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HYPONATREMIA IN VISCERAL LEISHMANIASIS

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SUMMARY

There are few reports linking hyponatremia and visceral leishmaniasis (kala-azar). This is a study of 55 consecutive kala-azar patients and 20 normal individuals as a control group. Hyponatremia and serum hypo-osmolality were detected in 100% of kala-azar patients. High first morning urine osmolality (750.0 ± 52.0 vs. 894.5 ± 30.0 mOsm/kg H_2O , $p < 0.05$), and high 24-hour urine osmolality (426.0 ± 167.0 vs. 514.6 ± 132.0 mOsm/kg H_2O , $p < 0.05$) demonstrated persistent antidiuretic hormone secretion. Urinary sodium was high (82.3 ± 44.2 vs. 110.3 ± 34.7 mEq/L, $p < 0.05$). Low seric uric acid occurred in 61.8% of patients and increased fractional urinary uric acid excretion was detected in 74.5% of them. Increased glomerular filtration rate was present in 25.4% of patients. There was no evidence of extracellular volume depletion. Normal plasma ADH levels were observed in kala-azar patients. No endocrine or renal dysfunction was detected. It is possible that most hyponatremic kala-azar patients present the syndrome of inappropriate antidiuretic hormone secretion.

KEYWORDS: Hyponatremia; Hypo-osmolality; Hypouricemia; Syndrome of inappropriate antidiuretic hormone secretion; Visceral leishmaniasis.

INTRODUCTION

Visceral leishmaniasis (kala-azar) is a zoonosis that affects predominantly young people, and which has extensive public health impact in tropical and subtropical regions of the world. It is estimated, that more than 12 million individuals are infected by various *Leishmania* species in 88 countries, with an estimated 1.5 to 2 million clinical cases⁴. The visceral form of the disease, fatal if not treated, is caused in Brazil by *Leishmania donovani chagasi*, species associated with endemic outbreaks. Kala-azar causes an intense immune dysfunction with polyclonal activation of B lymphocytes and depression in cellular and humoral immunities¹⁰. Visceral leishmaniasis progresses with intense inflammatory alterations in vital organs such as the lungs, liver, spleen, kidneys, digestive tract and bone marrow. Interstitial pneumonitis is common during the active phase of the disease, and necropsy studies have shown the prevalence of interstitial pneumonitis to be around 76.8% of human cases. A dry cough is a constant symptom of kala-azar, that persists from the onset of the disease throughout its entire clinical course. The parasitary etiology of the pneumonitis can be confirmed by immunohistochemical reaction using anti-leishmania polyclonal specific anticorps¹². Lobar pneumonia is a frequent complication of more debilitated patients, when secondary pulmonary bacterial infections occur. In a study involving 50 children with kala-azar, the diagnostic of lobar pneumonia occurred in 10% of cases and *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most frequent etiologic agents³⁶. Hyponatremia has been described in children with visceral leishmaniasis²⁵

and prospective studies of patients with chronic forms of kala-azar have shown the presence of hyponatremia and high daily sodium urinary excretion, characteristics that persist during all active phases of the disease^{20,21}, returning to normal serum levels after glucantime treatment. Hyponatremia and high sodium urinary excretion are features of the syndrome of inappropriate antidiuretic hormone secretion, of adrenal insufficiency or carriers of renal sodium wasting diseases^{5,15}.

The aim of the present study is to describe the characteristics of the hyponatremia observed in chronic forms of kala-azar.

PATIENTS AND METHODS

This study included 55 patients admitted to Hospital São José de Doenças Infecciosas and to the Hospital Geral de Fortaleza between 2002 and 2008. Diagnosis of kala-azar was confirmed by the finding of *L. donovani, subspecies chagasi* in bone marrow smears. Patients with arterial hypertension, systemic diseases and history of renal diseases are excluded. HIV positive patients or that having specific pulmonar diseases do not participate from the investigation. Patients with decreased renal function ($Ccr < 85$ mL/min/1.73m²) were rejected because the possibility of alterations of extracellular volume of these patients. Thirteen patients were excluded because they did not satisfy the criteria of the present investigation. All patients received a hospital diet with 2g/kg body weight of animal protein and a daily ingestion of 10 to 12g of sodium chloride. No medication was administered during the study period, and

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only physical measures were used to fever control. All patients were from the rural zones and were diagnosed as having had daily fever for several weeks, increased abdominal volume and great hepatosplenomegaly. No patient had received kala-azar treatment previously. All patients had thorax radiographies before hospitalization.

The control group consisted of 20 individuals that annually had health tests and worked in the hospital. There was no evidence of cardiovascular, renal disease or systemic disease. They received the same diet and had frequent clinical examinations. The study protocol was registered and approved by ethical committees of both hospitals, and is in accordance with the Helsinki Declaration of 2000. All subjects agreed to participate in the study.

Clinical and laboratorial parameters: The following clinical parameters were investigated: demographic data, pre-existing diseases and current drug use. A complete physical examination was performed. All laboratory tests were performed in the Instituto de Nefrologia do Ceará, on the first and second days after the diagnosis of visceral leishmaniasis. All studies were performed beginning at 7AM after an overnight fast, with patients supine for 12h. The following parameters were measured: full blood count, total serum proteins, albumin and globulins, serum sodium and uric acid; plasma renin, ACTH, cortisol, aldosterone, TSH and free T₄. First morning urine was collected simultaneously, and serum and urine osmolalities were determined. A daily urine sample was collected with patients on their usual diets for osmolality, sodium, urea and uric acid determinations. A second 24h-urine sample for 17-hydroxysteroids determination was collected using as conservation 20 mL of hydrochloric acid 8M. Creatinine clearance was calculated after fluid overload with 1500 mL of water drunk over 30 minutes. The bladder was empty and the time rigorously measured. There followed three periods of urine collection (one hour each) and mean creatinine clearance was calculated and adjusted to 1.73 m² body surface area. Urinary fractional excretions of sodium, uric acid and urea were calculated in daily urine samples. Plasma ADH and serum sodium were measured simultaneously with serum and first morning urine osmolality determination.

Analytic methods: Total serum proteins were determined by the Biuret method, and albumin by the green bromocresol technique. Plasmatic colloidosmotic pressure (COP) was calculated by the Landis-Pappenheimer equation: COP (mmHg) = 2.1(TP) + 0.16 (TP)² + 0.009 (TP)³, where TP = serum total proteins (g/dL). Physiological limits of plasmatic colloidosmotic power were 25.4 ± 2.3 mm Hg²⁶.

Serum and urinary osmolality were measured by cryoscopy with Precision Systems' Osmette A, USA. Creatinine was measured using modified Jaffé reaction, and uric acid was determined by the uricase method. Serum and urinary sodium and potassium were measured by ion selective electrode, AVL photometer model ISE 9180, USA. TSH, free T₄, ACTH and cortisol were measured by chemiluminescence; antidiuretic hormone (ADH) and aldosterone by radioimmunoassay. For urinary 17-hydroxysteroids, the Norymberski technique was used.

Statistical analysis: Clinical and laboratorial data were expressed as mean ± standard deviation (SD) or percentages. Differences between two independent variables were evaluated using the t test or Mann-Whitney test as appropriate. The Epi info 2002 (Centers for Disease Control and Prevention) and SPSS 10.0 (SPSS Inc. Chicago, IL, USA) were used in all analyses. A p-value < 0.05 was considered statistically significant.

RESULTS

All patients had daily fever, persistent nonproductive cough and splenomegaly. No cardiac disease was detected. Tachycardia was evident in routine electrocardiogram during feverish periods. Chest radiographies reveal increased reticular pattern of pulmonary fields, accentuated at bibasilar regions in 37 patients (67.2%). Clinical symptoms of pneumonia and radiological evidences of pneumonic infiltration were seen in nine patients (16.4%). Only one patient had detectable ascites. Mild low inferior limbs edema was present in thirteen patients (23.6%).

Demographic and clinical data were compared in kala-azar patients and controls (Table 1). Forty seven patients were male (85.4%), with a mean age of 28.6 ± 11.0 years (vs. controls 28 ± 11 years, p = 0.325) and eight (14.5%) were female with a mean age of 17.4 ± 8.1 years (vs. controls 16 ± 13 years, p = 0.152). Systolic and diastolic blood pressures were significantly lower in male kala-azar patients than in the control group. For females there was no difference. Supine blood pressure, lower than 100/60 mmHg was detected in 22 patients (40%). No patient had orthostatic hypotension. Body weight was significantly lower in kala-azar patients (50.3 ± 8.7 vs. 63.5 ± 11.4 kg, p < 0.005).

All patients had severe anemia with significant difference in hemoglobin levels in relation to control group (7.9 ± 1.4 vs. 14.2 ± 0.8 g/dL, p < 0.0001) (Table 2). Total serum proteins ranged from 6.6 to 12.1 g/dL and 20 patients (36.3%) had increased total serum proteins levels. All patients presented hypoalbuminemia (range 0.8-

Table 1
Demographic and clinical data of kala-azar patients and controls

	Kala-azar		Controls	
	n = 47	n = 8	n = 17	n = 3
Sex	Male	Female	Male	Female
Age (years)	28.6 ± 11.0 [§]	17.1 ± 8.0 [§]	28.0 ± 11	16.0 ± 13.0
Systolic blood pressure (mmHg)	101.7 ± 13.3 ^{***}	91.4 ± 14.6 [§]	120.3 ± 6.1	72.3 ± 5.6
Diastolic blood pressure (mmHg)	62.4 ± 10.6 ^{**}	52.8 ± 12.5 [§]	72.3 ± 5.6	65 ± 5.0
Body weight (Kg)	51.0 ± 7.8 ^{***}	39.8 ± 11.1 [*]	63.5 ± 11.6	59.9 ± 7.9

Results expressed as mean ± SD; Descriptive level: *p < 0.05, **p < 0.005, ***p < 0.0001, § = not significant.

3.6 g/dL), and there was statistical difference to controls (2.5 ± 0.6 vs. 4.6 ± 0.5 g/dL, $p < 0.0001$). Kala-azar patients had increased values of serum gammaglobulins (range 1.7-8.3 g/dL), and they were statistically different of controls (3.7 ± 1.6 vs. 1.0 ± 0.3 g/dL, $p < 0.0001$). Intravascular colloid osmotic pressure, calculated by Landis-Pappenheimer equation ranged from 22.8 to 64.7 mmHg, and it was higher in kala-azar patients (31.2 ± 9.7 vs. 26.4 ± 1.6 mmHg, $p < 0.005$). Twenty one patients (38.1%) had plasma colloid osmotic pressure in normal range (23-28 mmHg), and 34 patients (61.9%) had increased colloid osmotic pressure, with values above 28 mmHg. All patients had hyponatremia (sodium < 135 mEq/L). Serum sodium ranged from 120 to 134 mEq/L with a statistical difference to controls (129.3 ± 4.5 vs. 139.4 ± 1.6 mEq/L, $p < 0.0001$). None of them presented symptoms related to hyponatremia. All patients had plasma hypo-osmolality (Posm < 280 mOsm/kg H₂O), and significant difference with controls (269.5 ± 8.4 vs. 290.2 ± 5.3 mOsm/kg H₂O). First morning urine osmolality showed lower values in kala-azar patients than in controls (750.0 ± 52.0 vs. 894.5 ± 30.0 mOsm/kg H₂O, $p < 0.05$), but they may be considered as having good urinary concentration capacity.

Table 2

Laboratory findings of patients with kala-azar and controls

	Kala-azar n = 55	Controls n = 20
Blood hemoglobin (g/dL)	$7.9 \pm 1.4^{***}$	14.2 ± 0.8
Serum total proteins (g/dL)	$7.8 \pm 1.4^{\S}$	7.4 ± 0.4
Serum albumin (g/dL)	$2.5 \pm 0.6^{***}$	4.6 ± 0.5
Serum gammaglobulins (g/L)	$3.7 \pm 1.6^{***}$	1.0 ± 0.3
Plasma colloid osmotic pressure (mmHg)	$30.7 \pm 7.1^{**}$	26.4 ± 1.6
Serum sodium (mEq/L)	$129.3 \pm 4.5^{***}$	139.4 ± 1.6
Urinary sodium (mEq/L)	$82.3 \pm 44.2^{**}$	110.3 ± 34.7
Serum potassium (mEq/L)	$3.7 \pm 0.4^*$	4.0 ± 0.3
Urinary potassium (mEq/L)	$23.2 \pm 11.1^{***}$	39.4 ± 10.7
Serum osmotic pressure (mOsm/kg H ₂ O)	$269.5 \pm 8.4^{***}$	290.2 ± 5.3
1 st urine osmotic pressure (mOsm/kg/H ₂ O)	$750.0 \pm 52.0^*$	894.5 ± 30.0
Serum urea (mg/dL)	$29.3 \pm 11.3^{**}$	34.7 ± 2.8
Urinary urea (mg/d)	$18.2 \pm 8.1^{**}$	24.6 ± 6.5
Fractional urea excretion (%)	$47.3 \pm 11.4^{\S}$	53.8 ± 15.7
Serum uric acid (mg/dL)	$3.3 \pm 1.5^{**}$	4.4 ± 1.0
Urinary uric acid (mg/d)	$782.7 \pm 306.6^{**}$	575.2 ± 185.0
Fractional urinary uric acid excretion (%)	$18.7 \pm 13.6^{**}$	10.2 ± 3.1
Creatinine clearance (mL/min/1.73m ²)	$120.7 \pm 21.4^*$	110.4 ± 20.7

Results expressed as mean \pm SD; osm = osmolality ; Descriptive level: * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0001$, \S = not significant.

No patient presented urinary osmolality under 250 mOsm/kg H₂O, showing a lack of capacity to produce diluted urine⁷. Urine osmolality was inappropriately high in relation to serum osmolality, meaning the persistence of ADH secretion during the whole 24-hours period. Urinary sodium excretion was significantly lower in kala-azar patients than in controls (82.3 ± 44.2 vs. 110.3 ± 34.7 mEq/L, $p < 0.05$). No patient had urinary sodium concentration under 30 mEq/L. Fractional urinary sodium excretion (range 0.3 to 3.9%) was similar to controls: (0.9 ± 0.8 vs. $0.7 \pm 0.2\%$, $p = 0.2028$). Urinary potassium excretion was significantly lower in kala-azar patients than in controls (23.2 ± 11.1 vs. 39.4 ± 10.7 mEq/L, $p < 0.005$).

Hypochloremia (serum chlorum < 96 mEq/L) was found in 17 patients (30.9%).

Serum urea (29.3 ± 11.3 vs. 34.7 ± 2.8 mg/dL, $p < 0.005$), and 24-hour urinary urea excretion (18.2 ± 8.1 vs. 24.6 ± 6.5 g/d, $p < 0.005$) were lower in kala-azar patients than in the control group. Serum urea was lower than 20.0 mg/dL in 26 patients (47.2%). Fractional urinary urea excretion (47.3 ± 11.4 vs. $53.8 \pm 15.7\%$, $p = 0.627$) was not significantly different to the control group.

Serum uric acid (range 1.8-6.4 mg/dL) was lower than 4.0 mg/dL in 34 patients (61.8%)⁷. Mean serum uric acid (3.3 ± 1.5 vs. 4.4 ± 1.0 mg/dL, $p < 0.005$) was lower in kala-azar patients. Daily urinary uric acid excretion (782.7 ± 306.6 vs. 575.2 ± 185.0 mg/d, $p < 0.005$) was significantly higher in kala-azar patients. Fractional urinary uric acid excretion ranged from 6.1 to 77%, and it was increased in 41 patients (74.5%), significantly different to the control group (18.7 ± 13.6 vs. $10.2 \pm 3.1\%$, $p < 0.005$).

Creatinine clearance was significantly higher in kala-azar patients (120.7 ± 21.4 vs. 110.4 ± 20.7 mL/min/1.73m², $p < 0.05$). Patients with low creatinine clearances (Ccr < 85 mL/min/1.73m²) were excluded due the presence of water and electrolyte disturbances in low renal function patients. Increased glomerular filtration rate (Ccr > 130 mL/min/1.73m²) was present in 14 patients (25.4%).

Plasma ADH (Table 3) measured in 23 kala-azar patients (41.8%) was higher than controls, but had no significant difference: (5.6 ± 1.1 vs. 5.1 ± 3.4 pg/mL, $p = 0.0635$). Plasma ACTH ranged from 12 to 73 pg/mL, and it was within the physiological range. Plasma ACTH was not significantly different to the control group (38.6 ± 0.09 vs. 43.2 ± 12.3 pg/mL, $p = 0.840$). Eleven patients (20.0%) had normal ACTH plasma levels and low plasma cortisol concentrations. Plasma cortisol levels (range 13 to 34 μ g/dL) were significantly higher in kala-azar patients (19.0 ± 7.1 vs. 14.0 ± 3.9 μ g/dL, $p < 0.005$). Cortisol plasma levels were lower than 18 μ g/dL in 20.0% of patients, which had low daily urinary 17-hydroxysteroids too. Daily urinary 17-hydroxysteroids (25.5 ± 19.7 vs. 8.8 ± 1.2 mg/d, $p < 0.005$) were higher in kala-azar patients and they were increased (> 12 mg/d) in 44 patients (80%).

Plasma renin levels were significantly higher in kala-azar patients (3.1 ± 3.8 vs. 1.0 ± 0.2 ng/mL/h, $p < 0.05$). Plasma renin was increased (> 2.6 ng/mL/h) in 13 patients (23.6%). Plasma aldosterone levels were significantly lower in kala-azar patients (5.4 ± 3.6 vs. 11.6 ± 7.2 ng/dL, $p < 0.005$). Low plasma aldosterone levels (< 3.0 ng/dL) were observed in 18 patients (32.7%). Daily urinary aldosterone excretion (5.9 ± 3.5 vs. 5.5 ± 1.5 μ g/d, $p = 0.0623$) was not significantly different to controls.

Table 3
Laboratory findings of patients with kala-azar and controls

	Kala-azar n = 55	Controls n = 20
ADH (pg/mL)	5.6 ± 1.1 §	5.1 ± 3.7
ACTH (pg/mL)	39.8 ± 0.2*	30.2 ± 0.3
Renin (ng/mL/h)	3.1 ± 3.8*	1.0 ± 0.2
Aldosterone (ng/dL)	5.4 ± 3.6**	11.6 ± 7.2
Cortisol (µg/dL)	19.0 ± 7.1**	14.0 ± 3.9
Urine aldosterone (µg/d)	0.2 ± 0.1 §	0.16 ± 0.04
Urine 17-hydroxysteroids (mg/d)	25.5 ± 19.7 **	8.8 ± 1.2
TSH (µIU/mL)	2.8 ± 2.1 §	2.5 ± 2.0
T ₄ free (ng/mL)	1.2 ± 0.6 §	1.5 ± 0.3

ADH - antidiuretic hormone; TSH - Thyroid stimulating hormone, T₄ - free thyroxin; Results as mean ± SD. Descriptive level: *p < 0.05, **p < 0.005, ***p < 0.0001, § = not significant.

Thirteen patients (23.6%) had high plasma renin and 42 patients (76.4%) had normal plasma renin concentrations (5.7 ± 4.6 vs. 1.4 ± 0.7 ng/mL/h, p < 0.0001). Patients with high plasma renin levels had higher plasma aldosterone (7.2 ± 3.6 vs. 3.6 ± 2.8 ng/dL, p < 0.05). They also had high urinary sodium concentrations (100 ± 55 vs. 76 ± 39 mEq/L, p < 0.05). There were no statistical differences between two groups, when the levels of serum sodium (131 ± 3.8 vs. 128 ± 4.4 mEq/L), serum potassium (3.7 ± 0.3 vs. 3.8 ± 0.4 mEq/L), plasma colloid osmotic pressure (312 ± 107 vs. 313 ± 92 mmHg) and fractional urinary sodium excretion (0.6 ± 0.5 vs. 0.7 ± 0.5%) were compared. Patients with increased plasma renin concentrations, had no evidence of extracellular volume depletion. Eleven patients (84.7%) with high plasma renin concentrations had serum uric acid below 4.0 mg/dL (4.2 ± 1.3 mg/dL) and increased uric acid excretion fraction (22.2 ± 18.5%), showing no difference between kala-azar patients with normal and with increased plasma renin levels.

Thyroid-stimulating hormone (TSH) plasma levels of kala-azar patients was not statistically different (2.8 ± 2.1 vs. 2.5 ± 2.0 µIU/mL, p = 0.6274). Free T₄ plasma levels of kala-azar patients did not show significant difference from the control group (1.2 ± 0.6 vs. 1.5 ± 0.3 ng/mL, p = 0.3382).

DISCUSSION

Daily fever, sweating, diarrhea and vomiting are present in kala-azar patients and may be important features to induce water and electrolyte disturbances. These patients manifest accentuate weight loss, but paradoxically preserve a good appetite during all disease evolution, which assures them a regular intake of fluids and sodium chloride. Kala-azar patients present characteristically an enormous splenomegaly, that induces to severe anemia, leucopenia and thrombocytopenia. Low blood pressure values are frequently observed in kala-azar patients, without evidence of orthostatic hypotension. Recently hyponatremia has been described in kala-azar patients of different groups^{20,21,25}. All these features may be present in patients with extracellular volume depletion and hypovolemia. The physiological response to hypovolemia would be

vasopressin secretion, and through the stimulus of the renin-angiotensin-system, secondary aldosterone production.

Hyponatremic individuals, due to extra-renal causes and carriers of volume depletion, present low levels of urinary sodium, generally under 20 mEq/L⁸. Urinary sodium was high in all kala-azar patients, and fractional urinary sodium excretion stayed within the normal range, independently of the plasma renin concentration, ruling out the possibility of extracellular volume depletion. The urea excretion fraction of kala-azar patients was similar to the control group, a physiological parameter frequently decreased in patients with extracellular fluid depletion.

Nearly one fourth of kala-azar patients presented high levels of plasma renin, while their plasma aldosterone levels stayed in normal range, a possible evidence of decreased adrenal response to the high plasma renin levels or to the presence of a physiological block to aldosterone secretion, as hypokalemia, potassium depletion or expanded water space.

Patients with high and normal plasma renin levels showed no difference in relation to sodium and potassium serum levels, as to daily urinary sodium excretion and the plasma colloid osmotic pressure values. Tendency to low potassium serum levels are evident in kala-azar patients and probably indicate the coexistence of body potassium depletion.

Carriers of low adrenal activity frequently have hyponatremia with high urinary sodium concentrations, and characteristically increased serum levels of potassium, urea and creatinine. Kala-azar patients, on the other side, had low plasma concentrations of aldosterone, potassium, urea and creatinine.

Most kala-azar patients presented plasma cortisol values higher than 18 µg/dL¹¹ and increased daily excretion of urinary 17-hydroxysteroids, assuring the presence of good adrenal function and making remote the possibility of adrenal insufficiency. One fifth of patients present normal ACTH and cortisol plasma levels with normal 17-hydroxysteroids urinary excretion, their real adrenal activity being difficult to evaluate.

Blood acid-base studies in kala-azar patients had not detected the presence of metabolic acidosis as commonly observed in low adrenal activity patients²¹.

Normal TSH and free T₄ plasma levels indicated sufficient thyroid hormone secretion to supply the basic needs of the organism in kala-azar patients, rejecting the possibility of water retention and hyponatremia, due to thyroid hormone deficiency.

Hyponatremia has been also observed in malnourished patients. Kala-azar patients maintain an adequate food intake as observed by the daily urinary phosphate excretion²⁰. Malnourished patients differ from kala-azar patients, particularly because they manifest reduced glomerular filtration rate².

Kala-azar patients present many features of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This syndrome is described in normovolemic or hypervolemic patients, and results in excessive water retention at distal and collecting ducts, despite low levels of extracellular fluid osmolality. Its main characteristics are: hyponatremia and hypo-osmolality, persistently increased urinary

sodium excretion and urine osmolality, with preserved renal and adrenal functions^{6,30}.

Hyponatremia and hypo-osmolality were found in all patients with visceral leishmaniasis of the present study, and persisted throughout the active phase of the disease. Despite serum hypo-osmolality, kala-azar patients produced highly concentrated urine, as evidenced in the first morning samples, and in the 24-hourly urine collections. No patient had urine osmolality lower than 250 mOsm/kg H₂O, a necessary condition for sufficient free water formation and aqueous diuresis production, with consequent plasma hypo-osmolality correction⁷. Kala-azar patients had higher plasma ADH levels. They had high urinary concentration capacity, but lower than that of the control group. This discrepancy may result of the presence of interstitial nephritis as the predominant kidney lesion of kala-azar patients¹³.

Hypoalbuminemia is part of the classical form of chronic kala-azar, and was a constant in all kala-azar patients. It results from liver dysfunction, decreased albumin synthesis and reduction in intestinal absorption of proteins due to a protein losing enteropathy²⁷. Low serum albumin concentrations decrease the plasma colloid osmotic pressure, and may reduce intravascular negative charges induced to lower Na⁺ attraction into vascular space (Gibbs-Donnan equilibrium), accentuating the hyponatremia¹⁵.

Hypergammaglobulinemia was a typical feature of kala-azar patients, and results from intense production of polyclonal antibodies, particularly G immunoglobulins.

Very little research has been given to the intravascular volume status in visceral leishmaniasis. Blood volume determinations using radio-iron ⁵⁹Fe and radio-chromium ⁵¹Cr have evidenced normal values¹⁷. On the other side, expanded intravascular volume has been extensively documented using T-1824 dye method, in patients with splenomegaly and visceral leishmaniasis^{23,31}.

In vivo and in experimental research, the calculation of plasma colloid osmotic pressure using the Landis-Pappenheimer equation, gives excellent results. The values are similar to those directly measured with oncometers²⁸. The results nearly give an idea of the volemic state, when plasma albumin concentrations are above 1.0 g/dL, as that observed in the kala-azar patients²⁴. By applying the equation, all kala-azar patients have normal or predominantly increased colloid osmotic pressure. The presence of increased plasma gammaglobulin concentrations exceed the decreased contribution of the hypoalbuminemia, and produce a normal or increased colloid osmotic pressure in kala-azar patients. The expansion of the intravascular volume can explain the increased values of glomerular filtration rate observed in kala-azar patients.

Proximal tubular dysfunction affecting the reabsorption of proteins, light chains, sodium, potassium, magnesium, calcium, inorganic phosphate and glucose has recently been observed in kala-azar patients, and was also attributed to expanded water space¹⁹. Similarly, findings have been described in patients with different pathologies associated to the syndrome of inappropriate antidiuretic hormone secretion^{16,35}.

Increased plasma renin levels, low plasma aldosterone concentrations and low daily urinary aldosterone excretion were observed in one-third

of kala-azar patients. These alterations have been described also in critically ill and hypotensive patients³⁷. Total body water expansion and potassium depletion (vomiting, diarrhea, urinary potassium loss) may act as potent blocks to aldosterone secretion by adrenal glands in kala-azar patients. Hypochloremia and low urea serum levels may be evidence of decreased protein ingestion and/or body water expansion¹⁸. Hypouricemia and increased fractional urinary uric acid excretion are other features of kala-azar patients. Reduction of proximal uric acid reabsorption leads to increased uric acid delivery to distal and collecting ducts, resulting in a greater uric acid excretion^{1,7}.

The syndrome of antidiuretic hormone secretion in kala-azar patients may be started by interstitial pneumonitis described in 76.8% of necropsied patients¹². The widespread and intensive inflammatory state involving the lungs, the liver, the kidneys, the intestines and the lymphatic ganglia induced to increase production of plasma prostaglandins and renin^{9,29,33,34}. High serum levels of interleukin-6 have been detected in visceral leishmaniasis^{3,32} and can act as a potent stimulus of the hypothalamic-pituitary-adrenal axis and to arginine vasopressin (ADH) release too^{14,22}.

CONCLUSION

Kala-azar patients present malnutrition, anemia, hypoalbuminemia, and hypergammaglobulinemia. Hyponatremia, serum hypo-osmolality and high urine osmolality reflect persistent antidiuretic hormone secretion, without production of sufficient free water for plasmatic hypotonicity correction. Urine sodium excretion remains comparable to that of normal patients. Increased urinary uric acid excretion fraction, hypouricemia, and the absence of adrenal and thyroid insufficiency suggest the possibility of the syndrome of inappropriate antidiuretic hormone secretion in most kala-azar patients.

RESUMO

Hiponatremia no calazar

Existem poucos relatos relacionando hiponatremia com a leishmaniose visceral (calazar). Este é um estudo de 55 pacientes portadores de calazar e um grupo controle de 20 indivíduos normais. Hiponatremia e hipo-osmolalidade sérica foram detectados em 100% dos pacientes portadores de calazar. A presença de alta osmolalidade da primeira urina da manhã ($750,0 \pm 52,0$ vs. $894,5 \pm 30$ mOsm/Kg H₂O, $p < 0,05$) e da urina de 24h ($426,0 \pm 167,0$ vs. $514,6 \pm 132,0$ mOsm/Kg H₂O, $p < 0,05$), demonstraram a presença de persistente secreção de hormônio antidiurético. A concentração de sódio urinário foi elevada ($82,3 \pm 44,2$ vs. $110,3 \pm 34,7$ mEq/L, $p < 0,05$). Hipouricemia ocorreu em 61,8% dos pacientes e aumento da fração de excreção urinária de ácido úrico foi detectada em 74,5% dos casos. Aumento da velocidade de filtração glomerular estava presente em 25,4% dos pacientes. Não havia evidência clínica de depleção de volume extracelular. Valores normais de ADH plasmático foram observados nos pacientes com calazar. Não foi detectada disfunção renal ou endócrina. É provável, que a maioria dos pacientes com calazar apresente uma síndrome de secreção inapropriada de hormônio antidiurético.

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