3

Leptospirosis: Epidemiologic Factors, Pathophysiological and Immunopathogenic

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1. Introduction

Leptospirosis is a disease of worldwide distribution present on all continents except Antarctica (Adler & Montezuma, 2010) affecting wildlife, domestic and man. Leading consequently serious socio-economic and public health. It is currently the highest incidence of zoonosis in the world, also considers as an occupational disease, and reemerging infectious disease, occurring endemic and epidemic in developing countries with tropical and subtropical (Levett, 2001; Bharti et al., 2003, Ko et al , 2009). more frequently in tropical and developing countries (Bharti et al, 2003), acarrretando with this serious social and economic problems. The disease is an acute infection caused by a spirochete *Leptospiraceae* family, consisting of two genera, *Leptospira* and *Leptonema*. Recently, the genus *Leptospira* was divided into 17 species based on molecular classification (DNA), saprophytic and pathogenic species (Brazil 2002; Bharti et al. 2003). The pathogenic species are: *L. interrogans, L. alexanderi, L. fanei, L. inadai, L. kirschineri, L. meyeri, L. borgetersenii, L. weil, L. noguchi, L. santarosai,* Genomospecie 1, Genomospecie 4, 5 Genomospecie. The serotypes of *Leptospira* are interrogans Australis, Bratislava, Bataviae, Canicola, Hebdomadis, Icterohaemorrhagiae Copenhageni, Lai, Pomonoa, Pyrogenes, Hardjo and divided into serogroups (Ribeiro, 2006). The reservoir animals, mainly rats, are the most frequent disseminators, by eliminating spirochetes in the urine. *Leptospira* spp. can enter the body through intact skin or not, the oral mucosa, nasal and conjunctival (Kobayashi, 2001). The clinical manifestations of leptospirosis vary according to species, individual susceptibility, the pathogenicity and virulence of the serovar involved (Venugopal, 1990, Macedo 1991). After penetration of the bacteria likely, the organism spreads to the bloodstream to all organs (Hüttner et al, 2002). The incubation period is usually around 5-14 days, but have been described as short or long periods in some cases, such as 72 hours a month or more (Jezior, 2005). Leptospirosis is characterized by a vasculitis. The damage to capillary endothelial cells to the underlying cause of clinical manifestations such as renal tubular dysfunction, liver disease, myocarditis and pulmonary hemorrhage (Hill, 1997).

The clinical features are: a) kidneys: interstitial nephritis, tubular necrosis, decreased capillary permeability, and the combination of hypovolemia resulting in renal failure, b) in the liver: necrosis with central lobular proliferation of Kupffer cells and hepatocellular dysfunction c) in the lung, the lesions were secondary to vascular damage resulting in interstitial hemorrhage d) in the skin, the lesions occur as a result of vascular epithelial

injury, and) in skeletal muscle: the lesions were secondary to edema, vacuolation of the myofibril and damage of blood vessels, lesions of the vascular system in general, would result in capillary rupture, hypovolemia and shock (Jezior, 2005). In humans and dogs the most frequent clinical symptoms are severe hepatitis and nephritis (Mosier, 1957; Hagiwara et al., 1975). In dogs the most obvious symptom is jaundice (Greene et al. 1998; Sonrie et al., 2001), fever, myalgia, prostration and the evolution of the process, can present anuria, oliguria or polyuria, indicating different degrees of commitment renal (Masuzawa et al. 1991; Mcdonough, 2003). In cattle, the symptoms are related to the reproductive sphere as abortion and agalactia (Bercovich, 1989) and may have episodes of mastitis caused by serovar hardjo when determining the drop syndrome milk or "milk drop syndrome" (Higgins et al. , 1980, Pearson et al., 1980). In pigs, sheep and goats are seen sporadic reproductive disorders and, possibly, nervous and respiratory systems framework (Andre-Fontaine, 1985; Giles, 1993). Horses can be no abortion (Shapiro & Prescott, 1999) and ocular lesions (Jungherr 1944; Bohl and Ferguson 1952; Kemenes et al., 1985), such as recurrent uveitis, which have been observed after infection, particularly, by L. interrogans serovar pomona (Nick et al., 2000). The cats have to be refractory (Find and Szyfres, 1989). However, seroepidemiologic study in this species, conducted by different authors report seroconversion to multiple *Leptospira* spp (Langoni et al. 1998; Alves et al., 2003). From the epidemiological point of view, it is important to know the species of animals that act as reservoirs, and what the serovars prevalent in a given area. Some serovars have right choice for some species, so called primary hosts, in which cause mild disease with little damage. These can still host the leptospira in their renal tubules, where they remain free from the action of antibodies, and eliminate them through urine intermittently for long periods (Lamb et al., 1981), thus acting as a source of infection for man and other animals. The impact of leptospirosis in terms of public health is reflected in the high cost of treatment of humans afflicted with a fatality rate of about 5% to 20%. However, with regard to animal health, the consequences of infection are particularly the economic sphere, in view of the involvement of cattle, horses, pigs, goats and sheep, food producing animal species noble as meat, milk, and still products of industrial interest, such as wool and leather (Badke, 2001).

The disease course can vary from common symptomatic infection in endemic regions (Ashford et al., 2000), undifferentiated febrile illness, or syndrome to the presence of aseptic meningitis with low morbidity (Berman et al., 1973) or fulminant disease similar to toxic shock syndrome (Vernel-Pauillac and Merien, 2006) with jaundice, myocarditis, renal failure and cardiac hemorrhage, meningitis and death (Levett, 2001) have been described as epidemic in regions of severe leptospirosis in urban areas of Brazil (Ko et. al., 1999) The Jarisch-Herxheimer reaction is not an uncommon complication, when investigated (McBriede et al., 2005). The lung is a target organ that during leptospira infection, presents a hemorrhagic pneumonitis with varying degrees of severity. Under electron microscopy it is observed that the primary lesion is found in endothelial cells of capillaries (Huttner et al., 2002). Seijo et al (2002) classified the respiratory impairment present in leptospirosis in three groups: a) mild to moderate (20 to 70% of patients), pulmonary infiltrates frequently associated with jaundice and a slight alteration of renal function, b) with jaundice severe kidney disease and bleeding (Weill syndrome) occasionally death from kidney failure and myocarditis or cardiovascular collapse with extensive hemorrhage, c) pulmonary hemorrhage, often fatal, without the occurrence of jaundice, kidney disease or other bleeding.

Over the past year has been a frequent higher prevalence of leptospirosis with the observation of episodes of hemoptysis associated with pulmonary respiratory distress syndrome and death (Gill et al., 1992). The same authors, after review, mentioning that the death in Brazil is primarily linked with renal failure, 76.2% of cases, while 3.5% are related to pulmonary hemorrhage. In an outbreak of leptospirosis occurred in Nicaragua in 1995, 40% of fatal cases were associated with pulmonary hemorrhage (Trevejo et al. 1998).

The lung injury during inflammatory processes has been linked to excess stimulated cells in the lung, including alveolar macrophages, polymorphonuclear cells and production of reactive intermediates of oxygen and nitrogen, or other inflammatory mediators. The etiology of respiratory bleeding is unknown, however Nally et al. (2004) verified by immunofluorescence, the presence of immunoglobulins IgM, IgG, IgA and complement factor C3 deposited along the alveolar basement membrane, thus suggesting the existence of autoimmune process associated with the immunopathogenesis of pulmonary hemorrhage observed in fatal cases of leptospirosis.

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 (Knight et al., 1973). Vinh et al. (1986) extracted a glycoprotein (GLP) present in cell walls of a strain of serovar L.interrogans copenhageni that had 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 (Diament, et al. 2002). The mechanism by which leptospira activate the immune system has been the main focus of many studies, especially regarding the involvement of cytokines (Yang et al., 2000, Maragoni et al., 2004). High levels of TNF-α in serum of patients with leptospirosis were observed by Estavoyer et al. (1991) and Tajiki and Solomon (1996), and in the culture supernatant of macrophages from mice genetically selected Marinho et al. (2005, 2006) who also associated the severity of infection. Vernel-Pauillac and Merien (2006), tested 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. It is believed that the naturally acquired immunity may result from humoral-mediated response (Adler and Faine, 1977, Adler et al., 1980), which in turn serovar-specific (Adler and Faine, 1977). 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 (Werts et al., 2001). Klimpel et al. (2003), 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.

The humoral immune response, compared to the exposure to leptospires, is demonstrated by serological tests, where there is an increased activity of immunoglobulins IgG and IgM after natural infection or immunization. In men there was a greater prevalence of immunoglobulin class IgM (Adler et al, 1980; Petchclai et al. 1991; and Ribeiro et al, 1992), in all the patients, but not all produce agglutinins IgG, after infection. The cause of this individual variation is unknown, however it is observed more frequently in patients afflicted with Weill syndrome (Adler et al., 1980).

Other factors such as hemolysins (Lee et al., 2002), hyaluronidases, phospholipases and glycoproteins (Yang et al. 2001; Sitprija et al., 1980) are implicated in the pathogenesis of leptospirosis. The spiral movement itself would facilitate adherence to renal tubular

epithelial cells by lipoproteins wall as Lip41, Lip 36 and LPS (Dobrin et al. 1995). Pathogenic Leptospira present several surface proteins that mediate the interactions between the bacteria with the extracellular matrix and host cells, proteins that facilitate adhesion and invasion of host cell proteins that allow motility in connective tissue, secreted proteins such as enzymes degradation (collagenase, hemolysins, phospholipids and sphingomyelin) and pore-forming proteins. No leptospires in protein secretion of type III and IV, as used by Gram-negative bacteria for introducing proteins into host cells (Ko et al, 2009). The cell apoptosis, or programmed cell death plays an important role in modulating the pathogenesis of many infectious processes. The occurrence of apoptosis in the mechanism of tissue injury is a well known event in renal disease processes (Wong et al., 2001). Cell death by an apoptotic process would regulate the number of cells during induction and resolution of renal injury (Savill, 1994, Ortiz et al., 2002). Leptospira interrogans has been considered as an agent inductor of apoptosis of macrophages (Merian et al. 1997) and guinea pig hepatocytes (Merien et al., 1998) However, the mechanism responsible for cell death remains desconheciso. Jin (2009) showed that L. interrogans induces apoptosis in cell line J774A.1 via dependent on caspase 3 and 8. Caspases (*cysteine-dependent aspartate-specific proteases*) signal for apoptosis and cleave substrates leading to condensation and nuclear fragmentation, externalization of membrane phospholipids that will signal to these cells were engulfed by macrophages (Nicholson et al. 1997, Boatright et al ., 2003).

Fig. 1. *Leptospira* spp in dark field microscopy100 increased Microbiology Laboratory, Unesp Brazil Dr. Márcia Marinho /2011

The actual mechanisms that involve the immune response to leptospiral remain controversial and complex. The importance of understanding better the complexity of the mechanisms involved in leptospirosis, such as the virulence of the serovar, the immunocompetence of the host to the agent, the form of clinical manifestations presented, represents a major paradigm in the understanding of infectious diseases and factors related to imunofisiologia leptospirosis, foster the development of preventive and therapeutic strategies aimed at curbing the infection, contributing directly to reducing the prevalence of the disease. New studies are needed to determine the role of apotpose cell in the immunopathogenesis of leptospirosis and the mechanisms that underlie and induce

infection. Understanding these mechanisms and kinetics of their occurrence in the future will develop treatment strategies

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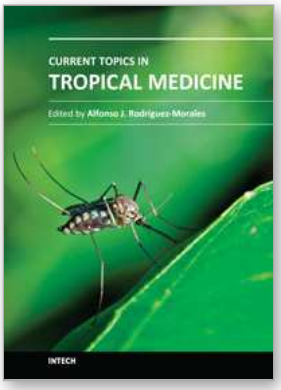

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