CASE REPORT

GROWTH RETARDATION DUE TO PANHYPOPITUITARISM AND CENTRAL DIABETES INSIPIDUS FOLLOWING RUSSELL'S VIPER BITE

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Abstract. Russell's viper envenomation and its related complications, especially acute kidney injury, is an important cause of morbidity and mortality in tropical developing countries of South Asia. Unusual complications, especially hypopituitarism, are rare and probably missed due to lack of clinical suspicion and diagnostic facilities. We report a rare presentation of growth retardation resulting from hypopituitarism due to Russell's viper envenomation along with central diabetes insipidus. Awareness of the fact that hypopituitarism may occur in this clinical setting is necessary for early diagnosis and treatment, especially among general care practitioners taking care of these patients.

Keywords: diabetes insipidus, empty sella syndrome, growth retardation, hypopituitarism, Russell's viper bite

INTRODUCTION

Snakebite envenomation is an important public health problem in South Asia, particularly in India, with 35,000-50,000 people dying annually according to World Health Organization (WHO) direct estimates (Chippaux, 1998). Russell's vipers are the leading causes of fatal snakebite in India, Pakistan, Sri Lanka, Burma, Thailand, and parts of Indonesia (Warrell, 1989).

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Snake venom can result in neurotoxicity, hemolysis, rhabdomyolysis, disseminated intravascular coagulation, acute kidney injury, hypotension, coagulopathy, damage to the local tissues, and even death (Sitprija, 2006). Pituitary dysfunction following snakebite is a rare presentation, and most of the clinical presentation is restricted to hypofunction of the anterior pituitary. Posterior pituitary dysfunction is a still rare presentation.

We present a case of a 20-year-old male patient who was bitten by a Russell's viper at the age of 12 years and who presented with an unusual presentation of growth retardation along with panhypopituitarism of both the anterior and posterior pituitary glands. This is the first

case report of growth retardation following a snakebite envenomation of which we are aware.

CASE REPORT

We present a case of a 20-year-old male patient who sustained a Russell's viper bite at the age of 12 years. There were no significant illnesses before this event, such as a history of head injury, central nervous system infections, any developmental delay, or morphological anomalies. Following the snakebite, he developed acute kidney injury and received seven sessions of hemodialysis along with supportive care for the snake bite. He also developed severe coagulopathy and hypotension necessitating vasopressors, plasma, and platelet transfusions. There was a history of mild altered sensorium (Glasgow coma score of 13, E3M6V4) that persisted for three days following which he improved without any neurological deficits. The renal dysfunction recovered after 15 days of hospital admission. He was lost to follow-up for the past eight years.

He recently presented with a history of growth retardation following the snakebite and a gain of just 2 cms in height over the past 8 years. His baseline height taken at 12 years of age was 133.5 cms, which was more than the 3rd centile in the height charts acceptable for Indian children (Khadilkar *et al*, 2007). He also had a history of generalized weakness, cold intolerance, constipation, failure to develop secondary sexual characteristics, and absence of penile erection. There is also a history of increased urinary volume and increased thirst. All these symptoms began after recovery from the snakebite. During this period, there were no other additional morbidities.

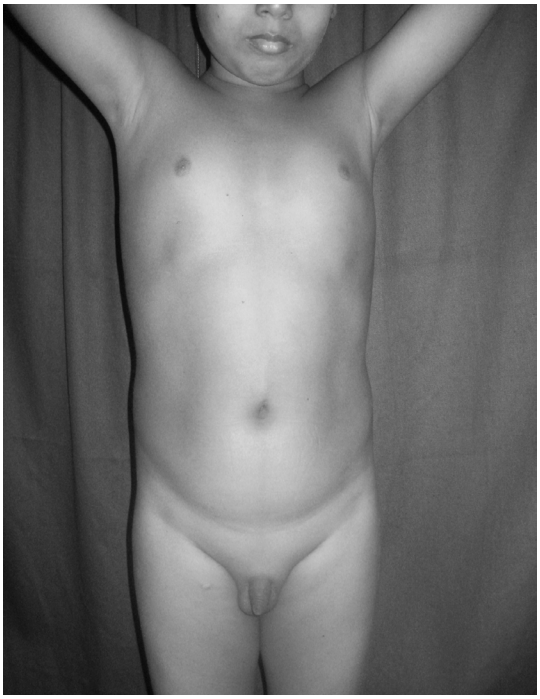

Fig 1–Photograph of the patient showing poorly developed secondary sexual characteristics (Tanner 1 stage of genital and pubic hair development). Also note the maintenance of normal body proportions.

On examination, the pulse rate was 72/min, and BP was 100/70 mmHg without any postural drop. His weight was 32.2 kgs and height was 135.5 cms (parental target height of 150 cms, <-2SD), with a normal upper segment/lower segment ratio of 0.9. He had an infantile voice with poorly developed secondary sexual characteristics (Tanner genital and pubic hair development: both Stage 1) (Fig 1). The renal function, liver function tests, serum electrolytes, and hemogram were all within normal ranges.

Urinalysis revealed absence of glucosuria with urine pH of 6. A 24-hour urine collection was done with a urine volume of 3,200 ml (99.37ml/kg body weight/day) and no proteinuria. The urinary excretions

Table 1
Pituitary function test of the patient.

Values	Observed value	Reference range
FSH	0.284 mIU/ml	0.7-11.1 mIU/ml
LH	0.382 mIU/ml	0.8-7.6 mIU/ml
Prolactin	1.84 ng/ml	2.5-17 ng/ml
FT4	0.427 ng/dl	0.8-1.9 ng/dl
TSH	2.95 IU/ml	0.4-4 IU/ml
6 AM Cortisol	4.4 g/dl	5-25 g/dl
IGF-1	42.3 ng/ml	182-780 ng/ml[a]
Testosterone	<20 ng/dl	245-1,600 ng/dl

[a]For a 16-24 year old male.
FT4, free T4; IGF-1, insulin like growth factor-1; FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.
All hormonal analyses were done using standard radio-immunoassay.

of uric acid, phosphate, calcium, citrate, and oxalate were also within normal limits. The serum osmolality was 298 mOsm/kg, but urine was hypoosmolic, with an osmolality of 132 mOsm/kg.

A pituitary function test was done, which showed panhypopituitarism (Table 1). Peak serum cortisol measured 6.2 g/dl within 60 minutes after an intramuscular dose of 250 g of synacthen, which was an inadequate response. This poor response might give a suggestion of a primary rather than a secondary adrenal insufficiency. However, a primary adrenal insufficiency was ruled out in view of the absence of clinical features suggestive of Addison's disease and normal serum electrolytes. Moreover, chronic pituitary failure itself leads to adrenal atrophy, which might explain the poor response to synacthen stimulation. Peak stimulated growth hormone level measured 3.2 ng/ml after injection of insulin Actrapid at a dose of 0.15U/kg intravenously which was inadequate. Both these tests firmly established the diagnosis of hypopituitarism.

An MRI of the pituitary gland showed a thinned-out gland with partial empty sella, normal infundibular stalk, and non-visualization of the T1 bright spot of the posterior pituitary (Fig 2). There was severe osteoporosis, especially of the lumbar vertebrae, with DEXA scan T-score of -4.3 of the L1-L4 vertebrae. The serum 25(OD) vitamin D measured 30.7 nmol/l (deficiency=≤25 nmol/l).

In view of the suggestive history, and the presence of polyuria and hypoosmolic urine, with normal serum osmolality in the presence of adequate thirst, a water deprivation test was planned. However, as it was not possible to do hourly AVP levels, and osmolalities of the urine and serum due to unaffordability, the test was modified.

We measured the baseline urine osmolality (132 mOsm/kg), body weight, and serum Na. Water deprivation began at 6:00 AM, with hourly measures of body weight, urine output, and serum Na. After 4 hours, the serum Na rose to 146 mmol/l, and the urine osmolality was measured as 200 mOsm/kg, with average urine output of 120 ml/hour. Arginine vasopressin 5U was then given subcutaneously, and urine osmolality was measured after 2

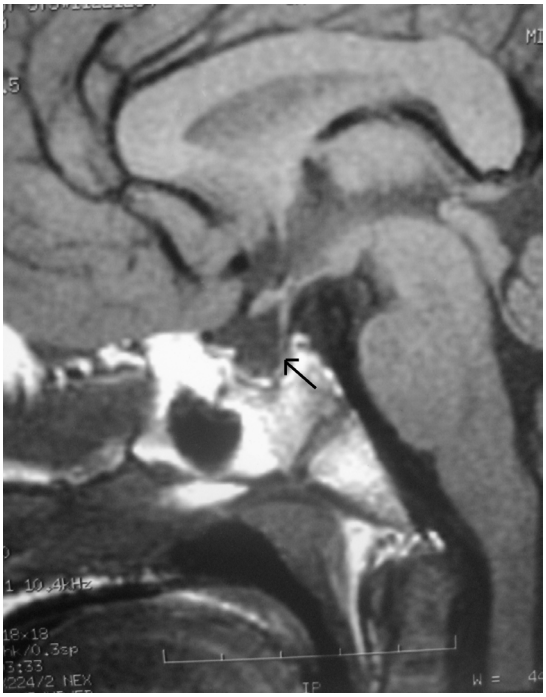

Fig 2–T1 weighted sagittal section MRI image showing a partial empty sella with thinned out pituitary (arrow). Infundibular stalk is normal and the posterior pituitary T1 bright spot is not visualized.

hours, which showed a >50% increase in the osmolality to 540 mOsm/kg. Thus, a diagnosis of Central Diabetes Insipidus was made for this patient.

Treatment was started with prednisolone 5 mg at 8:00 AM, levothyroxine 50 g daily, testosterone enanthate IM 200 mg every 2 weeks, intranasal desmopressin 10 g twice daily, calcium carbonate 500 mg twice a day, and calcitriol 0.50 g once a day. Unfortunately, the patient due to the cost of therapy declined growth hormone therapy. After one month of follow-up, there was a significant improvement of symptoms and general well being. The impact of the hormone replacement on the sexual development needs to be seen on follow-up.

DISCUSSION

Although Russell's viper bite is a very common occurrence in South Asia and is associated with significant mortality and morbidity, pituitary function abnormalities are a rare finding as is highlighted in a recent review (Antonypillai *et al*, 2011). As is well summarized in this review (Antonypillai *et al*, 2011), there have been only 49 reported cases of acute as well as chronic hypopituitarism following Russell's viper bite. Forty-eight patients included in this review (Antonypillai *et al*, 2011) had anterior pituitary dysfunction with one of the included case reports having both anterior as well as posterior pituitary involvement (Krishnan *et al*, 2001). There was only one case having an isolated posterior pituitary dysfunction (Gupta *et al*, 1992). Apart from the cases summarized in the review of Antonypillai *et al* (2011), there is one more case reported from South India where the etiology of central diabetes insipidus was attributed retrospectively to snake bite (Rajaratnam *et al*, 2000). Almost all of these cases have been reported from India and Burma.

The cases that have been reported in literature have had the expected symptoms of panhypopituitarism, with the common manifestations of weakness, lethargy, hoarseness of voice, swelling of the body, reduced body hair, loss of libido, and erectile dysfunction or menstrual disturbance. The time to diagnosis of these cases is variable, ranging from a few weeks to 20 years from the time of the snakebite. To the best of our knowledge, there are no reports of any case of growth retardation following a snakebite, making this the first case report. Our case is made more interesting by the presence of both anterior as well as posterior pituitary dysfunction.

There can be several mechanisms involved in patients sustaining Russell's viper envenomation that damages the pituitary gland. Pituitary lesions in snakebite survivors have been compared to classical Sheehan's syndrome following postpartum hemorrhage. The presence of a thrombotic tendency due to disseminated intravascular coagulation with deposition of fibrin in pituitary blood vessels, vulnerability to stagnant hypoxia/ischemia of the pituitary secondary to an episode of profound hypotension and the nondistensibility of the pituitary gland that confines the swelling in a closed space are features that are common in the classical Sheehan's syndrome and victims of severe Russell's viper bite envenomation (Antonypillai *et al*, 2011). After an acute damage to the pituitary gland, the persistence of this damage has been postulated to be due to the development of antigen-antibody complexes following the development pituitary antibodies developed due the initial insult (Goswami *et al*, 2002).

The etiology of anterior hypopituitarism in our case is probably due to secondary empty sella syndrome as sequelae of damage to the anterior pituitary resulting from the mechanisms described above. However, the presence of a posterior pituitary dysfunction is very unusual following a sellar pathology. This is probably due to the fact that synthesis of AVP occurs in the hypothalamus, and a sellar pathology does not destroy the magnocellular neurons causing an upward shift in the AVP secretory sites. Moreover, destruction of more than 80-90% of the magnocellular neurons of the hypothalamus is required to produce the clinical symptoms of CDI (Verbalis and Berl, 2008).

In our case, there was an absence of the posterior pituitary T1 hyperintensity, and there was no evidence of an upward shift of this intensity, which normally happens following a sellar pathology. Another case of an isolated CDI following snakebite in a 14-year-old patient who died following snakebite showed a pituitary hemorrhage on autopsy (Gupta *et al*, 1992). Thus, it appears that CDI may be related to hemorrhage and destruction of the anterior pituitary with resultant damage to the magnocellular neurons of the posterior pituitary that become chronic probably due to retrograde degeneration if the pituitary stalk section is high at the level of the infundibulum, as was shown in previous studies (Lipsett *et al*, 1956).

As is the finding in the majority of the case reports and also is the same in our case, acute kidney injury is seen in almost all of the cases that develop hypopituitarism following a snakebite envenomation. Hypopituitarism causes significant morbidity and is also associated with early mortality in cases with acute hypopituitarism. Snakebite envenomation is an entity of developing countries where the diagnostic facilities and access to health care is limited. Therefore, the prevalence of pituitary disorders in this patient population might be quite underestimated and the occurrence of this complication less known to the general practice physicians in the developing world.

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