LEPTOSPIROSIS: A CONTEMPORARY INFECTIOUS DISEASE

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ABSTRACT:Leptospirosis a Zoonotic disease first recognized in the last century. Leptospirosis is maintained in nature by chronic renal infection of carrier animals. The most important reservoirs are rodents and other small mammals. Human infection occurs through direct contact with urine. The mechanisms whereby leptospires cause disease are not clearly understood. Potential virulent factors include immune mechanisms, toxin production, adhesion and other surface proteins. Leptospirosis was described as a severe potentially fatal disease accompanied by any combination of renal failure, liver failure with hemorrhagic diathesis. Mortality rates in patients developing severe disease have ranged 5 % to 40 % .Organism may be identified by dark field examination, PCR assays are useful confirming diagnosis, direct culture methods, and indirect microscopic agglutination test. Treatment of mild leptospirosis by oral doxycycline .Treatment of moderate to severe disease should be with intravenous penicillin. Prevention consists of avoiding exposure to potentially contaminated water and reducing contamination by rodent control.

Key words: Leptospirosis,Transmission, Pathogenesis, Diagnosis.

INTRODUCTION

Leptospirosis or "Weil's disease was first described in Heidelberg in 1886.A syndrome of severe multisystem disease, presenting with profound jaundice and renal function impairment. The descriptions of disease that probably represent leptospirosis were made earlier ,but cause could not be definitively ascribed to leptospiral infection [1].The causative organism was isolated by Inada*et t al* , in 1915 .The role of rats as natural vectors was also demonstrated [2]. Leptospires were first visualized in autopsy specimens from a patient thought to have had yellow fever, but was not isolated until several years almost simultaneously, in Germany and in Japan [3,4].

Diagnostics confusion between severe icteric leptospirosis and yellow fever continued, with prominent researchers such as Stokes and Noguchi dying in their attempts to discover the causative agent[4]. The disease is underreported, particularly in tropical regions, but attempts at surveillance suggest that it may be the most common Zoonosis [5]. The disease is maintained in nature by chronic renal infection of carrier animals, which excrete the organism in their urine, contaminating the environment .Human infection occurs by direct contact with infected urine or tissues or, more commonly by direct exposure to the organisms in the damp soil or water. The spectrum of illness is extremely wide, ranging from undifferentiated febrile illness to severe multisystem disease with high mortality rates[6].This paper reviews the transmission, ,pathogenesis ,clinical manifestation ,diagnosis ,therapy and prevention of leptospirosis.

LEPTOSPIRA

Leptospira derives from the Greek l*epto* (thin) and latin*spira*(coiled) Because of their small diameter, leptospires are best visualized by dark field microscopy, appearing as actively motile spirochetes .Leptospira are readily cultured in polysorbate-albumin medium if specimens are obtained prior to initiation of antibiotic therapy [7]

The genus l*eptospira* was classified into two species, *L.interogans* and *L.biflexa*, comprised of pathogenic and nonpathogenic strains, respectively. Within each species, large numbers of serovars were differentiated using agglutinating antibodies. Serovar specificity is conferred by lipopolysaccharide (LPS) 0 antigens. More than 250 serovars of pathogenic *leptospire*s have been described; because of large number of serovars, antigenically related serovars were grouped into serogroups for convenience in serologic testing[8]. Some species contain both pathogenic and nonpathogenic strains. This classification is supported by 16S RNA gene sequencing, but is distinct from the former serological classification [9].The genome sequencing of several *Leptospira*species and strains have been determined, and sequencing of other strains is underway [10,11]

TRANSMISSION

Leptospirosis is endemic throughout the world .Human infections are endemic in most regions; the peak incidence in rainy season in tropical regions and the late summer in temperate regions .Outbreaks may follow periods of excess rain [12].The incidence of leptospirosis is probably grossly underestimated ,because of limited diagnosis capacity in the regions where the burden of disease is greatest [5].In the United States ,the highest incidence is found in Hawaii; with approximately 128 cases / 100,000 [13]. In Australia, the highest incidence reported in 1998,108 cases /100,000 of population compared to 2.2 per 100,000 in 1997 [14]. Leptospirosis is maintained in nature by chronic renal infection of carrier animals. The most important reservoirs are rodents and other small mammals, but livestock and companion animals are also significant sources of human infection .Infection of carrier animals usually occurs during infancy and ,once infected ,animals may excrete leptospires in their urine intermittently or continuously throughout life [15].

Infection occurs through direct or indirect contact with urine or tissues of infected animals .Direct contact is important in transmission to veterinarians working in milking sheds or dairy farms, abattoir works, butchers, hunters, and animal handlers. Transmission has been reported to occur to children handling puppies and to dog handlers. Recreational exposures have become relatively more important .often in association with adventure tourism to tropical endemic areas

.Several large point-source waterborne outbreaks have occurred after athletic events [16,17]. There has been an increase in leptospirosis cases in dogs in the eastern regions of North America and in Midwest, associated with a shift in the predominant serovar's causing disease [18-20]. New canine vaccines are available containing these serovar's.

PATHOGENESIS

Human infection is contracted almost exclusively from direct or indirect exposure to urine of carrier animals. Leptospires enter the body through cuts abrasions ,mucous membranes or conjunctivae, or aerosol of inhalation of microscopic droplets .Swallowing contaminated lake water was the only behavioral risk factor identified in a case-control study of a large leptospirosis outbreak at the 1998 Springfield Triathlon [16]. On entering the body, there is widespread hematogenous dissemination and penetration of tissue barriers, including invasion of the central nervous system and aqueous humor of the eye. The mechanisms whereby leptospires cause disease are not clearly understood. Potential virulence factors include immune mechanisms, toxin production, adhesion and other surface proteins. Human susceptibility to leptospirosis may be related to poor recognition of leptospiral LPS by innate immune system [21,22]. Human toll-like receptor (TLR) 4, which responds to extremely low concentrations of gram negative LPS (endotoxin), appears to be unable to bind leptospiral LPS [23], perhaps because of the unique methylated phosphate residue of its lipid A [24].Direct tissue damage may also be caused by production of hemolytic toxins, which may act as sphingomyelinases, phospholipases, or pore forming proteins [25].

Immune –mediated mechanisms have been postulated as one factor influencing the severity of symptoms [26].Investigation of Springfield triathlon outbreak identified the human leukocyte antigen (HLA) DQ6 as an independent risk factor for leptospirosis .The structural location of HLS-DQ6 polymorphisms associated with disease suggested that leptospires produce a superantigen that can cause nonspecific T-cell activation in susceptible individuals [27].In horses recurrent uveitis (moon blindness) it is shared by common equine pathogenic serovar's [28,29].

HUMAN DISEASE

Clinical manifestations of leptospirosis is associated with a very broad spectrum of severity of severity ranging from subclinical illness followed by seroconversion to two clinically recognized syndromes- a self- limited systemic illness seen in approximately 90 % of infections, and a severe potentially fatal illness accompanied by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis[2,30,31]. The mean incubation period is 10 days range,5 to 14 days ; determination of precise exposure may be difficult, leading to significant the first ten days of illness. Specimens should be collected before the antibiotic therapy is initiated. Urine also can be cultured after the first week of illness. Urine samples must be cultured within 1 hour of collection, becauseleptospires do not survive in the acidic environments [36,7].

Cultures are performed in albumin-polysorbate media such as Ellinghausen-McCullough-Johnson-Harris (EMJH) medium [6] Cultures are incubated at 30C for several weeks, before initial growth may be very imprecision in estimated incubation times. The acute systemic phase of illness begins abruptly with a high remittent fever (38^o to 40^o C) and headache, chills, rigors, and myalgias; conjunctival suffusion without purulent discharge; abdominal pain; anorexia, nausea and vomiting; diarrhea, and cough and pharynigitis; a pretibial maculopapular cutaneous eruption occurs rarely. Other less common signs include lymphadenopathy, splenomegaly, and hepatomegaly. The acute phase lasts from 5 to 7 days. Routine laboratory tests nonspecific but indicative of a bacterial infection.Leptospires can be recovered from the blood and spinal fluid (CSF) during the acute phase of illness, but meningeal signs are not prominent in this phase. Leptospires may also be recovered from urine, beginning about 5 to 7 days after the onset of the symptoms. Urinalysis reveals mild proteinuria and pyuria, with or without hematuria, and hyaline or granular casts. Death is rare in the acute phase of illness[15].

Aseptic meningitis with or without symptoms, is characteristic of the immune phase of illness, occurring in up to80 % of cases. In endemic areas, a significant proportion of all aseptic meningitis cases may be caused by leptospiral infection [32]. Severe neurological complications such as coma, meningoencephalitis, hemiplegia, transverse myelitis, or Guillain-Barre syndrome occur rarely [6].

The most distinctive form of severe illness that may develop after the acute phase of illness is Weil's disease, characterized by impaired hepatic and renal function. More severe cases may progress directly from the acute phase without the characteristic brief improvement in symptoms to fulminant illness, with fever higher than 40^o C and the rapid onset of liver failure, acute renal failure ,hemorrhagic pneumonitis ,cardiac arrhythmia, or circulatory collapse [31 Mortality rates in patients developing severe disease have ranged 5 % to 40 % [2,5,6,33].

LABORATORY DIAGNOSIS

Direct Detection Methods

Direct microscopic examination of leptospires in blood or urine by dark field examination in the early illness has been used for diagnosis. However the artifacts are commonly mistaken for leptospires, and the method has both low sensitivity (40.2 %) and specificity (61.5 %) [34]. Polymerase chain reaction (PCR) assays are useful is the prospect of confirming the diagnosis during early acute (letosopiremic) stage of illness, before the appearance of immunoglobulin M (IgM) antibodies, when treatment is likely to have the greatest benefit. In fulminating cases, in which death occurs before seroconversion, PCR may be of diagnostic value [35].

Isolation and Identification

Leptospires can be isolated from; blood, CSF, and peritoneal dial sate fluids during *slow.Isolatedleptospires are identified to serovar level by traditional serologic methods or by molecular methods, such as pulsed-field gel electrophoresis [37].*

Indirect Detection Methods

Leptospirosis case are diagnosed by serology, method is the microscopic agglutination test (MAT), in which live antigens representing different serogroups of leptospires are reacted with serum samples and then examined by dark field microscopy for agglutination[7].Diagnostic application of

the MAT is limited by the relatively low sensitivity when acute serum samples are tested [38].IgM antibodies are detectable after about the fifth day of illness.

THERAPY

***Antimicrobial therapy should be initiated as early in the course of the disease as suspicion allows .There have been few randomized or placebo controlled trials, [39].,and these have produced conflicting results. For treatment of mild leptospirosis and chemoprophylaxis doxycycline, ampicillin or amoxicillin.Treatment of moderate to severe leptospirosis, Penicillin G, Ceftriaxone and ampicillin [40].Jarish-Herxheimer reactions have been reported in patients treated with penicillin. Patients receiving penicillin should be monitored because of the increased morbidity and mortality of such reactions {41].Researchers in the endemic areas, found that penicillin was* effective from a larger than small dose [42].Other researchers in a controlled trial found oxytetracycline with good effect, including marked reduction in the duration of fever. [43].**

PREVENTION

Prevention involves, vaccination in cattle, swine, and in dogs is important to eliminate domestic reservoirs. Risky activities should be avoided, particularly swimming in or drinking from potentially contaminated water. Animal workers should wear boots and gloves. Rodents control is also important Weekly doxycycline has been used for those who cannot avoid prolonged exposure[44].Some rodenticides such as sodium fluoroacetate are too dangerous to use in open areas and so water- soluble anticoagulants, especially the sodium salts of warfarin and pival, are often used [1].

Human immunization is not widely practiced .Immunization is widely used in Asia to prevent large–scale epidemics in agriculture laborers. A vaccine containing serovarIcterohaemprrahagiae is available in France for workers in high risk occupations, and a vaccine has been developed for human use in Cuba [45].

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