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REVIEW ARTICLE

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Involvement of nervous system in cattle and buffaloes due to *Pasteurella multocida* B:2 infection: A review of clinicopathological and pathophysiological changes

Ali Dhiaa Marza[1,2], Faez Firdaus Jesse Abdullah[1, 3*], Ihsan Muneer Ahmed[4], Eric Lim Teik Chung[1], Hayder Hamzah Ibrahim[1, 5],Mohd Zamri-Saad[6], Abdul Rahman Omar[7], Md Zuki Abu Bakar[7], Abdul Aziz Saharee[1], Abdul Wahid Haron[1] and Mohd Azmi Mohd Lila[8]

[1]*Department of Veterinary Clinical Studies, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Serdang, Malaysia;*
[2]*Department of Veterinary Internal Medicine, College of Veterinary Medicine, Al-Qasim Green University, Iraq;*
[3]*Research Centre for Ruminant Diseases, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Serdang, Malaysia;*
[4]*Department of Microbiology, College of Veterinary Medicine, University of Mosul, Iraq;*
[5]*BabilTechnical Institute, Al Furat Al-Awsat Technical University, Iraq;*
[6]*Department of Veterinary Laboratory Diagnostics, Universiti Putra Malaysia, 43400 Serdang, Malaysia;*
[7]*Institute of Bioscience, Universiti Putra Malaysia, 43400 Serdang, Malaysia;*
[8]*Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Serdang, Malaysia.*
[*]*Corresponding author's e-mail: jessearіasamy@gmail.com*

ABSTRACT

Hemorrhagic septicemia (HS) is an acute septicemic disease principally affecting cattle and buffaloes caused by specific serotypes B:2 and E:2 of *Pasteurella multocida* in Asia and Africa, respectively. Despite continuing researches on pathogenesis of *P. multocida* for several decades, the mechanisms by which these bacteria develop the diseases are poorly understood. Although the involvement of the nervous system in the disease progress of HS is rare under natural conditions, few reports indicated the involvement of the nervous system in outbreaks of HS in cattle and buffaloes. Additionally, recent pathogenesis studies in both mouse and buffalo experimental models reported the involvement of nervous system due to *P. multocida* B:2, with bacteriological and histopathological evidences. In this review, we summarized and discussed the updates on the involvement of the nervous system in pathogenesis of HS focusing on clinical signs, pathological and pathophysiological changes.

Keywords

Acute phase proteins, Clinicopathology, Cytokines, Hemorrhagic septicemia, Nervous system, *Pasteurella multocida* B:2

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INTRODUCTION

Pasteurella multocida is a small Gram-negative coccobacillus that has been identified as a vital veterinary pathogen. *Pasteurella multocida* is responsible for numerous serious diseases in farm animals, including hemorrhagic septicemia (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). In human, wound abscesses and meningitis are predominantly following cat or dog bites (Armstrong et al., 2000; Green et al., 2002). Serological differences in both capsular and somatic antigens are used to designate a specific serotype of *P. multocida*. The capsular polysaccharides according to Carter (1955) are designated A, B, D, E and F. While cell wall lipopolysaccharides typing according to Namioka and Murata (1961) and Heddleston et al. (1972) are designated 16 somatic serotypes (Harper et al., 2006; Dziva et al., 2008). Hemorrhagic septicemia is an acute and highly fatal septicemic disease of cattle and buffaloes caused by specific serotypes B and E of *P.*

multocida in Asia and Africa, respectively (De Alwis, 1992; De Alwis, 1999; World Organization for Animal Health, 2012).

Most of the conducted studies on HS focused on respiratory and gastrointestinal tracts as main affected sites (Graydon et al., 1992; Dowling et al., 2002; Odugbo et al., 2005). 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 peracute form HS outbreak (Lane et al., 1992). Nevertheless, recent experimental studies on pathogenesis of HS re-emphasized the involvement of nervous system with successful 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 nervous system, especially that the pathogenic mechanisms involved in different diseases caused by *P. multocida* are, for the most part, poorly understood or completely unknown (Wilkie et al., 2012). Therefore, this review aimed to highlight the involvement of the nervous system in the pathogenesis of HS.

Virulence factors

Hemorrhagic septicemia is a result of complex interactions between specific host factors such as species, age, immune status and specific virulence factors of *P. multocida* B:2 such as lipopolysaccharides (LPS), outer membrane proteins (OMPs), capsule and adhesions (Harper et al., 2006; Boyce et al., 2012; Kharb and Charan, 2013). Buffaloes are generally more susceptible than cattle, and young animals are more prone to the disease than adults (De Alwis, 1992; De Alwis, 1999). The pathogenesis of HS is not clearly understood, however, it is believed that during stress conditions bacteria multiply and septicemia develops leading to death due to endotoxemia (Horadagoda et al., 2001; Harper et al., 2006).

The LPS of *P. multocida* constitutes the major components of the bacterial cell surface and it formed the basis for the most widely used classification systems due to the significant roles in a range of interactions between the bacteria and the hosts they infect or colonize (Harper et al., 2011; Harper et al., 2012). *Pasteurella multocida* synthesize two LPS glycoforms simultaneously, known as glycoforms A and B, although they share the same outer core but differ in their inner core structure (Harper et al., 2011). The LPS is involved in the avoidance of host innate immune responses including resistance to phagocytosis, complement-mediated killing, and the bactericidal activity of antimicrobial peptides. Additionally, LPS is a major antigen in the stimulation of adaptive immune responses to infection (Gonzalez and Maheswaran, 1993; Harper et al., 2006; Harper et al., 2012; Jesse et al., 2013d). The LPS of *P. multocida* has endotoxic properties, and the intravenous inoculation of LPS from serotype B:2 stains in buffalo proved to reproduce typical clinical signs of HS (Horadagoda et al., 2001, 2002). This means that the LPS has a major role in the disease pathogenesis. Similar results were obtained by Jesse et al. (2013d), where the injection of purified LPS from a serogroup B strain was able to mimic the clinical signs of HS. However, the humoral immune response to LPS varies and is dependent upon the host animal and on variations within the LPS structure (Harper et al., 2011; Hodgson et al., 2013). Although most of experimental infection using LPS of *P. multocida* B:2 focused on clinical and pathological changes in the respiratory and gastrointestinal tracts (Horadagoda et al., 2002; Abdullah et al., 2013a), less attention has been paid on the nervous system. However, recent study by Jesse et al. (2014) demonstrated the ability of LPS of *P. multocida* B:2 to induce histopathological changes in pituitary gland in male and female mice and finally change the hormonal levels. These findings support the ability of LPS to induce pathological changes in the nervous system.

Outer membrane proteins, on the other hand, function as selective barrier that prevents the entry of many toxic molecules into the cell, a step that is crucial for bacterial survival in several environments. In addition, the proteins embedded in the OMPs play a number of roles that are critical for the bacterial cell such as nutrient uptake, transport of molecules in and out of the cell, and interaction with the environment and host tissues. Indeed, despite progress in recent years, detailed knowledge of membrane proteins remains elusive (Hatfaludi et al., 2010). Nevertheless, recent studies showed the ability of *P. multocida* B:2 OMPs to induce the disease in both murine model and real hosts (Abubakar and Zamri-Saad, 2011; Abdullah et al., 2013b; Jesse et al., 2013a; Jesse et al., 2013d).

Another virulence factor is the capsule which has a significant role in pathogenesis due to its ability to resist phagocytosis (Boyce et al., 2000; Harper et al.,

2012). Boyce and Adler (2000) showed that the presence of the capsule is considered as a crucial virulence determinant and acapsular bacteria mutants were removed efficiently from the blood, spleen, and liver, while wild-type bacteria multiplied rapidly following intraperitoneal challenge of mice. Fimbriae, also found to play an important role in initial colonization or invasion (Fuller et al., 2000; Othman et al., 2012; Shivachandra et al., 2012). However, the study of fimbriae mostly restricted to vaccine development against *P. multocida* (Shivachandra et al., 2012). Evaluating the influence of the known virulence factors of *P. multocida* B:2 on the nervous system of buffalo as a main host is another window that needs attention. Indeed, this may lead to credible findings that could augment the understanding of the pathogenesis of HS.

Clinical and neurological responses associated with *P. multocida* B:2 infection

Hemorrhagic septicemia normally occurs in areas where husbandry practices are primitive and the animals are reared under free-range conditions. In such circumstances, the only reported sign after the disease onset may be sudden death because the animals are not under constant observation (De Alwis, 1999; Benkirane and De Alwis, 2002; McFadden et al., 2011). Therefore, the recorded clinical signs and neurological responses under natural conditions are seldom reported and/or investigated, and this possibly because nervous tissue is not often routinely examined (Lane et al., 1992).

Generally, the observed signs are temperature elevation, loss of appetite, nasal discharge, salivation and labored breathing, with edema in the submandibular region and spreading to brisket area (De Alwis, 1999; Odugbo et al., 2005; Khan et al., 2011). However, Lane et al. (1992) reported the presence of meningitis in an outbreak of HS among cattle without recording any nervous signs and this may be due to limited time available to monitor the animals in the peracute cases of the disease. Even though extensive experimental studies have been conducted on the pathogenesis of *P. multocida* using murine, cattle and buffaloes models (Odugbo et al., 2005; Jesse et al., 2013d; Annas et al., 2014b), most researchers focus on clinical signs other than the nervous system. Although manifestation of nervous clinical signs in *P. multocida* infection in animals is rare, lack of special interest in investigating the possible clinical and neurological responses following infection with *P. multocida* could be a major contributor to the rarity of such responses.

Three main phases are usually observed after experimental infection with *P. multocida* following short incubation period, one of temperature elevation, a phase of clinical signs and a terminal phase of recumbency (De Alwis, 1992; De Alwis, 1999; Abubakar and Zamri-Saad, 2011; 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 (Dowling et al., 2002; Horadagoda et al., 2002; Jesse et al., 2013d). Route of entry also affect the clinical phases duration, 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 (Odugbo et al., 2005; Abubakar and Zamri-Saad, 2011; Jesse et al., 2013d).

Nervous system examination is one of the most important factors that can precisely identify the neuroanatomic location or locations of any abnormalities (Jackson et al., 2002). Constable (2004) defined four functionally different anatomic regions of the nervous system that the clinician should consider during neurologic examination which include: cerebrum, cerebellum, brainstem and cranial nerves, and spinal cord and peripheral nerves. Therefore, deffects in a specific anatomic region of the nervous system could lead to affect the associated organ and finally produce the related clinical signs (Constable, 2004). In HS, clinical signs such as abnormalites in gait, dicrease rumen motility, defect in vision and recumbency at the final stage of the disease might related to the defect in the coresponding part of the nervous system. Gait abnormalities for example, could be result from cerebellar, brainstem, spinal cord, or peripheral nerve lesions (Jackson et al., 2002; Constable, 2004). 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. Recumbency and unable to rise were the most prominent signs of abnormal gait especially at the end stage of the endotoxic shock. Same results were obtained by Abubakar and Zamri-Saad (2011) with successful isolation of P. *multocida* B:2 from the brain. These results shed the light on the involvement of the nervous system in the pathogenesis of HS as a new research area need to be uncovered.

Bacterial isolation and PCR detection of *P. multocida* B:2 from the nervous system

Diagnosis of HS is mainly based on the clinical signs, post mortem findings and confirmatory diagnosis

which obtained through bacterial isolation from suspected samples or animals in addition to serological tests (De Alwis, 1999; Khan et al., 2011; Shivachandra et al., 2011; Taylor et al., 2015). Several laboratory diagnostic techniques for HS have been developed over the years for routine use (Dziva et al., 2008; El-Jakee et al., 2015). The bacterium could be identified directly through examination of blood smear from suspected or infected animal and can be isolated in suitable culture medium in the laboratory, while identification mainly depend on biochemical tests, serotyping and recently, molecular techniques such as polymerase chain reaction (PCR) (De Alwis, 1999; Zamri-Saad et al., 2006; Jesse et al., 2013c).

Successful bacterial isolation of *P. multocida* B:2 from nervous system especially from the brain has been reported in both natural outbreaks and experimental infection (Lane et al., 1992; Abubakar and Zamri-Saad, 2011; Abubakar et al., 2013; Abdullah et al., 2014a; Jesse et al., 2013c) (**Table 1**). However, most of these studies mainly focused on respiratory and gastrointestinal tracts as main sites and did not provide details about which part of the nervous system was involved and its relation to clinical signs and pathological changes during the disease course of HS. Lane et al. (1992) found typical bipolar, Gram-negative coccobacilli to rods in smears from brain of cattle suffering an outbreak of HS, and heavy growth of nearly pure culture of *P. multocida* was recovered from the brain of the affected animals. Moreover, the results were confirmed when all the experimentally infected mice with suspected materials died between 24 and 72 h post-inoculation, with signs of septicemia and *P. multocida* was re-isolated from the tissues of the dead mice. On the other hand, isolation of *P. multocida* B:2 from brain of experimentally infected mice has been reported by (Abdullah et al., 2014a; Khaleel et al., 2014). While Abubakar and Zamri-Saad (2011) and Abubakar et al. (2013) were be able to isolate *P. multocida* B:2 from brain of experimentally infected buffalo calves with presence of acute encephalitis.

The use of PCR added a further method to detect and confirm the presence of *P. multocida* from different types of samples (Townsend et al., 1998; Hunt et al., 2000; Ranjan et al., 2011; Jesse et al., 2013e).Using genus and species specific primers, *P. multocida* B:2 was identified in different sites and organs (Zamri-Saad et al., 2006; Shafarin et al., 2009). Recent experimental studies by Jesse et al. (2013c) and Abdullah et al. (2014a) reported the detection *P. multocida* B:2 from brain of infected mice in addition to other organs using PCR. These results confirm the ability of *P. multocida* B:2 to the cross blood brain barrier and support the evidence of bacterial meningitis and/or encephalitis (Scott, 2004; Stokol et al., 2009). Detailed study about the ability of *P. multocida* B:2 to invade different sites of the nervous system is necessary to provide better understanding of the pathogenesis of HS especially in buffaloes as a real host of the disease.

Cross pathology and histopathological changes in the nervous system due to *P. multocida* B:2 infection

In outbreaks of HS, the typical cross pathological findings are characterized by hemorrhages and congestions in different parts of the animal's carcass, especially the respiratory and gastrointestinal tracts, in addition to subcutaneous edema in submandibular and brisket areas (Khan et al., 2011; McFadden et al., 2011). On the other hand, the involvement of the nervous system was rarely reported in outbreaks and this may be due to the fact the nervous system in not routinely examined in such cases. However, Lane et al. (1992) reported meningitis as a constant feature in an outbreak of HS in cattle with successful bacterial isolation of *P. multocida*. In contrast, several experimental infection studies reported the involvement of the nervous system (Abubakar and Zamri-Saad, 2011; Abubakar et al., 2013; Jesse et al., 2013c) (**Table 1**). However, most of these studies did not present enough details about the involvement of the nervous system in the disease course of HS.

The pathological picture of HS depends upon many factors such as virulence of the strain used, inoculation dose and volume, route and duration of the disease (De Alwis, 1992; De Alwis, 1999). The inoculation dose and volume, in addition to route of infection have essential role in the development and pathology of the disease (Dowling et al., 2002; Odugbo et al., 2005; Dagleish et al., 2010). Abubakar and Zamri-Saad (2011) reported that oral infection with 50 ml of 10^9 cfu/mL of live wild-type *P. multocida* B:2 failed to produce a typical clinical signs of HS , while 5 mL of the same dose was able to induce severe clinical signs when intratracheal exposure was used. Route of infection also affect the extent and type of the lesions developed. Abubakar and Zamri-Saad (2011) found acute hemorrhagic encephalitis in buffalo calves after orally exposed to 10^9 cfu/mL of live wild-type *P. multocida* B:2 with mean histopathological score 2, while intra-tracheal exposure induce more sever lesion in the brain and the scored 3. Furthermore, respiratory route (intranasal infection by aerosols or intratracheal) and oral drenching results in

Table 1: Involvement of the nervous system due to *P. multocida* in different animals.

Organ	Lesion	Animal	Pathology	Bacterial isolation	PCR detection	Reference
Meninges	Meningitis	Cattle	ND*	+	ND*	Lane et al. (1992)
Brain	CNS perivascular hemorrhages	Calves	+	ND*	ND*	Hodgson et al. (2005)
Brain	Acute hemorrhagic encephalitis	Buffalo	+	+	ND*	Abubakar and Zamri-Saad (2011)
Brain	Acute hemorrhagic encephalitis	Buffalo	+	+	-	Abubakar et al. (2013)
Brain	Encephalitis	Mice	+	+	+	Abdullah et al. (2014a)
Brain	Encephalitis	Mice	ND*	+	+	Jesse et al. (2013c)
Brain	Encephalitis	Mice	+	ND*	ND*	Khaleel et al. (2014)
Brain	Encephalitis	Mice	+	ND*	ND*	Jesse et al. (2014)

ND, not done; CNS, central nervous system

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 (De Alwis, 1999; Odugbo et al., 2005; Jesse et al., 2013b; Annas et al., 2014). The duration of the disease further influence lesions type. In animals that died within 24-36 h of experimental inoculation, the gross pathology is limited to widespread petechial hemorrhages and generalized congestion of the lungs. When the duration was 36-72 h, hemorrhages are usually petechial or ecchymotic, and more pronounced (De Alwis, 1999; Odugbo et al., 2005).

The main histopathological lesions usually observed in various organs of animals affected by HS are degenerative changes and necrosis, inflammatory changes marked by leucocytic infiltration, edema, hemorrhage and thrombosis (Dowling et al., 2002; Abdullah et al., 2014a; Annas et al., 2014b; Khaleel et al., 2014). Organs including lungs, liver, heart, spleen, stomach and intestine are the most frequently selected to study histopathological changes (Dowling et al., 2002; Abubakar and Zamri-Saad, 2011; Jesse et al., 2013b; Annas et al., 2014a). In contrast, nervous tissues and organs are infrequently selected for histopathological studies of HS, and researchers rarely attempt to evaluate the involvement of the nervous system in the pathogenesis of HS.

In both natural and animal models of *P. multocida* infection, reports on involvement of the nervous system in the pathogenesis of the disease are rare (Horadagoda et al., 2002; Odugbo et al., 2005; Dagleish et al., 2010; Khan et al., 2011; McFadden et al., 2011). However, recent study by Abdullah et al. (2014a) reporteddistribution of inflammatory cell response, necrosis and haemorrhage in different organs including the brain in groups of mice inoculated orally with different doses of *P. multocida* B:2. Additionally, Khaleel et al. (2014) reported observed vascular congestion in the brain and neuronal necrosis, besides lesions in other organs, in mice model experimentally infected with river water contaminated with *P. multocida* B:2 (**Table 1**). These findings further give credence to the fact that certainly *P. multocida* infection has influence on the nervous system of infected animals. Although HS is well known as acute septicaemic disease affect the respiratory tract of the cattle and buffaloes (Graydon et al., 1992; Mathy et al., 2002; Jesse et al., 2013d), lesions involved the nervous system may result in abnormalities in mental status, behavior, posture and balance, gait and muscle tone, and the special senses (Constable, 2004). This assertion remains inconclusive until further studies are conducted to investigate the involvement of the nervous system in the pathogenesis of HS.

Cytokines and acute phase proteins effect due to *P. multocida* B:2 infection

Cytokines are small regulatory proteins utilized by cells for communication. They are produced by, and target, a remarkably diverse array of cell types and exert their regulatory effects mostly in the vicinity of their production sites (Praveena et al., 2010; Luzina et al., 2014; Stenken and Poschenrieder, 2015). Cytokines have an important role in pathogenesis of pasteurellosis (Iovane et al., 1998; Praveena et al., 2010). Cytokines, particularly TNFα, interleukins (IL-1β) and (IL-6) are produced by a range of cells, including macrophages, Kupffer cells, neutrophils, blood monocytes and endothelial cells (Hodgson, 2006; Dow et al., 2010; Praveena et al., 2010; Stenken and Poschenrieder, 2015). Cytokines affect organs involved in homeostasis, such as the central nervous system, the autonomic nervous system and the adrenal gland, to establish a rapid and intense protective or reactive response leading to systemic inflammatory reactions, including hormonal or metabolic, and resulting in a number of biochemical changes which potentiate the appearance of the main clinical changes characterized by fever, anorexia or weight loss (Dunn et al., 2005; Gruys et al., 2005; Tothova et al., 2013).

The role of cytokines in the pathogenesis of *P. multocida* infection has been studied using murine and buffalo models, and a surge in pro-inflammatory cytokines that

results in inflammatory reaction in the tissues were attributed in pathogenesis of the disease. In addition, the release of cytokines activates the acute phase response (APR) (Horadagoda et al., 2001; Praveena et al., 2010; Abdullah et al., 2013a). The most notable cytokines are TNFα, IL-1β, IL-6, IL-8 and IL-12 (Eckersall, 2006; Cray et al., 2009). However, IL1β, IL-6 and TNFα 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 pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α (Song and Wang, 2011).

Acute phase response, on the other hand is a nonspecific and complex reaction that occurs shortly after any tissue injury. The reactions of the APR are part of the non-specific immune system and thus the first line of defense against invading pathogens (Eckersall and Bell, 2010; Ceciliani et al., 2012; Tothova et al., 2013). Acute phase proteins (APPs) are blood proteins, produced by both hepatocytes and peripheral tissues, which their systemic levels increase or decrease in response to infection, inflammations or trauma (Eckersall and Bell, 2010; Mobasheri and Cassidy, 2010). The primary objective of the investigation of the APPs is to understand the pathophysiology of disease processes involved in the innate immune response to infections (Ceciliani et al., 2012). In addition, quantification of APPs provides valuable clinical information in the diagnosis, prognosis, treatment and monitoring of different pathologic processes (Eckersall, 2000; Murata, 2007; Eckersall and Bell, 2010; Abdullah et al., 2013b; Jesse et al., 2013a).

Acute phase proteins are believed to play major roles in several aspects of the systemic reaction to inflammation including the opsonization of several pathogens, the scavenging of potentially toxic substances and the overall regulation of different stages of inflammation. During the APR, the serum concentration of the APPs changes dramatically up to 100-1000 times (Eckersall, 2000; Eckersall and Bell, 2010; Ceciliani et al., 2012; Abdelbaset et al., 2014).There are basically two forms of APPs and these are the negative APPs and the positive APPs. The negative APPs include albumin (the major constituent of plasma protein), transferrin, transthyretin, retinol-binding proteins, antithrombin and transcortin. The negative APPs decrease during inflammation or infection and the physiological role of the decreased synthesis of such proteins in the phase of infection or inflammation is generally to save amino acids for the synthesis of positive acute-phase proteins more efficiently. On the other hand, the positive APP include serum amyloid A (SAA), haptoglobin (Hp), C-reactive protein (CRP), lipopolysaccharide binding protein (LBP) and α1-acid glycoprotein (AGP) (Ritchie et al., 1999; Skinner, 2001; Zweigner et al., 2006; Nikunen et al., 2007; Ceciliani et al., 2012; Plessers et al., 2015). The major biologic functions of SAA are thought to involve in host defense and lipid transport and metabolism. While the function of Hp as a haemoglobin-binding protein conserving the iron released following red cell haemolysis (Herpers et al., 2009; Eckersall and Bell, 2010; Tothova et al., 2013; Idoate et al., 2015).

The role of APPs in pathogenesis of *P. multocida* B:2 and it immunogens, LPS and OMPs, has 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 increase in SAA, Hp after experimental infection of buffalo calves with *P. multocida* B:2 and inoculation of its immunogens, LPS and OPMs. The concentrations of SAA and Hp were the highest in calves inoculated with LPS, followed by calves inoculated with OMPs, and finally, the calves infected with *P. multocida* B:2. The highest concentration of SAA and Hp in LPS and OMP treated groups could be due to longer duration and severity of tissue damage caused by these immunogens (Jesse et al., 2013a). A recent study by Abdullah et al. (2014b) have equally evaluated the SAA and Hp responses in experimental mice model following oral inoculation of graded doses of *P. multocida* B:2 and its lipopolysaccharide. The study concluded that there is a positive correlation between the dose of *P. multocida* type B:2 and its LPS and the increased level of APPs especially, Hp during the acute phase of infection.

Even though extensive researches have been done on cytokines and APPs using mouse and buffalo models infected with *P. multocida* B:2 which revealed valuable information about the pathophysiology of HS (Abubakar and Zamri-Saad, 2011; 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 in the pathogenesis of HS are new area need to be studied, especially with increased level of cytokine and APPs accompanied with the evidence of positive bacterial isolation and vascular congestion in the brain with neuronal necrosis in experimental mice model infected with river water contaminated with *P. multocida* type B:2 (Khaleel et al., 2013; Abdullah et al., 2014b; Ali et al., 2014; Khaleel et al., 2014).

CONCLUSION

Despite existence of extensive studies on the pathogenesis of *P. multocida* infection, gaps are still exist about possible involvement of the nervous system in the pathogenesis of *P. multocida* B:2. Since *P. multocida* has been isolated from the brain of infected animals under natural and experimental conditions, and lesions in the brain have been described, determination of virulence factors, and detailed investigation of clinical, bacteriological and pathological changes in the nervous system during the disease course would reveal significant information about the clinic-pathology and/or patho-physiology of *P. multocida* B:2 infection in cattle and buffaloes.

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