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Urinary Biochemical Changes, Histopathologic Effect of Kidney Damage Observed in Rats Infected with *Trypanosoma b. brucei*

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Introduction

Several investigations have used immunological techniques in elucidating the effect of host parasite relationship in animals to understand that of man. Sleeping sickness, a tropical disease in man is caused by *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. The related species *Trypanosoma brucei brucei* causes Nagana disease and rapid death in domestic animals. Trypanosomiasis causes land inhabitability, rapid tissue damage in animals and considerable effect on human nutrition (22).

FINNES (3) reported the occurrence of liver nephrosis and lung edema in cattle infected with *Trypanosoma congolense*. Alkaline phosphatase and muraminidase have been identified in human organs and secretions (1, 10). However, SIMAREN et al. (20) in single and concurrent infection of rats with *Trypanosoma congolense*, *Trypanosoma brucei* and rat hookworm (*Nippostrongylus brasiliensis*) reported fever, high degree of parasitemia, significant alteration in WBC, and loss of serum protein in the infected rats.

Since many unresolved pathological mysteries in African trypanosomiasis still exist, biochemical and electron microscopic studies of the kidneys of rats infected with *Trypanosoma b. brucei* were conducted in attempt to confirm possible occurrence of histopathological changes in the kidney, to establish the locations or site of the parasite in the tissue and the effect of infection by measurement of urinary volume, activity of alkaline phosphatase, acid phosphatase, muraminidase and protein concentration in the urine collected from infected rats, and to correlate the sensitivity and severity of these findings with the functional efficiency of the hosts' renal system. We are convinced that the results of this study will be of diagnostic value and a contribution to the advancement of knowledge in histopathology and chemical pathology of African trypanosomiasis.

Materials and Methods

Twelve white albino rats (11 weeks old) used in this study were selected from the parasite free in-bred colony maintained in our Parasitology Animal House, OBAFEMI AWOLOWO University, Ile-Ife. The rats were divided into two experimental groups. All rats were maintained on standard food pellet and water without restriction, each in a metabolic cage fitted with a plastic container placed below a metal gauze for the animal to urinate in.

All rats were intraperitoneally injected, each with 5,000 *Trypanosoma b. brucei* obtained from the rat which had been previously infected with our continuously maintained stock of the parasite. Modified method of LINICOMBE and WATKINS (10) was used for preparing the needed trypanosoma cells. During the infection, rats in the two experiments were starved on alternate days. Urine samples from every infected rat were collected every 24 hours. The volumes of urines were recorded and centrifuged at 1000 g for 10 minutes. The supernatants were used for the following biochemical tests. With Spectronic 20, total protein concentration was determined at 37° C by Biuret method and the results expressed in mg/ml excreted per hour (14); alkaline phosphatase and acid phosphatase activities were determined at 37° C and the unit expressed in nM/min/ml excreted per hour (WRIGHT et al. 1972); and muraminidase activity was also estimated at 37° C expressed in mcg/min/ml excreted per hour (6).

Electron microscopic study of the kidney of rat infected with the *Trypanosoma b. brucei* was conducted. One rat from each experiment was rapidly sacrificed 6th day after infection and the removed kidneys were dipped in a 100 ml beaker of 1% isotonic phosphate buffered osmium tetroxide fixative solution (12) at pH 7.3 for 2 hrs. Repeated washing at 4° C for 1 hour each was followed with dehydration through series of absolute alcohol at room temperature. The tissue sections were placed in propylene oxide repeatedly for alcohol clearance for 15 minutes after which they remained in 1 : 1 mixture of propylene oxide and epon for 4 hours; and in a 1 : 3 propylene oxide and epon mixture. The blocks were cured in the oven at 60° C for 36 hours to effect excellent polymerization. Ultrathin sections were cut with diamond knives on a Porter-Blue MT-2 Ultramicrotome. The sections were collected on 0.5% colloidon-coated grids (13) and stained in aqueous uranyl acetate or lead citrate (23) The grids were then examined and photographed with RCA EMU-2D electron microscope.

Results

The results of biochemical measurements of urinary volumes, protein concentration, activities of urinary serum muraminidase, acid phosphatase and alkaline phosphatase in collected urines from rats infected with *Trypanosoma b. brucei* are presented in tables 1 - 3.

There were progressive fluctuations in excreted urine during the infection. Progressive increases of urinary protein concentration were detected during the infection. The progressive increases in proteinuria found in the two experiments were higher than the control value. The slight decreases in urinary excretion corresponds to the time the animals were fed while the slightly sharp rises represented the period the animals were starved (Table 1).

No muraminidase activity was detected in the control urines. Marked increases in urinary serum muraminidase activity were detected in the urines of the infected rats (Table 3).

Similarly, significant sharp increases in urinary acid phosphatase activity detected were most marked on the 5th day post infection above the control value (Table 2).

Urinary activity of alkaline phosphatase increased above the normal control value with a sharp rise to a peak on the 5th day post infection (Table 2).

Ultramicrographs of the electron-microscopic study of the infected rats' kidney revealed the *Trypanosoma b. brucei* located in the kidney glomeruli, glomerular capillaries, interstitial glomerular spaces and the renal tubules (Fig. 1 - 3). Membranes around these organelles where the trapped parasites are localized showed irregular thicken-

TABLE 1
**Changes in Urinary Volume and Protein Concentration
 in Rats after Infection with *Trypanosoma b. brucei***

Days after Infection	Urine in ml/24 hrs.		Protein in mg/ml/hr.	
	Group I	Group II	Group I	Group II
1	4.17 ± 0.30	3.30 ± 0.2	0.28 ± 0.02	0.34 ± 0.02
2	3.73 ± 0.60	4.62 ± 0.4	0.25 ± 0.02	0.34 ± 0.02
3	5.25 ± 0.80	3.95 ± 0.9	0.35 ± 0.03	0.29 ± 0.04
4	4.60 ± 1.20	6.12 ± 1.1	0.40 ± 0.03	0.39 ± 0.09
5	10.28 ± 1.10	9.60 ± 1.4	0.59 ± 0.06	0.48 ± 0.08
Control	3.35 ± 0.12	3.27 ± 0.1	0.077 ± 0.01	0.074 ± 0.01

TABLE 2
**Changes in Urinary Acid Phosphatase and Alkaline Phosphatase
 in Rats after Infection with *Trypanosoma b. brucei***

Days after Infection	Acid Phosphatase in nM/Min/ml/hr.		Alkaline Phosphatase in nM/Min/ml/hr.	
	Group I	Group II	Group I	Group II
1	1.60 ± 0.15	0.85 ± 0.10	1.56 ± 0.25	0.84 ± 0.22
2	1.50 ± 0.01	1.56 ± 0.10	1.62 ± 0.16	1.36 ± 0.25
3	2.40 ± 0.20	1.34 ± 0.20	2.67 ± 0.35	1.10 ± 0.15
4	1.88 ± 0.20	2.14 ± 0.25	2.51 ± 0.50	3.02 ± 0.30
5	3.75 ± 0.30	5.00 ± 0.40	5.78 ± 0.50	3.88 ± 0.35
Control	0.60 ± 0.09	0.55 ± 0.08	0.68 ± 0.10	0.58 ± 0.10

TABLE 3
Changes in Urinary Muraminidase in Rats after Infection with *Trypanosoma b. brucei*

Days after Infection	ug/Min/ml/hr.	
	Group I	Group II
1	3.64 ± 0.5	2.20 ± 0.3
2	2.82 ± 0.4	2.97 ± 0.3
3	5.16 ± 0.6	2.68 ± 0.5
4	4.20 ± 0.3	8.50 ± 0.7
5	13.70 ± 1.0	20.56 ± 1.2
Control	0	0

ing, splittings and infoldings with scalloped appearance; small vesicles characteristics of lesions, inflamed mitochondria with or devoid of cristae and dense lipid droplets (Fig. 1 - 2).

Other ultrapathological features depicted in the micrographs of the diseased kidney and the trapped parasites included free ribosomes, increased lysosomes and glycogen particles, degenerating endothelial cells, inflamed degenerating cell membranes, fused golgi complexes, flagellar shafts and puffy elongated mitochondria uniting with agranular secretory reticulum (Fig. 1 - 3).



Fig. 1:

An oblique transverse section of a nuclear area of *Trypanosoma b. brucei* trapped in the border loop of a glomerular tubule and interstitial capillary network. Histopathologic effects are swollen mitochondria devoid of cristae, inflamed glomerular basement membrane with vacuolar lesions, increased free ribosomes and puffy lysosomes are displayed.

× 43,000

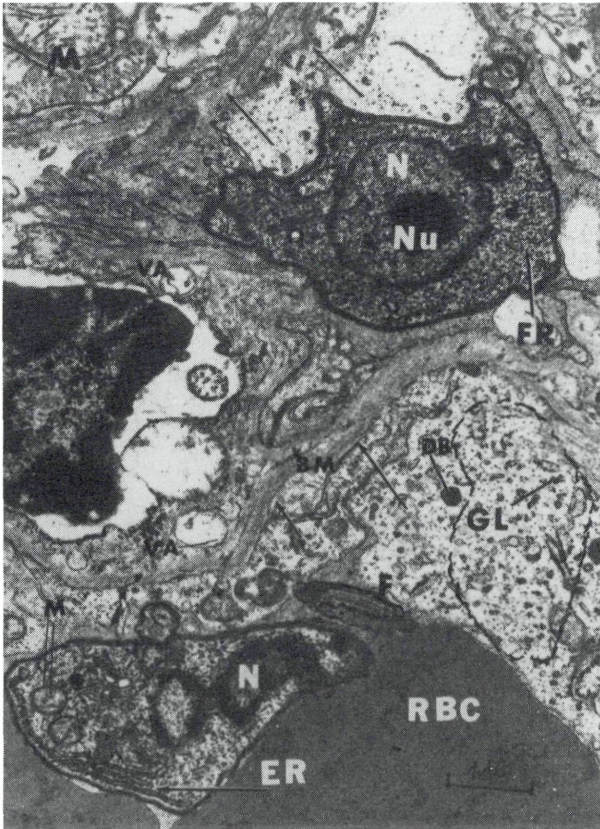


Fig. 2:

Longitudinal and transverse section of two *Trypanosoma b. brucei*. The top parasite is trapped between joined luminal surface of proximal segments of tubular nephrons and the bottom parasite is locked to one side of the basement membrane of a rich capillary by red blood cell. Effect of kidney damage are increased free ribosomes, glycogen granules, vacuoles dense bodies, elongated and inflamed mitochondria slantingly perpendicular to the infolding basement membranes.

× 18,000



Fig. 3:

An oblique transverse section of a *Trypanosoma b. brucei* trapped in interstitial capillary of glomerular tubule. The parasite is locked to the inflamed basement membrane of the capillary wall. Resultant kidney damage are swollen mitochondria devoid of cristae, increased glycogen granules, lysosome, free ribosomes, dense lipid bodies, and degeneration of cell membranes are displayed.

× 21,000

KEY TO ALL FIGURES

CM — Cell membrane	VL — Vesicles/lesions (arrows)
F — Flagellar shaft	BM — Basement membrane
SR — Secretory reticulum behind the nucleus	VA — Membrane bound vesicles
LY — Lysosome	FR — Free ribosomes
SP — Subpellicular microtubules	GL — Glycogen granules or particles
K — Kinetoplast	DB — Dense bodies
M — Mitochondria	ER — Endoplasmic reticulum
ME — Elongated mitochondria	RBC — Red blood cell
N — Nucleus	LP — Lipid droplets
NU — Nucleous	ED — Endothelial cell

Discussion

The recorded cellular changes in the infected kidney and the significant increases in urinary volume, proteinuria, alkaline phosphatase, acid phosphatase and muraminidase demonstrate clinical evidence that *Trypanosoma b. brucei* infection in rat causes renal damage and have caused damage in the proximal convoluted tubules of the kidney during the infection (Tables 1 - 3, Fig. 1 - 3).

The demonstrated histopathological changes occurred in sequential phases. First, the diuretic phase corresponds to the early period of progressive increases in urine and proteinuria occurrence during the infection. The 3rd and 4th day after infection represent the progressive phase when higher urinary excretions and rising proteinuria were recorded. The peaks of urinary volume and proteinuria of the 5th day post-infection corresponds to the polyuric phase when severe anaemia and renal insufficiency preceded death of the diseased rats (Table 1). The reported progressive proteinuria and other physiological findings are clinically parallel to the serum and cellular disorders reported in pregnant and non-pregnant rats infected with *Trypanosoma congolense* (19). These major findings include reduced total serum protein and calcium, unbalanced sodium and chloride electrolytes, normal potassium ion, and persistent hypoglycemia and hypercholesterolemia. Increases in urinary globulin and albumin in rabbits infected with *Trypanosoma brucei* have been reported (4, 7, 8). These authors reports are also support of our documented findings of significant increases of progressive proteinuria which confirmed the occurrence of renal syndrome during the infection.

The electron microscopic demonstration and localisation of *Trypanosoma b. brucei* in the glomeruli and glomerular capillaries of the kidneys of the infected rats and the histopathological changes found in the kidney cells around the trapped parasites are qualitative evidence that the parasitic infection causes renal damage and have also caused damages to the convoluted tubules of the kidney where absorption of the protein in the glomeruli takes place (Table 1, Fig. 1 - 3).

Muraminidase activity in normal urine hardly exists (24), but traces of its activity have been detected in human serum, lungs and kidney (11). No muraminidase activity was detected in the controls of our experiments. Our detection of initial muraminidase activity during the infection is in agreement with literature report. The subsequent increases of serum urinary muraminidase activity detected midstream of the infection were indicative signals of progressive renal insufficiency occurring in the infected rats (Table 3). There were marked increases in muraminidase activity around the 4th day post infection. The marked increases are distinctively higher than the reports of other workers that patients suffering from pyelonephritis, glomerunephritis and necrosis showed increased serum and urine muraminidase (5, 15). The significant higher increases in excreted muraminidase activity recorded on the 5th day of infection qualitatively showed that *Trypanosoma b. brucei* infection in rats caused glomerular damage. While

the histopathologic alterations depicted in the ultramicrographs of the diseased kidney are proofs of glomerular damage (Table 3, Fig. 2, 3). The pattern of urinary excretions of muraminidase documented in this investigation will be a useful sensitive index in quantifying glomerular damage of renal syndrome in African trypanosomiasis.

We have reported that progressive increases of acid phosphatase activity measured in the excreted urines of infected rats were most marked on the 5th day above the control value. The significance of this marked increases of acid phosphatase activity are confirmed by the demonstrated *Trypanosoma b. brucei* trapped in the proximal convoluted tubules of the infected kidney and the revealed histopathological changes of swollen mitochondria, abundant free ribosomes, increased number of lysosomes and glycogen particles in the kidney ultramicrographs. These pathologic changes and effects demonstrate beyond reasonable doubts that the lysosomal acid phosphatase of the convoluted tubules are deeply involved in the kidney damage (Table 2, Fig. 2, 3).

Presence of alkaline phosphatase in rat and human organs have been reported (8). Table 2 shows the detected sharp increases in urinary alkaline phosphatase activity above the control value. These activity increase of alkaline phosphatase was caused by the progressive damage the parasitic infection evoked on the proximal convoluted tubules of the kidney. The cellular changes ultrastructurally demonstrated in the tissues around the trapped parasite are also evidence of progressive histopathological damage caused by *Trypanosoma b. brucei* infection in the rats (Fig. 1 - 3).

Electron micrographs of the various sections of the infected kidney tissue have shown that the *Trypanosoma b. brucei* were trapped in the kidney glomeruli, glomerular capillaries, interstitial glomerular spaces and renal tubules (Fig. 1 - 3). SIMAREN (17) in ultrastructural studies of *Trypanosoma lewisi* in infected rats found the parasites trapped in liver sinusoids and space of Disse. In an extended study of this less pathogenic trypanosome in infected rat, SIMAREN (18) demonstrated the presence of *Trypanosoma lewisi* in kidney capillaries. He interpreted part of his observed cellular changes in the kidney cells and the parasite as possible indicators which can initiate kidney disorders in African trypanosomiasis. In this detailed investigation on *Trypanosoma b. brucei* infection, examined ultramicrographs of infected kidney sections prominently depict kidney cells parasitized by short and stumpy *Trypanosoma b. brucei* cells. Thick capillary and tubular basement membranes which enclosed these parasites also depict irregular thickening and splittings, swollen mitochondria with and devoid of cristae, puffy lysosomes, vesicular lesions, free ribosomes, abundant glycogen particles, and dense lipid inclusions. These cellular changes are demonstrated evidence of histopathological effect of the *Trypanosoma b. brucei* infection.

The displayed free ribosomes, glycogen particles, lysosomes, membrane bound vesicles and dense lipid droplets in the kidney cells and the trapped parasites are additional pathological features which confirmed glomerular damage and nephrotic syndrome during the infection. In the ultramicroscopic study, more short and stubby forms of *Trypanosoma b. brucei* were found localized in the infected kidney, unlike the many slender forms of *Trypanosoma lewisi* which were demonstrated in the liver sinusoids of the infected rat (17). This observation might be due to the mechanism of cyclical development in trypanosomes reported by VICKERMANN (21). A possibility that the parasites could have been transported to the prostrate glands during infection needs to be investigated.

From the results of this study, we categorically state that the enumerated urinary biochemical changes, and the demonstrated histopathological alterations and effects have established the occurrence of renal malfunction and insufficiency, and kidney damage during the infection of *Trypanosoma b. brucei* in rats. These qualitative and quantitative findings of progressive increases in proteinuria, significant increased

activity of alkaline phosphatase, acid phosphatase and muraminidase demonstrate pathological evidence that *Trypanosoma b. brucei* infection in rats causes renal damage and have also caused damages in proximal convoluted tubules of the kidney.

Summary

Experimental infection with *Trypanosoma brucei* was induced subcutaneously in 12 white laboratory rats divided into two groups. All the infected rats received the same standard dose of the parasite.

The mean criteria used to establish the effects of infection were measurement of urinary volumes, activity of alkaline phosphatase, acid phosphatase, muraminidase and protein concentration in urine collected daily from the infected rats.

Electron microscopic studies of infected rats were conducted in attempt to confirm possible occurrence of histopathological changes in the kidney, to establish locations or sites of the *Trypanosoma b. brucei* in the tissue and to correlate these findings with the functional efficiency of the host's renal system. The principal findings are as follows:

The fluctuation in excreted urinary volumes is an indication of progression of the parasitic disease, the occurring renal damage, and the physiological effect of feeding on alternate days during the infection.

There was a significant progressive proteinuria during the course of the infection. This progressive proteinuria is an indication that the parasitic infection causes renal damage in proximal convoluted tubules of the kidney where absorption of almost all the protein in the glomeruli takes place.

There was a marked increase in the activity of serum urinary muraminidase after infection which is also evidence of kidney damage in the infected rats.

There were increasing variations in the pattern of the acid phosphatase, most marked on the 5th day post infection. This significant increase above the normal value indicates or suggests that this lysosomal enzymes of the proximal convoluted tubules are involved in the kidney damage.

Urinary activity of the membrane bound alkaline phosphatase increased above the control value with a sharp rise to a peak on the 5th day post infection.

The micrographs of the electron microscopy revealed the presence of *Trypanosoma b. brucei* trapped in the kidney glomeruli, glomerular capillaries, interstitial glomerular spaces and the renal tubules. The membranes around these organelles where the trapped parasites are localized showed irregular thickening, splittings, vacuolar lesions and scattered lipid-like particles. Other ultrathin pathological features depicted in the micrographs of the diseased kidney and the trapped parasites included swollen mitochondria, free ribosomes, increased glycogen particles, increased number of lysosomes, degenerating endothelial cells, inflamed degenerating cell membranes, fused golgi complexes, broken flagellar shafts and puffy elongated mitochondria canals uniting with agranular secretory reticulum.

These electron microscopic changes confirm the presence of kidney damage following parasitic infection. Their presence indicates that infection by the parasite *Trypanosoma b. brucei* can cause glomerular damage and nephrotic syndrome in rats. It is possible that this parasite could have been transported to the prostate glands. This will be investigated.

Key words

Trypanosoma b. brucei infection, rats, urinary chemistry, blood chemistry, electron microscopy.

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Zusammenfassung

Biochemische und histopathologische Veränderungen als Folge einer Nierenschädigung bei mit *Trypanosoma b. brucei* infizierten Ratten

Bei 12 weißen Ratten wurde eine experimentelle Infektion mit *Trypanosoma brucei* durchgeführt. Alle Tiere erhielten die gleiche Anzahl von Parasiten subkutan. Zur Kontrolle der Nierenfunktion wurde täglich Harnvolumen, die Aktivität der alkalischen Phosphatase und der sauren Phosphatase, der Muraminidase sowie die Eiweißkonzentration anhand des gesammelten Urins der infizierten Tiere gemessen. Zur Feststellung von eventuellen histopathologischen Veränderungen der Nieren und der Lage der Parasiten im Gewebe wurden elektronenmikroskopische Untersuchungen vorgenommen. Dabei konnten folgende Befunde erhoben werden:

Die Veränderung des Harnvolumens ist ein Indikator für das Fortschreiten der parasitären Infektion, der dabei auftretenden Nierenschädigung sowie ein physiologischer Effekt der Fütterung an verschiedenen Tagen. Die Proteinurämie nahm während des Verlaufes der Infektion signifikant zu. Dies zeigt die zunehmende Schädigung der Niere durch die parasitäre Infektion v. a. in den proximalen Tubuli, wo die Eiweißrückresorption stattfindet. Auch der starke Anstieg der Muraminidase bei den infizierten Tieren ist ein Hinweis auf die ausgelöste Nierenschädigung. Ein signifikanter Anstieg der sauren Phosphatase, der am 5. Tag nach der Infektion besonders ausgeprägt ist, scheint darauf hinzuweisen, daß die lysosomalen Enzyme in den proximalen Tubuli von der Nierenschädigung besonders betroffen sind. Auch die membrangebundene saure Phosphatase zeigte einen Anstieg mit einem Gipfel am 5. Tag nach der Infektion.

Die elektronenmikroskopischen Schnitte zeigten das Auftreten von *Trypanosoma b. brucei* in den Glomerula, den glomerulären Kapillaren, im Interstitium der Glomerula und den Tubuli. Die Membranen der von Parasiten befallenen Organellen zeigten irreguläre Verdickungen, Spalten- und Vakuolenbildungen und verstreute, lipidähnliche Partikel. Die im Nierengewebe lokalisierten Parasiten zeigten vergrößerte Mitochondrien, freie Ribosomen, vergrößerte Glykogenpartikel, eine vermehrte Zahl von Lysosomen, degenerierte Endothelzellen, entzündlich degenerierte Zellmembranen, fusionierte Golgi-Komplexe, gebrochene Geißelschäfte und geschwollene mitochondriale Kanäle, verbunden mit einem agranulären sekretorischen Retikulum. Diese elektronenmikroskopischen Veränderungen bestätigen die durch die parasitäre Infektion hervorgerufene Nierenschädigung bei Ratten. Die gegenwärtige Studie zeigt insbesondere die Zerstörung der Glomerula und die Entstehung eines nephrotischen Syndroms als Folge der parasitären Infektion. Die Möglichkeit eines Transports der Parasiten in die Prostata soll noch untersucht werden.

Schlüsselwörter

Trypanosoma b. brucei-Infektion, Ratten, Nierenfunktion, Blutchemie, Elektronenmikroskopie.

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