Uveitis and Leptospirosis

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Introduction

Leptospirosis is a reemerging waterborne zoonotic disease that is common worldwide, especially in tropical countries with heavy rainfall. Adolf Weil described the disease as an acute process characterized by splenomegaly, jaundice and nephritis. The name Weil’s disease came to signify severe leptospirosis characterized by diverse clinical findings such as fever, jaundice, acute renal failure, refractory shock, and pulmonary hemorrhage. However, milder forms of leptospirosis or subclinical infection are more common than its severe Weil’s disease. Suspicion of diagnosis becomes easy in the epidemic settings with a focused history, however it is difficult to diagnose leptospira disease in sporadic form. Uveitis is an important ocular manifestation of leptospirosis in the latter immune phase of the disease.

Microbiology

Leptospires are highly motile, obligate aerobic spirochetes that share features of both Gram-positive and Gram-negative bacteria. The organisms cannot be seen by direct light microscopy. Dark-field or phase-contrast microscopy of wet preparations is required for direct visualization of leptospires in cultures or clinical specimens. Silver impregnation method (Warthin-Starry staining), immunohistochemistry, or immunofluorescence microscopy can be used to visualize the organism in tissue. Ellinghausen-McCullough-Johnson-Harris medium (EMJH) is the standard medium for isolation of Leptospira from clinical specimen. Similar liquid or semisolid media include Korthof’s, Fletcher’s and Stuart’s medium. Leptospires were originally divided into two groups, pathogenic leptospires grouped as “interrogans” complex and all other saprophytic strains were placed in the “biflexa” complex. Based on molecular phylogenetic analysis, this genus includes twenty species, of which nine are classified as pathogenic, five as intermediately pathogenic, and six as nonpathogenic (saprophytic). The pathogenic and intermediate Leptospira species cause disease in humans and animals.

Epidemiology

Leptospirosis is a widely distributed zoonotic disease with incidence of human infection higher in the tropics than in temperate regions. The pattern of leptospirosis transmission can be epidemic, endemic or sporadic. Epidemic outbreaks are common after rainfall or flooding. Endemic transmission occurs because of factors such as tropical humid environments and poor sanitation. Sporadic leptospirosis can occur among travelers, sewer workers, fish and poultry handlers, miners, butchers and tunnel digger. Human-to-human transmission does not occur but the most important sources of transmission to humans are rats, dogs, cattle, and pigs.

Systemic leptospirosis

Leptospires can directly penetrate and infect humans through the conjunctival and possibly oral mucosa or through abraded skin. The organisms can escape innate immune defenses such as epithelial barriers, phagocytic cells, complements and enter into bloodstream or extracellularly within organs where they multiply. Then can spread hematogenously to all organs. Average incubation period is 5–14 days. Leptospires can be isolated from blood during the leptospiremic phase of 3–10 days.

Systemic Leptospirosis is a multi-system disease, the clinical picture depends on the organs involved. Anicteric systemic illness occurs in majority (85 to 90%) of the cases. Pathognomonic ocular manifestations in the septicaemia phase include conjunctival chemosis and scleral icterus. Some develop icteric, septicemic leptospirosis or Weil’s syndrome. The most notable feature of severe leptospirosis is the progressive impairment of hepatic and renal function. Renal failure is the most common cause of death. Common systemic clinical findings include any of the following:

- Abrupt onset of fever and rigor
- Intense headache, fatigue and prostration
- Muscle tenderness (calf and lumbar areas)
- Jaundice, Conjunctival congestion without discharge
- Meningeal irritation, Delirium, psychosis
- Anuria or oliguria
- Multi organ hemorrhages and hypotension

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• Cardiac arrhythmia or failure, atrial fibrillation, flutter

The physicians easily miss the diagnosis, as symptoms are extremely variable, mimicking other infectious diseases. The differential diagnosis of systemic leptospirosis includes dengue fever, influenza, hanta virus infection, viral hepatitis, hemorrhagic yellow fever, malaria, typhoid, relapsing fever, meningitis, encephalitis and rickettsial disease1-4.

Leptospira completes its life cycle when it traverses the interstitial spaces of the kidney, the basement membrane of the proximal renal tubules, cross through proximal renal tubulonepithelial cells and become adherent to the proximal renal tubular brush border. After that, it is excreted in the urine. Chronic and persistent renal colonization can last for weeks or years. During immune phase, patient may develop uveitis, chronic aseptic meningitis, arthralgia, recurrent abortion or infertility. In second immune phase, appearance of antibody leptospires starts and only serology will be useful in this stage for the diagnosis9.

**Ocular Leptospirosis**

Febrile illness usually lasts for about a week or two. Development of immunoglobulins in the plasma coincides with rapid immune clearance of the organisms. However, even after clearance from the blood, leptospires remain in immunologically privileged sites, including the renal tubules, brain, and anterior chamber of the eye, for weeks to months. Uveitis is an important late complication of leptospirosis. It may manifest after 2 days - 4 years of systemic infection, usually around six months. The onset and severity of leptospiral uveitis is variable, the severity does not correlate with the severity of systemic disease. It may occur as single or recurrent episodes. Leptospiral uveitis manifests as either anterior or diffuse uveitis. Anterior uveitis is usually insidious and mild in contrast to acute and relapsing pan uveal inflammation5-9. The spectrum of clinical manifestation of ocular leptospirosis includes,

• Interstitial keratitis
• Non granulomatous Iritis
• Hypopyon
• Cataract
• Vitreous cells
• Membranous vitreous opacities
• Papillitis
• Retinal vasculitis
• Cranial nerve palsies

Leptospiral uveitis is one of the common causes of hypopyon in leptospiral endemic areas. Although rare, pearly white, rapidly progressing cataract may be seen in leptospiral uveitis10. The posterior uveal involvement is more characteristic, vitreous reaction may be of grade one to four; vitreous exudates and veil like membranous vitreous opacities are the hallmark of the disease. They may persist for several months, even after the patient regains visual acuity of 6/6. Hyperemic disc and optic neuritis are more common than cranial nerve paresis, which involves third, fourth, sixth, and seventh cranial nerves. Retinal vasculitis with perivascular sheathing of the vein is commonly seen in leptospiral uveitis, however occlusion and neovascularisation are not common. Differential diagnosis of leptospiral uveitis include,

• Uveitis associated with ankylosing spondilitis
• Behcets syndrome
• Sarcoïdosis
• Endogenous endophthalmitis
• Acute retinal necrosis

Patients presenting initially with unilateral uveitis with hypopyon and arthralgia can be misdiagnosed as HLA B27 associated uveitis and/or Behçet’s disease. Severe vitreous reaction, vasculitis and hyperemic disc can differentiate leptospiral uveitis from HLA B27 uveitis. Onset of Leptospiro uveitis is acute and of shorter duration, while Behcets uveitis is chronic, recurrent and insidious5. In addition, patchy perivasculitis is characteristic of leptospiral uveitis , in contrast to Behçet’s vasculitis which is often occlusive. Although the fundus pictures of sarcoidosis very closely mimic leptospirosis, sarcoidosis is a chronic granulomatous uveitis with ocular features which can be differentiated from the acute non-granulomatous uveitis of leptospirosis. Syphilis, Lyme disease and leptospirosis are differentiated with the help of history of exposure to their respective risk factors and by specific serology. Rarely endogenous endophthalmitis can be mistaken for leptospiral uveitis and vice versa in tropical countries, specifically when the patient gives a history of systemic febrile illness prior to ocular disease5-9.

**Diagnosis**

A high index of suspicion, exposure history and appropriate laboratory test are critical for confirmation of clinical diagnosis. Definitive diagnosis of systemic leptospirosis is possible only on isolation of the organism from the body fluids such as blood, urine or CSF. Isolation is possible during the early stage of illness, but successful only in 50% of cases 1-4,11,12. Antibodies are detectable after one or two weeks. The Micro Agglutination Test (MAT) is currently considered as the gold standard serological test where motile bacteria in liquid medium are treated with the titrated amounts of patients serum 1, 4. When the serum contains
antibodies, agglutination occurs and can be seen under dark field microscopy. This test is highly specific even in endemic populations. However IgM-ELISA is commercially available and is less labour intensive than MAT. Diagnosis of systemic Leptospirosis is considered confirmed when there is a fourfold or greater increase in leptospira agglutination titer between acute and convalescent-phase serum specimens. The diagnosis is considered probable, if the clinical picture is compatible with leptospirosis and an agglutination titer is greater than or equal to 1:200 dilution. Enzyme-linked immunosorbent assay, Indirect Hemagglutination, Dot-blot, and Lateral flow are other serologic tests on solid-phase assays, but has lower sensitivity compared to MAT.

**Treatment**

Early initiation of appropriate antimicrobial therapy in combination with supportive therapy reduces the mortality. Leptospires are sensitive to most antimicrobial agents including penicillin, amoxicillin, doxycycline and ceftriaxone. In practice, in severe systemic leptospirosis, intravenous penicillin G is administered at 1.5 million units every 6 hours for one week. Doxycycline may be given in doses of 100 mg twice daily for one week for mild to moderate cases. Steroids are the mainstay of treatment for leptospirosis uveitis. The preferred mode of delivery depends upon the severity, laterality and anatomical location of inflammation.

**Prognosis:** The mild forms of systemic leptospirosis are much more common than the severe forms and most patients with the mild form tend to recover within 1-2 weeks. The mortality due to leptospirosis varies from less than 1% to more than 20%. Fatal outcome is mainly related to renal failure. Leptospiral uveitis carries very good prognosis.

**Risk factors include:**

- Occupational exposure - rice field workers, mining ranchers, abattoir workers, veterinarians, sewer workers, and military personnel
- Recreational activities - fresh water swimming, canoeing, kayaking, and trail biking in warm areas
- Household exposure -- Infestation by infected rodents and exposure to infected pet dogs, domesticated live stock

**Prevention**

No vaccine is available for prevention of infection. Prophylactic antibiotic has a role depending upon the settings. It is beneficial for short termed, well defined exposures such as those involved in military training or recreational sports like swimming etc. Long term antibiotic therapy is not well established to work in high transmission endemic setting. General measures such as rodent and their infection control, self sanitation approach, avoidance of contaminated water reservoirs may be of use. However long term and strict maintenance for such measure is difficult to practice in tropical countries.

**Take Home Pearls**

- Ocular signs are variable and mimic other uveitis entities, which makes the diagnosis difficult.
- Commonly presents as unilateral or bilateral acute, non-granulomatous pan uveitis
- Important clinical signs include hypopyon, optic disc edema, retinal vasculitis and membranous vitreous opacities.
- Although the systemic morbidity is high, leptospiral uveitis carries good prognosis.

**References:**

1. Vinetz JM; Leptospirosis; Current Opinion in Infectious Disease 1997; 10: 357-361.
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Fig 1: Hypopyon in leptospiral uveitis

Fig 2: Rapidly maturing cataract with hypopyon in a young women with leptospiral uveitis

Fig 3: Disc oedema with vitreous veil attached to the disc

Fig 4: Leptospiral retinal vasculitis