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Pathogenesis of Leptospirosis: Important Issues

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Abstract

The leptospirosis is a re-emerging anthropozoonos is worldwide distribution. The immunopathogenesis of the disease is extremely complex. Which one the role of inflammatory mediatorys, cytokines, outer membrane proteins, apoptosis and others factors related with the virulence of the pathogen during the infection.

Summary

Leptospirosis is a re-emerging tropical infectious disease [1], is an important zooanthroponotic disease spread-worldwide [2]. The spirochetes of the genus *Leptospira* is responsible of human and animal leptospirosis characterized as mild febrile illness to severe multiorgan failure, especially pulmonary hemorrhage and renal failure [3]. Pathogenic leptospires are highly motile and invasive spirochetes that have the capacity to survive and grow in tissue by escaping natural defense mechanism [4]. The disease is transmitted to humans by direct or indirect exposure to contaminated urine from mammalian reservoir hosts as rodents but also farm, wild, and domestic mammals [5]. Asymptomatic form of leptospirosis with fever, headache, and myalgia that can spontaneously resolve is one of clinical presentations [3]. The most cases are probably inapparent and associated with host-adapted serovars such as Canicola in dogs, Bratislava in horses and pigs, Hardjo in cattle and Australis and Pomona in pigs [6-9].

In humans can vary in severity according to the infection serovar of Leptospira, and the age, health and immunological competence of the patient [2]. However, more severe cases, with sepsis and multiple organ failure, including hepatic and renal dysfunctions associated to pulmonary hemorrhage, are also reported [3]. Leptospires enter the body through small cuts or abrasions, via mucous membranes such as the conjunctiva or thorough wet skin. They circulate in the blood stream, with the bacteremic phase lasting for up to 7 days [2]. The second stage of acute leptospirosis is also referred to as the immune phase, in with the disappearance of the organism from the bloodstream coincides with the appearance of antibodies [5]. The mechanisms by which leptospires cause disease are not well understood. The presence of the virulence factors has been suggested. The involvement of toxins or toxic factors in the pathogenesis of leptospirosis has long been contemplated, since the absence of the microorganism at the site of tissue injury is a factor that strengthens this hypothesis [10,11] extracted a glycoprotein (GLP) present in cell walls of a strain of serovar *L.interrogans* Copenhageni that cytotoxic effect against the fibroblasts of mice (L929). Later it was demonstrated that GLP induced the production of cytokines, TNF-α and IL-10 by peripheral blood monocytes of healthy volunteers [12]. The mechanism by which *leptospira* activate the immune system has been the main focus of many studies, especially regarding the involvement of cytokines [13,14]. High levels of TNF-α in serum of patients with leptospirosis were observed and in the culture supernatant of macrophages [15-18], and also associated the severity of infection. Tests using the technique of quantitative real-time PCR, found elevated levels of inflammatory cytokines, IL-4 and IL-10 in the late stage of infection with *Leptospira interrogans* Icterohaemorrhagiae establishing a profile of involvement of cytokines in type 1 cellular immunity [19,20]. It is believed that the naturally acquired immunity may result from humoral-mediated response [21,22] which in turn serovarspecific [21]. The development of the humoral response is related to activation-dependent mechanism recetor Tool-like type 2 (TLR-2), via the innate immune system that would be activated by LPS leptospiral [23]. Other researchers [24], demonstrated that *Leptospira* can activate T cell proliferation and γ-δ α-β, suggesting therefore the involvement of these cell populations in host defense or in the pathology of leptospirosis. But the adhesion of leptospires to host tissue components is important as an initial and necessary step for infection and pathogenesis. Therefore, much recent leptopirosis research has focused on outer membrane proteins (OMPs) such as LipL32 [25], the bacterial immunoglobulin-like domain containing proteins (LigA-C) [26,27] the leptospiral endostatin-like proteins (LenA-F) [28]. Several studies recently showed that recombinant Lig proteins can mediate *in vitro* interaction with fibronectin, fibrinogen, collagen, laminin, tropoelastin, and elastin [29,30]. Others virulence factor might be of greater significance in the pathogenesis of leptospirosis would be the occurrence of apoptosis cellular or programmed cell death that is an essential mechanism for embryonic development and host response against many infectious and non-infectious disease [31] followed by tissues injury is well documented, including many renal diseases [32] *L. interrogans* serovar Icterohaemorrhagiae infection has been described to invade Vero cells and induce macrophages apoptosis [33]. Besides, *in vivo* apoptosis of hepatocytes of guinea pig infected by the same serovar has been described [34]. It has been demonstrated that *L. interrogans* induces apoptosis in J774A1 cells by activation of caspases-3 through activation of caspase-8 [35]. The clinical severity of the disease often appears to be out of proportion to the histopathological findings. Immune-mediated disease has been proposed as one factor influencing the severity of the symptoms [5]. The presence of the IgM, IgG and IgA and C3 along the alveolar basement membrane, were demonstrated, suggesting that as autoimmune process constitutes the etiology of fatal hemorrhagic complications due to leptospirosis [36]. A strong immunostaining of both Il-6 and TNF-ά was observed in addition to glomerular hypercellularity in Balb/c mice inoculated with Leptopira interrogans serovar Canicola [37]. Finally studies show that the expression of genes responsible for virulence factors in *leptospira* is pathogen-specific genes and that may be expressed or not depending

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on the pathogen's ability to attach to host tissues during infection. However, additional research is essential to understanding how, the mechanisms by which *leptospira* induces the tissue injury and what role that virulent factors on the pathophysiology of leptospirosis.

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