Review Article
Endocrine and Metabolic Manifestations of Snakebite Envenoming

Saptarshi Bhattacharya,1 Aishwarya Krishnamurthy,1,4 Maya Gopalakrishnan,2 Sanjay Kaira,3 Viny Kantroo,4 Sameer Aggarwal,5 and Vineet Surana6

1Department of Endocrinology, Max Super speciality Hospital, New Delhi, India; 2Department of General Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India; 3Department of Endocrinology, Bhatti Hospital, Kamal, India; 4Department of Respiratory Critical Care and Sleep Medicine, Apollo Hospitals, New Delhi, India; 5Department of Endocrinology, Apex Plus Super speciality Hospital, Rohtak, India; 6Department of Endocrinology, Manipal Hospital, New Delhi, India

Abstract. Snakebite envenoming is a neglected, public health problem in tropical and subtropical regions. Local tissue necrosis, neurotoxic, and hemo-vasculotoxic effects are well-recognized features, whereas the endocrine and metabolic derangements are not as well known. In addition to contributing to morbidity, some of these manifestations can be potentially life-threatening if not recognized early. The most prominent endocrine manifestation is hypopituitarism (HP), which can manifest acutely or remain asymptomatic and present years later. Unexplained recurrent hypoglycemia and refractory hypotension are early clinical clues to suspect corticotroph axis involvement in acute settings. Chronic pituitary failure may present, like Sheehan’s syndrome, several years after the bite. The occurrence of acute kidney injury, capillary leak syndrome, and disseminated intravascular coagulation are predictors of HP. Adrenal hemorrhages are documented in autopsy series; however, primary adrenal insufficiency is very rare and confounded by the presence of HP. Hyponatremia, hypokalemia or hyperkalemia, and dysglycemia can occur, but the mechanisms involved are only partially understood. Awareness, a high index of suspicion, correct interpretation of hormonal parameters, and timely treatment of these abnormalities can be lifesaving.

INTRODUCTION

Snakebite envenoming is a common but neglected health problem in tropical countries.1,2 The annual worldwide mortality attributed to snakebite is as high as 138,000.3,4 This is likely to be an underestimation, as snakebites are not notifiable in many countries, and several bite-related deaths may remain unreported. The estimated mortality from snakebite in India alone is approximately 58,000 per year.7

There are nearly 200 species of medically relevant venomous snakes, most of which belong to Elapidae and Viperidae family (and occasionally family Lampropidiidae and subfamily Atractaspidinae, and family Colubridae [sensu lati]).3 They differ in the chemical composition of their venom and the structure of the venom-delivery apparatus. Snake venom is a complex mixture of proteins, peptides, carbohydrates, lipids, amines, and other small molecules, with effects depending on the type of bite, the amount delivered, and several other factors.9,10 Usually, elapid bites (e.g., cobras, kraits, mambas, coral snakes and certain sea snakes) cause neurotoxic effects, whereas viperid bites cause local tissue destruction and vascular toxicity. This dichotomy in clinical manifestations is not absolute, with an occasional overlap in features of envenoming.11 Clinical manifestations may be local (swelling, blebs, and tissue necrosis) or systemic, involving the muscular system (paralysis and/or rhabdomyolysis), cardiovascular system (hypotension and collapse), and hemostatic system (disseminated intravascular coagulation [DIC]).12,13 Endocrine and metabolic derangements, which include pituitary gland (anterior and rarely posterior) dysfunction, adrenal involvement, dysglycemia, electrolyte abnormalities, and type 4 renal tubular acidosis (T4RTA), are lesser known systemic manifestations which contribute significantly to mortality and morbidity. This review focuses on endocrine and metabolic consequences of snakebite envenoming.

LITERATURE SEARCH STRATEGY

References for this review were identified through searches of PubMed for articles published till May 2020, by using the terms “snakebite,” “snake bite,” “snakebite envenoming,” “snakebite envenomation,” “snake envenoming,” “snake envenomation,” “snakebite poisoning,” “Russell’s viper (RV)” and “Russell’s viper (RVE) envenoming.” In combination with the words “endocrine,” “hormone,” “hypopituitarism (HP),” “pituitary insufficiency,” “hypocortisolism,” “hypothyroidism,” “hypogonadism,” “diabetes insipidus (DI)” “hypoglycemia,” “hyperglycemia,” “electrolytes,” “dyselektrolytemia,” “hyponatremia,” “hypermegmatria,” “hypokalemia,” “hyperkalemia,” “alkalosis,” and “acidosis.” Relevant articles were also identified through searches in the authors’ files and Google Scholar. Articles resulting from these searches and related references cited in those articles were reviewed. Articles published in the English language were included.

PITUITARY DISORDERS

Hypopituitarism is an uncommon but well-recognized complication of viperid envenomings, particularly of RV species (both Daboia russelii and Daboia siamensis).14–20 Hypopituitarism following snake envenoming was first described by Wolff in 1958 after bite of Bothrops jararacussu.14,15 Eapen et al.16 working in Angamaly, Kerala, provided the first reports from India, of both anterior and, later, posterior pituitary dysfunction following D. russelli bite. Tun-Te et al.17 first reported RVE-related acute and chronic pituitary failure from Myanmar. There are reports of both acute and chronic forms of HP from India, Myanmar, and Sri Lanka, but not from other South Asian countries (e.g., Pakistan, Bangladesh, Nepal, Thailand, Cambodia, China, Taiwan, and Indonesia), which are also home to this deadly species. This peculiar geographical difference in clinical features parallels the variation in venom composition of the same snake species.

* Address correspondence to Aishwarya Krishnamurthy, Department of Endocrinology, Max Super speciality Hospital, 108A IP Extension, Patparganj, New Delhi 110092, India. E-mail: aishwaryakr1410@gmail.com
inhabiting different geographic locations. This observation is further supported by geographic clustering of other clinical manifestations like conjunctival edema and capillary leak syndrome (CLS) in Myanmar and India, and rhabdomyolysis and presynaptic neurotoxicity in Sri Lanka and India.11,21–23 Recent venomics and proteomics-based analysis have demonstrated considerable compositional, functional, and immunological differences among geographic variants of RV venoms across the Indian subcontinent.24

Pathophysiology of pituitary insufficiency. The exact pathophysiology of HP following RVE is unknown. It is postulated that mechanisms may be similar to Sheehan’s syndrome (SS), where pituitary apoplexy occurs in an enlarged and vulnerable gland with limited vascular supply (Figure 1).18,19,25 The heightened vulnerability of the pituitary gland to vascular insults following RVE presumably results from two mechanisms:

1. Engorgement of the gland due to CLS.19,26
2. Direct stimulatory effects of RV toxin on pituitary cells—RV venom can stimulate a dose-dependent release of growth hormone (GH), adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH) from rat pituitary cell cultures, without cell lysis.27,28

Vascular insult to this stimulated and engorged pituitary gland may ensue from the following changes:

1. Microthrombi deposition or overt bleeding due to DIC, impairing pituitary vascular supply.26,29
2. Changes in pituitary intravascular pressure triggered by CLS.18,19,30
3. Susceptibility of anterior pituitary vasculature to compressive effects of even minor intrasellar pressure increments, owing to its location in an enclosed, bony sella turcica.31
4. Hypotension from circulatory shock.26
5. Increase in intracranial pressure.26

In an autopsy series of 52 patients, DIC was found to be a significant predictor of pituitary hemorrhage or necrosis.26 In another large series, increased whole blood clotting time (a quantitative indicator of DIC) at presentation was predictive for the development of HP.32 Thus, whereas the vascular insult is multifactorial in etiology, DIC plays an important role, with contribution from CLS.

Lastly, it has been hypothesized that identical to SS, there may be an additional, autoantibody-mediated slow destruction of the pituitary gland over time after the initial envenoming, that presents as delayed HP.19 Pituitary autoimmunity, triggered by the disclosure of “sequestered” pituitary antigens by pituitary tissue necrosis during the acute insult, could play a role in the pathogenesis of RVE-associated delayed HP. In SS, anti-pituitary and anti-hypothalamic antibodies have been demonstrated, suggesting a probable role of pituitary autoimmunity in anterior pituitary dysfunction.33,34 Literature search did not reveal that the presence of antibodies to pituitary has been studied in RVE-induced HP to date and remains an area of potential research.

Clinical features of pituitary insufficiency. Russell’s viper envenoming–related HP can occur acutely within 1 day to 2 weeks of the bite or be delayed as long as 24 years.17,19,35,36 Acute features are recurrent hypoglycemia and refractory hypotension, which respond to glucocorticoids.36,37 Chronic pituitary dysfunction may remain asymptomatic or present insidiously, weeks to years later, with fatigue, weight loss, and loss of appetite.17,32,38 Occasionally, HP is detected only by dynamic pituitary function testing.39,40 The mean time to diagnosis of delayed HP after viper bite was 8 years in a series from Southern India.38

---

**Figure 1.** Pathophysiology of hypopituitarism following Russell’s viper bite. DIC = disseminated intravascular coagulation; ICT = intracranial tension. This figure appears in color at www.ajtmh.org.
Chronic HP may or may not be preceded by acute pituitary dysfunction. On the other hand, acute pituitary insufficiency (API) can be transient or persist indefinitely. It is unknown whether the pituitary function remains normal, in the interval between initial envenoming and diagnosis of delayed pituitary dysfunction. In all probability, chronic HP may be a continuum of clinically manifest or occult pituitary damage, sustained at initial envenoming.

Cortisol and GH axes have been reported to be most commonly affected; however, this pattern of pituitary dysfunction is not universal. Naik et al. reported that somatotrophs (63%) are most commonly affected, followed by gonadotrophs (50%). In the setting of vasculotoxic bite somatotrophs (83%) are most commonly affected, followed by gonadotrophs and lactotrophs.32

In the series by Eapen et al.,16 of 600 cases of snakebite, only one had DI. In another report, a 20-year-old man was diagnosed with central diabetes insipidus (CDI), HP and growth retardation eight years after the bite. Another case of HP with CDI presented peculiarly with torsades de pointes.44 There is one reported case of isolated CDI, with normal anterior pituitary hormones in a 14-year-old boy.45 Diabetes insipidus was diagnosed in two of 13 patients with HP, in another cohort with AKI.32

Central diabetes insipidus occurs only when 80–90% of AVP-producing hypothalamic magnocellular neurons are lost because their capacity for AVP synthesis far exceeds the daily requirements. The posterior pituitary acts as a storage and secretory organ rather than a site of synthesis; thus, to cause CDI, the hypothalamus must be significantly affected. The anterior pituitary is supplied by a low-pressure hypothalamic-pituitary portal system from the superior hypophyseal artery. The posterior pituitary, however, receives direct arterial supply from the inferior hypophyseal artery. The intrasellar pressure changes that can accompany CLS or DIC may be insufficient to compromise posterior pituitary arterial circulation, as opposed to the low-pressure portal system in the anterior part. Thus, the posterior pituitary is resistant to vascular insults, and RVE-related CDI is rare.47
ENDOCRINE MANIFESTATIONS OF SNAKEBITE ENVENOMING

Table 1
Criteria used in various studies for the diagnosis of adrenal insufficiency after Russell’s viper envenoming

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Selection criteria</th>
<th>Diagnostic criteria</th>
<th>Number of HP cases</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golay et al. 37*</td>
<td>Clinical signs and symptoms which were relevant in the acute setting</td>
<td>A peak stimulated cortisol (after ACTH 250 μg) &lt; 18 μg/dL</td>
<td>2</td>
<td>Both persistent HP at 1 year and 13 months</td>
</tr>
<tr>
<td>Rajagopala et al. 36</td>
<td>1. Hypotension [SBP &lt; 90 mm Hg] and unexplained hypoglycemia (at least one episode of VBG level &lt; 55 mg/dL)</td>
<td>1. Random cortisol values &lt; 4.3 μg/dL</td>
<td>9</td>
<td>Three of five survivors had HP at 1 year follow-up, two not completed 1 year, and four died</td>
</tr>
<tr>
<td>Naik et al. 39</td>
<td>Envenoming by venomous snake</td>
<td>Plasma cortisol of less than 350 nmol/L (established from institute’s in-house assay) with inappropriately low ACTH</td>
<td>Five (three with secondary AI and two with primary AI)</td>
<td>At 6 months, secondary AI in 2 and primary AI in 1 (confirmed by provocation test)</td>
</tr>
<tr>
<td>Gopalakrishnan et al. 26</td>
<td>Circulatory shock defined as SBP &lt; 90 mm Hg despite intravenous fluid support of 20 mL/kg crystalloids and persistent oliguria (urine output &lt; 0.5 mL/kg/hour for &gt; 2 hours) or the need for vasopressor support to maintain SBP &gt; 90 mm Hg</td>
<td>Random serum cortisol &lt; 10 μg/dL</td>
<td>12 (63%) of 19 patients with circulatory shock. HP also diagnosed in 4/5 patients who had hypoglycemia, hypotension, and hyperkalemia</td>
<td>Not available</td>
</tr>
<tr>
<td>Bhat et al. 32</td>
<td>Patients with acute kidney injury following vasculotoxic envenoming</td>
<td>Serum cortisol &lt; 3μg/dL with low or inappropriately normal ACTH (OR) cosyntropin stimulated cortisol &lt; 18 μg/dL</td>
<td>11 (21%) of 51 in acute phase. None were symptomatic.</td>
<td>13 (two more) at 3 months</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotrophic hormone; AI = adrenal insufficiency; HP = hypopituitarism; SBP = systolic blood pressure; VBG = venous blood glucose.
* Of nine cases, two were diagnosed within first 2 weeks and considered as acute HP.

Pituitary imaging. Normal sellar appearance on magnetic resonance imaging (MRI), even in the presence of HP, is a common finding in snakebite patients. In the series by Golay et al.,37 seven of eight cases had no abnormality on pituitary imaging (five of whom were imaged within a year of envenoming). One of the cases diagnosed with HP and DI after eight years had findings of partial empty sella with a loss of posterior bright spot. In a series of delayed HP cases, MRI revealed normal findings in two and empty or partially empty sella in six.38 In a prospective study, Naik et al.39 documented empty sella in two patients and normal imaging in four patients at 6 months of follow-up. Rajagopala et al.36 have also described normal pituitary in the setting of acute HP following RVE. In the case of isolated CDI diagnosed 4 months after snake bite, the posterior pituitary bright spot was absent and lower infundibular stalk was thinned out, whereas anterior pituitary was normal.40 The current literature suggests that most HP cases have a normal sellar appearance in the first year, whereas those diagnosed later usually have partial or total empty sella.

Normal pituitary sellar imaging in RVE-induced pituitary dysfunction is contrary to findings in SS, where partial or complete empty sella is usually seen.49 In the early phase of SS, a non-hemorrhagic enlarged pituitary gland with a thin rim of enhancement is seen, following which the gland atrophies gradually, resulting in an empty sella typically by 1 year.50 The authors presume that a similar sequence of events occurs in HP induced by RVE, with a normal-appearing pituitary being observed in the initial year, with subsequent progression to partial or complete empty sella in later years. It is still unclear if this is indeed true and whether sellar imaging needs to be repeated after a year of initial envenoming to detect structural pituitary changes.

Autopsy findings. Unpublished reports of acute hemorrhagic necrosis affecting 25–35% of the anterior pituitary in patients surviving 8–72 hours after RVE have been discussed by Proby et al.35 In an autopsy series from South India, 46% of pituitary specimens demonstrated either ischemic or hemorrhagic necrosis.26 In another report, focal hemorrhages and small fibrin thrombi in the pituitary were observed along with microthrombi and histological evidence of acute tubular necrosis in the kidneys, suggesting that DIC may contribute to the pathogenesis of AKI and acute hemorrhagic necrosis of pituitary.29 Rajagopala et al.36 reported areas of ischemic necrosis with central hemorrhage in two patients. Another autopsy series from Myanmar showed pituitary hemorrhage and necrosis in 36 of 84 (43%) snakebite deaths.51 Thus, the most common pituitary findings in postmortem examination were ischemic necrosis and hemorrhage.

ADRENAL DISORDERS

Adrenal hemorrhage and primary AI are rare complications of snakebite envenoming. Two patients initially diagnosed with secondary AI in the acute phase were subsequently found to have primary AI as confirmed by recovery of ACTH levels along with the persistence of inadequate response to Synacthen stimulation test.39 A diagnosis of primary AI might be missed in the presence of HP.
Adrenal hemorrhages have been documented in several small autopsy series. Right-sided adrenal hematoma along with the right hemithorax, following the saw-scaled viper (Echis carinatus) envenoming, has been reported. In a large autopsy series, 25% had bilateral adrenal hemorrhage, and 6% showed ischemic necrosis. In a recent study, of 84 cases of lethal snakebite, the autopsy revealed AKI in 98%, pituitary hemorrhage/necrosis in 43%, and adrenal gland hemorrhage in 36%.

Like the pituitary, the adrenal gland is a highly vascular organ, and the etiology of hemorrhage and necrosis is likened to that of Waterhouse–Fridrichsen syndrome associated with severe bacterial sepsis with Neisseria meningitidis and Streptococcus pneumoniae infections. Snake venom has active constituents with both procoagulant and hemorrhagic effects that predispose to the development of DIC and, in turn, adrenal hemorrhage or necrosis. Bilateral adrenal hemorrhage may occur because of circulatory shock due to other causes such as bleeding or CLS in the setting of RVE.

**DYSGLYCEMIA**

Hyperglycemia has been reported in pediatric and adult populations with snakebite envenoming. Plasma glucose levels as high as 486 mg/dL at 2 hours and 223 mg/dL at 4 hours have been documented in an infant, after a lethal bite from the nose-horned viper (Vipera ammodytes ammodytes) in Croatia.

In a retrospective study of viper bites in a pediatric population, hyperglycemia was found to correlate with the risk of high-grade envenoming based on clinical severity criteria described by Audebert et al. Plasma glucose > 200 mg/dL has also been reported in seven of 44 cases of the many-banded krait (Bungarus multicinctus multicinctus) envenoming in Taiwan. One of the victims was later diagnosed to have diabetes mellitus.

Transient hyperglycemia has been reported with vipingid as well as elapid envenoming. Snakebite-related dysglycemia is believed to be pathophysiologically similar to autonomic dysfunction seen in severe scorpion sting poisoning or pheochromocytoma. Scorpion envenoming results in an autonomic storm with massive catecholamine release and increases in glucagon and cortisol levels. The counter-regulatory hormones oppose anabolic actions of insulin, leading to hyperglycemia. Catecholamine excess is known to have deleterious effects on glucose and insulin homeostasis. The transient nature of this dysglycemia further supports the possibility of autonomic dysfunction.

**ELECTROLYTE DISORDERS**

Electrolyte imbalance unrelated to pituitary or adrenal disorders has been reported in association with snakebite envenoming. Hyponatremia, hypokalemia, and hyperkalemia have been reported in the literature.

**Hyponatremia.** Hyponatremia is a potentially life-threatening complication of elapid as well as vipingi envenoming. There are isolated reports of hyponatremia following krait bite from Sri Lanka and the South American coral snake (Micrurus corallinus). Severe hyponatremia has been documented in 41% of 60 consecutive victims of Chinese krait bites (B. multicinctus) of the Elapidae family. Hyponatremia usually occurred on the second or third day following the bite and was associated with raised urine sodium levels. A similar observation was made in another series from Vietnam where 74% of cases of the Malayan krait (Bungarus candidus) envenoming developed hyponatremia with low serum osmolality inappropriately elevated urine osmolality with appropriately low ADH levels. Another series of 78 cases of krait bite from Thailand reported hyponatremia in 17.6%, with severe hyponatremia (< 120 mmol/L) in four pediatric patients, two of whom developed seizures.

**Recommendations for management of acute pituitary insufficiency following snakebite envenoming**

<table>
<thead>
<tr>
<th>Potential Risk Factors for Acute HP</th>
<th>Laboratory Tests for HP</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of clinical features such as capillary leak syndrome, disseminated intravascular coagulation, or AKI are risk factors for developing acute HP</td>
<td>Presence of clinical features such as capillary leak syndrome, disseminated intravascular coagulation, or AKI are risk factors for developing acute HP</td>
<td>In those with high index of suspicion, if immediate estimation of cortisol is not possible, then glucocorticoid supplementation can be started without waiting for the results after collecting a blood sample for random cortisol estimation</td>
</tr>
<tr>
<td>Plasma cortisol of &lt; 10 μg/dL or a delta cortisol (change in baseline cortisol at 60 minutes after cosyntropin 250 μg) of &lt; 9 μg/dL is consistent with the diagnosis of hypocortisolism (results not interpretable if glucocorticoid has been administered before testing)</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Consider shifting to oral glucocorticoid once clinically stable and oral intake is adequate</td>
</tr>
<tr>
<td>Intravenous hydrocortisone up to 400 mg/day in three to four divided doses can be administered.</td>
<td>Random plasma cortisol of &lt; 10 μg/dL in a critically ill patient of RVE can be considered to be diagnostic of hypocortisolism</td>
<td>Diagnosis of secondary hypothyroidism should be strongly suspected if serum T4 and T3 levels are low along with a low or inappropriately normal serum thyroid-stimulating hormone level, and thyroxine should be supplemented (in conjunction with corticosteroid axis affection, and, in its absence, sick euthyroid syndrome is a possibility)</td>
</tr>
<tr>
<td>Persistent or unexplained hypotension</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Rest of the pituitary and related hormones (LH, FSH, testosterone or estradiol, proactin, and IGF-1) should be analyzed, and diagnosis of hypocortisolism and hypothyroidism should be confirmed during a follow-up visit after 6–8 weeks of discharge</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Resource-limited settings</td>
</tr>
<tr>
<td>Persistent hyperkalemia</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>In those with high index of suspicion, if immediate estimation of cortisol is not possible, then glucocorticoid supplementation can be started without waiting for the results after collecting a blood sample for random cortisol estimation</td>
</tr>
<tr>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
</tr>
<tr>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
<td>Evidence of pituitary hemorrhage on imaging (magnetic resonance imaging)</td>
</tr>
</tbody>
</table>

FSH = follicle-stimulating hormone; HP = hypopituitarism; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; RVE = Russell’s viper envenoming; T3 = tri-iodothyronine; T4 = thyroxine.
Hyponatremia has also been described after envenoming from vipers, with reported cases following bites by the berg adder (Bitis Atrospos), endemic to South Africa, and the hump-nosed pit viper (Hypnale hypnale) from Sri Lanka. In a series of berg adder bite victims, hyponatremia was documented in eight of nine patients. The lowest documented sodium was 111 mmol/L, and hyponatremia occurred after 18–48 hours of envenoming, similar to the temporal profile of krait bite–induced hyponatremia. Detailed laboratory assessment of four cases revealed mean serum sodium of 123 mmol/L, mean urine sodium of 114.7 mmol/L, mean plasma osmolality of 262.2 mosm/kg, and mean urine osmolality of 663.2 mosm/kg. By contrast, another series describing 224 envenomings of the hump-nosed pit viper (Hypnale hypnale) from western Malabar coast of India did not describe hyponatremia in the clinical manifestations.

Early reports suggested that hyponatremia occurred because of the syndrome of inappropriate antidiuretic hormone (SIADH). Interestingly, fluid restriction, the standard management of SIADH, resulted in severe dehydration in three children, which ruled out SIADH as a possible cause and subsequent management of all hyponatremic patients with normal saline infusions yielded favorable response.

Hyponatremia can occur because of HP in vasculotoxic envenoming (e.g., RVE), whereas in neurotoxic envenoming, it is because of a different mechanism. It may be a direct effect of venom components per se, as natriuretic peptides (NPs) have been identified in the venom of several snake species. Dendroaspis NP has been isolated from venom glands of the green mamba (Dendroaspis angusticeps) and is found to have higher potency and stability than mammalian NP. It was investigated for therapeutic benefit in heart failure. Novel NPs have been isolated and characterized from venoms of other snakes such as the inland taipan (Oxyuranus microlepidotus), Iranian viper (Pseudocerastes persicus), Brazilian rattle snake (Crotalus durissus cascavella), blunt-nosed viper (Macrovipera lebetina), eastern brown snake (Pseudechis australis), and mulga snake (Pseudechis australis). Although most cases of hyponatremia observed after snakebite envenoming are acute in nature, but standard precautions related to slow normalization of serum sodium levels should be undertaken if there is any suspicion of chronic hyponatremia (> 48 hours), to avoid osmotic demyelination syndrome.

Hypokalemia. Hypokalemia can occur as a complication of neurotoxic envenoming and contribute to muscle weakness associated with these bites. Hypokalemia was previously presumed to be due to respiratory alkalosis from hyperventilation. A series of common krait (Bungarus caeruleus) bite from Sri Lanka found hypokalemia in 71% (n = 210), which was associated with metabolic acidosis and normal blood gases. The authors hypothesized that β-adrenergic stimulation from the autonomic dysfunction related to neurotoxic envenoming resulted in an intracellular shift of potassium, causing hypokalemia. This study, however, did not assess for external potassium losses and the possible role of other hormonal factors like insulin and aldosterone. This association between the potential pathogenic role of autonomic dysfunction in hypokalemia is supported by another report from India of hypokalemia following a Sind krait (Bungarus sindanus) bite where the patient had severe autonomic disturbances and cardiac complications.

Another report documented two victims of common krait bite, who developed deep coma and hypokalemia, with low renal potassium excretion and no evidence of gastrointestinal potassium loss (no diarrhea or ileus). The authors proposed that hypokalemia occurred due to an intracellular shift in a mechanism similar to barium poisoning. Barium ions increase the activity of Na+/K+ ATPase enzyme and block potassium channels to interfere with its passive diffusion, leading to a drop in extracellular potassium.

Hypokalemia has also been reported following Malayan krait bites in Thailand while being conspicuously absent in envenoming by banded kraits. However, the authors acknowledge the low numbers of banded krait victims (n = 9) as compared with Malayan krait bites (n = 68) in the series.

Although most reported cases of hypokalemia are from envenoming by elapids, it has also been reported from Hungary and Croatia following bites by Balkan adders (Vipera berus bosniensis). Despite belonging to the viperid family, this species predominantly causes neurotoxic manifestations. It has also been reported in RVE associated with API, which persisted for 5 days, despite high-dose intravenous potassium replacement. Because renal potassium loss was ruled out, a direct effect of components of RV venom per se, with or without contribution from stress-induced catecholamine release, was postulated to be responsible for the hypokalemia. The patient was treated with dexamethasone for API, which has no mineralocorticoid action (ruling out iatrogenic hypokalemia). Snake envenoming–induced redistributive hypokalemia should be managed similarly to hypokalemic periodic paralysis, and there lies a potential risk for rebound hypokalemia later.

Type 4 renal tubular acidosis. Type 4 renal tubular acidosis is characterized by hyperkalemia, normal anion gap metabolic acidosis, and inappropriately low urine transtubular potassium gradient (TTKG). There are three reports from SriLanka of T4RTA, following bites from the hump-nosed viper (Hypnale hypnale). The first patient developed AKI, required dialysis initially, and renal function gradually recovered over 10 weeks. Acute onset lower limb paraparesis occurred at 18 weeks, accompanied by hyperkalemia and mild renal dysfunction (eGFR-76 mL/minute), normal anion gap acidosis, urine pH of 5, and TTKG of 1.8. The findings suggested T4RTA, which was further corroborated by a response to fludrocortisone. Interestingly, this was transient, with a decrease in fludrocortisone requirement and complete recovery in the next 3 weeks. Two other cases were documented during the polyuric phase of recovery from AKI, with transient but severe intractable hyperkalemia (requiring dialysis) with normal anion gap metabolic acidosis and low TTKG.

It is unclear whether the mechanism of type 4 RTA in snake bite survivors is due to specific factors present in the venom or due to renal damage sustained at initial envenoming.

FUTURE DIRECTIONS

Many questions remain regarding endocrine and metabolic manifestations of snakebite envenoming. Early antivenom administration in RVE can prevent the progression of both coagulopathy and CLS, which are implicated in the pathogenesis of API. It is unclear whether this measure can prevent the occurrence of acute or chronic HP. Mortality benefits of early glucocorticoid administration in RVE, particularly in...
cases of refractory shock, merit exploration. Pathogenesis of electrolyte disorders and the role of pituitary autoimmunity in pituitary insufficiency are largely speculative. Specific interventions for these are possible only after a systematic investigation in larger populations. Advances in venom sequencing and next-generation proteomics may help identify specific venom components that cause particular clinical features.

CONCLUSION

Snakebite envenoming can cause major endocrine complications, which, if unrecognized, can be lethal. Acute pituitary insufficiency, hyponatremia resulting from natriuresis, and hypokalemia by the intracellular shift of potassium are emergencies that can occur after snakebite. Sometimes, the pituitary insufficiency may go unrecognized in the acute phase and manifest years later with chronic HP. Lacunae exist in our understanding of the mechanism of these abnormalities and remain to be explored. Awareness and knowledge of these conditions will decrease morbidity and mortality resulting from snakebite.

Received March 2, 2020. Accepted for publication June 2, 2020.

Acknowledgments: The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

Authors’ addresses: Saptarshi Bhattacharya and Aishwarya Krishnamurthy, Department of Endocrinology, Max Superspeciality Hospital, New Delhi, India, E-mails: saptarshi515@gmail.com and aishwaryakrishyakr141@gmail.com. Maya GopalaKrishnan, Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India, E-mail: mayagopala@gmail.com. Sanjay Kalra, Department of Endocrinology, Bharti Hospital, Karnal, India, E-mail: bridedk@gmail.com. Vinya Kantroo, Department of Respiratory Critical Care and Sleep Medicine, Indraprastha Apollo Hospital, New Delhi, India, E-mail: vinyakantroo@gmail.com. Sameer Aggarwal, Department of Endocrinology, Apex Plus Superspeciality Hospital, Rohtak, India, E-mail: drsameerendocrinology@gmail.com. Vineet Surana, Department of Endocrinology, Manipal Hospital, New Delhi, India, E-mail: vks183@gmail.com.

REFERENCES


