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Delayed hypopituitarism following Russell's viper envenomation: a case series and literature review

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Abstract

Purpose Hypopituitarism (HP) is an uncommon consequence of Russell's viper envenomation (RVE). Delayed hypopituitarism (DHP) presents months to years after recovering from snake bites (SB). The clinical presentation, manifestations, and outcomes of DHP following RVE have not been systematically studied. Here, we present a case series of HP following RVE with delayed diagnosis and conduct a literature review.

Methods We retrospectively reviewed data of eight DHP cases and literature to outline the presentation, manifestations, hormonal profiles, and radiological features of DHP following RVE.

Results Three men and five women, with a mean age at diagnosis of 39.5 ± 11.6 years, were included. The mean duration between snake bite (SB) and HP diagnosis was 8.1 ± 3.6 years. Secondary hypothyroidism and hypogonadotropic hypogonadism were present in all patients. Growth hormone deficiency (GHD) and secondary hypocortisolism were present in 6 (75%) patients. Magnetic resonance imaging (MRI) revealed empty sella and partially empty sella in three patients each (75%). The literature review revealed additional 20 DHP cases (mean age at diagnosis 32.4 ± 10.8 years), with 65% of patients being men. Fatigue, reduced libido, and loss of weight were the commonest symptoms among men. Secondary amenorrhea, fatigue, and loss of appetite were common manifestations among women. Acute kidney injury, GHD, secondary hypothyroidism, hypogonadism, and adrenal insufficiency were reported in 75%, 79%, 95%, 100%, and 85% of patients, respectively.

Conclusions DHP is an important complication of RVE, and a delay in its diagnosis is associated with significant morbidity. Patients with RVE should be followed up for a long term to identify DHP.

Keywords Russell's viper envenomation · Snake bite · Hypopituitarism · Delayed presentation · Pituitary necrosis · Amenorrhea

Introduction

SB is a significant health hazard for rural farmers of tropical countries [1], accounting for approximately 0.5% of all deaths in India. It is also associated with significant morbidity and long-term sequelae [2, 3]. India is home to > 200 species of snakes, of which approximately 60 species are poisonous [3]. However, four species of snakes, collectively referred to as the Big Four, the king cobra (*Naja naja*), Russell's viper (RV) (*Daboia russelii*), saw-scaled viper (*Echis carinatus*), and common krait (*Bungarus caeruleus*), are highly venomous, accounting for most poisonous bites and associated morbidity. RV and saw-scaled viper inhabit most of the Indian states, and the former is a leading cause of fatal SBs in India [4]. Vipers are vasculotoxic and the manifestations of viper envenomation include local cellulitis and tissue necrosis, bleeding, neurotoxicity, acute kidney injury (AKI), and shock [5]. Coagulopathy occurs in a large proportion of patients and is the main contributing factor to many complications. A polyvalent anti-snake venom serum (ASV), widely available in India, deactivates the venom of all major snake species and is administered to all SB patients. The early administration of polyvalent snake antivenom results in reduced mortality and acute complications of viper bite; however, its impact on long-term sequelae has not been assessed [6].

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Hypopituitarism (HP) is an uncommon consequence of Russell's viper envenomation (RVE). HP following RV bite was first reported in 1976 by Eapen et al. in three adults from South India, and subsequent isolated case reports from India and neighboring Asian countries have recognized this unusual complication [7]. Both acute and delayed presentations of HP following envenomation have been reported [8, 9]. Hypoglycemia, hypotension, and shock are presenting features of acute HP during the early hours of envenoming. Delayed HP (DHP) presents months to years after recovering SB, and manifestations are subtle and insidious [10]. Whether this delayed presentation represents an acute anterior pituitary insult that is diagnosed late or the slow and progressive destruction of anterior pituitary over months to years remains unknown. AKI following SB has been identified as a risk factor for HP development [11]. However, diabetes insipidus following viper bite has been rarely reported.

HP cases have only been reported from a few geographical locations, despite a wide distribution of vipers throughout Southeast Asia, raising concerns that many HP cases might be undiagnosed. Delay in the diagnosis can occur due to several reasons. First, the symptoms of HP are nonspecific and insidious. Second, HP symptoms in the elderly can be easily labeled as age-related physiological changes. Third, HP symptoms can be masked by other chronic ailments with similar manifestations. Untreated HP can have several adverse consequences and impaired quality of life. Prompt recognition and early institution of treatment can reduce the symptoms and consequences of hormone deficiency and improve the quality of life in chronic HP. As the disease is rare, characterization has been reported through case series, and the presentation, manifestations, and outcome of this complication have not been systematically assessed. Here, we present a case series of eight patients with HP following RVE where the diagnosis was significantly delayed. We also conduct a literature review to outline the clinical presentation, hormonal profile, and pattern and degree of hormonal deficiencies in patients diagnosed with DHP following RVE.

Methods

This case series is based on eight patients with delayed presentation of HP following RV SB. These patients were treated at the endocrine clinic of Vydehi Institute of Medical Sciences and Research Centre, Bangalore, India, between 2013 and 2018. We reviewed medical records of these patients to extract the relevant data. These patients were treated for SB elsewhere and recovered from acute complications. Patients presented to or were referred to our clinic for endocrine issues several months after SB. The snake species was confirmed based on the discharge summary of the acute episode, description of the snake, and corroboration with representative photos. All patients were surveyed with regard to their wellbeing after SB and questioned about HP symptoms (fatigue, loss of axillary and pubic hair, amenorrhea, reduced libido, infertility, dry skin, cold intolerance, puffy face, and breast atrophy). Fasting blood samples were obtained at 8 AM to measure free thyroxin (FT4), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin, total testosterone, and estradiol. We defined HP as deficiency of one or more pituitary hormones as follows: secondary hypothyroidism was defined as low FT4 (normal 0.64–1.12 ng/mL) with low or normal TSH (normal 0.5–4.2 IU/mL). Secondary adrenal insufficiency and GHD were defined as a peak stimulated cortisol of < 18 mcg/dL and peak GH < 3.0 µg/L, respectively, during the insulin tolerance test. Hypogonadotropic hypogonadism was defined as low testosterone (< 250 ng/dL) or low estradiol (< 15 pg/mL) in the setting of low or normal gonadotropins.

We surveyed the published literature in PUBMED, Google and EMBASE using the following terms: SB, HP, chronic HP, viper, RV and pituitary, in different combinations. We reviewed original articles published in English between 1995 and 2018 and included case series and isolated case reports with requisite information. Relevant articles were identified by title and abstract and/or full text review and screened for the completeness of clinical profile, radiological data and hormonal assays. Only those publications reported in English and included (i) patients with history of RV or saw-scaled viper bite (ii) delayed presentation of HP (iii) HP diagnosed by hormonal assays, and (iv) radiological imaging of pituitary either by MRI or computed tomography scan were selected. Data on demographic and geographic details, administration of ASV, history of AKI/hemodialysis following SB were collected. Cases with diagnosis of HP within 8 weeks after SB were excluded.

Data were tabulated and analyzed using Microsoft Excel (Microsoft Corp.). Descriptive data are expressed as mean ± SD, ranges and percentages. The percentage calculation was done by excluding the missing data for each variable analyzed.

Results

We identified eight cases (five women and three men) of delayed HP owing to RVSB (RV snake bite) over 5 years. Six cases were clinically suspected to have HP and underwent hormonal assessments. In two cases, diagnosis was established before the patients visited our clinic. The baseline characteristics and profile of pituitary dysfunction are presented in Table 1. The mean body mass index (BMI)

Table 1 Clinical, hormonal, and radiological features of eight patients with DHP owing to RVE

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	42	34	37	47	22	27	51	55
Sex	M	M	F	F	M	F	F	F
Age at snake bite (years)	29	28	34	37	18	15	43	46
Duration of symptoms	8	1	2	3	2	3	6	7
Clinical presentation	Weight loss, nausea, fatigue, loss of libido	Recurrent hypoglycemia, vomiting, fainting	Fatigue, hypotension amenorrhea, weight loss	Weight loss, amenorrhea, fatigue	Fatigue, cold intolerance, loss of libido	Weight loss, amenorrhea, infertility, fatigue	Headache, facial puffiness, early menopause, weight loss	Fatigue, cold intolerance, dry skin
BMI	18.3	16.9	15.01	16.8	22	19.8	20.67	22.8
Vision	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Free T4 (ng/dL)	0.34	0.47	0.44	0.46	0.57	0.61	0.52	0.36
TSH (μIU/mL)	0.69	1.55	0.03	6.31	0.04	2.84	0.2	4.84
LH (IU/L)	3.9	2.52	0.19	3.2	1.69	0.67	0.5	0.55
FSH (IU/L)	2.3	1.7	0.16	3.7	1.75	1.86	1.72	4.94
Total testosterone (ng/dL)	87.2	20.3	-	-	121.4	-	-	-
Estradiol (pg/mL)			7.5	11.3		4.5	NA	NA
ACTH (pg/mL)	8.1	12.2	15.5	20.2	6.4	31.3	17.8	3.48
Cortisol (mcg/dL)	1.76	1.32	1.84	5.91	1.53	5.81	1	0.13
Cortisol post ITT	4.78	2.8	3.2	18.9	4.9	21.2	7.4	1.2
GH (ng/mL)	0.05	0.2	0.02	0.07	0.03	0.27	0.03	0.07
GH post ITT	1.1	4.4	0.54	3.2	0.08	0.9	0.03	0.06
Prolactin (ng/mL)	3.2	2.1	3.8	4.8	4.2	3.8	2.9	8.9
Diabetes insipidus	No	No	No	No	No	No	No	No
Pituitary MRI	Partially empty sella	Empty sella	Empty sella	Normal	Partially empty sella	Normal	Partially empty sella	Empty sella

TSH thyroid-stimulating hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *ACTH* adrenocorticotropic hormone, *ITT* Insulin tolerance test

Reference norms: free T4—0.64–1.12 ng/mL, TSH—0.5–4.2 IU/mL, total testosterone: 250–800 ng/dL, ACTH—7.2–63 pg/mL, serum cortisol—5–23 mcg/dL, estradiol—15–350 pg/mL

was 19.03 ± 2.74. The mean age at diagnosis was 39.5 ± 11.6 years, and the mean duration between SB and HP diagnosis was 8.1 ± 3.6 years. The mean duration of symptoms that led to the diagnosis of HP was 4 ± 2.6 years.

Fatigue (2/3) and loss of libido (2/3) were the commonest symptoms among men. Among women, secondary amenorrhea was present in all the patients. None of the patients reported abrupt cessation of menses following SB. Weight loss (4/5) and fatigue (4/5) were other common symptoms among women. Weight loss was a complaint in six of our patients. Of six patients, prior BMI values were available only for three (1, 3, and 4), and the weight losses were 6.5, 11, and 8 kg, respectively. Two cases (5 and 8) did not complain of weight loss, and their BMIs at the time of snake bite were not available. Secondary hypothyroidism and hypogonadotropic hypogonadism were present in all the cases. GHD and secondary hypocortisolism were present in 6 (75%) patients. Two patients (cases 4 and 6) had cortisol levels > 18 mcg/dL post insulin tolerance test and two of them (cases 2 and 4) had normal GH axis. Hyperprolactinemia and

diabetes insipidus were not present in any of our patients. Radiological evaluation with pituitary MRI revealed empty sella and partially empty sella in three patients each and was normal in the remaining two patients.

Our systematic review identified two case series [11, 12] and 13 case reports [10, 13–24]. Full texts were available for all the articles reviewed. We analyzed the clinical presentation, hormonal profile, radiological picture and the management. In the first case series, two cases were excluded because HP was diagnosed within 8 weeks of SB. In the second case series, three out of four cases had to be excluded because of lack of hormonal assays and radiological data. A case report was excluded because of incomplete information [18]. In total, we were able to retrieve 20 cases of delayed HP due to RVE with requisite clinical, hormonal and radiological information. One of the cases was reported to be secondary to saw-scaled viper SB and the remaining cases were suspected to be due to RVE. In six case reports, GH axis was not assessed and in two reports, MRI data were not available; nonetheless, we included these cases in the review. All except one of these cases reported were from India. The demographics, disease manifestations, hormonal profiles and radiological evaluations are summarized in Table 2. The mean age at presentation was 32 ± 10.1 years (range 12–49), and 13 (65%) patients were men. The mean duration between the SB and diagnosis of HP was 5.2 ± 4.7 years (range 0.25–15). Fatigue, reduced libido and loss of weight were the three most common symptoms among men. Secondary amenorrhea, fatigue and loss of appetite were the three common manifestations among women. Unusual presentations included psychosis and thyrotoxicosis. History of AKI following SB was reported in 15 (75%) cases. GHD and secondary hypothyroidism, hypogonadism and adrenal insufficiency were reported in 11/14 (79%), 19/20 (95%), 19/19 (100%) and 17/20 (85%) cases, respectively. Pituitary MRI was reported to be normal, empty sella and partially empty sella in 8/18 (44%), 6/18 (33%) and 4/18 (22%) cases, respectively. Diabetes insipidus was reported in only two patients. A summary of hormonal profiles and radiological findings of our series and literature review is provided in Table 3. Secondary hypothyroidism and hypogonadism were almost universal while GHD and secondary adrenal insufficiency were present in nearly 80% of cases. Pituitary MRI revealed empty sella or partially empty sella in 16/26 (61.6%) patients.

Discussion

In this study, we reported the clinical presentation, manifestations, and outcomes of DHP following RVE and also performed a literature review. We found that DHP was an important RVE complication and that a delay in its diagnosis was associated with significant morbidity.

HP is an unusual complication of RV bite that has been reported in countries such as India, Burma, and Sri Lanka. In DHP, clinical manifestations of pituitary dysfunction are insidious on onset, subtle, and nonspecific, and in most patients, they commence months to years after recovering from SB. Apparent complete recovery from acute episodes of envenomation without any HP signs and delayed insidious onset of non-specific symptoms frequently leads to delayed diagnosis. This delayed presentation is somewhat similar to that of Sheehan's syndrome, where the anterior pituitary dysfunction in affected women may remain undiagnosed for years.

Tun-Pe et al. identified seven HP cases in 24 long-term survivors of severe RV bite envenomation, and subnormal responses to stimulation tests were reported in an additional four asymptomatic patients [8], suggesting a relatively high prevalence of HP following RV bite. However, given the number of SB and its fatalities (estimated to be 50,000 per annum in India), reports on DHP owing to SB have surprisingly been few and far since then [3], prompting us to present this case series and review the literature for cases of delayed HP owing to RVE.

In our case series, the presentation was insidious, starting several months after SB, most frequently with fatigue and hypogonadism symptoms such as reduced libido and secondary amenorrhea. In our cases, establishing the diagnosis and initiating therapy were significantly delayed. Half of the patients had a history of AKI during the acute episode. Two patients had repeated visits to the emergency department for hypoglycemia and hypotension before the condition was recognized. Panhypopituitarism was present in nearly 80% of patients with secondary hypothyroidism and hypogonadism in all the patients. None of our patients had diabetes insipidus and MRI of the pituitary revealed empty sella or partially empty sella in six patients. Based on the literature review, HP appears more common in men, although our case series had a female predominance. Fatigue, reduced libido, secondary amenorrhea, and loss of appetite were common presenting complaints. A high proportion of patients had AKI following envenomation. In the case series by Golay et al., approximately 10% of patients with viper bite developed HP. A history of hypotension and severe AKI requiring hemodialysis during the episode were also associated with HP. Development of chronic kidney disease on follow-up also predicted the development of HP [11]. Our analysis indicated that secondary hypogonadism and hypothyroidism occurred most frequently, followed by secondary adrenal insufficiency and GHD. Three hormonal axes were involved in $>80\%$ of patients. Diabetes insipidus was rare and was reported only in two cases. Normal pituitary imaging did not preclude DHP, and MRI findings were normal in nearly

Table 2 Case series and individual reports of DHP following viperine snake bite

Case no.	Patients (n)	Age (years)	Sex	Duration[a]	Presenting feature	AKI	Hypothyroidism	Secondary hypogonadism	GHD	Secondary Hypocortisolism	DI	MRI finding	Publication
1	1	35	F	0.25	Generalized edema, amenorrhea	–	+	+	NA	+	–	NA	James and Kelkar [12]
2	7	31	M	9	Fatigue, weight loss, cold intolerance	+	+	+	+	+	–	Normal	Golay et al. [11]
3		42	M	10	Decreased Libido	+	+	+	–	–	–	Normal	
4		35	M	0.33	Fatigue, decreased libido, loss of hair	+	+	+	–	+	–	Normal	
5		12	M	8	Growth retardation, generalized weakness, cold intolerance	+	+	+	+	+	+	Partially empty sella	
6		32	F	0.75	Fatigue, poor quality of life, loss of weight	+	+	+	+	–	–	Normal	
7		28	M	0.25	Generalized weakness, loss of libido, loss of weight	+	+	+	+	+	–	NA	
8		22	F	0.33	Fatigue, anorexia, constipation	+	+	+	+	–	–	Normal	
9	1	49	M	3	Generalized weakness, lethargy, reduced libido	–	+	+	–	+	–	Normal	Antony et al. [10]
10	1	45	M	8	Lethargy, loss of appetite	+	+	NA	NA	+	–	Empty sella	Srinivasan et al. [13]
11	1	28	M	3	Fever, drowsiness, loss of consciousness	–	+	+	+	+	–	Empty sella	Bandhyopadhay et al. [14]
12	1	20	M	8	Growth retardation, weakness, cold intolerance	+	+	+	+	+	+	Partially empty sella	Golay et al. [17]
13	1	25	F	5	Amenorrhea, loss of appetite, cold intolerance	+	+	+	NA	+	–	Partially empty sella	Prabhakar et al. [15]
14	1	42	M	15	Weakness, lethargy, coarse facial features	+	+	+	+	+	–	Empty sella	Kamath and Satish kumar [16]
15	1	19	F	0.25	Recurrent vomiting, weight loss, amenorrhea	+	–	+	NA	+	–	Normal	Shetty et al. [20]
16	1	35	M	5	Weakness, coarse facial features, loss of libido	+	+	+	+	+	–	Empty sella	Chakrabarthi [19]
17	1	37	F	0.91	Fatigue, amenorrhea, hypotension, depression	–	+	+	+	+	–	Normal	Sudulagunta et al. [21]
18	1	42	M	13	Hypopigmentation, psychosis	–	+	+	NA	+	–	Empty sella	Ratnakaran et al. [22]
19	1	43	M	NA	Fatigue, fainting, myalgia	+	+	+	+	+	–	Empty sella	Amalnath and Baskar [23]

Table 2 (continued)

Case no.	Patients (n)	Age (years)	Sex	Duration[a]	Presenting feature	AKI	Hypothyroidism	Secondary hypogonadism	GHD	Secondary Hypocortisolism	DI	MRI finding	Publication
20	1	18	F	0.33	Amenorrhea, lethargy, headache	+	+	+	NA	+	–	Partially empty sella	Majumdar et al. [24]
21	8	42	M	13	Weight loss, nausea, fatigue	+	+	+	+	+	–	Partially empty sella	Present series
22		34	M	6	Recurrent hypoglycemia, vomiting, fainting	+	+	+	–	+	–	Empty sella	
23		37	F	3	Fatigue, hypotension, amenorrhea, weight loss	+	+	+	+	+	–	Empty sella	
24		47	F	10	Weight loss, amenorrhea, fatigue	–	+	+	–	–	–	Normal	
25		22	M	4	Fatigue, cold intolerance, loss of libido	–	+	+	+	+	–	Partially empty sella	
26		27	F	12	Amenorrhea, infertility, fatigue, weight loss	+	+	+	+	–	–	Normal	
27		51	F	8	Headache, facial puffiness, early menopause, weight loss	–	+	+	+	+	–	Partially empty sella	
28		55	F	9	Fatigue, cold intolerance, dry skin	–	+	+	+	+	–	Empty sella	

DHP delayed hypopituitarism, *NA* Not available, *AKI* acute kidney injury, *GHD* growth hormone deficiency, *DI* diabetes insipidus

[a]Duration between snake bite and diagnosis of HP in years

Table 3 Hormonal deficiencies and radiological findings in 28 cases of DHP

	N = 28
Age (years; mean ± SD)	34.1 ± 11.0
Sex: male (%)	16 (57%)
Duration between SB and diagnosis of HP in years: (mean ± SD)	5.8 ± 4.6
Renal failure: n (%)	19 (68%)
Hypothyroidism: n (%)	27 (96.4%)
Hypogonadism: n (%)	27 (100%)
GHD: n (%)	17 (77%)
Secondary adrenal insufficiency: n (%)	23 (82%)
Diabetes insipidus: n (%)	2 (7%)
Pituitary MRI	Empty sella: 9 (34.6%) Partially empty sella: 7 (27%) Normal: 10 (38.4%)

SB snake bite, *GHD* growth hormone deficiency

one-third of cases. This is in contrast to Sheehan's syndrome where a high proportion of patients have empty or partially empty sella [25]. Moreover, no correlation was observed between the presence of empty sella and the severity of hormonal deficit with respect to the number of hormonal axes involved.

RV venom has several biologically active procoagulant enzymes and hemorrhagins that result in coagulopathy and disseminated intravascular coagulation [26]. Fibrin deposition in the pituitary blood vessels and hypoxic–ischemic damage to the pituitary owing to hypotension contribute to pituitary dysfunction, and micro thrombi and hemorrhages are observed in the pituitary gland [27, 28]. Another postulated hypothesis is increased vascular permeability that causes pituitary swelling in the confines of sella with associated hypoxia, ischemia, or bleeding causing pituitary necrosis such as that in Sheehan's syndrome [10, 29].

Although it is unclear whether the delayed presentation represents acute anterior pituitary insult that is diagnosed late or the slow and progressive destruction over months to years, based on the literature review, it appears that both factors could be relevant in different cases. In some cases, the onset of HP symptoms started immediately after recovery from the acute episode, and HP diagnosis was established within 6–12 months. The likely underlying mechanism is acute pituitary necrosis. In other reports, patients completely recovered from acute episodes and remained asymptomatic for months to years before the onset of HP symptoms, with the latter mechanism being operative in these patients. One potential mechanism that could be operative in these cases includes the release of pituitary antigens during acute episodes, leading to the development of autoantibodies with slow destruction of anterior pituitary over years. Anti-pituitary antibodies and anti-hypothalamus antibodies were demonstrated in patients with Sheehan's syndrome and may play a role in the development of DHP [30, 31]. However, further studies are required to elucidate the exact pathophysiological mechanisms of pituitary damage in these cases with delayed presentation.

RV is distributed throughout the Indian subcontinent, S-E Asia, China, and Taiwan. Saw scaled viper has a wider distribution in North Africa, Arabia, India, Sri Lanka, and Southwestern Asia. To date, a vast majority of case reports on HP due to SB have focused on RV bite. A few cases of HP due to saw scaled viper envenomation have also been reported. Apart from these, only one case of HP due to *Bothrops jararacussu* envenomation has been reported from Brazil [32]. There is a significant variation in the toxic composition of snake venom of vipers in different parts of the world, which is largely attributed to differences in toxin-encoding genes and a complex interaction between genetic and postgenomic factors acting on toxin genes [33]. This variability results in differences in venom-induced pathology and lethality. Therefore, vipers in other continents are not similar to RV in terms of the composition of venom. We do not believe that the results of this paper are generalizable beyond their geographic distribution. However, we suspect a high burden of undiagnosed HP in the areas of their distribution.

The need for early diagnosis and treatment of HP cannot be over-emphasized. Untreated HP can result in impaired quality of life, significant morbidity, and increased mortality [34–36]. HP is associated with increased mortality even after standard hormone replacement therapy [35, 37]. Untreated GHD was also associated with increased mortality in patients with HP [38]. HP is associated with a poor quality of life and significant reduction in life expectancy, and fertility outcomes in women with HP are poor [39, 40]. HP diagnosis necessitates complex hormonal treatment regimens and burdens the healthcare economy.

This review has a few limitations. While we believe that weight loss and low BMI are direct consequences of delayed diagnosis and treatment of HP, the contribution of low BMI to the progression/worsening of central hypothyroidism and hypogonadism cannot be ruled out. In patients in whom prior MRIs were not available, a remote possibility exists that empty sella/partial empty sella was a pre-existing condition rather than a result of the snake bite.

DHP is an important complication of RVE, and delay in its diagnosis is associated with significant morbidity and impaired quality of life. Patients with RVE require long-term follow-up to identify DHP. AKI following envenomation is a predictor of future DHP development. Fatigue, reduced libido, amenorrhea, unexplained hypoglycemia, or

hypotension should prompt evaluation for HP in patients with history of RVE. HP can be present even in the face of normal pituitary imaging findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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