after the introduction of steroids, it is worth investigating for DI. It is also important to follow these patients up for at least 6 months with regard to hypopituitarism. Chronic ill health in those who survive the acute episode should alert the physician to the possibility of hypopituitarism.

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