IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 24, Issue 10 Ser. 6 (October. 2025), PP 70-74
www.iosrjournals.org

Blindness In Weil's Disease - An Immunological Phenomenon

Author

Abstract
Background: *Leptospirosis is the most common zoonotic infection, frequently encountered in the tropics especially during monsoon, and less commonly in the western countries during temperate climates. This makes it essential to have a complete knowledge about the manifestations and major as well as minor complications of the disease, especially in the background of an epidemic, which has occurred multiple times in the past. It is usually transmitted via contaminated rat urine, through non intact skin and possibly intact mucosa, owing to the burrowing motility, and hyaluronidase which may be the virulence factors in play. It is a disease of epidemic potential, especially after heavy rainfall, or floods. Most patients give a positive history of contact with dirty or stagnant water, explaining why it is more common in the third world.*
Case Presentation: *A 49-year-old male, with no comorbidities, construction worker by occupation, was brought with fever, myalgia, hepatorenal dysfunction, and desaturation, and a positive history of contact with dirty water. He was clinically diagnosis as tropical fever syndrome, which was supported by a positive serology for leptospirosis. He developed rapidly progressive bilateral loss of vision during the second week of illness, which was diagnosed as optic neuropathy which is extremely rare in the setting of leptospirosis. After detailed evaluation of CSF, and serum and taking into consideration the clinical features, a diagnosis of leptospirosis related optic neuropathy was made. Though managed early with steroids, the prognosis was poor.*
Conclusion: *Acknowledging the potential of Leptospira species to produce a severe morbidity such as optic neuropathy is crucial, especially in the background of a possibility of epidemic during times of floods or heavy rainfall.*

Date of Submission: 20-10-2025 Date of Acceptance: 30-10-2025

I. Introduction

Leptospirosis, has a number of colloquial names describing the likely source of infection such as mud, swamp, Fort Bragg, etc. It is caused by pathogenic spirochete bacteria belonging to family *Leptospira*. It was first detected in the renal tissue of a victim believed to have died of yellow fever in 1907. Many cases are mild to moderate, which might not even be detected, but the more severe form known as Weil's disease is characterised by severe thrombocytopenia and bleeding, hepatic dysfunction resulting in jaundice, pulmonary hemorrhage, and renal failure, the latter of which is the most common cause for fatality. Other complications include myopericarditis and hypotension, acute respiratory distress syndrome (ARDS), pancreatitis, and Diffuse Alveolar Hemorrhage. Most ocular manifestations are uncommon such as conjunctival congestion, and subconjunctival hemorrhage, but more adverse events such as uveitis, and neuroretinitis, though rare, are possible. This also reinforces the essentiality of hygiene as well as chemoprophylaxis of the disease among manual labourers and farmers.

II. Case Report

A 49-year-old previously healthy male, construction worker by occupation, presented to the emergency unit as a referral from a secondary care centre with a history of fever, myalgia of 6 days duration, and oliguria with yellowish discolouration of eyes since past 4 days. There was history of contact with stagnant water about 10 days back, no history of animal or pet exposure, no history of PTB or contact with TB. On day 4 of the illness, he had reported to the local hospital, where he was tested positive for leptospirosis (IgM ELISA positive). He was initiated on intravenous Crystalline Penicillin and Doxycycline from the district hospital, and underwent 2 cycles of haemodialysis in view of persistent hyperkalaemia with worsening AKI and oliguria. Four bags of platelet concentrate were transfused in view of cutaneous bleed. Patient developed AF and hypotension which resolved on HD, and ECHO showed no evidence of myocarditis. He was referred to our centre in view of desaturation and worsening condition. At admission to our medical college, patient was conscious, tachypnoeic, dyspnoeic, and icteric. Bilateral crepitations were heard over basal lung fields on auscultation, with a saturation of 94% with 4L O_2, and urine output of 200ml over last 24 hours. There were ecchymotic patches over the abdomen, and petechiae

over both extremities. He was continued on doxycycline, ceftriaxone, and platelet concentrate. Patient developed abdominal pain, and pancreatic enzymes were markedly elevated. It resolved spontaneously after 48 hours of NPO and oral feeds were reintroduced successfully. CT abdomen was normal- contrast study deferred in view of AKI. On day 10 of illness, he developed hypotension and was transferred to ICU, started on inotropes, ventilatory support, and continued on Sustained low-efficiency dialysis in view of anuria and hyperkalaemia, via right IJV catheter. Repeat ECHO showed evidence of myocarditis with positive cardiac enzymes. On day 2 of ICU stay (day 12 of illness), he noticed painless bilateral blurring of vision, with no restriction of extraocular movements, which progressed to complete loss of vision over the next 24 hours. Though Putscher retinopathy was suspected, fundus was normal on direct ophthalmoscopy.

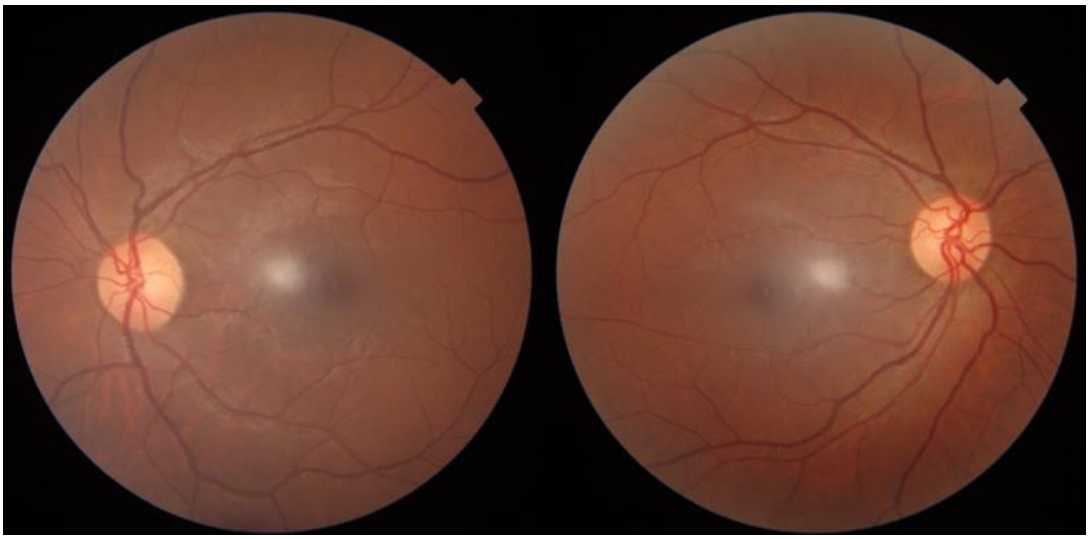


Figure 1: Fundus Photography Showing Normal Fundus (Both Eyes).

Methyl prednisolone 1gm pulse therapy was given for 5 days after hiking antibiotics to meropenem in renal adjusted dose, suspecting leptospirosis related optic neuritis. VEP was done which showed flat line. MRI Brain with orbit and optic nerves showed normal optic nerves and brain parenchyma. Workup for optic neuritis were done, including CSF study for fungal and viral aetiology which came back negative including HSV 1 and 2, VZV, HHV 6 and 7, EBV, CMV, Adenovirus, Parvovirus B19, Par echovirus, and Enterovirus, CBNAAT for tuberculosis, and VDRL. CSF Cryptococcal antigen was suspicious but India ink stain was negative. CMV IgM was borderline reactive, with negative CSF study. CSF test for common causes of optic neuritis were done came back negative for antibody to AQ-4, oligoclonal bands and oligodendrocytes.

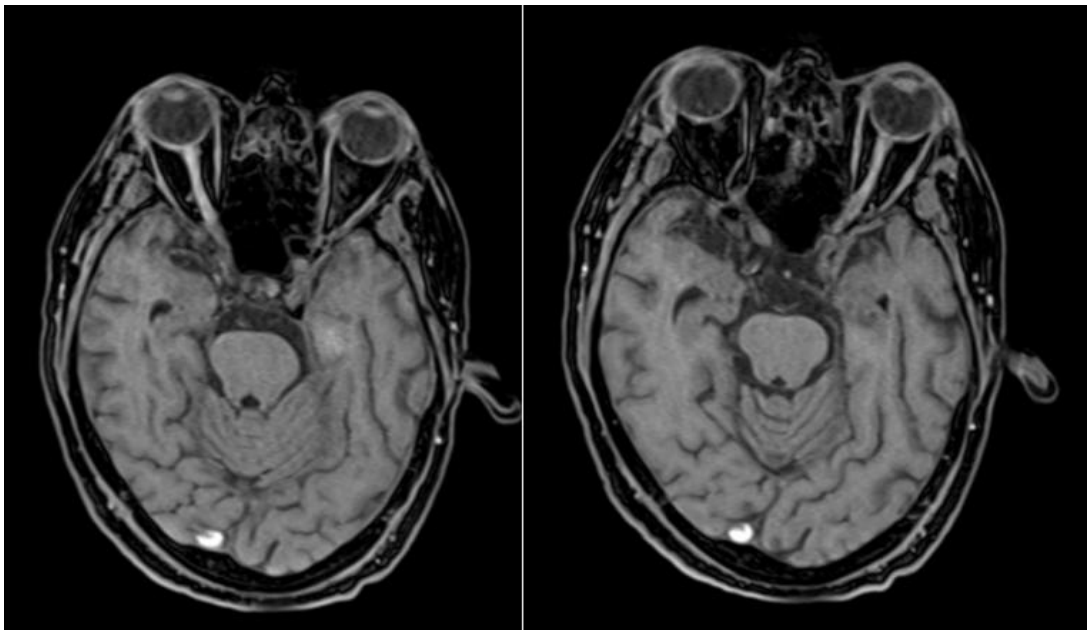
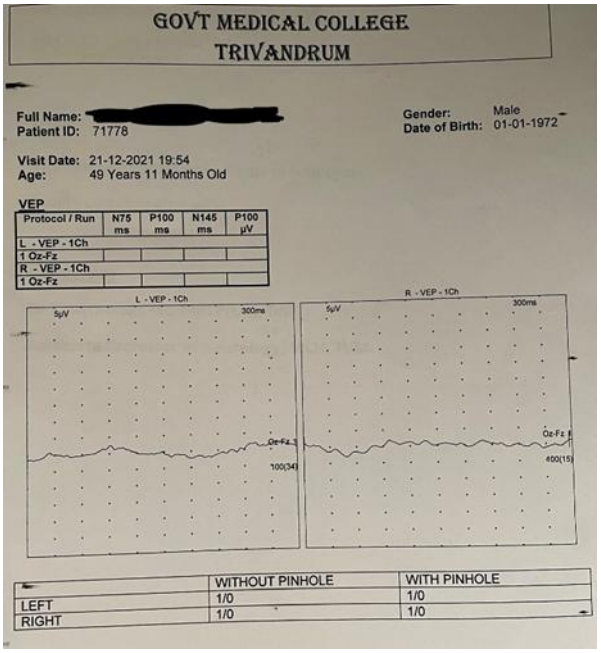


Figure 2: Mri T1 Weighted Image Showing Normal Optic Nerves.


GOVT MEDICAL COLLEGE
TRIVANDRUM

Full Name: [redacted]
Patient ID: 71778
Gender: Male
Date of Birth: 01-01-1972

Visit Date: 21-12-2021 19:54
Age: 49 Years 11 Months Old

VEP

Protocol / Run	N75 ms	P100 ms	N145 ms	P100 µV
L - VEP - 1Ch				
1 Oz-Fz				
R - VEP - 1Ch				
1 Oz-Fz				

L - VEP - 1Ch
R - VEP - 1Ch

	WITHOUT PINHOLE	WITH PINHOLE
LEFT	1/0	1/0
RIGHT	1/0	1/0

Figure 3: Visual Evoked Potential (Vep) Showing Flat Lines.

Serology was negative for toxoplasma, EBV, HSV, HIV, HBsAg, HCV, and syphilis. Vasculitic and autoimmune workup including ANA and ANCA were negative. Serology came back positive for CMV (IgM ELISA- 1.3), but was negative in CSF. He was continued on maintenance dose of steroid- prednisolone 1mg/kg/day. Repeat VEP after pulse therapy showed no improvement. Patient developed steroid induced hyperglycemia, which was controlled with insulin. A total of 12 cycles of hemodialysis was done, following which creatinine improved from 7.5 to 3.2mg/dL (no pre illness values were available to assess baseline creatinine before the illness), and urine output was maintained. Pancreatic enzymes, liver function, troponin, and CRP returned to normal. He was weaned off inotrops after 2 weeks (day 24 of illness). He developed a swelling over left forearm at the site of iv cannulation- was diagnosed with iatrogenic abscess- drained and dressing done. Steroids were continued in tapering doses, and planned to taper over the next 4-6 weeks. Two weeks post discharge, ophthalmologic evaluation showed normal fundoscopic examination and FFA with no improvement in vision.

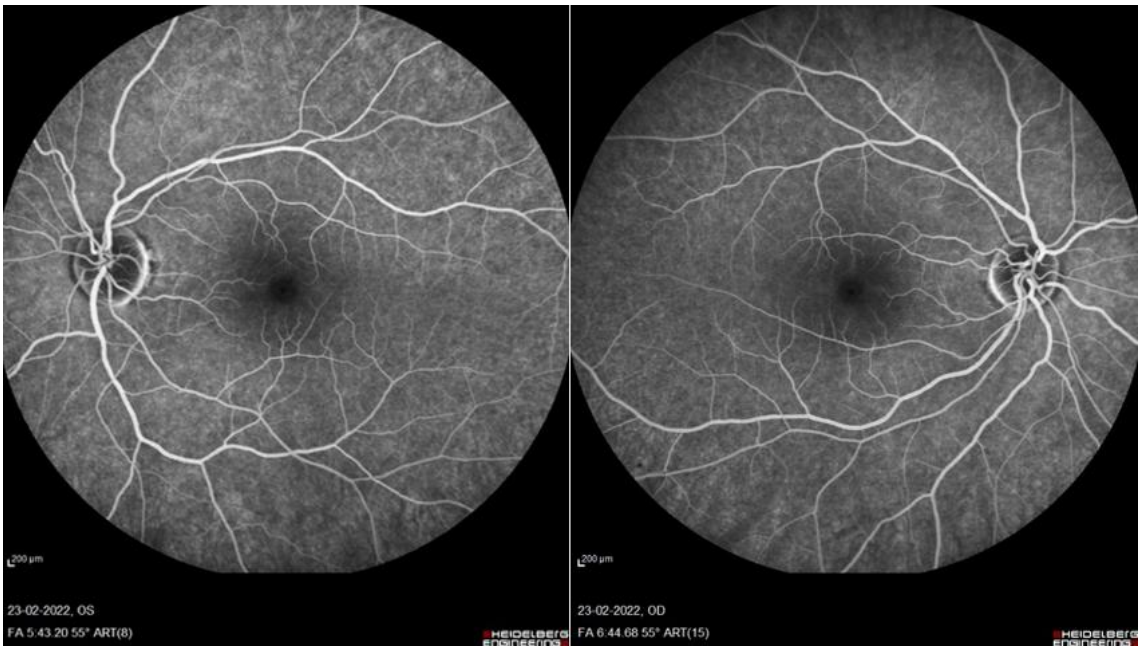


Figure 4: Fundus Fluorescein Angiography Showing Normal Vessels

Patient developed catheter related UTI, with culture growing E. coli sensitive to imipenem, which was managed with intravenous antibiotics. Patient started ambulating with support, and weekly follow up renal function tests were stable at creatinine 3.1mg/ dL. The abscess site at the hand was cared with daily dressings, and was granulating with healthy tissue, and planned for closure after 2 weeks. Five weeks after discharge, on one morning, the patient developed acute onset cough and breathlessness following which he collapsed within 6 hours, during transit to the hospital. Patient could not be resuscitated. Post mortem swab came positive for Covid 19. Autopsy was not done.

III. Discussion

This report describes a patient with optic neuropathy, secondary to Weil's disease (Leptospirosis), which was diagnosed with serology, and as a diagnosis of exclusion. Prevalence of optic neuritis in leptospirosis is low, and very rarely encountered in clinical practice, and has been reported with extreme rarity in literature. With multiple, yet rare differential diagnoses at play, the diagnosis of leptospirosis related optic neuropathy was made as a diagnosis of exclusion.

CMV neuroretinitis

Cytomegalovirus is well known to cause a characteristic cottage cheese/ pizza pie retinopathy in immunocompromised patients such as HIV. Some have isolated optic nerve involvement, which may include isolated optic neuritis [2,3], retrobulbar optic neuritis associated with meningoencephalitis and bilateral PORN (Progressive Outer Retinal Necrosis) [4], and bilateral retrobulbar optic neuritis following haploidentical hematopoietic stem cell transplantation [5]. Cases of CMV papillitis have been reported with much rarity among immunocompetent individuals. This responds readily to steroids and antivirals, when treatment is initiated early in the disease course, though prognosis maybe poor if treatment is delayed. A negative CSF study for CMV, with normal fundus examination and MRI, and negative response even after early administration of steroids makes this diagnosis least likely.

Cryptococcus related optic neuritis

This occurs mostly in immunocompromised patients, and may cause acute vision loss, as seen in our patient, or chronic vision loss. The former is attributed to direct invasion of the optic nerve by cryptococcal parasite and latter by an increased intracranial pressure during chronic therapy. [1] In immunocompetent individuals, it mostly presents acutely, as immune mediated optic nerve dysfunction, probably secondary to arachnoid adhesions causing nerve compression, oedema or inflammatory cell-mediated damage. In such cases, the associated features include cranial nerve palsies (6^{th} nerve), high cryptococcal antigen titres, optic atrophy which carrier poor visual prognosis. The absence of these features, with normal intracranial pressure and negative CSF India Ink stain and MRI Brain, in the background of a typical tropical fever syndrome makes this diagnosis less likely.

Leptospirosis related optic neuropathy- an immunological phenomenon

In the clinical setting of fever with hepatorenal dysfunction, ARDS, and myocarditis, with a history of contact with stagnant waters, in the tropics, the most probable diagnosis is Weil's disease. This diagnosis was further supported by positive serology. After the initial bacteraemic phase which presents as myalgia, persistently high fever, and vomiting, during the Immune Phase (second phase) of Weil's, meningeal, pulmonary, cardiac and hepatorenal manifestations occur. Rarely, meningitis, characterised by mild protein elevation, few lymphocytes, and normal glucose levels occur. This phase involves host immune response, which may result in immune complex mediated glomerulonephritis, and endothelial injury leading to vasculitis. Furthermore, platelets may adhere to and aggregate at the endothelium. Ocular manifestations of leptospirosis may occur in first and second phase of the disease. [6]The bacteraemic phase manifestations usually may include conjunctival congestion, subconjunctival hemorrhage, and scleral icterus. The latter phase may manifest more serious entities such as cranial nerve palsies, retinal vasculitis, non-granulomatous uveitis, keratitis, and very rarely optic neuropathy. Though vision loss is rarely encountered in Weil's disease, the occurrence of the same during the second week of illness, along with other complications of immune phase points towards a probable immune phenomenon, which may directly affect the optic nerve, or maybe secondary to a vasculitic phenomenon. The poor response to steroids despite early initiation may favour an ischemia of the optic nerve secondary to vasculitic phenomenon, rather than direct inflammatory optic neuritis, which usually responds better to steroids in neuritis of other aetiology. Though MRI Brain with orbit and optic nerve showed normal optic nerves, neuritis cannot be excluded as contrast was deferred in view of AKI. Brain parenchyma showed small nerve ischemic changes, which might be reminiscent of a vasculitic phenomenon. Since the pre illness values of creatinine was not available to assess baseline function, it could only be assumed that the renal functions were normal in the background of nil comorbidities, with normal size and corticomedullary differentiation of kidneys in imaging. Whether the worsening of creatinine, not

completely returning to normal, is also part of a similar immune phenomenon, affecting the nephrons as well as the microvasculature, synergistic to that in an immune mediated glomerulonephritis, is a mystery that shall remain unsolved, as biopsy could not be taken. Incomplete recovery of renal function and vision possibly points towards a common underlying pathology.

Another possibility is loss of vision secondary to uremic optic neuropathy, which has a much diabolic progression in acute worsening of kidney function [8]. Usually occurring secondary to chronic kidney diseases, with eGFR<12 ml/hr, it commonly affects large nerve fibres, distal, sensory and motor, and axonal. Most common cranial nerve affected is vestibulocochlear, with reversal of deafness after haemodialysis or renal transplant. The complete loss of vision despite early initiation of haemodialysis and steroid therapy makes this diagnosis highly unlikely.

Ocular and renal development during organogenesis, share many common genes, such as WT-1, BMPJ, Pax-2, and many others. This might be why many syndromes which are caused by mutations of such genes result in oculorenal manifestations. As to whether the pathogenic antigens in Leptospira such as LipL32 have a common site of infection owing to this developmental ancestry needs further studies. Another possible mechanism is that of molecular mimicry, as in rheumatic fever. [7]Leptospira antigens such as LruA and LruB share immune-relevant epitopes with eye proteins such as vimentin, which is also involved in chronic allograft nephropathy in renal transplant patients. These have been studied in Leptospira related uveitis in animal models, but studies are rare probably because of the scarcity of optic neuropathy in leptospirosis, and hence treatment always needs to be individualized, as there are no protocols for the same.

IV. Conclusion

As optic neuropathy is extremely rare, species identification might be a necessary step in patients presenting with the same. Though more common ocular and systemic manifestations of leptospirosis are mild, and reversible, rare complications such as an optic neuropathy or an irreversible kidney injury may amount to a hugely comorbid life for the patient. Hence, the knowledge of such a complication, even among the most inexperienced practitioner becomes most essential. Furthermore, patients with acute vision loss should be screened for leptospirosis, for instilling early treatment. As with any infectious disease, the importance of this entity may only be evident during an epidemic, with utmost importance to tropical countries. Leptospirosis epidemics may occur in the aftermath of floods, such as that which occurred in the state of Kerala in August 2018, which cost many lives. Acknowledgement of such rare, yet severe complications help in early recognition and treatment of the same.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.

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