

Generalized Fatigue, Amenorrhea Due
to Snake Bite?Sreenivasa Rao Sudulagunta^{1*}, Mahesh Babu sodalagunta², Hadi Khorram³,
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Article Information

Received date: May 22, 2015

Accepted date: Jul 02, 2015

Published date: Jul 08, 2015

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Key words Hypopituitarism; Viper bite

Abstract

Introduction: Hypopituitarism is a clinical syndrome characterized by deficiency of pituitary hormone production. Snake bite is an uncommon cause of hypopituitarism. Envenoming by poisonous animals is an occupational hazard often faced by farmers and farm laborers in tropics. Viperine snake bites cause local cellulitis, tissue necrosis, bleeding manifestations, disseminated intravascular coagulation (DIC), acute kidney injury (AKI), shock, cardiac arrhythmia, neurotoxicity, coma, and death. Worldwide estimates vary from 1.2 to 5.5 million snakebites, 421,000 to 2.5 million envenomings, and 20,000 to 125,000 deaths.

Case Report: We report case of a 37-year-old female who was bitten by a Saw scaled viper snake and developed chronic hypopituitarism diagnosed after 11 months. Patient improved with treatment of essential hormones.

Conclusion: Hypopituitarism after a snake bite is often insidious in onset and a rare complication. Diagnosis is often delayed due to unawareness causing significant morbidity. Physicians should have a low threshold to suspect hypopituitarism in snake bites.

Introduction

Hypopituitarism is a clinical syndrome characterized by deficiency of pituitary hormone production. Disorders that involve pituitary gland, hypothalamus, or surrounding structures may cause it. Panhypopituitarism refers to involvement of all pituitary hormones; usually, only 1 or more pituitary hormones are involved, resulting in isolated or partial hypopituitarism. Hypopituitarism is an uncommon disorder as described by National Institutes of Health (NIH), affecting <200,000 individuals in the United States. Worldwide, estimated incidence is 4.2 cases per 100,000 per year and prevalence is 45.5 cases per 100,000 without gender difference.

Regal et al. [1] reported incidence and prevalence of hypopituitarism in northwestern Spain where they studied an adult population of 146,000 and prevalence was found to be 45.5 cases per 100,000 population. Four studies from the United Kingdom and Sweden revealed that mortality increases by 1.3- to 2.2-fold in hypopituitarism patients, compared with age and sex-matched cohorts [2]. Snake bite is an uncommon cause of hypopituitarism.

Out of all the snake species identified till now (about 3000), 300 species are found to be venomous. In India 57 species of snakes are venomous out of a total of 216 known species [3]. The poisonous snakes in India are classified in to Elapidae which includes common cobra (*Naja Naja*), king cobra and common krait (*Bungarus caeruleus*, Banded krait, Sind krait), *Echis carinatus* (saw scaled or carpet viper) (Figure 1), viperidae (Russell's viper) (Figure 2), and pit viper and hydrophiidae (sea snakes) [4]. Envenomation due to bites of cobra and krait causes paralysis of the ocular, bulbar, and limb girdle muscles whereas viper bites cause bleeding from muco-cutaneous sites, hemolysis, acute kidney injury, and shock [5].

Centre for Global Health Research and Registrar General of India conducted first national survey of death causes (Million Death Study) done in 2001-03 estimates snakebites causing 46,000 deaths per year. However, Central Bureau of Health Intelligence of Government reports only 1,350 deaths for the period from 2004 to 2009 which is grossly underestimated [6]. Global estimates range from 1.2 to 5.5 million snakebites, 421,000 to 2.5 million envenomings, and 20,000 to 125,000 deaths [7,8]. Each year, approximately 8,000 venomous snakebites occur in the United States. Between 1960 and 1990, no more than 12 fatalities from snake venom poisoning were reported annually.

One source of snake in rural areas is Chulha which is a mud made furnace used for cooking. The ash retained is warm in winters and cool in summers and is thus a pleasant environment for krait and cobra to stay during night hours (Figure 3). Here, we report a case of middle aged female who was bitten by saw scaled viper 11 months ago and presented with recurrent hypoglycemia,



Figure 1: Saw scaled viper. Licensed under the Creative Commons Attribution-Share Alike 4.0 International license from Wikimedia [16].



Figure 2: Russell's viper. Licensed under the Creative Commons Attribution-Share Alike 4.0 International license from Wikimedia [17].

hypotension and loss of libido as a consequence of snake bite.

Case Report

A 37yr old female presented to the Medicine outpatient department with 11 months history of generalized fatigue, lethargy, reduced libido, amenorrhea and depression. Patient had history of Saw scaled viper snake bite 11 months ago in her house while try to cook food in a Chulha. Patient did not consult a doctor and was given local medicine. She was altered sensorium with mucosal bleeding following the snake bite for 20 days. Patient improved over a period of 1 month after which she developed generalized fatigue and

Table 1: Investigation report showing hormonal levels during first and second visits.

Date	First visit (09/12/14)	Second visit (05/02/15)
TSH	0.04 mIU/mL	0.87 mIU/mL
Reference range	0.30-5.5	
Free T3	0.5 pg/mL	2.8 pg/mL
Reference range	1.7-4.2	
Free T4	0.42 ng/dL	1.20 ng/dL
Reference range	0.70-1.80	
Thyroxine Dosage	25 mcg	100 mcg

Table 2: Investigations of patient showing hypopituitarism.

Serial no.	Hormone Profile	Observed value	Normal range
1	ACTH	4.08	7.3-65pg/mL
2	8AM CORTISOL	0.00	6.1-19.8mg/dL
3	FSH	0.1	0.3-10.0 mIU/mL
4	LH	<0.10	1-18 mIU/dL
5	GROWTH HORMONE	<0.05	0.00-10ng/mL
6	IGF1	<25	101-268 ng/ml
7	IGF-BP3	0.99	3.30-6.60ug/ml
8	PROLACTIN	1.4	2.0-25.0ng/mL



Figure 3: Chulha. Licensed under the Creative Commons Attribution-Share Alike 4.0 International license from Wikimedia [18].

amenorrhea. Patient continued to work in the cultivation of crops with progressive increase in fatigue.

Patient consulted in local hospital after 2 months and was diagnosed with hypothyroidism and started on levothyroxine 25 mcg. Her symptoms persisted, for which levothyroxine dosage was changed many times (increased and decreased) and multivitamins were prescribed. She had recurrent episodes of hypoglycemia during this period which responded to dextrose. Her hypoglycemic episodes were associated with anxiety, tremors, mental confusion, sweating, palpitations and loss of consciousness. She also had 4 episodes of generalized tonic clonic seizures (GTCS) associated with hypoglycemia. Patient had no prior history of Diabetes mellitus, infections, alcohol consumption, surgeries and chronic illness.

Her investigations revealed hemoglobin of 10.6 gm/dL, total leukocyte count of 9,100 mm³ (with differential of 70% Polymorphonuclear leukocytes, 21% lymphocytes), and platelet count of 200,000 mm³.MRI Brain revealed no abnormality. Toxicology screening was normal. Serological testing was done for cytomegalovirus (CMV), herpes simplex virus (HSV), epstein-barr virus (EBV), varicella- zoster (VZV), mycoplasma pneumoniae, hepatitis B and C, haemophilus influenzae and campylobacter

jejuni which revealed no infection. Other laboratory test results were serum Creatinine, 1.1 mg/dL; urea, 28 mg/dL; sodium, 141 mEq/L; potassium, 4.1 mEq/L; aspartate aminotransferase (AST), 133 IU/L; alanine aminotransferase (ALT), 171 IU/L; total bilirubin, 0.49 mg/dL; albumin, 3.26 gm/dL; and total protein, 6.7 gm/dL. Abdominal ultrasonography (USG) revealed no abnormality. Her other investigations revealed hypopituitarism (Table 1 and Table 2) which was assumed due to viper bite that happened 11 months ago. Patient was supplemented with levothyroxine of 50 mcg which was later increased to 100 mcg, estrogen, progesterone and prednisone. Posterior pituitary hormonal tests (vasopressin levels) were normal.

Differential diagnoses considered were hyponatremia, hypothyroidism, Kallmann Syndrome, Idiopathic hypogonadotropic hypogonadism, Pituitary macroadenomas and microadenomas,

Septo-optic dysplasia and polyglandular autoimmune syndromes. They were excluded by investigations. Other causes of hypopituitarism were also excluded.

Discussion

Common Causes of pituitary insufficiency include pituitary adenomas, intrasellar or parasellar tumors, traumatic brain injury (TBI), inflammatory or infectious destruction of pituitary, surgical removal, radiation-induced destruction, subarachnoid hemorrhage and postpartum pituitary necrosis (Sheehan syndrome). Among hypothyroidism causes, head trauma in many studies showed an incidence of 15-40% [9]. But, Kokshoorn et al. found the incidence of posttraumatic hypopituitarism to be lower than assumed [10]. Almost no case reports are described regarding saw scaled viper envenomation causing hypopituitarism.

Saw scaled viper is the smallest member of the Big four snakes in India and is responsible for causing most of the snakebite cases and deaths, due to frequent occurrence in highly populated regions, and inconspicuous nature [4]. This species produces on the average of about 18 mg of dry venom by weight, with maximum of 72 mg. It may inject as much as 12 mg, whereas lethal dose for an adult human is only 5 mg [11].

Viper venom contains pro-coagulant enzymes that activate factor V and X and other steps in the blood coagulation cascade leading to defective hemostasis causing cross-linkage fibrin and deposition of micro thrombi in the microvasculature [12]. The coagulant effect of venom is also due to an enzyme, arginine esterase hydrolase, similar in action to thrombin, which clots fibrinogen and aggregates platelets and conversion of prothrombin to thrombin. The hemorrhagic necrosis of the anterior pituitary gland was pathologically demonstrated in patients of viper bites in a study done by Proby et al. [13] Than et al., and Tun et al., who reported presence of adrenal hemorrhage apart from pituitary hemorrhages in some patients of viper bites [14,15]. Normal MRI brain and no neurological deficits in our patient showed no possibility of intracranial bleed due to disseminated intravascular coagulation (DIC) as a cause of seizures. No electrolyte imbalance was found during the episodes.

Possible mechanisms described for pituitary damage following snake bite are thrombosis of pituitary vessels as a part of DIC, peripheral vascular collapse followed by spasm of pituitary vessels, thrombosis of local venules causing ischemic pituitary infarction or damaged vascular endothelium, impaired platelet function, depletion of clotting factors, and secondary fibrinolysis leading to pituitary hemorrhages.

Conclusion

Hypopituitarism after snake bite is a rare entity confined to tropics of the world. Diagnosis is often delayed if not suspected as in our patient who was diagnosed 11 months after snake bite. Most cases described are due to Russell's viper bites and very few reports due to saw scaled viper which is of more common occurrence. Patients presenting with fatigue, hypoglycemia, menstrual disturbances have to be evaluated for hypopituitarism.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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