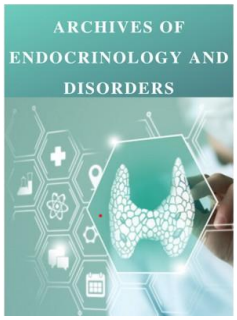

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Review Article

Absent Functionally Active Adenohypophysis Following Viperine Snake Bite: Victim Surviving 19 Years After the Primary Insult Without Supplementation

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Abstract

Acquired chronic panhypopituitarism is an insidious onset, gradually progressive endocrine defect triggered usually by infective, auto-immune or vascular insult to the pituitary. In tropics and south-east Asian countries viperine snakebite is one of the common causes of such Pituitary insults but usually remain undiagnosed for months to years which might not only cause significant compromise to the quality of life but also cause sudden deaths. These patients usually perform well if timely diagnosis is made and adequate hormonal supplementation instituted. We report a 45 year old male patient who had almost no Pituitary Hormonal reserve after incurring a Hemotoxic snakebite at the age of 26 and remained without any Hormonal supplementation for 19 years. The patient even almost forgot the triggering event due to severe memory loss and was elaborated only by his relatives on the second visit to the attending clinician. Victims of Hemotoxic snakebites need to be followed up by basic hormonal profile evaluation at least every six months initially and annually thereafter. A detailed history taking from patient as well as relatives is essential to confirm the etiological diagnosis and thereafter formulate management strategies to prevent future complications.

Keywords: Chronic Panhypopituitarism; Amnesia; Viperine Snakebite; Empty Sella; Consumptive Coagulopathy

Abbreviations:

MR: Magnetic Resonance; IGF-1: Insulin like Growth Factor-1; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; TSH: Thyroid Stimulating Hormone Free; T4: Thyroxine; DEXA: Dual X-ray Absorptiometry

Introduction

A case of chronic panhypopituitarism with absent anterior Pituitary hormones, post snake-bite envenomation diagnosed after 19 years of the event. The victim survived for 19 years without any hormonal supplementation with absent Anterior pituitary function which makes the clinical scenario extremely rare in the literature.

Clinical Case

A 45-year-old unmarried male presented to the house physician with generalized weakness, lack of energy, easy fatigability and apathy. Serum testosterone estimation was done which was low. The patient was thereafter referred to the endocrinologist for further evaluation and came for consultation unaccompanied by relatives. When enquired about his ailments, he was apathetic

and produced the serum testosterone report as a reason for attending the clinic. It was deciphered that the patient is unemployed and prefers a solitary life.

On clinical examination, the patient was thin built, had an alabaster skin tan with wrinkling around the orbit, large ears, facial puffiness and dry skin (Fig. 1). However, he had no facial, axillary or pubic hair. The stretched penile length and testicular volume were inappropriate for his age (Table 1) (Fig 2). The scrotum however had rugae and pigmentation indicating a probable secondary etiology (Fig 3). The anthropometric parameters are depicted in Table 1 and the hormonal profile indicating panhypopituitarism is illustrated in Table 2. The complete blood Count of the patient was normal with a Hemoglobin of 13.4 gm/dl with other cell lines normal.

Figure 1: Depicts the vivid facial features of Panhypopituitarism.

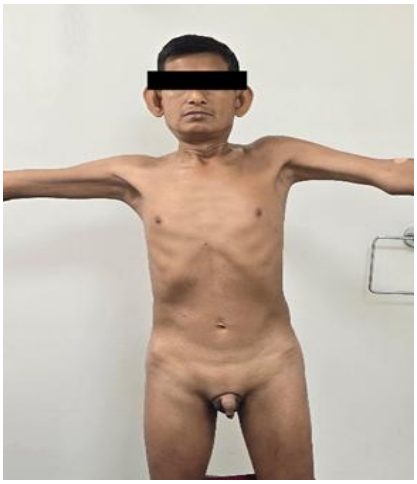

Figure 2: Total loss of axillary and pubic hair with inappropriately small genitilia and gonads.

Figure 3: Pigmented scrotum with rugations but absent pubic hair.

In the second interaction, the patient was accompanied by his brother-in-law. During this visit, the relative revealed that the patient was hospitalized at the age of 26 years for two weeks following a snakebite and transient renal shutdown. During the hospitalisation, he received several units of fresh frozen plasma. Following recovery, the patient gradually lost all his body hair and currently does not require shaving at all. The patient never had any symptoms suggestive of posterior pituitary dysfunction as recalled by his relative viz. polyuria, polydipsia.

Sl. No.	Parameters	Measurements and Description
1	Height	160 cm
2	Arm Span	162 cm
3	Upper Segment: Lower Segment	76 cm: 84 cm
4	Tanner Staging	P2
5	Stretched Penile Length	6 cm
6	Testicular Volume and Consistency	8 ml with normal consistency
7	Scrotum	Pigmented, rugae present

Table 1: Basic anthropometry and Sexual Maturity Rating (SMR).

Sl. No.	Hormonal Parameters	Value	Normal Range
1	TSH	0.01 μIU/ml	0.35-4.94 -μIU/ml
2	Free T4	0.49 ng/dl or 6.306 pmol/Ltr	0.7-1.48 ng/dl or 9.009- 19.047 pmol/Ltr
3	FSH	0.54 mIU/ml	0.95-11.95 mIU/ml
4	L.H	<0.04 mIU/ml	0.57-12.07 mIU/ml
5	8 am testosterone	0.04 nmol/L	9.36-37.1 nmol/L
6	Prolactin	0.431 ng/ml or mcg/Ltr	4.04-15.2 ng/ml or mcg/Ltr
7	S.IGF-1	20 ng/ml or 2.614 nmol/l	101-267 ng/ml or 13.20-34.90 nmol/l
8	S. Cortisol	<1.0μg/dl or <27.6 nmol/L	3.7-19.4μg/dl or 102.12-535.44 nmol/L
IGF-1: Insulin like Growth Factor-1; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; TSH: Thyroid Stimulating Hormone Free; T4: Thyroxine			

Table 2: Baseline hormonal profile of the patient.

A DEXA (Dual X-ray Absorptiometry) study revealed severe loss of bone mass with T- score of -4.5 at the lumbar spine and -2.9 at the neck of the femur, characteristic of long-standing untreated hypogonadism.

Fig. 4,5 both the Image depicts an empty Sella with thin rim of remnant pituitary tissue at the floor.

Contrast MR (Fig. 4,5) of pituitary revealed empty sella, with a thin rim of anterior pituitary at the floor of Sella, probably non-functional as evident from the Hormonal profile. The posterior pituitary and infundibulum had normal location, morphology and thickness. Grossly, the rest of the brain was normal. The MR features are likely to be due to anterior pituitary infarction secondary to micro-thrombi deposition as is evident in the works of Than, et al., on autopsy findings of Viperine bite victims [1].

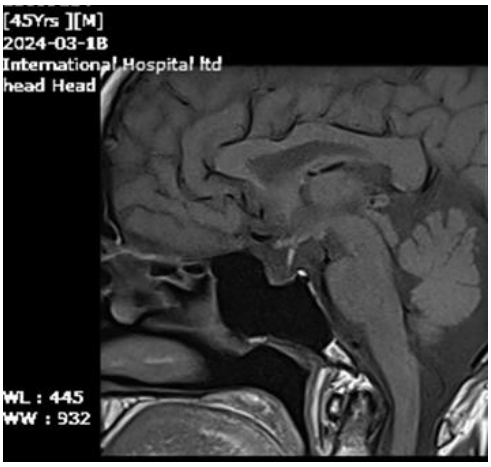

Figure 4: Pre-Gadolinium T1 sagittal image.

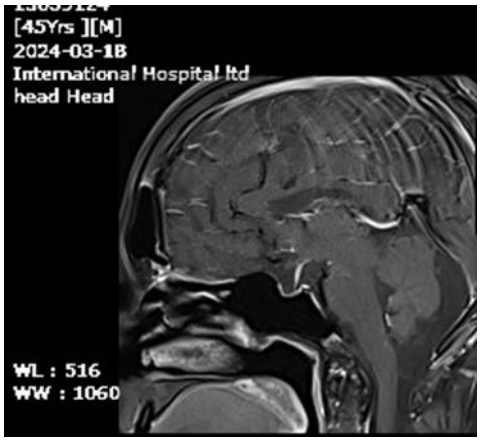

Figure 5: Post Gadolinium T1 sagittal image.

Treatment

The patient was started with hormonal supplementation with tablet hydrocortisone at a dose of 7.5 mg on awakening, 5 mg at 12 noon and 2.5 mg at 5 pm. Levothyroxine was initiated at a dose of 75µgms in empty stomach. Testosterone is being administered in an available combination of 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate in 1 mL arachis oil making it 250 mg injection every 21 days. Growth Hormone therapy was offered but patient did not accept the therapy due to financial constraints.

Follow-up

A marked change in overall attitude has been observed in the patient after 2 months of therapy. He has found employment in a local factory. The patient is currently talking and discussing much more fluently. A thicker line of Mustache is currently visible and there is androgenic hair growth in face, axilla and pubis. We are in the process of continuous follow-up.

Discussion

The patient of panhypopituitarism following a viperine snakebite is unique in few aspects. The patient remained without supplementation in spite of being totally deficient in anterior pituitary hormones for almost 19 years. In this period the patient also survived a COVID infection though requiring hospitalization. Probably, the use of steroids in the hospital helped the patient to cope with the crisis. The patient did however never complain of polyuria throughout the entire course denoting preserved posterior pituitary functions.

Panhypopituitarism is a rare but known complication of snakebite. According to recent Indian studies, majority of the pituitary insults occur in the immediate period following the bite but are clinically diagnosed anywhere between two weeks to ten years. In a cohort of sixty patients, the hormonal profile of only six patients simulated anterior pituitary insult during the acute phase.

The remaining patients did not have any alterations in hormonal profile in the next six months follow-up [2]. There have been around thirty-six cases of panhypopituitarism, mostly from India, chiefly from identified bites of D. Siamensis and D. Russelii [3,4]. Our patient lost all his facial, pubic and axillary hairs within days of the envenomation depicting total loss of Gonadotrophs early in the course.

Our patient uniquely had profound memory loss and the entire episode of envenomation was recalled only by his relative, which might be explained by a severe chronic secondary hypothyroidism. Also, the patient did not complain of the classical symptoms of panhypopituitarism such as easy fatiguability, loss of libido or weight loss, since he did not perceive them as issues requiring medical attention. The patient however had all the clinical signs of panhypopituitarism as described. The history suggestive of acute kidney injury is one of the strongest clues to the subsequent development of panhypopituitarism. Younger age, increased number of haemodialysis sessions and raised 20 minutes whole blood clotting time are the strongest predictors of future development of panhypopituitarism in snakebite patients [5]. Our patient not only had acute kidney injury and received few dialysis sessions but also was administered fresh frozen plasma suggesting a possible consumptive coagulopathy.

Our case, although a male, has features similar to Sheehan's Syndrome patients who have variable deficiencies of Anterior Pituitary Hormones reported and remain asymptomatic [6]. Our case however differs from Sheehan's in few aspects. The total absence of Anterior Pituitary Hormones as in our case is not common in Sheehan's which has variable degrees of deficiency ranging from deficiencies in a single axis to insidious involvement of multiple axis. Zargar, et al., documented that there was a significant lapse of approximate 9.74 years prior to the involvement of all the Pituitary axis which is quite similar to our case in which although the Gonadotrophs were destroyed early but probably the Corticotroph destruction followed a prolonged and gradual course aiding survival. On the contrary, Sheehan's patients usually have gradual involvement of gonadal axis or at times no involvement at all. Menstruation and even Pregnancy have been reported in documented cases of Sheehan's [7]. Sheehan's is prevalent in the developing world with poor health infrastructure. Robust data on the Anterior Pituitary profile and their correlation with patient symptoms are still lacking. Laway, et al., analyzed 3 cases where they documented the Variability of Anterior Pituitary profile with the patient with severe deficiency of Adreno-cortical axis requiring hospitalization [8]. Sert, et al., documented a case series of 28 Sheehan's patients where they found 9 cases of the 22 cases requiring 3 or more Hormonal replacements required hospitalization at Diagnosis. Our Case survived for 19 years undetected without supplementation probably highlights the basic pathology of gradual loss of Adrenocorticotrophs. Also, because adrenal mineralocorticoid secretion is largely unimpaired in Secondary adrenal insufficiency, our patient somehow escaped Adrenal crisis, although Adrenal crisis has been well reported even in secondary adrenal insufficiency [9]. Our case report demonstrates that patients with absent Anterior Pituitary functions might survive for years after the initial insult, irrespective of any gender bias. These patients might even have complete amnesia of the inciting event [10].

Conclusion

In any developing country, particularly in the tropics, panhypopituitarism due to hemotoxic snakebite is a definite possibility. The patients might remain undiagnosed for years owing to insidiousness of symptoms. This in turn not only increases the chances of unexpected sudden mortality but also morbidity, thereby increasing the financial burden of the family. A basic hormonal profile in snakebite survivors in the initial months of follow-up and thereafter annually for the initial few years might go a long way in detecting post snakebite panhypopituitarism. A detailed history from the patient as well as the relatives is extremely essential not only for the etiological diagnosis but also for anticipation of future complications and there after formulating adequate supplementation.

Learning Points

- Chronic Acquired Panhypopituitarism is an insidious state and requires high index of suspicion for Diagnosis. Post Viperine snake-bite, Panhypopituitarism might develop after months to years, therefore careful clinical vigilance is mandatory
- Significant reversible Dementia associated with Hypothyroidism and apathetic attitude might result in patients forgetting the triggering event. Detailed history from patients and relatives is essential
- Acute kidney Injury requiring Renal Replacement Therapy is one of the important predictors of Pituitary Insult
- Chances of Acute adrenal crisis is rare in secondary adrenal insufficiency because of retained adrenal mineralocorticoid activity

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

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Authors Contributors
All the authors have made contributions in their own way. SP was involved in the review of Literature. The diagnosis of the case and write-up was prepared by SCSP involved the MR imaging and detection of Empty Sella. Finally, the write-up was edited by A.M and D.M.

Consent of Patient
Signed informed consent was obtained directly from the patient.

Data Availability
Original data that was generated and analysed have been included in the write-up.

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