UNIVERSITI PUTRA MALAYSIA

CLINICOPATHOLOGICAL CHANGES OF THE NERVOUS SYSTEM FOLLOWING INOCULATION OF PASTEURELLA MULTOCIDA B:2 AND ITS IMMUNOGENS IN BUFFALO CALVES

ALI DHIAA MARZA

FPV 2017 2

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By

ALI DHIAA MARZA

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

January 2017

DEDICATION

To my family who made my professional progress possible

To my instructors, teachers, mentors who made it a reality

To the fellow researchers who may be able to use the results of this research

I dedicate my work to all with love and gratitude.

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

CLINICOPATHOLOGICAL CHANGES OF THE NERVOUS SYSTEM FOLLOWING INOCULATION OF *PASTEURELLA MULTOCIDA* B:2 AND ITS IMMUNOGENS IN BUFFALO CALVES

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January 2017

Chairman : Associate Professor Faez Firdaus Jesse Abdullah, PhD
Faculty : Veterinary Medicine

Haemorrhagic septicaemia (HS) is an acute, highly fatal septicaemic disease affecting cattle and buffaloes with high morbidity and mortality rates. *Pasteurella multocida* E:2 (African serotype) and B:2 (Asian serotype) are responsible of the disease in Africa and Asia, respectively. Despite continuing researches on the pathogenesis of *P. multocida*, the mechanisms by which these bacteria and its lipopolysaccharide (LPS) and outer membrane proteins (OMPs) immunogens develop the diseases are poorly understood. It is well known that HS affects mainly the respiratory and digestive tracts of cattle and buffaloes. However, involvement of other sites such as the nervous system in the pathogenesis of HS has been reported in previous studies, including outbreaks and pathogenesis studies of HS, without details. Therefore, this study was conducted to investigate in details the involvement of the nervous system towards *P. multocida* B:2 and its lipopolysaccharides (LPS) and outer membrane proteins (OMPs) immunogens in buffalo calves.

Twenty one clinically healthy, non-pregnant and non-lactating swamp buffalo calves were used in this study and divided into 7 groups of 3 buffaloes in each one. Buffaloes calves of group 1 (Ctrl) was inoculated orally with 10 ml of sterile phosphate buffered (PBS) as a negative control. Group 2 (Pmor) and group 3 (Pmsc) were inoculated with 10 ml of 1×10^{12} cfu/ml of *P. multocida* B:2 whole bacteria orally and subcutaneously, respectively. Group 4 (LPSor) and group 5 (LPSiv) were inoculated with 10 ml of LPS broth extracted from 1×10^{12} cfu/ml of *P. multocida* B:2 orally and intravenously, respectively. Group 6 (OMPor) and group7 (OMPsc) were inoculated with 10 ml of OMPs broth extracted from 1×10^{12} cfu/ml of *P. multocida* B:2 orally and subcutaneously, respectively. All calves in Pmor, LPSor, LPSiv and OMPor and Ctrl groups survived during the experiment and euthanized at the end of the experiment at 504 h (21 days) post inoculation, while calves in Pmsc and OMPsc groups had to be euthanized after 12 h and 72 h post infection,

respectively as they develop sever clinical signs of HS according to the guideline of the Institutional Animal Care and Use Committee (IACUC). In order to monitor both general clinical and neurological responses during the experiment, detailed clinical examination were performed based on modified scoring system including; total general clinical score (TGCS) and total nervous clinical score (TNCS). The TGCS includes scores of mean rectal temperature (MRT), mean respiratory rate (MRR) and mean heart rate (MHR), in addition to scores of demeanour, appetite, nasal discharge and nature of respiration. While TNCS includes scores of mentation, gait abnormalities, fixation reflex, menace response, pupillary light reflex, perineal reflex, photomotor reflex, tongue tone test, gag reflex, swallowing reflex, panniculus reflex, pedal reflex, patellar reflex and palpebral reflex. In addition, pathophysiological changes in the cerebrospinal fluid (CSF) were also evaluated which include selected proinflammatory cytokines and acute phase proteins. After euthanization of the calves, complete post mortem, microbiological and histopathological examinations were conducted on the calves in the studies groups.

Clinically, significant differences ($P<0.05$) in both TGCS and TNCS were found among the studies groups compare with Ctrl group. However, Pmsc and OMPsc groups developed severe clinical signs and recorded sharp increase in both TGCS and TNCS that lead to euthanization of the calves in these groups at 12 and 72 h post inoculation, respectively, and this indicates direct associated of increased nervous clinical signs with disease severity. While less severe TGCS and TNCS were recorded in Pmor, LPSor, LPSiv and OMP groups and calves in these groups were able to survive until the end of experiment at 504 h post inoculation, and this indicates that calves in these groups were able to overcome the infection with *P. multocida* B:2 or inoculation of its LPS and OMPs immunogens.

At necropsy, different levels of significance ($P<0.05$) in mean gross lesion score (MGLS) were recorded in buffalo calves in the studied groups including the cerebrum, cerebellum, brainstem and spinal cord when compared with calves of Ctrl group. However, the cerebrum and brainstem being the most affected sites of the nervous system. On the other hand, examination of the cranial and spinal nerves did not reveal any significant changes. The pattern of the pathological lesions reflect the severity of the clinical signs where Pmsc and OMPsc groups represented the per acute stage of the disease and congestion and hemorrhage in the brain and spinal cord were the most prominent lesions. However, oedema was noted in the brain of the buffalo calves in OMPsc rather than Pmsc group. While the pathological changes were different in LPSiv group in which oedema was more prominent than congestion and hemorrhage. Less MGLS were observed in the Pmor, LPSor and OMPor groups indicating the less effect of the oral route on the nervous system. Additionally, positive bacterial re-isolation and polymerase chain reaction (PCR) confirmation of *P. multocida* B:2 from different parts of the nervous system in calves of Pmsc group confirm the ability of these bacteria to cross blood brain barrier (BBB) especially at the per acute stage of the disease and support the involvement of the nervous system in the pathogenesis of HS.

The histopathological examination of the nervous system of the inoculated groups reflect the previously observed gross pathological findings, and significant increase (P<0.05) has been found in the total mean histopathological lesion score (MHLS) of the treated groups: Pmor, Pmsc, LPSor, LPSiv, OMPor and OMPsc when compared with calves of Ctrl group. The histopathological changes recorded in this study included; inflammatory cells infiltration, oedema and spongiosis, gliosis, congestion and hemorrhage, in addition to necrosis and degeneration and confirm the ability of *P. multocida* B:2 and its LPS and OMPs immunogens to cross the BBB and induce their pathological effects. While the most affected sites of the nervous system were the cerebrum and brainstem. Although various histopathological lesion were reported in different parts of the nervous tissues, the route of inoculation was observed to play a significant role in determination of the severity of the lesion as subcutaneous and intravenous routes in Pmsc, OMPsc and LPSiv groups showed the most pronounced and higher lesion distribution than respected orally inoculated groups.

Pathophysiological changes including; classical parameters, proinflammatory cytokines and acute phase proteins (APPs) also showed various levels of difference in the studied groups. Classical parameters showed significant differences (P<0.05) with high values recorded in the CSF total leukocytic count (CSF-TLC) and CSF total protein (CSF-TP) especially Pmsc and OMPsc groups as indication of acute body response to the disease produced. Significant increase also observed in the levels of CSF cytokines including; tumor necrosis factor-α (CSF-TNF-α), interleukins (CSF-IL-1) and (CSF-IL-6) in addition to CSF APPs including; haptoglobin (CSF-Hp), serum amyloid A (CSF-SAA) and C-reactive protein (CSF-CRP) concentrations which indicate that the subcutaneous route of inoculation would induce more severe reactions rather than oral route.

According to presented evidences, it can be concluded that *P. multocida* B:2 and its LPS and OMPs immunogens were able to cross the BBB and induce pathological changes in different sites of the nervous system. The produced neuropathological changes could make alteration in animal behavior with the evidence of absence of some of the neurological responses especially in Pmsc and OMPsc groups, and this was supported by the increased concentrations of proinflammatory cytokines and APPs in the CSF in these groups. Accordingly, these results provide for the first time strong evidence of the involvement of the nervous system of buffalo calves experimentally inoculated of *P. multocida* and its immunogens in the pathogenesis of HS, and shows that the type of inoculum and route of inoculation strongly affect the induced pathological changes of the nervous system and also the severity of disease produced.

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

PERUBAHAN KLINIKOPATHOLOGI SISTEM SARAF BERIKUTAN INOKULASI DENGAN *PASTEURELLA MULTOCIDA* B:2 DAN IMUNOGEN DALAM ANAK KERBAU

Oleh

ALI DHIAA MARZA

Januari 2017

Pengerusi : Profesor Madya Faez Firdaus Jesse Abdullah, PhD
Fakulti : Perubatan Veterinar

Hawar berdarah (HS) adalah akut, penyakit septisemia yang membawa maut yang melibatkan lembu dan kerbau dengan morbiditi dan mortaliti kadar yang tinggi. *Pasteurella multocida* E: 2 (serotype Afrika) dan B: 2 (serotype Asia) adalah bertanggungjawab ke atas penyakit masing-masing di Afrika dan Asia. Walaupun kajian berterusan ke atas patogenesis *P. multocida*, mekanisme bakteria ini dan lipopolisakarida (LPS) dan protein membran luar (OMPs) immunogens yang menyebabkan penyakit ini kurang difahami. Adalah diketahui umum bahawa HS memberi kesan terutamanya kepada salur pernafasan dan pencernaan lembu dan kerbau. Walau bagaimanapun, penglibatan bahagian lain seperti sistem saraf dalam patogenesis HS telah dilaporkan dalam kajian sebelum ini, termasuk wabak dan kajian patogenesis HS tetapi tanpa butiran yang terperinci. Oleh itu, kajian ini telah dijalankan untuk mengkaji secara terperinci penglibatan sistem saraf terhadap *P. multocida* B: 2 dan lipopolisakarida (LPS) dan protein membran luar (OMPs) immunegen bagi anak kerbau.

Dua puluh satu ekor kerbau yang sihat secara klinikal, tidak hamil dan bukan menyusu telah digunakan dalam kajian ini dan dibahagikan kepada 7 kumpulan dimana 3 anak krbau dalam setiap satu kumpulan. Anak kerbau dari kumpulan 1 (Ctrl) telah disuntik secara oral dengan 10 ml bufer fosfat steril (PBS) sebagai kawalan negatif. Kumpulan 2 (Pmor) dan kumpulan 3 (Pmsc) telah disuntik keseluruhan secara oral masing-masing dengan 10 ml larutan 1×10^{12} cfu/ml bakteria *P. multocida* B:2. Kumpulan 3 (LPSor) dan kumpulan 4 (LPSiv) telah disuntik keseluruhan secara3 oral masing-masing dengan larutan ekstrak daripada 1×10^{12} cfu/ml *P. multocida* B: 2. Kumpulan 6 (OMPor) dan kumpulan 7 (OMPsc) telah disuntik keseluruhan secara oral masing-masing dengan larutan ekstrak daripada 1×10^{12} cfu/ml *P. multocida* B: 2. Semua anak kerbau dalam kumpulan Pmor, LPSor, LPSiv dan OMPor dan kawalan terselamat semasa eksperimen dan

dikorbankan pada akhir eksperimen pada 504 jam (21 hari) selepas inokulasi, manakala anak-anak kerbau dalam kumpulan Pmsc dan OMPsc terpaksa dimatikan masing-masing selepas 12 jam dan 72 jam selepas inokulasi, kerana mereka menunjukkan tanda-tanda klinikal HS yang teruk dan mengikut garis panduan Jawatankuasa Penjagaan dan Penggunaan Haiwan Makmal (IACUC). Dalam usaha untuk memantau kedua-dua tindak balas klinikal dan neurologi umum semasa eksperimen , pemeriksaan klinikal secara terperinci telah dijalankan berdasarkan sistem pengskoran yang diubahsuai termasuk; jumlah skor umum klinikal (TGCS) dan jumlah skor klinikal saraf (TNCS). TGCS termasuk purata skor suhu rektum (MRT), purata kadar pernafasan (MRR) dan purata kadar jantung (KSM), sebagai tambahan kepada skor sikap, selera makan, pengeluaran dari hidung dan jenis pernafasan. TNCS termasuk puluhan status mentaliti, keabnormalan gaya berjalan, penetapan refleks, tindak balas ancaman, tindakbalas cahaya, tindakbalas palpebral, tindakbalas photomotor, ujian nada lidah, tindakbalas gag, tindakbalas menelan, tindakbalas refleks, tindakbalas panniculus, tindakbalas pedal, tindakbalas patellar dan tindakbalas perineal. Di samping itu, perubahan patofisiologikal dalam cecair serebrospina (CSF) juga telah dinilai termasuk sitokine proinflamator yang dipilih dan protein fasa akut. Selepas anak kerbau dikorbankan, bedah siasat lengkap, mikrobiologi dan peperiksaan histopatologi dijalankan ke atas anak kerbau dalam kumpulan kajian ini.

Secara klinikal, perbezaan ketara ($P<0.05$) dalam TGCS dan TNCS telah dijumpai dalam kumpulan kajian berbanding kumpulan kawalan. Walaubagaimanapun, kumpulan Pmsc and OMPsc telah menunjukkan tanda-tanda klinikal yang teruk dan direkodkan meningkat dalam TGCS dan TNSC dimana menyebabkan banyak anak dalam kumpulan ini masing-masing dikorbankan pada 12 dan 72 jam selepas inokulasi dan ia menunjukkan berkait rapat dengan peningkatan tanda saraf klinikal dengan penyakit berjangkit. Manakala pengurangan dalam kumpulan TGCS dan TNCS telah direkodkan dalam kumpulan Pmor, LPSor, LPSiv dan OMP dan anak kerbau dalam kumpulan ini mampu untuk bertahan sehingga akhir eksperimen iaitu pada 504 jam selepas inokulasi dan ini menunjukkan bahawa anak kerbau dalam kumpulan ini mampu untuk mengatasi kesan dengan *P. multocida* B:2 atau inokulasi LPS dan OMPs immunogens.

Pada ujian nekropsi, kadar perbezaan ketara ($P<0.05$) dalam purata skor lesi kasar (MGLS) telah direkodkan dalam kajian kumpulan anak kerbau termasuk serebrum, serebellum, saraf otak dan serat tunjang apabila dibandingkan dengan kumpulan kawalan. Walaubagaimanapun, serebrum dan saraf otak adalah paling banyak terkesan dalam sistem saraf. Disamping itu, pemeriksaan pada saraf kranial dan saraf spinal tidak menunjukkan sebarang perubahan. Paten kajian patalogikal menunjukkan, kadar jangkitan pada tahap penyakit yang merebak secara pesat dan gangguan dalam otak dan sarat tunjang adalah paling banyak dalam kajian. Walaubagaimanapun, oedema telah dinyatakan dalam otak anak kerbau adalah tinggi dalam OMPsc berbanding kumpulan Pmsc. Manakala perubahan secara patologikal adalah berbeza dalam kumpulan LPSiv dimana oedema adalah lebih banyak berbanding kongest and pendarahan. MGLS telah didapati kurang dalam kumpulan Pmor, LPSor dan OMPor dimana menunjukkan kurang kesan secara oral pada sistem saraf. Tambahan, bakteria positif yang diasingkan dan sistem penjujukan DNA

(PCR) telah mengesahkan bahawa *P. multocida* B:2 daripada bahagian lain pada sistem saraf dalam anak kerbau bagi kumpulan Pmsc menunjukkan kemampuan bakteria ini untuk mengatasi banteng darah otak terutamanya pada peringkat penyakit berjangkit dan menyokong penglibatan sistem saraf dalam patogenesis HS.

Pemeriksaan histopatologikal pada sistem saraf bagi kumpulan inokulasi telah menunjukkan perkaitan pada penemuan pathologi kasar, dan secara perbezaan ketara telah meningkat ($P<0.05$) telah ditemui dalam purata skor histopatologikal (MHLS) bagi kumpulan rawatan: Pmor, Pmsc, LPSor, LPSiv, OMPor dan OMPsc berbanding kumpulan kawalan anak kerbau. Perubahan histopatologikal telah direkodkan dalam kajian ini termasuklah kehadieran sel radang, oedema dan spongiosis, gliosis, kongesi dan perdarahan, tambahan nekrosis dan penglibatan telah mengesahkan kemampuan *P. multocida* B:2 serta LPS dan OMPs immunogens untuk melawan BBB dan menyebabkan kesan pathologikal. Manakala yang paling terkesan ialah pada serebrum dan sistem saraf. Walaubagaimanapun, kepelbagaian histopathologikal telah dilaporkan dalam pelbagai laporan pada sistem saraf, kadar inokulasi telah memainkan peranan dalam penentuan tahap penyakit subkutaneous and intravenous bagi kumpulan Pmsc, OMPsc and LPSiv telah menunjukkan peningkatan dalam ketaburan lesi penyakit berbanding kumpulan inokulasi yang lain.

Perubahan pathofisiologikal termasuklah: parameter klasikal, sitokine dan tahap akut proteins (APPs) telah menunjukkan pelbagai tahap perbezaan dalam kumpulan kajian. Parameter klasikal menunjukkan perbezaan ketara ($P<0.05$) dengan nilai tinggi direkodkan dalam CSF jumlah leukosit (CSF-TLC) dan CSF jumlah protin (CSF-TP) terutamanya kumpulan Pmsc dan OMPsc dimana menunjukkan tindakbalas badan kepada penyakit telah dihasilkan. Perbezaan ketara juga telah dijumpai pada CSF sitokine, termasuklah nekrosis otak, factor –α (CSF-TNF-α), interleukine (CSF-IL-1) dan (CSF-IL-6) tambahan kepada konsentrasi CSF APPs termasuklah ; haptoglobin (CSF-Hp), serum amyloid A (CSF-SAA) dan C-reactive protein (CSF-CRP) dimana menunjukkan inokulasi subkutis boleh menyebabkan banyak tindakbalas berbanding secara oral.

Berdasarkan kepada penemuan, ia boleh disimpulkan bahawa *P. multocida* B:2 dan LPS serta OMPs immunogens mampu untuk melawan BBB and membawa kepada kesan perubahan pathologikal pada bahagian berbeza dalam sistem saraf. Perubahan neuropathologikal juga mampu untuk mengubah tindakbalas terutamanya dalam kumpulan Pmsc dan OMPsc, dan ia telah disokong oleh penigkatan konsentrasi proinflamatori sitokien dan kumpulan APPs dalam CSF. Tambahan, keputusan yang dihasilkan telah menyokong secara kuat bahawa penglibatan sistem saraf dalam anak kerbau yang telah diinokulasi dengan *P. multocida* dan immunogens dalam pathogenesis HS telah menunjukkan bahawa inokulasi memberi kesan kepada perubahan pathologikal bagi sistem saraf dan meyebabkan penghasilan penyakit.

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I certify that a Thesis Examination Committee has met on 20 January 2017 to conduct the final examination of Ali Dhiaa Marza on his thesis entitled "Clinicopathological Changes of the Nervous System Following Inoculation of *Pasteurella multocida* B:2 and its Immunogens in Buffalo Calves" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Noordin bin Mohamed Mustapha, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Hazilawati binti Hamzah, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Siti Khairani binti Bejo, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Peter David Eckersall, PhD
Professor
University of Glasgow
United Kingdom
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 22 March 2017

This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Faez Firdaus Jesse Abdullah, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Abdul Rahman Omar, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Zuki Abu Bakar, PhD
Professor
Faculty of Veterinary Medicine
Universiti Malaysia Kelantan
(Member)

Mohd Zamri-Saad, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
Professor and Dean
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- the research conducted and the writing of this thesis was under our supervision;
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Signature: _____
Name of Chairman of Supervisory Committee: Associate Professor Dr. Faez Firdaus Jesse Abdullah

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Abdul Rahman Omar

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Zuki Abu Bakar

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Mohd Zamri-Saad

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APP	Acute phase proteins
APTT	Activated partial thromboplastin time
BHI	Brain heart infusion
cfu	colony forming units
CSF	Cerebrospinal fluid
Ctrl	Control
ELISA	Enzyme linked immunosorbent assay
h	hour
Hp	Haptoglobin
HR	Heart rate
HRP-avidin	Horse radish peroxidase avidin
HS	Haemorrhagic septicaemia
IACUC	Institutional Animal Care and Use Committee
ICR	Institute of Cancer Research
IL-1	Interleukins-1
IL-6	Interleukins-6
LPS	Lipopolysaccharide
LPSiv	LPS of *P. multocida* B:2 in occulted via intravenous route
LPSor	LPS of *P. multocida* B:2 inoculated via oral route
MHLS	Mean histopathological lesion score
ml	millilitre
MSLS	Mean surface lesion score
min	minute
ng	nanograms

nm	nanometers
OD	Optical density
OMPor	OMP of *P. multocida* B:2 inoculated via oral route
OMPs	Outer membrane proteins
OMPsc	OMP of *P. multocida* B:2 inoculated subcutaneous route
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
pg	picogram
Pmor	*P. multocida* B:2 inoculated via oral route
Pmsc	*P. multocida* B:2 inoculated via subcutaneous route
rpm	revolutions per minute
RR	Respiratory rate
RT	Rectal temperature
SAA	Serum amyloid A
Sec	second
SDS-PAGE	Sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SIM	Sulphur indole motility
TGCS	Total general clinical score
TMB-Substrate	Tetramethylbenzidine liquid substrate
TNCS	Total nervous clinical score
TSI	Triple sugar iron
VRI	Veterinary Research Institute

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Pasteurella multocida is the causative agent of a wide range of diseases in many species of animals, including haemorrhagic septicaemia (HS) in cattle and buffalo, atrophic rhinitis in swine, fowl cholera in poultry and respiratory disease in ungulates and rabbits (De Alwis, 1999; Harper *et al.*, 2006; Wilkie *et al.*, 2012). It also affect human and causes wound abscesses and meningitis especially after cat or dog bites (Wade *et al.*, 1999; Green *et al.*, 2002). Haemorrhagic septicaemia (HS) is an acute septicemic disease principally affecting cattle and buffaloes caused by specific serotypes B:2 and E:2 of *P. multocida* in Asia and Africa, respectively (De Alwis, 1999; World Organization for Animal Health, 2012; Jesse *et al.*, 2013d). The disease has economic impact due to high mortality rates among the affected animals especially buffaloes (De Alwis, 1999; Annas *et al.*, 2015a). It is a well-known fact that HS occurs most commonly in cattle and buffaloes. However, buffaloes are thought to be more susceptible than cattle, and young animals have been observed to be more susceptible than adults (Horadagoda *et al.*, 2002; Annas *et al.*, 2015a). Moreover, predisposing factors such as movement of animals, poor husbandry conditions and weather changes could vastly affect the immunostatus of the animals and finally result in explosive outbreaks (De Alwis, 1992b; Benkirane and De Alwis, 2002; McFadden *et al.*, 2011).

Complex interactions between specific host factors such as species, age and immune status, and virulence factors of *P. multocida* B:2, mainly lipopolysaccharides (LPS), outer membrane proteins (OMPs), capsule and adhesions are thought to play a key role in causing HS (Harper *et al.*, 2012; Othman *et al.*, 2012; Jesse *et al.*, 2013a; Jesse *et al.*, 2013d; Kharb and Charan, 2013). The LPS of *P. multocida* constitutes the major components of the bacterial cell surface and it has a major role in the disease pathogenesis (Horadagoda *et al.*, 2001; Harper *et al.*, 2012; Jesse *et al.*, 2013a). Additionally, outer membrane proteins of *P. multocida* are thought to have a role in the disease pathogenesis (Hatfaludi *et al.*, 2010), and recent studies showed the ability of *P. multocida* B:2 OMPs to induce the disease in both murine model and real hosts (Abdullah *et al.*, 2013a; Jesse *et al.*, 2013f). Furthermore, in experimental studies related to pathogenesis of HS, different routes of inoculation of *P. multocida* B:2 or its immunogens LPS and OMPs have been found to induce different pathogenesis pathways and finally might affect the produced clinical and pathological pictures of the disease (Dowling *et al.*, 2002; Horadagoda *et al.*, 2002; Jesse *et al.*, 2013d; Annas *et al.*, 2014b). Respiratory route (intranasal infection by aerosols or intratracheal) and oral drenching results in a longer course of disease and more profound lesions, while subcutaneous inoculation results in rapid onset of disease, a shorter course and less marked pathological lesions mainly describes as peracute form (Dowling *et al.*, 2002; Abubakar *et al.*, 2013; Jesse *et al.*, 2013d; Annas *et al.*, 2015b).

Buffaloes affected by HS outbreaks usually show short clinical course lasting a few hours with signs of severe depression, dyspnea, elevated temperature, salivation, nasal discharge followed by swelling of the ventral cervical region and brisket, respiratory distress and finally death (Carter and De Alwis, 1992; Khan *et al.*, 2011).

On the other hand, in experimental infection studies using *P. multocida* B:2, three main phases usually could be observed following short incubation period, one of temperature elevation, a phase of clinical signs and a terminal phase of recumbency (De Alwis, 1999; Dowling *et al.*, 2002; Jesse *et al.*, 2013d). Nevertheless, in many cases, overlap between the clinical phases are occur with varying degrees with less define phases when the disease course is short (Odugbo *et al.*, 2005; Jesse *et al.*, 2013d). Examination of the nervous system is one of the most important factors that can precisely identify the neuroanatomic location or locations of any abnormalities (Jackson *et al.*, 2002b). Accordingly, any defect in a specific anatomic region of the nervous system could lead to affect the associated organ and finally produced the related clinical signs (Constable, 2004). Signs such as abnormalities in gait, decreased rumen motility, defect in vision and recumbency at the final stage of the disease might be related to the defect in the corresponding part of the nervous system. Rumen hypomotility 0/min after 4 h post infection has been reported by Jesse *et al.* (2013d) in a study involved buffalo calves inoculated intramuscularly by 1×10^{12} cfu/mL of *P. multocida* B:2. In the same manner, recumbency and inability to rise were the most prominent signs of abnormal gait especially at the end stage of the endotoxic shock (De Alwis, 1999; Abubakar and Zamri-Saad, 2011). Although manifestation of the nervous clinical signs of animals affected by *P. multocida* B:2 is rarely reported, lack of special interest in investigating the possible clinical and neurological responses following infection with *P. multocida* B:2 could be a major contributor to the rarity of such responses (Marza *et al.*, 2015).

During necropsy examination, the main focus of the examiner is usually paid on the pathological changes of the respiratory and gastrointestinal tracts as main affected sites of animals affected by HS, and this render the examination of other parts of the body seldom investigated (Dowling *et al.*, 2002; Odugbo *et al.*, 2005; Jesse *et al.*, 2013d). However, recent studies reported the involvement of urinary tract as new localization site of *P. multocida* B:2 in buffalo surviving experimental HS, suggesting their role in the pathogenesis of HS. (Annas *et al.*, 2014a; Annas *et al.*, 2014b). While the involvement of the nervous system due to *P. multocida* has been reported mainly in human (Zaramella *et al.*, 1999; Green *et al.*, 2002), few studies reported the presence of meningitis or encephalitis in outbreaks of HS as central nervous tissues are not often routinely examined (Lane *et al.*, 1992). Nevertheless, recent experimental studies on pathogenesis of HS re-emphasized the involvement of nervous system with successful bacterial isolation of *P. multocida* B:2 from the brain (Abubakar and Zamri-Saad, 2011; Jesse *et al.*, 2013c; Khaleel *et al.*, 2014). These findings rise a question about the ability of this enigmatic pathogen to involve other sites like the nervous system (Marza *et al.*, 2015).

Besides clinical and pathological changes, pathophysiological responses have been investigated in the pathogenesis studies of HS using murine and buffalo models (Abdullah *et al.*, 2013b; Abdullah *et al.*, 2014b; Ali *et al.*, 2014). Cytokines including interlukine-1β (IL-1β), interlukine-6 (IL-6) and tumor necrosis factor-α (TNF-α) have been shown able to reproduce toxic effects induced by LPS of *P. multocida* (Horadagoda et al., 2001; Harper et al., 2011; Abdullah et al., 2013a; Abubakar et al., 2013; Ali et al., 2014). Moreover, administration of LPS has been reported to induce neuroinflammation and increases proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α (Song and Wang, 2011). Acute phase proteins (APPs) also have been investigated extensively as potential biomarkers for detection of HS (Horadagoda *et al.*, 2001; Abdullah *et al.*, 2013b; Khaleel *et al.*, 2013). Jesse *et al.* (2013a) reported an increased in serum amyloid A (SAA), haptoglobin (Hp) after experimental infection of buffalo calves with *P. multocida* B:2 and inoculation of its immunogens, LPS and OPMs. Although extensive studies have been done on cytokines and APPs using different animal models (Abdullah *et al.*, 2013b; Jesse *et al.*, 2013a; Khaleel *et al.*, 2013; Abdullah *et al.*, 2014b; Ali *et al.*, 2014), cytokine and AAPs responses and their effect on the nervous system, especially the cerebrospinal fluid (CSF), are new area need to be studied (Marza *et al.*, 2015).

According to the previous facts, it is clear that there are clinical, pathological and pathophysiological evidences about the involvement of the nervous system in the pathogenesis of *P. multocida* B:2 infection. Such evidences have been generated from different studies. However, these studies lack detailed information about the effect of *P. multocida* B:2 on different parts of the nervous system and further studies are needed for better understanding of the pathogenesis of such devastating disease.

1.2 Problem statement

Despite continuing researches on pathogenesis of *P. multocida* B:2 for several decades, the involvement of the nervous system as a newly investigated localization site during the disease course of HS has not been studied in details yet in buffaloes as a natural host

1.3 Hypothesis of the study

Experimental infection of buffaloes with *P. multocida* B:2 and its LPS and OMPs immunogens via different routes could induce clinical, pathological and pathophysiological changes in the nervous system.

1.4 Objectives of the study

The objectives of the study were:

1. To evaluate clinical signs and neurological responses of buffaloes inoculated with *P. multocida* B:2 whole bacteria and its LPS and OMPs immunogens extracts using oral, subcutaneous and intravenous routes.

2. To detect the presence of *P. multocida* B:2 in nervous tissues and cerebrospinal fluid (CSF) of buffaloes inoculated with *P. multocida* B:2 via various route using standard bacterial culture and polymerase chain reaction (PCR).

3. To determine pathological and histopathological changes of different anatomic regions of the nervous system of buffaloes inoculated with *P. multocida* B:2 whole bacteria and its LPS and OMPs immunogens extracts using oral, subcutaneous and intravenous routes.

4. To evaluate classical parameters, cytokine and acute phase proteins (APPs) responses in the CSF of buffaloes inoculated with *P. multocida* B:2 whole bacteria and its LPS and OMPs immunogens extracts using oral, subcutaneous and intravenous routes.

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