UNIVERSITI PUTRA MALAYSIA

PATHOGENESIS OF NEPHRO-AND TESTICULOPATHIES INDUCED BY THE MALAYSIAN ISOLATE OF Trypanosoma evansi IN RABBITS

YASAMEEN SAHIB GUMAR

FPV 2015 5

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By

YASAMEEN SAHIB GUMAR

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

January 2015

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TO MY

PARENTS, BROTHERS

AND

SISTER

FOR THEIR ENDLESS LOVE AND SUPPORT

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Doctor of Philosophy

PATHOGENESIS OF NEPHRO-AND TESTICULOPATHIES INDUCED BY THE MALAYSIAN ISOLATE OF *Trypanosoma evansi* IN RABBITS

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January 2015

Chairman: Professor Noordin Mohamed Mustapha, PhD.

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Trypanosoma evansi, the causative agent of Surra, is a severe parasitic infection of animals leading to morbidity and mortality among livestock. The pathogenesis of surra is obscured and not fully elucidated with regards to nephro-and testiculopathies along with anaemia in the chronically infected laboratory model. This forms the basis of the present investigation. This study was designed to provide partial explanation on histopathological alterations, detection and distribution of trypanosomal antigen during the progress of the disease in rabbits experimentally infected with *T. evansi*.

Thirty five male rabbits with an average weight of approximately 2-2.3 kg were divided randomly into seven experimental groups comprising of five rabbits each. Animals from trypanosome-infected groups were inoculated intravenously (I/V) with 1×10^5 trypanosome/ml while the control group received phosphate saline glucose (PSG) buffer via the same route. Parasitaemia was estimated twice weekly for six months post infection (p.i.). Body temperatures were measured prior to blood sampling. The weights of the rabbits in each group were measured every 10 days. Standard haematological and biochemical parameters including Hb, PCV, RBC, WBC and differential counts were done. Five rabbits from each group were sacrificed and examined at 1, 2, 3, 4, 5 and 6 months pi.

The protozoan was found in the blood of the infected rabbits as early as 72 hours p.i. Haemogram showed an obvious drop in Hb, PCV, total erythrocyte count and leucocytosis. Anaemia was followed by the first wave of parasitaemia which continued until the end of the experimental period. Differential WBC counts showed heterophilia, lymphocytopaenia, monocytosis and eosinophilia. Biochemical analysis showed a significant increase in serum levels of urea, creatinine, ALT, AST, GGT, globulin, total protein plus a decrease in albumin and glucose. At necropsy, nephropathy, hepatomegaly, splenomegaly and testiculopathy were observed.

Microscopical observations in the kidney include moderate to severe tubular degeneration and necrosis, shrunken glomeruli with increase Bowman's spaces and membranous glomerulonephritis. Amylidiosis were demonstrated at 5 and 6 months

p.i. Testicular changes especially that of severe degeneration and aspermia were observed by the first month p.i. All changes were consistent with trypanosome infection and were confirmed by presence of trypanosomes in these tissues by immunohistochemistry and immunoflourescent techniques.

The data denotes that the pathogenesis of Malaysian isolate of trypanosomosis in rabbit model is associated with a pronounced biochemical and morphological changes in the kidneys and testicles, in addition to chronic hematological disorders such as anaemia.

The *T. evansi* was demonstrated by an immunohistochemical technique in formalin-fixed tissues of rabbits. The immunopositive antigenic expression of *T. evansi* was clearly disseminated in the parietal layer of Bowman's capsule together with glomerular capillaries; the same expression was seen in the renal interstitial of the blood vessels. In the testicles, the antigenic expression was prominent in the seminiferous tubules, in the testicular blood vessels and in the testicular interstitial connective tissue. Moreover, immunopositive reaction was seen in the epithelium lining of the epididymis.

Electron microscopy showed electron-dense deposits and podocyte fusions. Also, the presence of swelling mitochondria denoting oxidative damage due to lipid peroxidation, which was visualized in the kidneys and testicles of *T. evansi* infected rabbits.

The IgG and IgM antibody levels were elevated following infection while the C3 activation by antigen-antibody complexes during the infection also resulted in hypocomplementaemia. Cytokines such as IL-1, IL-6, TNF-α, INF-γ and IL-10 were measured and compared with the level of anaemia. Although the pathogenesis of anaemia in *T. evansi* infection is not obviously well-defined, the study showed that elevated levels of these cytokines together with the haematological findings may explain the pathological mechanism of *T. evansi* on the host with resultant organ damage and anaemia.

It was concluded that rabbits intravenously injected with the Malaysian isolate of *T. evansi* developed end stage kidney disease and very severe testicular and epididymal damage that could result in infertility. Furthermore, rabbits play an important role as a model to study the chronic pathological effects of *T. Evans* which mimics the natural infection. Immunohistochemistry technique is an important diagnostic method to confirm the infection even when the parasites become undetectable in the peripheral blood.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PATOGENESIS NEPHRO-DAN TESTICULOPATI YANG DIARUH ISOLAT *Trypanosoma evansi* MALAYSIA PADA ARNAB

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Trypanosoma evansi merupakan parasit penyebab jangkitan Surra pada haiwan yang menjurus kepada kemorbidan dan kemortalan ternakan. Patogenesis penyakit yang kurang jelas terutama terhadap nefro- dan testikulopati bersama anemia menjadi asas kajian ini. Ia dibentuk untuk menerang secara separa perubahan histopatologi, pengesanan dan taburan antigen tripanosom ketika perkembangan penyakit pada arnab yang dijangkiti secara ujikaji.

Sebanyak 35 ekor arnab jantan dengan purata berat 2.-2.3 kg diagih secara rawak kepada tujuh kumpulan rawatan yang mengandungi 5 ekor arnab setiap kumpulan. Haiwan dari kumpulan terjangkit-tripanosom diinokulat secara intravena (I/V) dengan 1×10^5 tripanosom/ml manakala kumpulan kawalan menerima glukosa salina fosfat (PSG) buffer melalui kaedah yang sama. Parasitemia dianggar setiap dua minggu selama enam bulan pasca jangkitan (p.i.). Suhu badan disukat sebelum pengambilan darah. Berat arnab dari setiap ditimbang setiap 10 hari. Parameter piawai hematologi dan biokimia termasuk Hb, PCV, RBC, WBC dan kiraan pembedaan juga dibuat. Lima ekor arnab dari setiap kumpulan dikorbankan dan diperiksa pada 1, 2,3,4,5, dan 6 bulan p.i.

Protozoa ditemui dalam darah seawall 72 jam p.i. Hemogram menunjukkan penurunan ketara pada Hb, PCV, kiraan eritrosit penuh dan leukositosis. Anemia terkesan oleh arus parasitemia pertama yang berlarutan hingga ke akhir tempoh kajian. Kiraan perbedaan RBC menunjukkan heterofilia, limfositopenia, monositosis dan eosinofilia. Analisis biokimia menunjukkan pengingkatan aras urea, kreatinina, ALT, AST, GGT, globulin, protein penuh serum termasuk penurunan albumin dan glukosa. Ketika nekropsi, nefropati, hepatomegali, splenomegali dan testikulopati dilihat.

Ujian mikrosokopi pada ginjal merangkumi penjanarosotan dan nekrosis pertengahan dan teruk, pengecutan glomerulus beserta peningkatan ruang Bowman dan glomerulonefritis bermembran. Amiloidosis kelihatan pada 5 dan 6 bulan p.i. Perubahan testis terutama penjanarosotan teruk dan apermia dilihat pada bulan

pertama p.i. Kesemua perubahan adalah selari dengan jangkitan tripanosom dan disahkan oleh teknik imunohistokimia dan inmunopendafloran.

Data menunjukan bahawa pathogenesis tripanosom isolate Malaysia pada model arnab berkait dengan perubahan ketara biokimia dan morfologi pada ginjal dan testis disamping gangguan hematologi kronik seperti anemia.

T. evansi yang ditunjukkan oleh teknik imunohistokimia pada tisu arnab terawet-formalin. Penterjemahan antigen imunopositif *T. evansi* dengan jelas tersebar di lapisan luar kapsul Bowman bersama dengan kapilari glomerulus, dengan kesan yang sama pada salur darah intersitium renal. Pada testis, penterjemahan antigen ketara pada tubul seminiferus, salur darah testis dan tisu intersitium. Lebih lagi, tindakbalas imunopositif dilihat pada epithelium selaput epididimis.

Mikroskopi electron menunjukkan mendakan legap-elektron dan pengabungan podosit. Begitu juga dengan kehadiran pembengkakan mitokondria membuktikan kerosakan oksidatif akibat pengkosidaan lipid yang dilihat pada ginjal dan testis arnab terjangkit.

Aras antibody IgG dan IgM meningkat lanjutan dari jangkitan manakala pengaktifan C3 oleh kompleks antigen-antibodi ketika jangkitan membawa kepada hipokomplementemia. Sitokin seperti IL-1, IL-6, TNF-α, INF-γ dan IL-10 disukat dan disbanding dengan aras anemia. Walaupun pathogenesis anemia akibat jangkitan *T. evansi* agak samar, kajian ini menunjukkan peningkatan aras sitokin bersama penemuan hematologi yang menerangkan mekanisma patologi *T. evansi* pada perumah dengan kesan kerosakan organ dan anemia.

Adalah dirumuskan bahawa arnab yang disuntik dengan isolate *T. evansi* isolate Malaysia akan membentuk penyakit ginjal peringkat akhiran dan kerosakan testis dan epididimis yang teruk yang boleh menjurus kepada kemandulan. Lebih lagi, arnab memainkan peranan penting sebagai model untuk kajian kesan patologi kronik *T. evansi* yang menyerupai jangkitan semulajadi. Imunohistokimia merupakan teknik diagnosis penting untuk mengesahkan jangkitan walaupun parasit tidak dapat dikesan dalam darah periferi.

ACKNOWLEDGEMENTS

All the praises and thanks are to ALLAH the compassionate, the Merciful, the only creator of the universe and the source of all knowledge and wisdom.

Foremost, I would like to express my sincere gratitude to my supervisor Professor Dr Noordin Mohamed Mustapha for the endless support and encouragement, for his patience, motivation, enthusiasm, and for the huge knowledge he has shared with me. His supervision was inimitable and comprehensible. He understands, caring, kind and great person to work with. I could not have imagined having a better supervisor and mentor for my Ph.D study.

I would like to thank the rest of my thesis supervisor, committee: Dr. Reuben Sharma Prof. Dr. Md. Zuki Abu Bakar for their encouragement.

Special thanks go to Miss. Jamila, Miss latifa, Mr. Ghazali, Mr. Abarao for their excellent assistance and Electron Microscope staff in IBS for their help and indispensable support, especially Miss Almazian, Miss Amina and Mr. Rhafi. My thanks to Mr. Nooraziman from animal house of Faculty of Veterinary Medicine for his invaluable help and support. Special thanks to my labmates for giving hand in solving problems.

Special thanks go to all my family, dear sister, and brothers for their confidence in me and for being always interested in my well-bein, for providing unfailing support to finish this work. I thank all my international friends for their prayer and moral support, Finally, to those not mentioned here, I would like to thank you for your direct or indirect effort and contribution to this study.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy.
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LIST OF ABBREVIATIONS

Ab-ELISA	Antibody-detection enzyme-linked immunosorbant assay
Ag-ELISA	Antigen-detection enzyme-linked immunosorbant assay
ALT	Alanine Aminotransferase
APOL1	Apolipoprotein L1
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BCT	Buffy Coat Techneque
BUN	Blood Urea Nitrogen
CKD	Chronic Kidney Disease
CRD	Chronic Renal Disease
°C	Degree Celsius
C3	Complement 3
CATT	Card Agglutination Test
CATT / *T. evansi*	Card Agglutination Test for *Trypanosoma evansi*
CFT	Complement Fixation Test
CRF	Corticotropin Releasing Factor
DAB	3,3′- Diaminobenzidine
DEAE	Diethylaminoethyl cellulose
dH2O	Distilled water
ddH2O	Deionized distilled water
DME	Direct Microscopic Examination
DF	Dilution Factor
Dpi	Day post infection
DNTB	5-5'-dithiobis 2-nitrobenzoic acid
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Linked Immunosorbent Assay
EPO	Erythropoietin

ESRD	End stage renal disease
et al	And others
fL	femtoliters
GGT	Gamma-Glutamyl Transferase
GFR	Glomerular Filtration Rate
g/L	gram/litter
G	Group
GGT	Gamma Glutamyl Transpeptidase
GSH	Glutathione
GSH-Px	Glutathione Peroxidase
H_2O_2	Hydrogen peroxide
Haematocrit	Hct
Hb	Haemoglobin
HMI-9	Hirumis modified Iscove's medium-9
HCT	Haematocrit Centrifugation Technique
HRP	Horseradish peroxidase
HSD	Honest significant difference
IFAT	Indirect Fluorescent Antibody Test
IFT	Immunofluorescence Test
IgA	Immunoglobulin alpha
IgG	Immunoglobulin gamma
IgM	Immunoglobulin mu
IHC	Immunohistochemistry
IL	Interleukin
INF-γ	Interferon-gamma
i.p.	Intraperitoneally
I/V	Intravenously
kDNA	Kinetoplast DNA
LAT	Latex Agglutination Test

MAECT	Mini-anion exchange chromatography
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MDA	Malondialdehyde
MetHb	Methemoglobin
MHCT	Microhaematocrit Centrifugation Test
MIT	Mouse Inoculation Test
NO	Nitric Oxide
NO_3	Nitrate
NO_2	Nitrite
O_2^-	Superoxide anion
OD	Optical Density
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate Buffered Saline
PCR	Polymerase Chaine Reaction
PCT	Proximal convoluted tubule
PCV	Packed Cell Volume
p.i.	post infection
PSG	phosphate saline glucose buffer
R	Pearson's correlation coefficient
R^2	Linear regression analysis
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RoTat 1.2	Rode Trypanozoon Antigen Typa 1.2
Rpm	round / minute
SEM	Scanning Electron Microscope
SAA	Serum amyloid A
SOD	Superoxide dismutase
SD	standard deviation

SH	Sulfhydryl group
TBA	Thiobarbituric acid
TEM	Transmission Electron Microscopy
TEP	1,1,3,3-Tetraethoxypropane
Th1	T helper type 1 cell
Th2	T helper type 2 cells
T Lymphocyte	Thymus Dependant Lymphocyte
TMB	3,3',5,5'-Tetramethylbenzidine
VSG	Variable Surface Glycoprotein
WBC	White Blood Cell
µl	Microliter
µm	Micron
µM	Micromolar
%	Percentage

CHAPTER ONE

INTRODUCTION

Trypanosoma evansi is a single cell parasite which discovered and identified as a causative agent of animal trypanosomosis. It is mechanically transmitted via blood sucking flies such as those of tabanids and *Stomoxys*. In the tropics and subtropics, *T. evansi* infection causes Surra, the severe protozoal disease in the animals (Hoare, 1972; Losos, 1980) leading to poor performance (Ahmad *et al.*, 2004; Dargantes *et al.*, 2005a). Nevertheless, the infection is not only limited to bovine but spills over to equine, canine, feline, lapine and large murine (capybaras) and humans (Herrera *et al.*, 2004; Joshi *et al.*, 2005; Silva *et al.*, 1995a; Tonin *et al.*, 2011; Eberhardt *et al*., 2014). Surra decreases the productivity of livestock leading to financial losses (Sekoni, 1994; Al-Qarawi *et al.*, 2004) . Sadly, these losses are not fully estimated because of insufficient data and misdiagnosis, in addition of farmers' reluctance or delay in reporting mortalities (Dobson *et al*., 2009).

In camelids, it has an acute and a chronic onset, while in equines the infection with *T. evansi* commonly demonstrates an acute entity ensuing to death within two to eight weeks post-infection. Conversely, in bovines (buffaloes and cattle) the infection leads to a chronic form where infected animals may live without overt signs for about three years p.i. (Luckins, 1988; Lun *et al.*, 1993). In other animals like rabbits, trypanosomosis also has a chronic course that is characterised by apathy, pale mucous membranes and oedema of eyelids and ears with irregular prolong peaks of parasitaemia (Costa *et al.*, 2012). Therefore, these clinical characteristics renders rabbits as suitable experimental models of chronic trypanosomosis due to the low and prolonged parasitaemia (Ramírez-Iglesias *et al.*, 2011).

The complex and multifactorially-induced anaemia is the most common sign of trypanosomosis that is present in almost all animals (da Silva *et al.*, 2011a; Habila *et al.*, 2012) due to extravascular haemolysis (Anosa, 1988a; Mbaya *et al.*, 2012). Additionally, immunologically-mediated mechanism (Assoku, 1975; Mbaya *et al.*, 2012) and erythrocyte peroxidation are factors which play a role in the development of anaemia in acute and chronic trypanosomosis (Igbokwe *et al.*, 1994; da Silva *et al*., 2009a; Wolkmer *et al.*, 2009). Lipid peroxidation of the erythrocytes causes membrane injury, osmotic fragility and destruction of the red blood cell (RBC) making anaemia a hallmark of the pathology of *T. evansi* infections (Habila *et al*., 2012). Acute infection of *T. evansi* in rats is associated with oxidative stress in erythrocytic membranes peroxidation (Wolkmer *et al.*, 2009). Erythrocytic of the infected rabbits may comprise of poikilocytes, macrocytic, anisocytosis, hypochromic, Howell-Jolly bodies, stomatocytes, Burr cells, as well as target cells are present (Silva *et al.*, 1999).

The importance of kidney damage in the pathology of trypanosomosis has been described in monkeys (Facer *et al.*, 1978), mice and rabbits (Uche and Jones, 1992) experimentally infected with *T. rhodesiense* and *T. brucei*, respectively. It is related to the deposition of immune complexes within glomeruli along with tubular degeneration, congestion and cellular infiltration (Bal *et al*., 2012).

Red fronted gazelle (Mbaya *et al.*, 2011), sheep and goats infected by *T. vivax* (Sekoni *et al.*, 2004) and dogs experimentally infected with *T. brucei* (Obi *et al.*, 2013) developed testicular degeneration. Lesions caused by trypanosomosis can lead to varying degrees of seminal deterioration with total lack of spermatogenesis causing infertility (Sekoni *et al.*, 1988; Ngeranwa *et al.*, 1991; Adamu *et al.*, 2007). The effects of *T. evansi* are more virulent and devastating on reproductive performance in dromedary bulls which could be linked with the formation and precipitation of immune complexes in seminiferous tubules, pituitary dysfunction and testicular degeneration (Al-Qarawi *et al.*, 2004).

Hepatomegaly and hepatic congestion occurs in goats infected by *T. evansi* (Dargantes *et al.*, 2005a). Histologically, irreversible changes composing of necrosis, pseudo-lobule formation and haemorrhage in sinusoids of liver are observed (Biswas *et al.*, 2001).

In trypanosomosis, interferon-gamma (IFN-γ) stimulates macrophages to induce the pro-inflammatory cytokines production such as TNF-α, IL-1, IL-6 and IL-10 that plays a significant role in the replication process of the parasite and in the immune response of the host (Paim *et al.*, 2011). Furthermore, a positive relationship exists between cytokines and oxidative stress in the development of anaemia (Voulgari *et al.*, 1999; Morceau *et al.*, 2010). These cytokines are described as inhibitors to erythropoiesis which is connected with anaemia of chronic diseases (Weiss and Goodnough, 2005). The essential role of interleukin-6 in the pathogenesis of anaemia of chronic disease proposes that it may be the main therapeutic aim, that is accessible for the treatments of the target tumour necrosis factor alpha and interleukin- 1 (Raj, 2009).

This research hypothesised that the rabbit can act as models for trypanosomosis with evidence of nephropathy and testiculopathy via involvement of oxidative stress with the following objectives to:

i. elucidate haematological changes and related mechanisms of anaemia in rabbits experimentally infected with *T. evansi*.

ii. determine the histopathology, immunohistochemistry, immunofluorescence and ultra-structural changes in the kidney and testicles of rabbits infected with *T. evansi.*

iii. evaluate the pathological effects of the parasites on the immune system and its pathogenetic mechanism on oxidative stress.

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