SNAKEBITE ENVENOMATION AND ENDOCRINE DYSFUNCTION

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ABSTRACT

Snakebite envenoming (SBE) is a life-threatening medical emergency encountered in tropical parts of Asia, Africa, and Latin America. Toxins in the venom cause local damage and multi-organ dysfunction, predominantly affecting neurological, hematological, and vascular systems. Endocrine anomalies are less frequently reported and often masked by more severe disorders. Anterior pituitary insufficiency is the most common endocrine manifestation and mainly observed after Russell's viper (*Daboia russelii* and *D. siamensis*) bite. SBE-induced hypopituitarism can manifest early or have a delayed presentation. Primary adrenal insufficiency, hyponatremia, hypokalemia, hyperkalemia, and hyperglycemia are also described. These complications are uncommon and under-reported, as SBE occurs in remote areas and medical facilities for endocrine assessment might not be available. Timely identification and management of these problems are critical for optimum medical outcome.

INTRODUCTION

Snakebite envenoming (SBE) occurs predominantly in rural parts of Asia, Africa, and Latin America (1,2). The World Health Organization (WHO) included SBE in the priority list of neglected tropical diseases in 2018. According to the WHO, 4.5–5.4 million people get bitten by snakes annually, but many cases are not reported as people living in remote areas with limited healthcare access are affected. Clinical illness from SBE develops in 1.8–2.7 million, and the annual mortality is around 81,000 to 138,000 (3).

Toxins in snake venom can cause local tissue destruction, neurological damage, hemorrhagic tendency, renal failure, and cardiovascular compromise. Endocrine dysfunctions are uncommon but can have ominous consequences if not recognized. Anterior pituitary insufficiency (API) after Russell's viper (RV) envenomation (RVE) is the most common endocrine manifestation of SBE. Electrolyte disturbances and hyperglycemia are the other complications described (4). Timely recognition and appropriate management of endocrine derangements like hypocortisolism and electrolyte imbalances can save lives.

SPECIES OF SNAKES AND SNAKE VENOM

The medically relevant poisonous snakes usually belong to the Elapidae and Viperidae families. Rare cases of envenoming from Atractaspididae and Colubridae families are also described. The common Elapidae snakes include cobras, mambas, kraits, coral snakes, death adders, and sea snakes. The Viperidae snakes of significance are vipers, including RV, adders, asps, and pit vipers. The general notion that

Elapidae envenomation results in neuroparalytic manifestation and Viperidae bite induce local reaction and vasculotoxicity does not always hold.

Snake venoms contain mixtures of polypeptides, amines, carbohydrates, lipids, phospholipids, nucleosides, and minerals. The principal constituents are proteins belonging to the four families: phospholipase A2, metalloprotease, serine protease, and three-finger peptides. Additional secondary protein families include cysteine-rich secretory proteins, l-amino acid oxidases, kunitz peptides, C-type lectins/snaclecs, disintegrins, and natriuretic peptides (5).

Snake venom toxicity can be classified into three main categories: vasculotoxic, neurotoxic, and cytotoxic. Various proteins with enzymatic properties such as phospholipase A2, hyaluronidases, peptidases, and metalloprotease can cause local tissue destruction. Phospholipase A2, metalloproteases, and other protein components can cause neurotoxicity, damage the coagulation cascade, induce muscle necrosis, and sometimes exert cardiotoxic and nephrotoxic effects (6). Cardiac compromise and acute kidney injury (AKI) can also emerge as secondary complications. Endocrine disorders after SBE are uncommon and pathophysiologic mechanisms are incompletely understood.

ANTERIOR PITUITARY INSUFFICIENCY

Anterior pituitary insufficiency (API) is the most well-recognized endocrine manifestation of SBE. Most cases are from Sri Lanka, India, and Myanmar and occur after RVE (*Daboia russelii* and *D. siamensis*).

Etiology

Wolff first narrated SBE-induced hypopituitarism in 1958 after bite from *Bothrops jararacussu* (7). The first description of API following RVE in the Indian subcontinent came from Eapen *et al*. (8). Although RV is found in many south Asian countries, most accounts of RVE-induced API are almost exclusively from Myanmar, India, and Sri Lanka (9–16). It could be related to the geographic variation in venom composition among the same snake species. The incidence of API in a study from northern India was 14.6% (6/41) among patients admitted with vasculotoxic snakebites (presumed RVE) (12).

Pathophysiology

The pituitary gland is a highly vascular structure enclosed in a bony cavity called the sella tursica. The low-pressure hypothalamic-pituitary portal system originating from the superior hypophyseal artery provides blood supply to the anterior pituitary. The hypophyseal portal system is susceptible to compressive effects from an enlarged or engorged gland and renders the anterior pituitary vulnerable to vascular insults after stimulation from any cause.

Sheehan's syndrome and RVE-induced hypopituitarism share similar pathophysiology (16,17). In Sheehan's syndrome, hemorrhagic infarction of the pregnancy-induced hyperplastic gland occurs during severe postpartum bleeding-related hypovolemic shock (18). Predisposition to vascular damage in RVE could result from gland engorgement due to a generalized increase in capillary permeability as in capillary leak syndrome (19–21). Additionally, the toxins in RV venom can stimulate pituitary cells as suggested by in-vitro studies, further increasing the susceptibility to damage (22).

The vascular supply to an engorged and stimulated gland might be compromised due to microthrombi deposition or hemorrhage from disseminated intravascular coagulation (DIC) (16,23), circulatory or hypovolemic shock (14), thrombotic occlusion of major vessels including cerebral venous thrombosis (24,25), and increased intracranial pressure (14). Autoimmune damage has been postulated to contribute to delayed pituitary injury in Sheehan's syndrome (26,27). The role of similar immune-mediated damage in the

development of delayed hypopituitarism after RVE has not been studied.

Clinical Features

ACUTE HYPOPITUITARISM

Acute onset API has been observed after RVE in several series and can present as early as the first day (11,12,15). In one series of nine patients, API occurred after a median interval of nine days (range 2-14 days) (15). The usual manifestations of RVE include local reaction, coagulopathy, neuromuscular paralysis, and AKI (28,29). Circulatory shock, another feature of RVE, is multifactorial in etiology (14). In the acute phase, adrenal insufficiency (AI) dominates the clinical presentation of API. The symptoms of AI often get masked by other systemic effects of RVE. Clinical clues could be refractory hypotension and the presence of hypoglycemia or hyponatremia.

Central hypothyroidism may coexist with secondary AI and is diagnosed if serum thyroid-stimulating hormone (TSH) is low or normal along with decreased serum thyroxine levels. TSH can also get suppressed due to sick euthyroid syndrome and glucocorticoid administration. The diagnosis of central hypothyroidism is difficult to discern in the acute phase, and a follow-up test after recovery is necessary for confirmation. Reassessment of hypothalamic-pituitary-adrenal (HPA) and additional evaluation of the gonadotrophic and growth hormone (GH) secretion should be performed after 4-6 weeks. Acute hypopituitarism is sometimes transient, but the typical outcome is a permanent disease (12,13).

DELAYED HYPOPITUITARISM
API is often diagnosed years after RVE (30–33). The symptoms depend on the hormone axis involved and the extent of hormone deficiency (34). Delayed hypopituitarism often presents as secondary amenorrhea and infertility in females. In males, hypogonadotropic hypogonadism usually manifests as loss of libido and erectile dysfunction. Loss of secondary sexual characteristics can be present in both genders.

Standard features of secondary hypothyroidism include cold intolerance, weight gain, constipation, dry skin, and hoarseness. Secondary AI presents as fatigue, loss of appetite, and orthostatic dizziness (34). Involvement in early childhood can cause stunted growth and delayed or absent puberty (31). In a case series of delayed API, secondary hypothyroidism and hypogonadotropic hypogonadism were present in all the cases (8/8); and GH and secondary AI were present in 75% (6/8) (30). Table 1 depicts the recent case series describing API.

Predictors of Hypopituitarism

The presence of acute kidney injury (AKI) most consistently correlates with the development of API after RVE (13,30). Bhat *et al*. found that in patients (n=51) with vasculotoxic snakebite-associated AKI, the risk factors for API were younger age, the number of hemodialysis sessions, and 20-min whole blood clotting time (13). There was a history of AKI in 75% of cases of delayed hypopituitarism in another series (30). In a study describing nine patients with acute API, the predictors were multi-organ dysfunction, lower platelet counts, and more bleeding with a requirement for transfusions (15). However, coagulopathy, AKI, hemodialysis, and clinical severity scores failed to show any association with hypopituitarism in a prospective study (12).

Table 1. Case Series of Hypopituitarism After Snakebite Envenoming					
Author, year	Region	Snake species	No. of patients	Onset, Time	Clinical features/ hormone axes involved/ comments
Tun Pe, 1987(10)	Myanmar	Not defined	Snakebite – 220 Acute API – 3 PH (on autopsy) – 4 Delayed API – 11	Acute: 21 hr - 9 d Delayed: 2 wk - 24 yr	Acute - C, GH, PRL Delayed Symptomatic - 7 Asymptomatic – 4
Proby, 1989 (35)	Myanmar	RV	Acute API (probable) – 20 Delayed API – 11/12	Acute, NA Delayed – 8 - 226 wk	C - 10/15 T - 19/20 G -12/17
Golay, 2014 (11)	West Bengal, India	Vasculotoxic snakebite	API - 9/96 cases of snakebite associated AKI	Acute and delayed, 2 wk - 10 yr	C - 6/9 G, GH, T - 9/9 1 empty sella, rest normal
Rajagopala, 2014 (15)	Puducherry, India	Vasculotoxic snakebite	9/989 cases	Acute, 2-14 d	Hypoglycemia (100%), hypotension (67%) C - 9/9 Partial empty sella in 6/9
Naik, 2018 (12)	India	Vasculotoxic snakebite	9/41 cases	Acute (10%), Mean - 32 hr	Primary AI - 2/6, C, GH, G - 6/6 PRL - 2/6
White, 2019 (36)	Myanmar	RV (85.4%), Rest - cobra, krait, green pit viper, others	20/948 cases	Acute (2%)	Coagulopathy - 68.9%, AKI - 72.2%
Gopalkrishnan, 2018 (14)	India	RV, saw-scaled viper	SB - 248 AI – 12 API - 4	Acute	C -19/48 Autopsy - 52. PH or ischemic necrosis - 46% Bilateral adrenal hemorrhage - 26%, Adrenal ischemic necrosis – 6%

| Shivaprasad, 2018 (30) | Karnataka, India | RV | Delayed API - 8 | Delayed, 5-11 yr | C, GH - 6/8 T, G - 8/8 |
| Bhat, 2019 (13) | West Bengal, India | Vasculotoxic snakebite | API - 11/51 at 7 d and 13/33 at 3 mn after snakebite associated AKI | Acute and delayed, 7 d – 3 mn | C – 12/13 PRL – 9/13 G – 9/13 GH – 5/13 T – 4/13 |

RV - Russell's viper, C - cortisol, GH - growth hormone, G - gonadotropin, PRL - prolactin, T - thyroid, API – anterior pituitary insufficiency, AI - adrenal insufficiency, PH – pituitary hemorrhage, AKI – acute kidney injury, SB- snake bite

Diagnosis

ACUTE HYPOPITUITARISM

It is challenging to diagnose API during the acute phase. The indicators associated with API are summarized in table 2. The assessment of the HPA axis is required to decide the necessity for glucocorticoid replacement. Hypocortisolism in the acute phase is diagnosed from random cortisol or with the cosyntropin stimulation test. In remote areas, if a delay is anticipated in obtaining the cortisol report, hydrocortisone replacement should be started in suspected cases. The different criteria that have been used to diagnose hypocortisolism in the acute phase are (a) fasting serum cortisol < 3 µg/dL (83 nmol/L) (13), (b) random serum cortisol < 5 µg/dL (138 nmol/L) in suspected pituitary apoplexy (37), (c) random serum cortisol < 10 µg/dL (275 nmol/L) in a critically ill patient

(14), (d) post-cosyntropin peak cortisol < 18 µg/dl (500 nmol/L), and (e) post-cosyntropin delta cortisol < 9 µg/dL (250 nmol/L) (38). Note in very ill patients serum cortisol levels can be artifactually low secondary to a decrease in cortisol binding protein.

The interpretation of the thyroid function test can be problematic in the acute phase. Low luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin might be indicative but not diagnostic of API. The gonadal axis and sex hormone secretion (testosterone in males and estradiol in females) is usually suppressed during any severe illness. The pituitary function should be reassessed after 4-6 weeks of recovery. The MRI findings reveal a normal gland on imaging in acute cases (11,12,15). Pituitary hemorrhage has been demonstrated in autopsy findings but is seldom observed in imaging studies (15).

Table 2. Features Suggestive Of or Associated with Acute Hypopituitarism after Russell's Viper Bite		
Clinical features	**Laboratory results**	**Imaging**
Persistent or unexplained hypotension	Hypoglycemia	Pituitary hemorrhage or infarct on MRI
Acute kidney injury	Hyponatremia	
Capillary leak syndrome		
Disseminated intravascular coagulation		

DELAYED HYPOPITUITARISM

Acute hypopituitarism may progress to chronic disease or manifest insidiously years later (11,12,30). It may be prudent to perform periodic surveillance to rule out the development of API following RVE. Hypogonadism has been described in 100% of cases, central hypothyroidism in 96.4%, secondary AI in 82%, and GH deficiency in 77% (30). Central diabetes insipidus (CDI) is very rare and discussed next. The clinical presentation depends on the age, the hormone axes involved, and the mode of onset. The tests recommended for the diagnosis of pituitary hormone deficiency are outlined in table 3. However, facilities for the dynamic tests may not be available in remote areas where SBE is prevalent (34). MRI usually reveals a normal pituitary during the initial year, but partial or complete empty sella may be found later on (4).

Table 3. Investigations for Diagnosis of Chronic Anterior Pituitary Insufficiency		
Hormone	Tests	Interpretation/comments
ACTH	Cortisol, ACTH between 8- 9 AM	Serum cortisol values < 3 µg/dL (83 nmol/L) at 8–9 AM on 2 occasions strongly suggest AI in an appropriate clinical setting. Intermediate levels (3-18 µg/dl; 83 – 497 nmol/L) require cosyntropin stimulation test. Concomitant normal or low ACTH levels indicate secondary AI.
	Cosyntropin (Synacthen) stimulation test	Cosyntropin injection 250 µg (i.v. or i.m.) followed by serum cortisol at 30 min and 60 min. Peak cortisol < 18 µ/dl (500 nmol/L) is suggestive of AI.
	Insulin tolerance test	Serum cortisol < 20 µg/dL (550 nmol/L) at the time of insulin induced hypoglycemia < 40 mg/dL (2.2 mmol/L). Extreme caution required, not practiced in many centers.
TSH	T4 (total or free), TSH	Low T4 with low or normal TSH suggests the diagnosis of central hypothyroidism
GH	IGF-1	Low IGF-1 suggestive but not diagnostic.
	GH stimulation test	Adults: Insulin tolerance test, arginine, GHRH stimulation test, Macimorelin stimulation test, glucagon stimulation test. Children: Clonidine stimulation test in addition to tests used for adults.
Gonadotrophin (Males)	LH, FSH, testosterone (total), SHBG	Low total testosterone (<300 ng/dl (10.41 nmol/L)) between 8–9 AM, preferably on 2 occasions along with low or normal LH, FSH is suggestive of gonadotrophin deficiency. SHBG and free or bioavailable testosterone measurement should be considered in borderline cases.
Gonadotrophin (Females)	LH, FSH, estradiol	Low estradiol in the setting of low or normal LH and FSH in the appropriate clinical setting (amenorrhea/ oligomeorrhea) suggests gonadotrophin deficiency.

Prolactin	Prolactin	Low levels found in hypopituitarism

ACTH – adrenocorticotrophic hormone, AI – adrenal insufficiency, TSH – thyroid-stimulating hormone, T4 – thyroxine, GH - growth hormone, IGF-1 – insulin-like growth factor 1, LH – luteinizing hormone, FSH – follicle-stimulating hormone, SHBG – sex-hormone binding globulin

Management

Acute hypopituitarism typically occurs in critically ill patients with severe envenomation from RV. Intravenous hydrocortisone is required if AI is suspected or diagnosed. Thyroxine supplementation for hypothyroidism should be started only after correcting AI. There is a risk of precipitating adrenal crisis because of the accelerated metabolic clearance of cortisol, if thyroxine is administered before treatment of AI (39). Monitoring of electrolytes, and slow correction of hyponatremia when present, in order to prevent central pontine myelinolysis, are important adjuncts.

If oral intake is proper and the patient is hemodynamically stable, intravenous hydrocortisone can be substituted by oral glucocorticoids. Hormonal evaluation of the entire pituitary axes should be performed after 4-6 weeks of recovery. Replacement of deficient hormones as per standard practice should be instituted if API persists (34).

Post-mortem Findings

Pituitary hemorrhage and ischemic necrosis have been described in autopsy studies of 43% (36/84) cases of RVE in Myanmar (40). Areas of ischemic necrosis with hemorrhage at the center were observed in studies from India (15). Deposition of fibrin microthrombi in the pituitary and other organs, including the kidney, suggests a possible role of DIC in the pathogenesis of API (23).

DIABETES INSIPIDUS

Involvement of the posterior pituitary gland is exceedingly rare in SBE. There are only a few case reports of central diabetes insipidus (CDI) after RVE (13,31,41,42). The posterior pituitary receives direct arterial supply from the inferior hypophyseal artery and is resistant to vascular damage. On the other hand, the anterior gland is susceptible to vascular compromise as it is supplied by the low-pressure hypophyseal-portal system (43). Moreover, CDI occurs when more than 80% of arginine vasopressin (AVP)-producing hypothalamic magnocellular neurons are lost. The posterior pituitary acts as a storage and secretory organ, and persistent CDI ensues only in the presence of significant damage to the hypothalamus (44). Polyuria, a cardinal feature of CDI, may be obscured due to concomitant hypocortisolism and manifest only after glucocorticoid replacement (45). CDI should be treated with nasal or oral desmopressin.

ADRENAL DISORDERS

Etiopathogenesis

Secondary AI from hypopituitarism is the classically described adrenal disorder resulting from SBE. Primary AI is exceptionally uncommon, though adrenal hemorrhage (AH) has been described in imaging studies and autopsy findings. There are cases of AH occurring after RVE and saw scale viper (*Echis carinatus*) bite (40,46,47).

The pathophysiology of AH is related to DIC and has been postulated to resemble Waterhouse–Friderichsen syndrome (48). The adrenal gland is a highly vascular structure that derives its arterial supply from three arteries but is drained by only one adrenal vein and has a dense internal network of capillaries (49). The causal factors behind predisposition to AH after RVE are summarized in table 4 (14,50,51).

Table 4. Factors Predisposing to Hemorrhage after Russell's Viper Envenomation
Intrinsic predisposition of adrenal vascular structure due to arterial supply by 3 vessels but drainage by one vein
Rich subcapsular plexus with limited drainage by venules forming a "dam"
Disseminated intravascular coagulation and hemorrhagic toxins in the venom increase bleeding tendency
Formation of microthrombi in venules impair venous drainage and cause pooling of blood
Pooling of blood due to capillary leak syndrome
Stress-induced trophic effect of adrenocorticotrophic hormone induces adrenal cortical hyperplasia and increase vascularity
Stress-induced catecholamine secretion causes adrenal venous constriction resulting in pooling of blood in the adrenal gland

Diagnosis And Treatment

AH has been described in 36% of cases in an autopsy series, though primary AI is rare (40). Refractory hypotension, hypoglycemia, hyponatremia and hyperkalemia should raise suspicion of primary AI. The presence of associated secondary AI can confound the diagnosis. Bilateral AH with transient AI has been described following RVE. The hemorrhage and adrenal function resolved in weeks (47). Cases depicting chronic AI have been published after vasculotoxic SBE (12). Diagnosis and treatment are similar to secondary AI; the primary differentiating point is elevated plasma ACTH. Mineralocorticoid supplementation may be additionally required in primary AI.

HYPERGLYCEMIA

Etiopathogenesis

Hyperglycemia, an infrequent endocrine complication after SBE, has been described following both elapid (*Bungarus multicinctus multicinctus*) and viper envenomation (*Vipera ammodytes* ammodytes, European viper spp) (52–54). In rat models, common krait (*Bungarus caeruleus*) venom produces hyperglycemia (55). Intraperitoneal injection of saw-scaled viper (*Echis carinatus*) venom in rats suppressed plasma insulin and depleted liver glycogen stores (56). The hyperglycemic effect of Egyptian cobra (*Naja haje*) was also associated with concomitant depletion of liver and kidney glycogen stores. The mechanism of hyperglycemia is presumed to be triggered by a massive surge of catecholamines, a phenomenon observed after scorpion envenomation and in pheochromocytoma (4,57). Scorpion toxins stimulate sodium and inhibit potassium channels leading to intense and persistent excitation of the autonomic nervous system and release of neurotransmitters from the adrenal medulla, activating parasympathetic (early hours) and sympathetic nerve endings (4–48 hours). Catecholamine-mediated activation of the alpha receptors inhibits insulin secretion and contributes to hyperglycemia (54,58).

Clinical Features and Management

In a series of 83 children, viper envenomation resulted in hyperglycemia starting 4 hours after the bite, was moderate in severity, and usually transient. Moreover, hyperglycemia at presentation was a marker of high-grade envenomation (54). Severe hyperglycemia up to 480 mg/dl (26.7 mmol/L) occurred in a 45-day baby

after two hours of bite from a nose-horned viper (*V. a. ammodytes*). (53). A retrospective study from Taiwan found hyperglycemia in 15% (7/44) patients of *Bungarus multicinctus* envenomation. Only one of them had persistent diabetes after recovery (52). Acute pancreatitis can result from the bite of the adder (*Vipera berus*), but associated hyperglycemia was not observed (59,60). Insulin and other antihyperglycemic drugs should be administered for management of hyperglycemia as and when necessary.

ELECTROLYTE DISTURBANCES

Hyponatremia

ETIOPATHOGENESIS

Envenomation by Malayan krait (*Bungarus candidus*), banded krait (*Bungarus fasciatus*)), and vipers can result in hyponatremia (61–68). Hyponatremia sometimes occur secondary to anterior pituitary insufficiency (API) after vasculotoxic envenoming but it has also been reported in the absence of API (4). Initial descriptions suggested that the syndrome of inappropriate antidiuretic hormone secretion (SIADH) could be responsible for hyponatremia (64). However, subsequent accounts revealed that urinary salt loss from natriuretic peptides in venom, rather than SIADH, is the pathogenic mechanism. The urinary salt loss is secondary to venom-derived natriuretic peptides, similar to endogenous natriuretic peptides, and acts on the renal tubules to decrease sodium and water reabsorption (69). Cerebral salt wasting has also been postulated to cause hyponatremia (61). An unusually high prevalence of hyponatremia (89%) was observed in a series of 14 patients with berg adder (*Bitis atropos*) bite in South Africa (67). Many-banded krait (*Bungarus multicinctus*) envenomation caused hyponatremia in 42% of cases (63).

Natriuretic peptides are found in the venom of Elapidae species such as *Bungarus candidus, Bungarus multicinctus, Dendroaspi sangusticeps, Oxyuranus microlepidotus, Pseudonaja textillis,* and *Pseudechis australis* and a few Viperidae species e.g. *Hypnale hypnale, Psudocerastus persicus,* and *Macrovipera lebetina* (66).

CLINICAL FEATURES

The presentation of hyponatremia depends on the severity and acuteness of onset. The clinical profile ranges from asymptomatic hyponatremia to varying alteration in sensorium to frank coma (61,62). Seizures occur in severe cases (62). Usually there are associated systemic features but isolated hyponatremia, hypovolemia, urinary salt loss, and generalized tonic-clonic seizures, following hump-nosed pit viper bite (*Hypnale hypnale*) has been described (66). In a case series of 42 patients admitted in Vietnam, 31 people (73.8%) had hyponatremia, the lowest values occurring an average of two days after the bite. Approximately 42–50% of patients who did not receive antivenom developed significant hyponatremia (< 130 mmol/L) 2–3 days post-bite. (70). Another series of 78 cases of krait bite from Thailand reported hyponatremia in 17.6%, with severe hyponatremia (< 120 mmol/L) developing in four pediatric patients, two of whom developed seizures (71).

MANAGEMENT

Hyponatremia resulting from natriuretic peptides should be corrected by intravenous saline administration. SIADH is not the cause of hyponatremia, and fluid restriction is not recommended. If chronic hyponatremia is suspected, the correction rate should not exceed 10-12 meq/L in any 24 hours to avoid osmotic demyelination (72). If primary or secondary AI is the cause of hyponatremia, glucocorticoid supplementation is necessary.

Hypokalemia

ETIOPATHOGENESIS
Hypokalemia results from both elapid (73,74) and viper envenomation (75–77). Patients with

hypokalemia after RV, common krait (*Bungarus caeruleus*), and Balkan adder (*Vipera berus*) bite demonstrated low trans-tubular potassium gradient (TTKG) ruling out renal potassium loss. The intracellular redistribution of potassium has been suggested as the likely pathophysiological mechanism, as gastrointestinal loss was also unlikely. Beta-adrenergic stimulation from toxin-mediated autonomic dysfunction leads to the intracellular shift of potassium and is the likely cause of hypokalemia (74,75). Concomitant hypomagnesemia and high urinary magnesium excretion were also observed in patients with hypokalemia, following Viperidae bite, presumably resulting from the direct toxic action of venom on the renal tubules (77). A high incidence (71%) of hypokalemia (<3.5 mmol/l) was found in a series of 210 patients from Sri Lanka during the first 48 hours. It was accompanied by metabolic acidosis but not respiratory alkalosis (78).

CLINICAL FEATURES AND MANAGEMENT

Hypokalemia manifests as muscular cramps or weakness, constipation, abdominal bloating, polyuria, and sometimes cause life-threatening complications like arrhythmias, rhabdomyolysis, hypokalemic paralysis, diaphragmatic palsy, and respiratory failure (75). The treatment strategy is similar to that of hypokalemic periodic paralysis. Rebound hyperkalemia is a potential complication during recovery. Potassium should be replaced orally or intravenously, along with appropriate monitoring. Magnesium deficit should be corrected if present (79).

Hyperkalemia

ETIOPATHOGENESIS

Hyperkalemia can complicate envenomation by nose-horned viper (Vipera ammodytes ammodytes), European viper (*Vipera berus*), and hump-nosed viper (*Hypnale hypnale*) (53,80–83). Severe envenomation from these snakes causes hyperkalemia secondary to rhabdomyolysis and AKI, and can be fatal (53,80). Hyperkalemia was present in 7% of cases of SBE in 258 patients from Thailand (77).

Type 4 renal tubular acidosis (T4RTA) is another possible cause of hyperkalemia. It was described during the recovery phase of bite by hump-nosed viper (81,82). Renal biopsy from these patients showed tubular atrophy and focal segmental glomerulosclerosis pattern (81). The underlying cause could be thrombotic microangiopathy caused by toxins in venom leading to patchy cortical necrosis with delayed or partial recovery of renal functions (83).

CLINICAL FEATURES AND MANAGEMENT

Hyperkalemia associated with rhabdomyolysis and AKI can cause life-threatening arrhythmias. The presence of hyperkalemia along with hyperchloremic metabolic acidosis and low trans-tubular potassium gradient (TTKG) is suggestive of T4RTA and has been described in victims of hump-nosed viper bites during recovery from AKI. Fludrocortisone has been used successfully in such cases. T4RTA, in most cases, was transient (82). Hyperkalemia associated with rhabdomyolysis and AKI will require potassium lowering therapy and, in severe cases, dialysis.

Table 5. Summary of Snakebite Envenoming Induced Endocrine Dysfunctions				
Endocrine manifestation	Pathophysiology	Onset of symptoms	Clinical features	Management
Acute hypopituitarism	Hemorrhagic infarction of the anterior pituitary (pathogenesis similar to Sheehan's syndrome)	Hours to days	Hypotension not responding to standard therapy, hypoglycemia, hyponatremia	Glucocorticoid +/- thyroxine replacement
Delayed hypopituitarism	Sequalae of vascular insult to pituitary during acute phase	Months to years	Amenorrhea, hypogonadism, hypothyroidism, secondary adrenal insufficiency, growth hormone deficiency	Replacement of deficient hormones
Diabetes Insipidus	Very rare, possible vascular insult during acute phase	Immediate or delayed	Polyuria, polydipsia	Desmopressin
Adrenal insufficiency	Hemorrhage with or without infarction in the adrenals secondary to coagulopathy	Hours to days	Hypotension and circulatory collapse	Glucocorticoid +/- mineralocorticoid replacement
Hyperglycemia	Massive catecholamine surge	First 4-6 hours	Children more than adults	Standard treatment of hyperglycemia
Hyponatremia	Venom derived natriuretic peptides – renal salt wasting	First 2-3 days	Asymptomatic to varying alteration in sensorium to coma, seizures	Intravenous saline
	Pituitary or adrenal insufficiency			Glucocorticoid replacement
Hypokalemia	Intracellular redistribution of potassium secondary to autonomic dysfunction. Venom-mediated renal tubular damage	Within first 24 hours	Muscle cramps, constipation, abdominal bloating, paralysis, respiratory failure, arrhythmia	Replacement of potassium with precaution to avoid rebound hyperkalemia
Hyperkalemia	Venom mediated thrombotic microangiopathy in the kidneys leading to type 4 renal tubular acidosis	Weeks	Arrhythmia	Fludrocortisone

	Rhabdomyolysis or kidney injury related	Days		Supportive, dialysis in severe cases

CONCLUSION

Endocrine dysfunctions associated with SBE are rare. However, missing the diagnosis can have life-threatening consequences. Acute or delayed anterior pituitary insufficiency is the most common manifestation. Establishing the diagnosis of hypocortisolism and timely glucocorticoid initiation in acute hypopituitarism are critical. Reports of adrenal dysfunction are scarce, though adrenal hemorrhage following RVE has been described more often in autopsy series. Electrolyte abnormalities should be anticipated and managed appropriately. Awareness and appropriate treatment of endocrine dysfunctions in resource-limited settings are necessary for optimal outcome.

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