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Effect of Vasculotoxic Snake Bite on Anterior Pituitary Function: Study from a Tertiary Teaching Hospital from Eastern India

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ABSTRACT

Background & Aim: Snake bite (SB) is a major public health problem in tropics and subtropics. Vasculotoxic SB can cause cellulitis, coagulopathy, acute kidney injury (AKI), shock and even death. Pituitary dysfunction is a rare complication of SB and is often unrecognised. Aims and Objectives: To assess the anterior pituitary functions in vasculotoxic SB patients and their association with complications of SB. **Methods**: This was a hospital based cross-sectional study evaluating vasculotoxic SB patients admitted consequtively to a tertiary care teaching hospital of Eastern India. Each enrolled patient underwent routine investigations on the first day of hospitalisation. Coagulation profile and hormones evaluating anterior pituitary function which included serum levels of follicle-stimulating hormone(FSH), luteinizing hormone(LH), thyroid stimulating hormone(TSH) and morning cortisol were estimated on 3rd day of admission. Data analysis was done using standard statistical methods. **Results**: Evaluation of anterior pituitary hormones in sixty-one cases of vasculotoxic SB revealed higher morning cortisol level in 21(34.4%) cases followed by TSH in 6(9.8%) and LH in 5(8.2%) cases.It further revealed lower levels of FSH in maximum patients 29(47.5%), followed by LH in 26(42.6%), cortisol in 5(8.2%), and TSH in 02(3.2%) cases respectively. Normal values of TSH were found in most of the patients 53(86.8%) followed by corisol in 35(57.3%), FSH in 31(50.8%) and LH in 30(49.2%) cases.Thirty-eight cases (62.3%) revealed biochemical evidence of hypopituitarism (HP). The deficiency of both FSH and LH was noted in 21(55.3%) patients followed by FSH in 6(15.79%), LH in 5 (13.16%), cortisol in 3 (7.89%) cases respectively. Out of 15 cases of AKI, 10(66.6%) cases developed biochemical evidence of HP. Twenty out of 28 cases (71.4%) of DIC, developed biochemical evidence of HP. In both the groups, deficiency of combination of FSH and LH was recorded the most and TSH deficiency was the least. Study of association of variation of FSH, LH, cortisol and TSH values with variables such as total platelet count(TPC), D.dimer, blood urea and serum creatinine showed a strong association between FSH with TPC (P<0.05) and creatinine (P <0.05), LH with TPC(p<0.05), and cortisol with creatinine (p<0.05). Hence FSH and cortisol were strongly associated with AKI. TSH showed no significant association with any of the variables. **Conclusion**: Pituitary dysfunction, especially asymptomatic HP is not an uncommon but often unrecognised complication following vasculotoxic SB.Whether this is a transient phenomenon due to envenometion and stress following SB or persistent needs long term follow up study.

Keywords: Snake bite, vasculotoxic, hypopituitarism, DIC, acute kidney injury.

INTRODUCTION

Snake bite (SB) is still a health hazard in tropics and subtropics causing substantial morbidity and mortality. Global neglect of this condition and lack of sufficient epidemiological data prompted the World Health Organization (WHO) to recognize it as a "neglected tropical disease" in 2009.[1] There has been few epidemiological studies on the global impact of SB specially focussing on mortality but the results are variable.[2,3] According to the Million Deaths Study, an epidemiological study on mortality in India, SB are responsible for about 45,900 deaths annually (0.47% of all deaths) with an annual age-standardized rate of 4.1/100,000 with higher rates in rural areas.[4] In India, almost two-thirds of SB are attributed to saw-scaled vipers, about one-fourth to Russell's viper and only a small proportion to Cobras and Kraits.[5]

In India, vasculotoxic snake-bites are commonly seen following bites of the Russell's viper and saw scaled vipers, clinically manifested by local cellulitis and systemic complications like acute kidney injury (AKI), disseminated intravascular coagulation (DIC), haemorrhagic manifestations, intra vascular haemolysis, rhabdomyolysis and shock.[6]

Most of the literatures on SB have highlighted the acute complications like AKI, bleeding manifestations, DIC or fatality. However, there are many other acute complications which are less studied that can cause significant morbidity and

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mortality. One of them include pituitary insufficiency or hypopituitarism (HP).[1,7] Pituitary damage and HP is one of the unusual complication seen predominantly in India and Burma.[6] Vasculotoxic SB (Russell's viper) is known to cause acute and chronic HP and diabetes insipidus (DI). HP is a relatively uncommon complication of vasculotoxic SB and only 49 cases have been reported worldwide.[6] HP is the partial or complete insufficiency of anterior pituitary hormone secretion and may result from pituitary or hypothalamic disease.[8] Patients with acute HP may present with hypotension and hypoglycemia during the acute phase of envenoming, if unrecognized is potentially fatal. Those with chronic HP have a delayed presentation after recovered from acute envenoming, if unrecognized can be debilitating.[6]

Immediate and long-term effects on hormone levels of anterior pituitary following bites by the Burmese Russell's viper was studied by Proby C et al.[7]Twenty patients at the stage of acute illness were studied using a single blood sample for assays of several hormones of anterior pituitary.None showed normal levels of all hormones measured.Tweleve survivors were assessed at 8-226 weeks after envenoming, by measurement of basal pituitary hormone levels combined with pituitary reserve function.All but one showed deficit in pituitary hormone secretion which indicates that acute pituitary insufficiency was persistent except one where the same was transient.7 This transient,subclinical perturbations in pituitary hormones following viperine SB could be due to effects of envenomation or acute stress following SB.

It is surprising that, although vasculotoxic SB are seen over a wide geographical distribution, reports on acute HP is scanty and localised to few regions.Chronic HP following vasculotoxic SB is a rare but well recognized clinical entity.The clinical presentations, associations, treatment and outcome of SB induced acute HP are not well described so as so the levels of different stress related hormones,anterior pituitary hormones in particular and their effects on milleau-interior during the earliest part of acute phase of illness.This could be due to lack of awareness amongst physicians of this complication and under reporting. Hence, it is essential that the physicians should be aware of this complication of vasculotoxic SB in order to make an early diagnosis and hormonal replacement therapy to decrease the morbidity and mortality. Since this region of Odisha is fairly suffered by SB, and there is no published data on the prevalence of HP, we conducted a hospital based study to evaluate the effect of vasculotoxic snake bite on pituitary function in patients admitted to this largest tertiary teaching hospital of Odisha.

MATERIALS & METHODS

This was a hospital based cross-sectional study conducted in the Post Graduate Department of Medicine, SCB Medical College and hospital, Cuttack, Odisha. Sixty-one cases of vasculotoxic snake bites admitted consecutively to the first unit of this department from September 2014 to November 2015, of both genders and age group >15 year were enrolled for the study. Patients were selected as cases of vasculotoxic SB based on the history of type of SB, features of local envenoming, with bleeding/clotting disturbances, shock or acute kidney injury.[1] Other categories of snake bites (neurotoxic, sea snake, non-poisonous or past history of snake bite), known cases of endocrine disorders (thyroid, Addison's disease, Cushing's disease), those who are on steroid or hormonal therapy were excluded from the study.Informed consent was taken from all patients. DIC was defined according to the International Society for Thrombosis and Hemostasis criteria.10AKI was diagnosed as per the kidney Disease Improving Global Outcome (KDIGO) 2012 guidelines for acute kidney injury.[11]

Each patient underwent detailed history taking and complete clinical examination. Vasculotoxic snake bite was confirmed by abnormal 20-minute whole blood clotting test (20 WBCT), considered as the most reliable test of coagulation.[1] Other relevant tests done include complete blood count (CBC), urine routine and microscopic examination, blood glucose level, blood urea, serum creatinine, liver function test, serum electrolytes, coagulation profile which includes prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer. Hormonal profile to assess the anterior pituitary function which include follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and serum cortisol (8 AM) were done using a single blood sample on third day of admission irrespective of the presence of features of acute HP (hypoglycemia, hypotension) to search for biochemical or subclinical evidence of changes of post SB pituitary hormone prifile. Further, evaluation for growth hormone (GH) deficiency was not done as it would not translate to therapy and also prolactin due to financial constrains.Estimation of TSH,FSH,LH were done by chemiluminescence (CLIA) method using ABBOTT 1 2000 SR kit, serum cortisol was estimated by electro-chemiluminescence (ECLIA) using COBAS E411 (ROCHE). The reference values of different hormones are TSH 0.27 - 4.2 µIU/ml, FSH(mIU/ml)-Female: Follicular phase 3 - 18, luteal 2 - 15, midcycle 15 - 70, post -menopausal 30 - 210, Male: 4 - 18, LH (mIU/ml) -Female: Follicular 4 - 18,luteal 4 - 18, midcycle 30 – 90, postmenopausal 20 - 114, male: 4 - 18, cortisol

(8AM)- 171 - 536 nmo/L. D-dimer estimation was done by immunoassay test,value of >200ng/dL was considered as positive.

HP was defined as deficiency of one or more pituitary hormones and pan hypopituitarism was defined as deficiency of three or more pituitary hormone[9]

All patients received the standard care for SB envenomation including polyvalent anti-snake (ASV) and renal replacement therapies as and when necessary.[1]

Statistical analysis was done using SPSS statistical package version 20. Quantitative variables were described as mean + standard deviations (SD) unless otherwise indicated.Qualitative variables were described by percentage. Association between different variables were studied using chi square test & the means of different variables were compared using ANOVA. For all statistical tests, P value <0.05 was considered significant.

RESULTS

Table 1: Baseline demographic characters, clinical and biochemical parameters in study population

Variables	Values
Age (Years)	41.75 ± 14.34
GENDER (Male/Female)	44/17
Systolic Blood Pressure (mm Hg)	118 ± 17
Diastolic Blood Pressure (mm Hg)	74 ± 08
Pulse (Rate/minute)	83 ± 08
Signs of cellulitis	61(100%)
Major Bleeding	09(14.75%)
Acute Kidney Injury	15(24.6%)
Disseminated Intravascular Coagulation	28(45.9%)
Total Leucocyte Count (cell/cmm)	12034.43 ± 3871.97
Total Platelet Count (Lakh/cmm)	2.12 ± 0.54
Blood Urea (mg/dL)	55.28 ± 39.04
Serum Creatinine (mg/dL)	1.9 ± 2.36
Total Bilirubin (mg/dL)	1.34 ± 1.22
D-dimer(ng/dL) of DIC patients	302.56+127.07
FSH(mIU/mL)	13.67+25.68
LH(mIU/mL)	10.55+10.82
TSH (µIU/mL)	3.72+10.31
Cortisol(nmol/L)	832.13+1243.35

Our study is a hospital based cross-sectional study and reflects the prevalence of pituitary dysfunction in vasculotoxic SB patients in the in-patient setting. Sixty-one cases of vasculotoxic SB were enrolled in this study, out of which 44(72.2%) were male and 17 (27.8%) were female patients, M: F(2.58:1). Most of the patients were from the age group of 30 - 49 years (41%). The age of the patients studied ranged between 16 - 72 years, with a mean age of 41.75 (± 14.34) years. Majority of the bites were in outdoor (59%), more during evening hours and night (45.9%) and most common involved site was lower limb (78.6%).The baseline characteristics, clinical features and biochemical parameters are shown in [Table 1].The mean values of hormones of anterior pituitary evaluated in all patients are shown in [Table1] which indicates that all the hormones were within normal limits except the mean morning serum cortisol level which was higher. The values (low/normal/high) of hormonal profile in this study are shown in [Table2] which showed lower serum levels of FSH in maximum number of patients (47.54%) followed by lower levels of LH, cortisol, and TSH in 46.62%,8.2%,and 3.28% of patients respectively.High values of morning serum cortisol was recorded in maximum (34.43%) number of patients followed by patients with higher levels of TSH, LH and FSH in 9.84%, 8.20%,and 1.64% of patients respectively. Normal values of TSH were found in most of the patients (86.88%) followed by cortisol, FSH and LH respectively.

Table 2: Values of hormonal profile in patients of snake bite

Serum hormones	Low values No(%)	Normal Values No(%)	High values No(%)	Total Cases
FSH	29 (47.54%)	31 (50.82%)	1 (1.64%)	61
LH	26 (42.62%)	30 (49.18%)	5 (8.20%)	61
TSH	2 (3.28%)	53 (86.88%)	6 (9.84%)	61
Cortisol	5 (8.20%)	35 (57.38%)	21 (34.43%)	61

Table 3: Hormones Affected in cases of post snake bite hypopituitarism

FSH alone	6 (15.79%)
LH alone	5 (13.16%)
Cortisol alone	3 (7.89%)
FSH and LH	21(55.27%)
FSH and TSH	1 (2.63%)
FSH,LH and TSH	1 (2.63%)
FSH,LH and Cortisol	1 (2.63%)

Table 4(a): Pituitary Hormones affected in AKI

Hormones decreased in AKI	Number of cases (%),n=10
FSH alone	3 (30%)
FSH and LH	6 (60%)
FSH,LH and TSH	1 (10%)

Table 4(b): Pituitary Hormones affected in DIC (biochemical)

Hormones decreased	Number of cases(%) in DIC(n=20)
FSH alone	3 (15%)
LH alone	3 (15%)
Cortisol alone	1 (5%)
FSH and LH	10 (50%)
FSH and TSH	1 (5%)
FSH,LH and TSH	1 (5%)
FSH,LH and Cortisol	1 (5%)

Table 5: Duration between snake bite and hospitalisation and complications

Duration	No of cases	Hypopituitarism	AKI	DIC
< 12 hours	42(68.85%)	26(68.42%)	7(46.66%)	21(75%)
>12-24 hours	12(19.67%)	9(23.69%)	4(26.67%)	6(21.43%)
> 24 hours	7(11.48%)	3(7.89%)	4(26.67%)	1(3.57%)
Total	61	38	15	28

Table 6(A): Association of variation in FSH values with other variables.

		Sum of Squares	df	Mean Square	F	p-value
TPC	Between Groups	.933	2	.466	7.396	.001
	Within Groups	3.657	58	.063		
	Total	4.590	60			
TLC	Between Groups	.358	2	.179	.702	.500
	Within Groups	14.790	58	.255		
	Total	15.148	60			
D dimer	Between Groups	.620	2	.310	1.238	.297
	Within Groups	14.527	58	.250		
	Total	15.148	60			
Serum urea	Between Groups	.371	2	.186	.728	.487
	Within Groups	14.776	58	.255		
	Total	15.148	60			
Serum creatinine	Between Groups	1.774	2	.887	5.395	.007
	Within Groups	9.537	58	.164		
	Total	11.311	60			

Table 6(B): Association of variation in LH values with other variables

		Sum of Squares	df	Mean Square	F	p-value
TPC	Between Groups	.577	2	.289	4.172	.020
	Within Groups	4.013	58	.069		
	Total	4.590	60			
TLC	Between Groups	.381	2	.190	.748	.478
	Within Groups	14.767	58	.255		
	Total	15.148	60			
D dimer	Between Groups	.635	2	.317	1.268	.289
	Within Groups	14.513	58	.250		
	Total	15.148	60			
Serum Urea	Between Groups	.386	2	.193	.758	.473
	Within Groups	14.762	58	.255		
	Total	15.148	60			
Serum Creatinine	Between Groups	1.106	2	.553	3.144	.051
	Within Groups	10.205	58	.176		
	Total	11.311	60			

Table 6(C): Association of variation in cortisol values with other variables

		Sum ofSquares	df	Mean Square	F	p-value
TPC	Between Groups	.381	2	.190	2.622	.081
	Within Groups	4.210	58	.073		
	Total	4.590	60			
TLC	Between Groups	.252	2	.126	.491	.614
	Within Groups	14.895	58	.257		
	Total	15.148	60			
Serum Urea	Between Groups	1.319	2	.659	2.766	.071
	Within Groups	13.829	58	.238		
	Total	15.148	60			
Serum Creatinine	Between Groups	1.788	2	.894	5.443	.007
	Within Groups	9.524	58	.164		
	Total	11.311	60			
D dimer	Between Groups	.405	2	.202	.796	.456

In this study, 38 (62.3%) out of 61 cases, showed biochemical evidence of HP, out of which male were 30 (68.18% of total male) and female 8 (47.06% of total female). Considering the site of bite, 32 (66.67%) out of 48 cases of lower limb bites and 6 (46.15%) out of 13 upper limb bites developed HP.

Of the hormones disturbed in HP, the deficiency of combination of FSH and LH was noted in most (55.3%) of patients followed by isolated deficiencies of FSH, LH, and cortisol in 13.16%, 15.79%, and 7.89% patients respectively as shown in table-3. Out of 15 cases of AKI, 10 (60.7%) developed HP, whereas 20 (71.4%) cases out of 28 cases of DIC, developed HP. In both the groups, the deficiency of combination of FSH and LH was found in highest number of patients followed by

isolated deficiencies of FSH, LH and TSH as shown in table-4a and 4b.

In this study, majority of the patients presented to hospital within a time period of <12 hours after the bite and also developed AKI, DIC and HP the most followed by the patients admitted during the next 12 hours and more than 24 hours respectively as shown in table-5. Table-6A, 6B, 6C shows the association of variation in FSH, LH, and cortisol values with other variables such as total platelet count (TPC), total leucocyte count, D-dimer, and serum creatinine, which shows a strong association between variation in FSH values with variation in TPC (P value=0.001), and s.creatinine level (P value=0.007), LH with TPC (P value =0.020) and cortisol with s.creatinine (P value=0.007). There was no statistically significant association between variations in TSH values with any other above tested variables.

DISCUSSION

As most of the mortality following vasculotoxic snake bite are related to acute complications due to organ failure or venom itself, the role of other complications is not well studied. Both functional and structural damage to pituitary gland is an uncommon complication of SB envenomation.Such pituitary abnormality may result from acute stress or venom itself leading to perturbation in pituitary hormone profile immediately after snake bite and may contribute to significant morbidity and mortality.

Russell's viper can release many toxins and active procoagulant enzymes which activate factors V, X and other steps in the blood coagulation cascade. This leads to the formation of cross linked fibrin in the blood stream, most of which is immediately broken down by the body's own fibrinolysis system. Ultimately the levels of clotting factors become so depleted by disseminated intravascular coagulation that consumption coagulopathy develops. Russell's viper also contains a metalloproteinase 'haemorrhagin' which damages vascular endothelium and toxins that causes platelet dysfunction. These venom induced disturbances leads to thrombosis and spontaneous haemorrhages at diverse organs including upper and lower digestive tract, the lungs, the retroperitoneal space, the genito-urinary tract are seen in patients of viper envenomation.[6,12] Microvascular thrombin deposition and focal haemorrhages in the pituitary may be responsible for haemorrhagic infarction of the anterior pituitary and functional consequences of acute and chronic HP.[6] Some venom components cause vasodilation and capillary leakage syndrome which alone or along with the hypovolemia resulting from acute bleeding may cause arterial hypotension and shock.[13] Other mechanisms by which pituitary dysfunction occurs may be due to direct action of venom on anterior pituitary or swelling of pituitary gland within the confines of its indispensible pituitary fossa due to increased generalised vascular permeability.[6] Development of acute renal failure may be related to DIC, hypovolemia, shock, rhabdomyolysis and direct nephrotoxicity causing acute tubular necrosis.[14]

Clinical manifestations of HP depends on the extent of hormone deficiency and may be nonspecific, such as fatigue, weakness, dizziness, nausea, vomiting, hypotension or more indicative such as growth retardation or impotence and infertility in Growth hormone (GH) and gonadotropin deficiency, respectively.[8] The diagnosis of HP relies on the estimation of basal and stimulated secretion of anterior pituitary hormones and of the hormones secreted by pituitary target glands.[8]

Analysing the mean values of the hormones of all the SB patients [Table1], it revealed that morning cortisol level was on higher level and rest others were almost within normal limits. Higher cortisol level could be a result of acute illness following SB resulting in stress. Stress activates pituitary-adrenal axis resulting in hypothalamic secretion of corticotrophin-releasing factor (CRF) which in turn stimulates the pituitary to adrenocorticotrophic (ACTH),8-lipotropin and 3-endorphin.[15] Plasma levels of these hormones can increase by two- to five fold during stress in humans.Raised plasma ACTH facilitates release of endogenous glucocorticoids from adrenal cortex.[15]The values of hormonal profile of anterior pituitary [Table2] showed that lower values of FSH was found in maximum number of patients followed by patients with lower levels of LH,cortisol and TSH respectively. The low gonadal hormones could be due to stress related suppression of circulating gonadotropins and gonadal steroid hormones.[9] Stress induced endogenous glucocorticoid release acts directly on hypothalamus to suppress production of 'gonadotrophin releasing hormone' (GnRH), which ultimately leads to suppressed production of FSH and LH from anterior pituitary.[16] Recent evidences suggests that stress induced glucocorticoid release also enhances hypothalamic release of 'gonadotrophin-inhibitory hormone'(GnIH) which inhibits hypothalamic release of GnRH and pituitary release of gonadotrophins. Thus stress induced glucocorticoid release suppresses GnRH and boosts GnIH, a double whammy on reproductive system suppressing the entire tract.[17] Low cortisol level (8.2% cases) may be due to acute pituitary failure leading to decreased release of ACTH resulting in acute adrenal insufficiency which couldn't be established here without estimation of peak stimulated cortisol level after ACTH stimulation.8 In most of the cases (86.8%) TSH level was

normal.Only a few cases (3.28%) had low TSH. Low TSH could be due to secondary hypothyroidism due to acute pituitary failure following SB, which is suggested by low serum FT4 levels and inappropriately normal or low basal TSH levels that don't rise normally after TRH.8 Further, secondary hypothyroidism is a rare disease and we couldn't prove this as FT4 estimation and TRH stimulation was not done here.Thyroid function is usually down regulated during stressful conditions. Stress related immunological changes affect the immune respose to TSH receptor through modulation of cytokines,hormones and neurotransmitters.Stress induced glucocorticoid release inhibits TSH secretion through its action on central nervous system.[18] Defect of antigen-specific suppressor T-lymphocytes, defect in immunologic surveillance leading to production of TSH receptor antibodies and shifting of Th1-Th2 immune balance away from Th1 towards Th2 in genetically susceptible individuals are some propositions which may be responsible for suppressed TSH production.[19-21] At the same time, it is very difficult to rule out the possibility of presence of mild,undiagnosed thyroid hyperfunction already present in these patients.

Further, higher levels of cortisol were found in maximum number of patients followed by patients with higher values of TSH and gonadotrophins.The reason behind stress related glucocorticoid release is already discussed. High levels of TSH could be due to stress related release of catecholamines which stimulated hypothalamic secretion of thyrotrophin releasing hormone (TRH) leading to increased TSH production by anterior pituitary.[22] Apart from TSH, raised LH and FSH levels were also found. It has been shown that stress induced release of glucocorticoids also protects gonadotropin release than suppress it. This is attributed to specific mechanisms by which glucocorticoids regulate prostaglandin in the brain which mediate the suppressive effect on LH pulsality by suppression of hypothalamo-pituitary-gonadal axis(HPG axis).[23] Inhibin and Activin, members of the Transforming Growth Factors (TGFs), found in the gonadal fluid have the ability to suppress or stimulate respectively the FSH secretion from anterior pituitary.[24] Glucocorticoid can further increase FSH secretion by decreasing plasma concentration of Inhibin.[25]

In this study, 38 out of 61 cases (62.3%) revelaed biochemical evidence of pituitary insufficiency as none of the patient had evidence of hypotension or hypoglycemia during hospital stay as the clinical manifestations depend on the extent of hormone deficiency and may be non-specific, liable for missing.[8] Male out numberd female as male are more exposed to out door and agricultural activity. A systemic review of SB induced acute HP by Rajagopala et al. showed male gendere was predominant 95.2% (20/21), and all patients 100% (9/9) of HP of his case series were male.[26] In our series all the cases (100%) of HP had received bite over extremities (upper and lower) which is similar to that reported by Rajagopala et al. i.e. 88.9% (8/9).[26] None of our patients showed evidence of recurrent hypoglycemia or hypotension which are the important manifestations of acute HP. Rajagopala et al. in their series reported the prevalence of hypotension during hospitalization to be 66.6% (6/9) and recurrent hypoglycemia to be 100% (9/9).[26] Systemic review by Rajagopala et al. of patients (no=21) with AHP following Russell's viper envenomation reported hypotension at the time of diagnosis of AHP to be 76.2% (16/21 patients), and recurrent hypoglycemia in 92.9% (12/13) of patients.[26]

Of the hormone decreased in HP in our series, the deficiency of combination of FSH and LH was found in most (55.27% cases) followed by deficiency of FSH (15.79%), LH (13.16%) and cortisol alone in (7.89%) of cases respectively. TSH was affected the least in combination with FSH, and LH. Combination of hormones FSH/TSH, TSH/FSH/LH, and cortisol/FSH/LH each affected in 2.63% cases [Table 3].Tun-Pe et al. From Burma studied 9 patients with features of AHP following Russell's Viper bite but finally diagnosed 3 cases as AHP with inappropriately low baseline cortisol, growth hormone and prolactin levels.[27] Among 336 patients studies in Srilanka by Kularatne et al. no patients had clinical features suggestive of acute cortisol insufficiency.28 This variation could be due to variable ethnic, genetic and virulence of SB factors.

In our study, out of 15 case of post snake bite ARF, 10 cases (66.6%) developed HP whereas among 28 cases of DIC, 20 cases (71.4%) developed HP.This may be due to the fact that the pathophysiology of these three conditions are related.In both the scenario, the deficiency of combination of FSH and LH was recorded in maximum mumber of victims, and the least were deficiency of TSH and cortisol as shown in [Table 4a and 4b]. Proby C, et al. studied 20 patient during acute phase with post viper bite AKI and DIC. In this study 10/15 patients had inappopriately low cortisol, 19/20 (95.0%) patients had low TSH and thyroxin concentrations, 12/17 (70.5%) males had low serum testosterone with low or inappropriately normal gonadotrophin concentrations and 1/3rd females had low serum oestrogen concentrations. The majority of these patients were on either prednisolone or hydrocortisone which reacted with the assay used in the study. Thyroid observations may be interpreted as sick-euthyroid syndrome during acute illness.[7] The observation on gonadal hormones is at par with our observations. There is a visible difference in the percentage of patients showing low levels of TSH and cortisol, may be

due to varied sample size and ethnic variation in response to envenomation or stress. According to Golay V et al. from Eastern India who conducted a prospective observational study on survivors of SB-AKI found 9 patients (9.37%, n = 96) had evidence of HP. Low gonadal hormones, TSH and cortisol were found in 100%, 100%, 66.6% cases respectively.[9] This is similar to our observation on gonadotropins but conspicuous difference in affection of TSH and cortisol, which would be due to genetic or ethic variation in response to stress or envenomation.

In this study, majority of patients presented to hospital within a time period of <12 hours after the snake bite and also developed AKI (46.66%), DIC (75%) and HP (68.42%) followed by the patients admitted during the next 12 hours and more than 24 hours respectively following SB as shown in table-5. More complications during early hours may be related to acute severe illness following severe envenomation may be associated with anterior pituitary failure. An additional mechanism may be direct action of the venom upon the function of anterior pituitary cells.[7] Delay in institution of ASV therapy may be another factor.All three complications were found raised simultaneously during same period possibly because of the fact that all three are the manifestation of same pathogenic mechanism.[6]

The decline in the complications in patients admitted to hospital > 24 hours may be due to the fact that these patients were treated in nearby health care centre at the earliest, received ASV and referred to our medical college after 24 hours. Golay et al. also had similar observations in their series where the bite to ASV therapy time was 5 (28) hours in SB patients with AHP and 6 (10) hours in SB patients without AHP.[9] Systemic review of patients with AHP (n=21) by Rajgopala S et al. revealed the time of onset of hypotension after admission was 3 days (21 hours – 14 days) and recurrent hypoglycemia after admission was 9 days (21 hours – 14 days) and recurrent hypoglycemia after admission was 9 days (21 hours – 14 days), which are the indicators of onset of AHP.[26] Of their own series (N= 09) onset of hypotension after admission was 8.5 (1-14) days, onset of recurrent hypoglycemia was 9(2-14 days).

Study of the association of variation in FSH, LH and cortisol values with other variables; total platelet count (TPC), total leucocyte count (TLC), d-Dimer, blood urea, serum creatinine shows a strong association between variation in FSH values with TPC (P value <0.05) and serum creatinine level (P value <0.05), LH with TPC (P value <0.05), and cortisol with serum creatinine (P value <0.05). Hence FSH and cortisol were strongly associated with AKI.

Limitations of the study:

HP in this study was biochemical as the patients were asymptomatic.Whether this was transient following post SB acute severe illness due to stress or persistent due to acute HP needs further follow up with basal and stimulated secretion of anterior pituitary hormone and of the hormones secreted by pituitary target glands.As the progressive loss of pituitary hormone secretion is usually a slow process,which can occur over a period of months or years,short hospital stay of the patients was the main limitation.All hormones except GH,and prolactin were studied.

CONCLUSION

Pituitary dysfunction,especially asymptomatic HP is not a rare but often unrecognised entity following vasculotoxic SB envenomation.It was more common in those who developed complications like AKI and DIC.This state could be either due to stress following acute severe illness having profound effect on the level of these hormones, or severe envenomation / direct effect of venom on function of anterior pituitary cells resulting in anterior pituitary failure.This needs further long term studies on a larger cohort.

REFERENCES

1. WHO. Snake-bite (internet).(Cited 2017. July 09). Available from: http://www.who.int / neglected - diseases/snake bites/in
2. Chippaux JP. Snake-bites: appraisal of the global situation. Bull World Health Organ 1998; 76:515-24.
3. Kasturiratne A, Wickremasinghe AR, de Silva N et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLOS Med 2008; 5:e218
4. Mohapatra B, Warrel DA, Suraweera W, Bhatia P, Dhingra N, et al. Snakebite mortality in India: a nationally representative mortality survey. PLoS Negl Trop Dis 2011;5(4): e1018
5. Saini RK, Sharma S, Singh S, Pathania NS. Snake-bite poisoning: a preliminary report. J Assoc Physiscians India. 1984; 32(2):195-7
6. Antonypillai CN, Wass JAH, Warrel DA, Rajaratnam HW. Hypopituitarism following envenoming by Russell's vipers (Daboia Siamensis and D. russelii) resembling Sheehan's syndrome: First case reported from Sri Lanka, a review of the literature and recommendations for endocrine management. QJM 2011; 104:97-108.
7. Proby C, Tha A, Thet W, Hla M, Burrin JM, Joplin GF.Immediate and long-term effects on hormone levels following bites by the Burmese Russell's Viper.Q J Med 1990;75:399-411
8. Ascoli P, Cavagnini F. Hypopituitarism. Pituitary 2006; 9:335-42.
9. Golay V, Roychowdhary A, Dasgupta S, Pandey R. Hypopituitarism in patients with vasculotoxic snake bite envenomation related acute kidney injury:a prospective study on the prevalence and outcomes of this complication. Pituitary 2014; 17 : 125-31.
10. Takemitsu T, Wada H, Hatada T, Ohmori Y, shikura K,Takeda T, et al. Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. Thromb Haemost 2011;105:40-4

11. Acuye Kidney Injury Work Group. Kidney disease: Improving Global outcomes (KDIGO) - clinical practice guidelines for Acute Kidney Injury. Kidney Inter 2012; 2:1-138
12. Del Brutto OH, Del Brutto VJ. Neurological complications of venomous snake bite:a review.Acta Neurol Scand 2012;125:363-72
13. Otero-Patino R. Epidemiological, clinical and therapeutic aspects of Bothrop's asper bites. Toxicon 2009; 54:998-1011.
14. Sitprija V. Animal toxins and the kidney. Nat clin Pract Nephrol 2008; 4:616-27.
15. Hargreaves KM. Neuroendocrine markers of stress. Anesth Prog 1990; 37:99-105.
16. Whirledge S, Cidlowski JA, Glucocortioid, stress and fertility. Minerva Endocrinol 2010; 35(2):109-25.
17. Kirby ED et al. Stress increases putative gonadotrophin inhibitoryhormoneand decrease luteinizing hormone in male rats.Proc Natl Acad sci USA 2009 ;106 (27):11,324-9.
18. Helmreich DL, Parfitt DB, Lu Xy, Akil H,Watson SJ. Relation between the hypothalamic-pituitary-thyroid(HPT) axis and the hypothalamic-pituitary-adrenal(HPA) axis during repeated stress.Neuroendocrinology.2005;81:183-92
19. Mizokami T, Li AW, El Kaissi S, Wall JR. Stress and thyroid autoimmunity. Thyroid 2004; 12:1047-55
20. Davies TF.Pathogenesis of Graves' disease. In: Braverman LE, Utiger RD (Eds).Werner and Ingbars The Thyroid: A fundamental and clinical text. Philadelphia USA: Lippincott Williams and Wilkins; 2005.pp.457-73
21. Tsatsoulis A. The role of stress in the clinical expression of thyroid autoimmunity. Ann N Y Acad Sci 2006; 1088:382-95
22. Economidou F., Douka E, Tzanela M, Nanas S, Kotanidou A . Thyroid function during critical illness. Hormones 2011; 10 (2): 117-24.
23. Matsuwaki T,et al.Maintenance of gonadotrophin secretion by glucocorticoids under stress conditions through the inhibiton of prostaglandin synthesis in the brain. Endocrinology 2006; 147(3) : 1087-93.
24. Mc Cullagh DR: Dual endocrine activity of the testes Science 1932; 76 (1957): 19-20.
25. Tohei A, Kogo H. Dexemethasone increasing follicular stimulating hormone secretion via suppression of inhibin in rats. Eur J Pharmacol 1999; 386 (A): 69-74.
26. Rajagopala S, Thabah MM, Ariga KK, Gopalkrishnan M. Acute hypopituitarism complicating Russell's viper envenomation: case series and systemic review. QJM 2015; 108 (9) 719-28.
27. Tun-Pe, Phillips RE, Warrell DA, Moore RA, Tin-Nu-Swe, Myint-Lwin, et al. Acute and chronic pituitary failure resembling Sheehan's syndrome following bites by Russell's viper in Burma. Lancet 1987; 2 : 763-7.
28. Kularatne SA. Epidemiology and clinical picture of the Russell's viper (Daboia russelii russelii) bite in Anuradhapura, Sri Lanka: a prospective study of 336 patients. Southeast Asian J Trop Med Public Health 2003; 34 : 855-62.

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