Ocular Manifestations of Leptospirosis

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ABSTRACT

Leptospiral uveitis is a common entity in tropical countries. Ocular manifestations are noted in the second phase of illness, but these remain under-diagnosed mainly because of the prolonged symptom-free period that separates the systemic manifestations from detection of ocular manifestations.

Varying ophthalmic presentations and the intrinsic nature of different types of uveitis to mimic one another also challenge the accuracy of the diagnosis. Of the individual ocular signs, the combination of acute, non-granulomatous, panuveitis, hypopyon, vasculitis, optic disc edema, membranous vitreous opacities and absence of choroiditis or retinitis have high predictive value for the clinical diagnosis of leptospiral uveitis. Geographic location of the patient, occupation, socio-economic status, risk factors related to exposure, past history of fever or jaundice also aid in diagnosis.

Steroids are the mainstay of treatment for leptospiral uveitis. Depending upon the severity and anatomical location of inflammatory lesion, topical, peri-ocular and/or systemic steroids are given. The prognosis is generally good, even when the inflammation is severe.

Leptospirosis, Borreliosis, and Syphilis are three important spirochaetal diseases, which can cause systemic infectious disease and after a latent period they result in uveitis, an immunological disorder. [1,2] Leptospires are very thin, spiral-shaped, tightly coiled, gram-negative aerobic, spirochetes with a unique flexuous type of motility. The genus is divided into two species: the pathogenic leptospires, L. interrogans and non-pathogenic leptospires, L. biflexa. Infected rodents and other animals pass the bacteria in their urine contaminating the soil and water reservoirs. They enter the humans through an intact mucosa or abraded skin, resulting in a bacteraemia, disseminating into various organs such as the kidneys, liver, lungs, heart and the central nervous system. A febrile illness, headache, severe fatigue and muscle pain may be the clinical features of the leptospiremic acute phase; however the severity of fever varies from asymptomatic presentation to mild, moderate or severe form and is not sufficiently characteristic for an early diagnosis. [1,3] After 4 to 7 days of the initial bacteraemia, the leptospires are rapidly eliminated by the immune system from all host tissues except from immunologically privileged places like the brain and eyes. This results in immunological diseases like uveitis, which may manifest after 2 days - 4 years after the systemic infection. Usually, uveitis begins around three to six months after the initial leptospiral illness. [2,4-7]

Ocular involvement is seen both in the systemic bacteraemic phase as well as in the immunological phase. The incidence of ocular signs during acute systemic phase varies from 2% to 90%. However, in some instances, the ocular manifestations may be sub-clinical or of such low order as to be overlooked; they are usually found by those who search for it. [2,8-11] During this stage one may also see conjunctival congestion without any conjunctival discharge, chemosis, and sub-conjunctival haemorrhage. Presence of yellow sclera and circum-corneal congestion is regarded as pathognomonic sign of severe systemic leptospirosis. Martins reported a high incidence of additional ocular signs in the acute phase of leptospirosis including optic disc oedema, retinal vasculitis, retinal haemorrhage and hard exudates. None of these patients with leptospirosis had uveitis in the systemic phase. [9]

Uveitis is a potentially blinding inflammatory disease of the eye and it includes a large group of diverse etiologies. [11-13] Leptospiral uveitis was first reported by Weil in 1866 in his original article and subsequently, several authors found its varying presentations. [7-32] The precise incidence of uveitis in systemic leptospirosis is not known and it ranges from 3% to 92%. [1] European authors reported an incidence of 10% to 44%, while Brand and Heath reported figures of 13% and 2% from Israel and the United States, respectively. [12,21] In a uveitis clinical set up, Vassilev, as cited by Duke Elder, reported leptospiral uveitis to contribute to 10% of all uveitis cases. [21] But the incidence probably depends largely on the awareness with which the ocular signs are searched for. [36] Although it is one of the common entities in tropical countries, it remains under diagnosed. The prolonged symptom-free period between the systemic and ocular manifestations makes it difficult for the ophthalmologist...
to link uveitis to leptospirosis. Lack of laboratory facilities further challenges the accuracy of the diagnosis. Sturman et al. in their exhaustive review of related world literature have cited numerous reports of leptospiral uveitis, and have identified a broad spectrum of clinical manifestations that includes iritis, iridocyclitis, papillitis, membranous vitreous opacities, vasculitis and panuveitis. Edward, Feigh, Woods, Duke Elder, and others also have contributed informative and extensive descriptions of leptospiral uveitis. Two recent studies from South India have identified non-granulomatous uveitis, hyppopyon, cataract, vitreous inflammatory reaction, retinal vasculitis and papillitis as more common ocular manifestations of leptospirosis [Table 1].

Leptospiral uveitis commonly affects the young and middle-aged patients, men more often than women, mainly because of the increased chance of exposure to leptospirosis-contaminated water or soil. It may occur as single, self-limited or recurrent episodes. Bilateral and unilateral presentations are found to be equally prevalent. The primary anatomical location of inflammation is either the anterior segment or panuveitis involving anterior, middle and posterior segment of the eye. Doret classified leptospiral uveitis into a mild anterior uveitis and a severe panuveitis with noticeable vitreous opacities. Anterior uveitis is usually insidious and mild in contrast to pan-uveal inflammation, which may be acute, severe and relapsing. The onset and severity of leptospiral uveitis is variable, with its severity not necessarily correlating with that of systemic disease.

Slit lamp bio-microscopic examination of the anterior segment of the eye revealed the presence of inflammatory cell collection or non-granulomatous keratic precipitates (KPs) at the back of the cornea. Like Fuch’s heterochromic iridocyclitis, these KPs are fine, white and often diffusely distributed on the corneal endothelium, however presence of acute circum corneal congestion, inflammatory cells and flare in anterior chamber can indicate leptospiral uveitis and differentiate this from Fuch heterochromic uveitis. Inflammatory reaction of the anterior chamber ranges from moderate to severe scale. In case of severe inflammation, the cells gravitate down to form hyppopyon. Hyppopyon has been noted to occur in 12 % of patients with leptospiral uveitis [Figure 1]. In tropical countries, leptospiral uveitis is one of the common causes of hyppopyon uveitis in contrast to Mediterranean countries where the presence of hyppopyon usually indicates Behcets syndrome, an autoimmune uveitis. HLA B27-related uveitis is another cause for the hyppopyon, which is also common in young males and these two can be differentiated from leptospirosis with the help of history and systemic examination. Other ocular immunological manifestations include interstitial keratitis, which was seen in 18% of patients. Similar corneal lesions were also seen in equine recurrent leptospiral uveitis of horses.

Cataract is a well-recognised complication of uveitis and the steroid treatment of uveitis. Once the inflammation is controlled, a majority of uveitic cataracts remain stable or progress only slightly. In a previous study 14% of patients with sero-positive leptospiral uveitis developed cataract, of them 76% of the patients had visually significant cataract on their first visit even before the steroid treatment. The spontaneous absorption of opacified lens material is rare except in patients with traumatic cataract, congenital rubella and in age related leaking Morgenian cataract. Holloway and Gowen reported a case of spontaneous absorption of cataract. The patient also had vitreous veils and vitreous opacities. However etiological diagnosis of uveitis was not known. Progression of cataract in leptospirosis was rapid in these young patients and the lens material was found absorbed in 2.5% of patients with leptospirosis. There is a single case report from the United States of a missing lens nucleus in a 31-year-old patient who suffered from leptospiral uveitis. Horses are well recognised to develop severe uveitis associated with rapid cataract formation in the setting of equine recurrent leptospiral uveitis. Laboratory studies have demonstrated the presence of anti-Leptospira serum antibodies in these horses that react with lens antigens, suggesting the presence of an antigenic relationship between the lespories and lens antigens; the mechanism of cataract formation in human is not known. The leptospiral uveitis usually responds promptly to treatment and cataract removal and intra-ocular lens implantation result in complete recovery of vision.

The posterior uveal involvement appears to be more characteristic—inflammatory cell collection in vitreous is an important clinical sign. In fact, Sturman uses different terminology to denote the viritis, including vitreous floaters, exudates, precipitates and vitreous membranes. All these observations were also noted in the recently published large series of leptospiral uveitis from south India: 76% of cases were found to present with significant vitreous reaction. Vitreous inflammatory cells may be of grade one to four, they may aggregate to form vitreous exudates floating in vitreous. In some of these patients, these vitreous exudates were arranged in a linear pattern resembling a string of pearls, as seen in sarcoid uveitis. In the severe form of the disease, so-called vitreous precipitates or inflammatory cell collections at posterior vitreous face were seen. Parsplana snow balls can also be seen. Initial transient clouding of the vitreous with inflammatory cells may be associated with the formation of peculiar membranes. These vitreous veil-like membranous opacities are either attached
to the disc or they freely float in the vitreous.\textsuperscript{6,7} [Figure 2]. Feign and Doret described membranous vitreous opacities to be the hallmark of the disease.\textsuperscript{3,18} These membranes may persist for several months, even after the patient regains visual acuity of 6/6.\textsuperscript{10,41} In spite of severe grade III or IV vitreous infiltration, on presentation, when the inflammation gets under control, marked clearing of inflammatory cells is possible; the total permanent opacification vitreous is rare in leptospiral uveitis.\textsuperscript{3,9} Such severe vitreous inflammatory reaction may also be seen in other uveitis including toxoplasmosis, sarcoidosis, acute retinal necrosis and endogenous endophthalmitis. Toxoplasmosis, sarcoidosis and acute retinal necrosis are differentiated from leptospiral uveitis with the presence of retinal and choroidal inflammatory lesions, which are absent in the latter. It is often quite difficult to differentiate leptospiral uveitis from endogenous endophthalmitis, especially when the vitreous cells measure up to 4+, as both are acute in nature and fundus in both entities are not visible on presentations.

Several investigators noted the presence of hyperaemic disc in leptospirosis\textsuperscript{2,7,16,11,27,30} and it was seen in 3% - 64% of cases of ocular leptospirosis in previous studies [Figure 3]. Levin reported a case of hyperemic optic disc with blurred margins, parapapillary venous sheathing, and vitreous haze. Fluorescein angiography revealed disc leakage and visual-evoked potential testing disclosed a delayed response demonstrating the oedema. Neuroretinitis is another clinical entity where inflammations of optic nerve and peripapillary retinal layers result in a macular star. There are several causes for neuroretinitis and the infectious causes include leptospirosis.\textsuperscript{42} Optic neuritis and retrobulbar neuritis were seen in few patients and they demonstrated colour vision defect or field abnormalities.\textsuperscript{10} Other neurological manifestations of the disease that can cause visual symptoms include encephalitis, optic neuritis and cranial nerve paresis involving third, fourth, sixth, and seventh cranial nerves.\textsuperscript{6,19,27,30} Chronic headache usually follows aseptic leptosomal meningitis. Hyperemic disc or papillitis is seen also in few other uveitic entities like VKH syndrome, sympathetic ophthalmia, multiple sclerosis, pars planitis and sarcoidosis. Absence of bilateral exudative retinal detachment or choroidal thickening of VKH and sympathetic ophthalmia, absence of CNS involvement and MRI finding of multiple sclerosis, absence of characteristic chronic snow banking of pars planitis, absence of bilateral granulomatous uveitis of sarcoidosis help the clinician to rule out these entities when a patient with leptospiral uveitis presents with disc oedema.

Vasculitis of renal vessels and cerebral pan arteritis, have been reported in systemic leptospirosis.\textsuperscript{43,44} Likewise, retinal vasculitis was seen in 4.8% to 51% of patients with leptospiro uveitis [Figure 4]. It mainly affects the veins and 1% of them also had arteritis.\textsuperscript{7,31} Other common causes of uveitis with reti-
nal vasculitis are Behcet’s syndrome, sarcoidosis and Eales’ disease. Behcet’s vasculitis is occlusive in nature; the optic disc becomes pale during its chronic course. However, the retinal vasculitis of leptospirosis is of perivasculitis type, vascular occlusions and optic atrophy are not seen in this entity. Eales’ disease is characterised by the absence of uveal inflammation, neo-vascularisation and recurrent vitreous haemorrhage while in leptospiral uveitis, uveal inflammation is the predominant feature and it neither causes neovascularisation nor recurrent haemorrhage. In general, vasculitis of leptospiral uveitis responds well to steroid treatment. [7] The studies on pathogenesis of vascular damage in experimental leptospirosis in the guinea pigs revealed evidence of swollen endothelium, dilated endoplasmic reticulum and enlarged mitochondria; open junctions seemed to be the initial lesions followed by endothelial necrosis. [8] The exact mechanism of vascular involvement in humans is not known.

**Differential diagnosis**

Although leptospiral uveitis is one of the common entities, it remains underdiagnosed mainly because of protein manifestations of both systemic as well as ocular presentations. Further the notorious ability of uveitic entities to mimic each other creates a diagnostic challenge. Other non-granulomatous uveitis entities that can mimic leptospiral uveitis are uveitis associated with ankylosing spondilitis and Behcets syndrome. Both of them may present with a non-granulomatous hypopyon uveitis, in young male patients, with or without arthralgia. However, the systemic history can help in differentiating these disorders; moreover the Behcet’s syndrome has a chronic and insidious course while leptospiral uveitis is acute on its presentation. As far as the posterior segment is concerned, the disc oedema, vitreous reaction and vasculitis of leptospiral uveitis closely mimic the uveitis of sarcoidosis. Here again the sarcoidosis is a chronic granulomatous uveitis and can be differentiated from acute non-granulomatous uveitis of leptospiro­sis. Endogenous endophthalmitis can rarely be mistaken for leptospiral uveitis and vice versa, specifically when the patient suffered from a febrile illness and was treated with intravenous fluids; both these histories are known risk factors for leptospiriosis and endogenous endophthalmitis, respectively. The laboratory work including Microscopic Agglutination Test (MAT) for leptospirosis, blood and vitreous culture for other bacterial and fungal causes of endogenous endophthalmitis will help in the definitive diagnosis.

**Laboratory techniques**

Confirmation of clinical diagnosis of leptospirosis relies on laboratory testing specifically when the clinical signs are not pathognomonic. In the case of systemic leptospirosis, isolation of the organisms confirms the diagnosis. However, ocular manifestations occur in the immune phase after a symptom free latent interval challenging the isolation techniques. The attempt to isolate the organisms from ocular fluids has rarely succeeded in human beings, [17] although several investigators isolated the leptospires from aqueous fluid and vitreous of horses. [16, 47] MAT is currently considered a gold standard test. However, methodological complexities, including the requirement for a continuous supply of live organisms, high specificity for individual sero-groups leading to false negativity, and subjective errors in the reading limit its use in several ophthalmic hospitals. The results of MAT have to be considered carefully as it may offer a false negative result if the infecting serovar is not present in the panel. A false positive result may occur due to the presence of residual antibody in endemic areas. [9] In this test 12 to 18 serovars that are known to be common in a geographic area are included in the panel. The motile bacteria in liquid medium are treated with the titrated amounts of patients serum and it is examined under dark field microscopy. When the serum contains antibodies, agglutination is seen under dark field microscopy. Analysis of paired serum is recommended, either seroconversion or a four-fold or greater rise in antibody titre is considered diagnostic for systemic leptospirosis, whereas in the chronic stage or in ocular leptospiriosis, a titre above 1:100 dilutions is taken as significant. [48] Other commercially used tests which use the cross reacting antigens are ELISA, macroscopic agglutination, indirect haemagglutination, lepto dipstick, microcapsule agglutination tests, and lateral flow assay. [1, 3, 4, 9] Several studies are being done to find out better antigen and to improve serological methods. Recently lipoprotein L 32 and an LPS antigen have been identified as important serological markers. [9, 50] Molecular techniques such as PCR based method are also under evaluation for rapid identification. [51, 52]

**Pathogenesis of leptospiral uveitis**

Leptospiral uveitis is a widespread disease that affects humans as well as domestic and wild animals. Pathological study in human ocular tissues in this disease is not yet available. [1, 3, 6] however extensive studies are available in veterinary science. Horses infected with *Leptospira* present with several ocular manifestations, including recurrent iridocyclitis also known as periodic ophthalmia or moon blindness or equine recurrent uveitis (ERU). Ocular signs in horses include blepharospasm, lacrimation, corneal edema, corneal opacities, hypopyon uveitis, vascularisation, retinal detachment, cataract formation and lens dislocation. The common endpoint of ERU is blindness. Several investigators isolated leptospires from vitreous samples of horses that suffered from equine recurrent uveitis. [9] The rabbit eye model for leptospiral uveitis revealed early vitreous invasion by neutrophils, macrophages, plasma cells and lymphocytes in 10 days and the antibody formation appeared after the 14th day. The appearance of antibodies in the aqueous humor coincided with the appearance of intra-ocular plasma cells. Severe and acute fibrinous uveitis was noted on re-infection. [15] Gsell demonstrated a significant amount of antibodies for *Leptospira pomona* in aqueous suggesting a possibility of local antibody production. [13] Based on the presence of local antibody production, ERU is believed as an organ-specific autoimmune disease. Kalsow reported immuno histopathological studies on acquired and experimentally induced leptospiral uveitis in horses. The study recognises the disease as a distinct subset of equine uveitis of post-infectious immuno-pathogenesis; it also emphasises a possible relevance to human uveitis. [54] A study by Parma et al, used the immuno-
blotting technique, to bind serum antibodies from horses, immunised with leptospiral serovars with antigenic fractions from both the comma and lens of the horses. The study hypothesised an antigenic mimicry between leptospiral proteins and horse ocular antigens.\textsuperscript{40} This antigenic mimicry was suggested as a possible cause for recurrent uveitis in horses. Of note the DNA sequence related to the antigen mimicry was detected in pathogenic serovars, and not in non-pathogenic serovars.\textsuperscript{45} Molecular studies on human eyes are not yet available.

### Complications

When uveitis is transient, complete healing is the rule, but in cases with severe inflammation, cataract and occasionally steroid induced glaucoma complicate the prognosis. Cataract extraction with intraocular lens implantation and anti glaucoma treatment carries good prognosis.\textsuperscript{7,10}

### Treatment

Treatment with anti-microbial agents (for example, Penicillin, Amoxyccillin, Doxycycline or Ceftriaxone) is indicated in systemic leptospirosis early in the course of the disease, and intravenous Penicillin or Ampicillin is used in severe systemic illness.\textsuperscript{5,56} Steroids are the mainstay of treatment for uveitis. Depending upon the severity, laterality and anatomical location of inflammation, topical, periocular and systemic steroids are given.\textsuperscript{7} It is not known whether the systemic antibiotic treatment during the systemic phase has any protective role on long-term complications like uveitis and there is no double blind study on the need for additional antibiotic treatment in leptosporial uveitis.

### Conclusion

Leptospirosis has a worldwide distribution. Diagnosis of systemic leptospirosis is often missed at peripheral centres; subsequently the uveitis is misinterpreted as idiopathic uveitis by the ophthalmologists. There exists a definite possibility of underestimating the incidence of uveitis associated with leptospirosis. If the diagnosis is misinterpreted, young patients with hypopyon uveitis with a history of joint pain (during systemic leptospirosis) may mislead the ophthalmologist to diagnose other uveitic entities that are associated with arthralgia such as Behçet’s syndrome or HLA B27 related uveitis. There is a definite need for development of clinical prediction rules to detect the initial ocular presentation of leptosporial uveitis and more specific and accessible molecular methods to confirm the clinical diagnosis.

### References