

Original Article

Leptospiral uveitis: A late complication of systemic leptospirosis

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Background and objectives: Leptospirosis is an important animal borne disease that primarily affects farmers in tropical countries. As a late complication, it causes ocular inflammation, uveitis. We are presenting ocular signs of leptospiral uveitis.

Methods: In this retrospective observational study, we have reviewed the data from clinical and laboratory records of microscopic agglutination test (MAT) positive, uveitis patients seen between 1994 and 2017 at the uveitis department of a university affiliated ophthalmology postgraduate institute in Tamil Nadu, South India.

Results: Out of a total of 75,150 new uveitis cases with different aetiologies seen in 24 years, 3,658 (4.9%) had clinical diagnosis of leptospiral uveitis. Of them, 1,268 (34.7%) patients were positive for leptospiral serological test. Of them, follow-up details were available for 876 patients. Of 876, 650 (74.2%) were men, 482 (55%) were farmers. 1224 eyes of 876 patients were found to have uveitis. The most common ocular signs were vitreous membranous opacities seen in 814 eyes (66.5%) followed by retinal phlebitis in 347 (28.4%), optic disc hyperaemia in 260 eyes (21.2%), and hypopyon in 208 eyes (17%). Active choroiditis/retinitis were never seen. Topical, oral or periocular steroid injections were used to treat uveitis. Inflammatory control was achieved in 96% of the patients. Two or more-line visual improvement was seen in 700 out of 740 (94.5%) eyes.

Interpretation and conclusions: Ocular involvement is an important immunological complication of systemic leptospirosis. Recognition of this entity is vital, especially in young males in whom other immunological uveitis are also common.

Keywords Hypopyon; Leptospiral uveitis; Ocular leptospirosis; Retinal vasculitis; Vitreous membranes

Leptospirosis is a common animal borne, tropical disease, with an estimated annual global burden of nearly 1 million patients and 60,000 fatalities.¹ In the last two years, new outbreaks have been reported even in temperate climate.^{2,3} However, the definitive diagnosis of leptospirosis remains challenging because of varying clinical manifestations. Apart from fever, leptospirosis can involve any organ or multi organs, presenting with varying clinical manifestations, making the diagnosis a challenge. The diagnosis is often missed unless the physician includes leptospirosis in the differential diagnosis and investigates to confirm.⁴ After three to six months of systemic leptospirosis, the patients develop late ocular complications, such as uveitis.⁵⁻⁷ Primarily patient fails to give the history of a fever that occurred 3-6 months prior to eye problem. And there is no etiological diagnosis in their medical report even if they had one. Hence ophthalmologist

fails to give importance to the past history of fever. Additionally, the uveitis presents with varying severity and clinical signs either in one or both eyes, either as anterior uveitis or pan uveitis. Consequently, the ophthalmologist too fails to add leptospirosis in their differential diagnosis. Thus, ocular complications of systemic leptospirosis are underdiagnosed to a great extent. This paper presents ocular manifestations of 1224 eyes of 876 serology positive patients with leptospiral uveitis seen between 1994-2017.

Methods

We carried this retrospective observational analysis at the department of Uveitis, Aravind Eye Hospital and postgraduate institute of ophthalmology affiliated with The Tamil Nadu Dr. M.G.R. Medical University, Tamil Nadu, India. The study analysed ocular presentation,

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treatment details, visual status before and after treatment, and recurrence rate. Institutional review board approval was obtained for retrospective analysis of all patients. Patient's consent was obtained to use the clinical data anonymously. Data were entered initially in Foxpro followed by MS Access. Same data entry operators entered all the data. Data cleaning were carried out regularly. The STROBE⁸ (Strengthening the Reporting of Observational Studies) guidelines are used in this paper and the checklist is included as **Supplementary Table I**.

Inclusion and exclusion criteria: As per the literature,⁵ patients who presented with acute anterior or pan uveitis with hypopyon, retinal vasculitis and or floating vitreous membranes with past history of fever were subjected to micro agglutination test (MAT). Patients who tested positive were included.

Clinical work up: The clinical diagnosis was arrived on a complete evaluation of the patient's past and present history, exposure history to risk factors and ocular symptoms and signs. Slit lamp examination was used to examine the anterior segment inflammation. Posterior segment was examined with indirect ophthalmoscope.⁹ Laboratory tests were done to rule out other causes as needed. Demographic details, history and ocular findings were documented. Two uveitis specialists studied all case sheets independently, any discrepancy raised was resolved by a third uveitis specialist. Inter-observer agreement between the two reviewers were assessed using Cohen's kappa for categorical variables and the Intraclass correlation coefficient for continuous variables. The overall kappa values ranged from 0.86 to 0.94, indicating excellent agreement, and ICC values ranged from 0.88 to 0.97, indicating high reliability. There were two data entry operators. To minimise data entry errors, we implemented regular training and employed double data entry with automated validation checks. Periodic audits ensured consistency across the dataset.

Serological tests for leptospirosis: Two mL of serum from clinically diagnosed cases of leptospiral uveitis was stored in a -80°C deep freezer. Initially, MAT was performed at a regional laboratory at the Tamil Nadu Veterinary College, Chennai, (1994)⁶ and at the Leptospirosis Reference Laboratory at the Centers for Disease Control and Prevention (CDC), USA (1994–1997).⁷ Subsequent samples were tested at the Indian National Leptospirosis Reference Laboratory (NRL) in Andaman (1998). Later with the help of WOTRO-grant id: WM-93- 370, a regional leptospirosis

laboratory was started at our center, with 21 serovars. MAT was performed as per the standard technique of Kmety and Dikken.¹⁰ The results were confirmed by a research associate trained in Royal Tropical Institute. A titer ≥ 1 in 100 dilution was counted positive for the infecting serogroup.¹⁰ Since 2005, the condition of leptospiral cultures was annually evaluated through the International Leptospirosis MAT Proficiency Testing Scheme performed by Royal Tropical Institute.¹¹

All uveitis patients were treated with topical, oral or systemic steroids based upon the inflammatory status. As it is late immunological complication, they were treated only with steroids, antibiotics were not given. Average duration of this uveitis was only one to 3 months. Steroids were given only till the inflammation was active. Vision and inflammatory control were recorded before and after treatment. As per standardisation of uveitis nomenclature for reporting clinical data, changes in best corrected vision were defined as Improved (increase of 2 lines in Snellen Chart), Stable (with in one line), or Worse (loss of 2 or more Snellen visual acuity chat).⁹

Statistical analysis: Frequency (percentage) and mean (standard deviation) were presented for all demographic and clinical characteristics as appropriate. Visual acuity (VA) was converted to logarithm of minimum angle of resolution (Logmar units). Shapiro-Wilk test was used to assess the normality of the data. Wilcoxon Signed rank test was used to compare VA from baseline to post-treatment. Chi square test and Fisher's exact test was used to compare the proportions. Missing data were handled using imputation (predictive mean matching) and sensitivity analyses were done by complete dataset to assess the robustness of the imputed dataset. No difference in the results were found between the imputed dataset and complete dataset. Mixed linear effects model was used to compare the visual acuity between the groups adjusting for eye-level correlation. All hypotheses were tested two-sided and P -value < 0.05 was considered as statistically significant. All the analyses were done by using STATA v17.0 (StataCorp, Texas, USA).

Results

Over the course of 24 years, 3,658 (4.9%) cases had a clinical diagnosis of leptospiral uveitis and of them, only 1,268 (34.7%) patients were positive by MAT for leptospirosis. Among them, follow up details were available for 876 patients. Of 876, 650 (74.2%) were, men, 482 (55%) were farmers. 1224 eyes of 876

Table I. Demographic and clinical variables of patients with leptospiral uveitis Anterior vs. Intermediate, posterior and pan uveitis

	Overall (n=876); n (%)	Anterior uveitis (n=241); n (%)	Other uveitis* (n=635); n (%)	P value
Demographic variables (in persons)				
Age (yr)				
≤20	118 (13.5)	41 (17.0)	77 (12.1)	
21-60	731 (83.5)	139 (57.7)	376 (59.2)	
>60	27 (3.1)	61 (25.3)	182 (28.7)	0.144 [†]
Gender				
Female	226 (25.8)	69 (28.6)	157 (24.7)	
Male	650 (74.2)	172 (71.4)	478 (75.3)	0.238 [†]
Occupation				
Others	394 (45.0)	114 (47.3)	280 (44.1)	
Farmer/Other risk	482 (55.0)	127 (52.7)	355 (55.9)	0.394 [†]
Laterality (no. of persons)				
Unilateral	528 (60.3)	169 (70.1)	359 (56.5)	
Bilateral	348 (39.7)	72 (29.9)	276 (43.5)	<0.001 [†]
Duration between systemic and ocular leptospirosis				
>90 days	64 (7.3)	22 (9.1)	42 (6.6)	
≤90 days	812 (92.7)	219 (90.9)	593 (93.4)	0.202 [†]
Ocular findings (n=1224 eyes)	n=1224	n=310	n=914	
Visual acuity (in logmar units)				
Mean (SD)	0.60 (0.77)	0.65 (0.91)	0.59 (0.71)	
Min – max	0 – 3.2	0 – 3.2	0 – 3.2	
Median (IQR)	0.3 (0 – 0.78)	0.18 (0 – 1)	0.30(0 – 78)	0.954 ^a
Anterior segment				
Non-granulomatous uveitis	1169 (95.5)	290 (93.6)	879 (96.2)	0.058 ^{††}
Posterior Synechiae	248 (20.3)	69 (22.3)	179 (19.6)	0.311 [†]
Hypopyon	208 (17.0)	76 (24.5)	132 (14.4)	<0.001 [†]
Cataract	235 (19.2)	89 (28.7)	146 (16.0)	<0.00 [†]
Posterior segment				
Vitreous membranous opacities	814 (66.5)	73 (23.6)	741 (81.1)	<0.001 [†]
Vitreous cells and exudates	378 (30.9)	7 (2.3)	371 (40.6)	<0.001 [†]
Retinal Phlebitis	347 (28.4)	5 (1.6)	342 (37.4)	<0.001 [†]
Optic disc hyperaemia	260 (21.2)	8 (2.6)	252 (27.6)	<0.001 [†]
Lost to follow-up rate (n=876)	359 (41.0)	109 (45.2)	250 (39.4)	0.115 [†]

*posterior/intermediate/pan uveitis; [†]Chi square test; ^{††}Fisher's exact test; ^aMixed linear effects model

patients were found to have uveitis. Flow diagram of patient recruitment is given in **Supplementary Figure 1**. The most common ocular signs were vitreous membranous opacities in 814 eyes (66.5%), followed by retinal phlebitis in 347 eyes (28.4%) optic disc hyperemia in 260 eyes (21.2%) and hypopyon in 208 eyes (17%). Elevated intraocular pressure and cystoid macular edema were rarely seen while active choroiditis/retinitis were never seen. Topical, oral or periocular steroid injections were used to treat uveitis.

Demographic details and clinical data are given in **Table I**. Vision before and after treatment is given in **Table II**. The quality of our leptospiral culture results were found good by Royal Tropical Institute. The **Figure** presents the serovars over the 24-year period. Detailed year wise serovar prevalence is given in the **Supplementary Table II**. However, seropositivity slowly declined over years. In 2000 we had *L. louisiana*, as predominant serovar however there was big peak of negative cases in 2000 possibly due to emergence of

Table II. Comparison of visual acuity: Before and after treatment

Visual acuity (in logmar units)	Overall	Anterior uveitis	Other uveitis*	P value
Baseline				
No of eyes	1224	310	914	
Mean (SD)	0.60 (0.77)	0.65 (0.91)	0.59 (0.71)	
Median (IQR)	0.3 (0 – 0.78)	0.18 (0 – 1)	0.30(0 – 78)	0.954 ^a
Post treatment				
No of eyes	741	169	572	
Mean (SD)	0.24 (0.52)	0.25 (0.61)	0.24 (0.49)	
Median (IQR)	0 (0 – 0.3)	0 (0 – 0.18)	0 (0 – 0.3)	0.876 ^a
P value	<0.001 ^b	<0.001 ^b	<0.001 ^b	

Visual acuity improved in both the groups after steroid treatment. Group wise differences in visual acuity were not statistically significant.
^aposterior/intermediate/pan uveitis; ^aMixed linear effects model; ^bWilcoxon Signed rank test

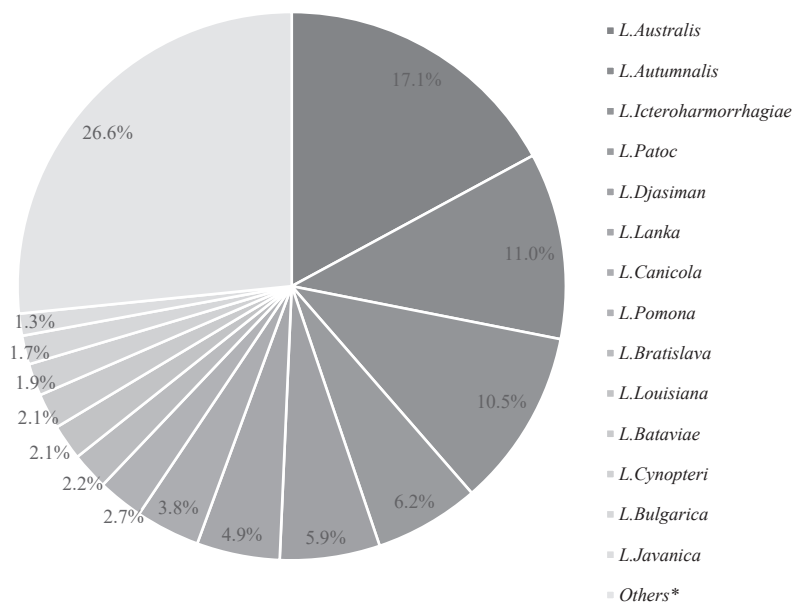


Figure. Leptospiral serovar distribution over 23 years in leptospiral uveitis patients. Serovar names are given in descending order in the figure. Here, *Others includes *L. hebdomadis*, *L. panama*, *L. hardjo*, *L. grippityphosa*, *L. sarmin*, *L. tarassovi*, *L. ballum*, *L. georgia*, *L. wolffi*, *L. shermani*, *L. andaman*, *L. celledoni*, *L. Jegthlara*, *L. medanensis*, *L. ranarum*, *L. sejroe*, *L. copenhageni*, *L. pyrogenes*, *L. robinsoni*.

other serovars which were not in our panel. A figure showing the yearly distribution and trend of serovars over 24 years is given in **Supplementary Figure 2** enabling the reader to appreciate temporal trends. Out of 876 patients, 516 (58.9%) returned for follow-up for three months, accounting for 740 eyes out of 1224 eyes. 235 eyes out of 1224 developed cataract during the course. All of them needed cataract extraction with intra ocular lens implantation. The surgical prognosis was very good. Visual acuity (VA) data was recorded for the 740 eyes with three-month follow-up. Visual recovery of these patients is given in **Tables I and II**. Stable, two or more line improvement was seen in 700 out of 740 eyes (94.5%) of eyes. None of the patient

had recurrence of uveitis. Irrespective of anterior or pan uveitis, visual recovery was good (**Table II**). As per standardised uveitis nomenclature,⁹ inflammatory control was achieved in 96% of the patients.

Discussion

Leptospiral uveitis in our study population presented with simple non granulomatous anterior uveitis or with severe pan uveitis, hypopyon, cataract, vitreous membranes, retinal vasculitis and optic disc hyperemia (**Table I**). Absence of acute retinitis and choroiditis was consistently seen in all cases; hence their presence can rule out the diagnosis of leptospiral uveitis. Cystoid

macular oedema and glaucoma were very rarely seen. Free floating membranous opacities were seen in vitreous. Rapidly progressing unilateral or bilateral white cortical cataracts in young farmers were another unique pathognomonic clinical sign. Leptospiral uveitis is widely studied and published which reveal similar clinical picture.^{5,12-25} The cataract progression was so rapid, that the cortex of the lens may get absorbed leaving the capsule intact.^{25,26} From leptospiral uveitis patients, the lens materials were gathered during cataract extraction. They showed globular degeneration of the lens fibres on haematoxylin eosin stain, while the controls showed regular uniform arrangement of lens fibres.²⁶ Leptospiral uveitis patient's serum contains antibodies that cross-react with multiple lens proteins such as retinal dehydrogenase 1 and crystallins (α -B, α -A2, β -B2). Retinal dehydrogenase 1 of human lens is homologous to the leptospiral protein, betaine aldehyde dehydrogenase. These antigens and their antibodies can act as a potential initiation for cataract formation.²⁷

Barkay *et al*¹⁵ and Sturman *et al*²⁰ have done an elaborate review on leptospiral uveitis. The article identifies a broad spectrum of clinical manifestation that includes iritis, iridocyclitis, papillitis, membranous vitreous opacities, vasculitis and panuveitis as in our study population. As in our study, Sturman classified leptospiral uveitis into a mild anterior uveitis and a severe pan uveitis with vitreous opacities.²⁰ Keratic precipitates (KPs) of leptospiral uveitis were non granulomatous in nature like in Fuch uveitis. However, KPs of Fuch's uveitis, are reported to be fine, white and diffusely distributed on the corneal endothelium without circumcorneal congestion.²¹ Hypopyon uveitis is seen also in Behcet's syndrome and in HLA B27 related uveitis. Both the entities can be differentiated from leptospiral uveitis with the help of history and systemic examination.²¹ Cataract is a well-recognised complication of uveitis. Uveitic cataracts remain stable or progress gradually. In leptospiral uveitis, rapid progression of cataract or even spontaneous absorption of opacified lens material was seen. Such phenomenon is seen only after trauma and in congenital Rubella.⁵ Initial clouding of the vitreous with inflammatory cells may be followed by the formation of peculiar membranes.¹³ These vitreous veil-like opacities are either attached to the disc or seen as free-floating vitreous membranes.²⁰ Sturman described these membranous vitreous opacities to be characteristic of the disease.²⁰ Several investigators noted the presence

of hyperaemic disc in leptospirosis. Levin Hypenemic disc or papillitis is seen also in few other uveitic entitis like, VKH syndrome, sympathetic ophthalmia, multiple sclerosis parsplanitis and sarcoidosis.²² Appropriate clinical signs and investigations can differentiate them from leptospiral uveitis.⁷ The intermittent periphlebitis of this entity is appreciably different from the occlusive vasculitis of Behcet syndrome. This picture also differs from Eales disease, which commonly manifests as a primary peripheral vasculitis without panuveal inflammation. The prognosis of vision in ocular leptospirosis is reportedly good, often with complete recovery.⁷

Limitations include, we performed MAT in different international and national laboratories initially as MAT was not available in our city before establishing our laboratory. False negativity increased by 2018 as cultures became old as they went through many subcultures.⁴

Important implications of our study is, there were sporadic reports on leptospiral uveitis from other countries and none were from India. Clinical signs of our patients allowed us to characterise the ocular leptospirosis. Specific implication of this study is to increase the awareness of ocular complications of systemic leptospirosis to general physicians and enable them to refer to ophthalmologist when their patients develop ocular symptoms.²⁸

In conclusion, leptospiral uveitis is an important delayed complication of leptospirosis. It can manifest as both unilateral and bilateral pan uveitis rather than as unilateral anterior uveitis. It should be considered in the differential diagnosis of acute uveitis in patients with past history of fever, especially when they are from endemic areas, from lower socioeconomic groups and from rural areas. These patients have a good visual prognosis. This entity should be differentiated from other severe uveitides, like Behcet syndrome, especially when it manifests with hypopyon and joint pain. Awareness of this entity has to improve.²⁸ Ocular leptospirosis has very good prognosis with topical and oral steroids.⁶

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शोध-संदेश

लेप्टोस्पायरोसिस एक पशुजनित रोग है, जो उष्णकटिबंधीय देशों में विशेष रूप से किसानों को प्रभावित करता है। इसके देर से होने वाले जटिल प्रभावों में आंखों की सूजन (यूवाइटिस) भी शामिल है। प्रस्तुत अध्ययन में लेप्टोस्पाइरल यूवाइटिस से प्रभावित रोगियों में आंखों से संबंधित लक्षणों का विवरण प्रस्तुत किया गया है। अध्ययन के निष्कर्ष दर्शाते हैं कि आंखों का प्रभावित होना, लेप्टोस्पायरोसिस की एक महत्वपूर्ण प्रतिरक्षात्मक जटिलता है। विशेष रूप से युवा पुरुषों में, जहां अन्य प्रकार के यूवाइटिस भी सामान्य हैं, इसकी समय पर पहचान अत्यंत आवश्यक है।

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