Post Fever Uveoretinal Manifestations in an Immunocompetent Individual

Abstract

Background: Post fever uveoretinal sequelae (PFURS) are the various uveoretinal manifestations seen after a systemic febrile illness in an immunocompetent individual caused by bacteria, viruses, and protozoa. These may be the result of a direct invasion by the pathogen or by indirect mechanism mediated through immune mechanisms.

Method: The authors aim to review the ocular manifestations, utility of relevant diagnostic tests, management, and prognosis of PFURS. A comprehensive literature search was conducted on PubMed and Google Scholar databases with the search words “retinitis”, “choroiditis”, “neuroretinitis”, “maculopathy”, “multifocal retinitis”, “neuroretinitis”, “retinitis”, “rickettsiosis”, “typhoid”, and “West Nile”. Only articles published or translated into English language were considered. The key data were extracted, evaluated, and combined.

Results: The authors search yielded 95 articles for the period between 1986 and May 2020. Painless blurring of vision was the most common symptom. Patients can have varied posterior segment manifestations, including vitritis, focal and multifocal patches of retinitis which could be unilateral or bilateral, optic nerve involvement, serous detachment at the macula, macular oedema, and localised involvement of the retinal vessels in the form of beading of the vessel wall, tortuosity, and perivascular sheathing.

Conclusion: PFURS presents with a similar morphological pattern irrespective of the aetiology and follows a preset natural course before resolution. Treatment may or may not be required. Treating physicians need to be aware of this important ophthalmic condition even after complete resolution of fever.

INTRODUCTION

Post fever uveoretinal sequelae (PFURS) is used for describing the various uveoretinal manifestations seen 2–4 weeks after a systemic febrile illness in an immunocompetent individual with positive serology for bacteria, viruses, or protozoa. These manifestations may be the result of a direct invasion by the pathogen or by indirect mechanism mediated through immune mechanisms.
through immune mechanisms. Ocular symptoms include sudden, painless diminution of vision, black dots, flashes of light, loss of one-half of visual field, and central black outs. Patients can have varied uveoretinal manifestations including solitary and multifocal patches of retinitis, serous detachment at the macula, macular oedema, and localised/generalised involvement of the retinal vessels in the form of beading of the vessel wall, tortuosity, and perivascular sheathing and optic nerve involvement. Irrespective of the cause of the fever, clinical presentations of cases are similar with predominant signs at the posterior pole of the retina and a favourable response to steroids may suggest a possible immunological basis for this condition.

Epidemic retinitis (ER) is a retinitis post-febrile illness commonly caused by *Rickettsia*, dengue, chikungunya, West Nile virus (WNV), and several other as yet unknown organisms, generally seen in tropical countries. ER has been previously described by different authors as “post-fever retinitis” or “acute multifocal retinitis.” Herein, various pathogens implicated in PFURS are discussed. Table 1 summarises various studies in medical literature.

**VIRAL**

Chikungunya, dengue, and Zika viruses have emerged as increasingly important arboviruses that cause ophthalmic manifestations. The global expansion of these arboviruses was preceded by the global spread of their vectors. These arboviruses have common and very similar symptoms such as fever, skin rashes, malaise, headache, neutropenia, and lymphopenia. Dengue maculopathy is a common posterior segment condition and its incidence may correlate with the severity of systemic disease. Common ophthalmic manifestations include subconjunctival, vitreous, and retinal haemorrhages; anterior and posterior uveitis; optic neuritis; and maculopathies such as foveolitis, haemorrhage, and oedema. Main symptoms include blurring of vision, scotomata, metamorphopsia, and floaters.

Symptoms of dengue maculopathy start at a mean of 6.9 days after the onset of fever. Poorer visual acuity may be seen in patients with macular oedema or foveolitis, and this correlates with the severity of macular oedema. There may be presence of well-defined, yellowish subretinal lesions in the macula along with retinal striae radiating around the fovea (foveolitis). These lesions may represent disruption of photoreceptors, the outer neurosensory retina, and the inner segment/outer segment (IS/OS) junction, along with dot and blot and macular haemorrhages which corresponds to areas of scotomata.

The presence of foveolitis in patients with maculopathy was 7%. In the study by Pang and Loh, four out of six patients had bilateral disease. Some eyes had concurrent findings of superior temporal branch vein occlusion and macular oedema, while some had associated foveolitis and vasculitis suggestive of an inflammatory pathophysiology. Haemorrhagic retinopathy associated with dengue haemorrhagic fever is related to the induced thrombocytopenia. The onset of visual symptoms is usually observed within 1 day from the resolution of fever and at the nadir of the thrombocytopenia. Secondary dengue infection may manifest as retinitis with signs of microvascular occlusions in the retina. Changes such as anterior uveitis, exudative maculopathy, choroidal effusion, Roth spots, vasculitis, exudative retinal detachment, and panophthalmitis are rare. Mean complement C3 levels were lower in subjects with dengue maculopathy than in those without. The appearance of maculopathy 1 week after onset of fever suggests that dengue maculopathy is the result of an immune-mediated process and not a direct consequence of viral invasion of ocular tissue. Acute macular neuroretinopathy (AMN) has been recently reported to be an unusual manifestation of dengue maculopathy. AMN presents with hyper-reflectivity of the outer retina (outer plexiform layer and outer nuclear layer), and disruption of ellipsoid zone, external limiting membrane, and interdigitation zone.

Fundus fluorescein angiography is a useful imaging modality to determine the extent and severity of retinal manifestations such as maculopathy and retinal vasculitis. Foveolitis appears as retinal pigment epithelial hyperfluorescence that appears in the early phase and persists till the late phase.
Table 1: Summary of the case report/series published in the medical literature.

| Paper                  | Design          | Number of cases | Age/sex       | Interval between fever and ocular symptom | Infection      | Ocular symptoms                                      | Ocular signs                                                                 | Investigations                                                                 | Treatment                          | Follow-up | Outcome                                                                 |
|------------------------|-----------------|-----------------|---------------|--------------------------------------------|----------------|-----------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------|-----------|-------------------------------------------------------------------------|
| Lalitha et al., 2007   | Case series     | 37              | M:F 21/16     | 33 days                                    | Chikungunya    | Photophobia, retrobulbar orbital pain, and conjunctivitis. | Granulomatous and nongranulomatous anterior uveitis, optic neuritis retrobulbar neuritis, dendritic lesions, and retinitis. | Single positive IgM chikungunya serologic test by ELISA.                        | Topical and systemic steroids      | 3 months  | VA improved in 11 patients, remained same in 12, and worsened in 3.     |
| Relhan et al., 2014    | Case report     | 27-year-old M   | 6 weeks       | Decreased vision 4 weeks after the onset of treatment, BCVA 20/125 N36 RE and 20/20 N6 LE. Grade 1 RAPD in the RE. Defective colour vision in the RE. | Typhoid fever  | RE clear media with slight disc pallor with area of vasculitis superior to disc associated with multiple whitish fluffy areas of deep retinitis and a large NSD in the macular area. LE clear media, normal disc and foveal reflex, one discrete CWS superior to the disc, and a nasal area of retinal venous sheathing. | RE highly reflective and disorganised inner retinal layer with back scattering and underlying serous retinal detachment on OCT. Negative for HIV, tuberculosis, syphilis, connective tissue disorders, SLE, and rheumatoid arthritis. | Prednisolone (1 mg/kg body weight/day). Steroids were tapered over 2 months with regular monitoring. | 6 months  | BE Complete resolution of all retinal lesions with pigmented changes. Mild disc pallor in the RE. OCT at 6 months showed residual thinning of inner retinal layers over the lesion along with complete resolution of subfoveal NSD in the macula. |
| Su et al., 2007        | Case series     | 197             | M:F 119:78    | 7 days                                     | Dengue fever   | Retinal or choroidal vasculopathy with macular swelling, small white or yellow dots usually on the papillomacular bundle or close to the fovea, and intraretinal haemorrhages at the macula. | Blood samples: to evaluate complement C3 and C4 levels. Urine samples: quantification of urinary microalbumin by immunoturbidimetric method. FFA: mild arteriolar and/or venular leakage. | Supportive therapy                                                      | 1 month | 27 had dengue maculopathy and 15 had significant morbidity with severe visual impairment. |
| Koundanya et al., 2019 | Case report     | 42-year-old F   | 7 years       | BOV in the RE for 5 days (VA 6/24 N8 RE and 6/6 N6 LE). | Dengue fever   | Dilated and tortuous super-temporal ven with multiple intraretinal haemorrhages and a patch of retinitis measuring approximately 2-disc diameter along the super-temporal arcade along with a serous detachment of the macula. | FFA of RE: areas of blocked fluorescence corresponding to the retinal haemorrhages and early hyperfluorescence with late hypofluorescence along the super-temporal arcade in right eye. OCT of RE: showed subfoveal fluid and hyperreflectivity of the inner retinal layers with loss of architecture over the patch of retinitis. NS-1 antigen test for dengue virus was positive but was negative for chikungunya, West Nile virus, and yellow fever. Dengue IgG: IgM ratio was 1.8, suggestive of secondary dengue infection. | Oral corticosteroids (1 mg/kg)                                                      | 2 months  | VA in RE improved to 6/6 N6. Resolving retinal haemorrhages and retinalits patch. OCT of the RE showed a decrease in the thickness of the inner retinal layers and resolving oedema. |
| Paper                  | Design          | Number of cases | Age/sex | Interval between fever and ocular symptom | Infection      | Ocular symptoms                                      | Ocular signs                                                                 | Investigations                                                                                   | Treatment                                                                                     | Follow-up | Outcome                                               |
|-----------------------|-----------------|-----------------|---------|------------------------------------------|----------------|-----------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------|-----------|-------------------------------------------------------|
| Mahendradas et al., 2008 | Case series     | 9               | M:F 5:4 | 4–12 weeks (median: 6 weeks)             | Chikungunya   | Vitritis and a hyperaemic disc with an area of confluent retinal opacity suggestive of retinitis in the posterior pole with surrounding retinal and macular oedema. | FFA: early hypofluorescence and late hyperfluorescence with disc leakage. OCT: increased reflectivity in the NFL zone corresponding to the areas of retinitis with after shadowing. Fluid-filled spaces in the outer retina with subfoveal serous detachment. Serum: chikungunya IgM antibody. Serological tests for HSV (IgG and IgM), CMV (IgM), dengue IgM, and ELISA for HIV I and II were negative. | Systemic acyclovir; prednisolone (40 mg/day orally for 1 week), which was then tapered over a period of 6 weeks along with topical 0.1% diclofenac sodium four times a day. | 6 weeks | VA improved with resolving retinitis. |
| Mahesh et al., 2009   | Case report     | 48-year-old F   | 2 weeks | Chikungunya                              | BOV, VA 20/80 N18 RE, 20/60 N6 LE. | Few vitreous cells, optic disc oedema, intraretinal haemorrhages, peripapillary CWS, and areas of retinitis with macular star in BE. | FFA: leakage from disc margins and from peripapillary vessels and blocked fluorescence due to retinal haemorrhage. | ESR: 61 mm in 1 hour (Westergren’s method). Haemoglobin: 12.5 gm%. Total count: 14,000 cells/mm³. Differential count showed polymorphs 62%, lymphocytes 28%, eosinophils 8%, and basophils 2%. Platelet count: 1.8 lakhs/mm³. Random blood sugar: 240 mg%. Blood urea: 30 mg%; serum creatinine: 0.8 mg/dL. SGOT: 42 U/L; SGPT: 67 U/L. ELISA test for HIV and VDRL test were negative. Chikungunya (Card) IgM ELISA test was positive. PCR test: confirmed the presence of chikungunya virus infection. | Tablet Prednisolone 1 mg/kg body weight which was started and tapered over 6 weeks. | BCVA improved to 20/30, N6 in RE and 20/20, N6 in LE. Bilateral resolution of disc oedema with decrease in the retinal haemorrhages and CWS. |
| Prabhushankar et al., 2017 | Case report | 59-year-old M | 28 days | Typhoid fever                             | Diminution of vision in RE (VA 2/60 RE, 20/20 LE). | RE: showed white fluffy lesions along the superior and inferior arcades with superficial haemorrhages in around the macula with a macular star suggestive of retinitis. | OCT: RE underlying macular serous retinal detachment was noted. Blood tests were done to rule out VDRL and HIV status. X-cyton analysis of the AC aspirate was negative for organisms including Mycobacterial tuberculosis, Toxoplasma gondii, HSV, CMV, and VZV. | Oral prednisolone 1 mg/kg body weight which was tapered over 2 months. | 3 months | Improvement in the BCVA in RE to 6/6 which was maintained on further visits. Fundus examination revealed resolving lesions in BE and OCT of the RE showed resolution of the serous detachment. |
| Paper                  | Design     | Number of cases | Age/sex | Interval between fever and ocular symptom | Infection            | Ocular symptoms                                                                 | Ocular signs                                                                 | Investigations                      | Treatment                                                                 | Follow-up | Outcome                  |
|-----------------------|------------|-----------------|---------|-------------------------------------------|----------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------|------------|--------------------------|
| Fusco et al., 2017    | Case report| 23-year-old M   | 20 days | 20 days                                   | Salmonella typhi     | Blurred disc margins especially in the nasal half, arterial narrowing, venous dilatation with increased tortuosity, exudates of varying size and flame haemorrhages localised at the posterior pole and in the midretinal periphery. | VF: sector scotoma involving blind spot.  
Colour vision: yellow blue defect.  
CBC: leukopenia.  
ESR: raised.  
Widal’s test: positive at significant titres.  
Stool culture: grew S. typhi.  
Patient was allergic to chloramphenicol so he was treated with 2 g ampicillin 6 hourly for 4 weeks and locally long-acting corticosteroids retro bulbar injection. |                                                                      | Haemorrhages and exudates significantly diminished.  
Some gain in VA.        | 3 months            |
| Murthy et al., 2008   | Case report| 35/M            | 21 days | 21 days                                   | Chikungunya         | RE: areas of retinitis and haemorrhages in the posterior pole and hyperaemia and blurring of the disc margins (neuroretinitis).  
LE: a patch of retinitis was seen nasal to the optic disc. | FFA: areas of capillary nonperfusion corresponding to the retinitis lesions.  
OCT: area of retinal destruction.  
ESR: 38 mm/hour.  
Haematological and rheological parameters, coagulation profile, blood sugar, liver and renal function, urine analysis, and chest X-ray were normal.  
VDRL test for syphilis and Mantoux test were negative.  
ELISA: IgM and IgG positivity for HSV, and only IgG positivity for CMV and VZV.  
ELISA: HIV and toxoplasma were negative.  
Aqueous: positive for HSV.  
Intravenous acyclovir 1,500 mg/m²/day.  
Oral steroids 1 mg/kg body weight.  
Oral acyclovir and intravitreal ganciclovir 2 mg in 0.05 mL in BE. |                                                                      | Retinal lesions had healed well and his BCVA was 20/120 and 20/20 in the RE and LE, respectively. | 5 months            |
| Siqueira et al., 2004 | Case report| 1/M             | 13 days | 13 days                                   | Dengue fever        | No AC or vitreous cells BE; preretinal haemorrhages at equator; CWS at macula; and peripheral vascular sheathing BE. | FFA areas of CNP in both the equator and macula; MRI brain and carotid Doppler studies: normal.  
Oral anti-platelet therapy: LE Pars plana vitrectomy; RE PRP. |                                                                      | Poor VA in LE; no further retinal vasculitis. | 2 years            |
| Paper                | Design          | Number of cases | Age/sex | Interval between fever and ocular symptom | Infection           | Ocular symptoms                                                                 | Ocular signs                                                                 | Investigations                                                                 | Treatment                                                                 | Follow-up   | Outcome                          |
|----------------------|-----------------|-----------------|---------|-------------------------------------------|---------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|----------------------------------|
| Lim et al.           | Case series     | 20              | M:F     | 6.8 days                                  | Dengue fever        | BOV (90.9%); VA range from 6/6 to HM; vitreous cells (18.2%); RPE changes (27.3%); RPE discoloration (39%); retinal haemorrhage (36.4%); retinal vasculitis (91%); intra-retinal white lesions (18.2%); macular oedema (54.5%). | AC cells (18.2%); vitreous cells (18.2%); RPE changes (27.3%); RPE discoloration (39%); retinal haemorrhage (36.4%); retinal vasculitis (91%); intra-retinal white lesions (18.2%); macular oedema (54.5%). | FFA: arteriolar focal knobby hyperfluorescence in the macula with mild vascular wall staining and leakage (27.3%); early hyperfluorescent spots at the level of the RPE (36.4%); and transmission defects (36.4%). ICG: Diffuse choroidal hyperfluorescence (81.8%). | No treatment (1 case); steroid therapy (1 topical, 2 periocular, 2 oral). | 2 weeks to 4 months | RPE discoloration over affected areas; partial recovery of VA (3 cases); VA stable (3 cases). |
| Sanjay et al.        | Case Series     | 21              |         |                                            | Dengue fever        | Diminution of vision from 6/6 to CF; impaired colour vision, scotomas, enlarged blind spot. | Retinal oedema, retinal haemorrhages, CWS, optic disc swelling, and optic disc atrophy. | mfERG: centrocecal scotoma. pVEP: delayed P100 latency and absent response. MRI: oedema of optic nerve sheath complex. HVF: central scotoma, paracentral scotoma, enlarged blind spot | 6 months to 1 year | 6/9 with impaired colour vision and paracentral scotoma (1 eye). No PL RE and resolved VF defects in LE (1 case). 6/6 with signs and symptoms completely reduced (1 case). |
| Shanmugan et al.     | Case report     | 17/M            |         | 2 weeks                                   | Rickettsia          | Diminished vision in BE for 10 days, 6/36 RE, and 1/60 LE. | RE soft exudates and haemorrhage suggestive of retinitis. LE retinal whitening and retinal haemorrhages. | RE OCT: vitreous cells and NSD at fovea. OCTA: distortion of the FAZ with CNP areas in SCP and DCP. Choriocapillary layer in the RE: signal void areas corresponding to soft exudates. LE OCT: vitreous cells and NSD at fovea SCP and DCP showed multiple CNP areas, pruning of vessels temporal to the disc, and signal void areas. Choriocapillary slab in the LE: absence of signals at areas corresponding to soft exudates. Positive forOX-2 antigen and negative forOX-K andOX-19. | Oral doxycycline and oral prednisolone. | 6 months | BCVA was 6/9 RE and 6/12 LE. Complete resolution of soft exudates and haemorrhages was noted in BE. RE: SCP and DCP showed enlarged FAZ, reduction in the CNP area, and reorganisation of the capillary network. LE: SCP showed reorganisation of capillary network at macula with decrease in CNP area and disappearance of abnormal vessels temporal to the disc. LE: DCP showed decrease in CNP area with minimal distortion of FAZ. |
| Haritoglou et al.     | Case report     | 1/F             |         | 1 day                                     | Dengue fever        | BOV BE; VA 6/150 BE; colour vision severely affected. | Small haemorrhages atNFL, exudative maculopathy BE. | Electrophysiological exam: prolonged latencies, reduced amplitude of visually evoked cortical responses, mild reduction of amplitudes in mERG BE. | No treatment. | 8 weeks | VA improved: RE 6/30 LE 6/9.5. |
Table 1 continued.

| Paper | Design | Number of cases | Age / sex | Interval between fever and ocular symptom | Infection | Ocular symptoms | Ocular signs | Investigations | Treatment | Follow-up | Outcome |
|-------|--------|----------------|-----------|------------------------------------------|-----------|----------------|-------------|---------------|-----------|-----------|---------|
| Yamamoto et al., 2002 | Case report | 1/M | 24 days | Dengue fever | BOV BE; VA OF BE. | Fundoscopy was normal; optic neuropathy suspected as the cause of visual disturbance. | MRI brain: no abnormalities in the optic nerves, cerebellum, or cerebrum. | IVMP. | NA | Mild visual disturbance BE. |
| Cruz-Villegas et al., 2003 | Case report | 1/M | 3 days | Dengue fever | BOV BE; VA; RE 6/24; LE 6/120; scotomas BE; ocular pain BE. | AC cells BE; AC shallow BE; extensive bilateral choroidal effusions. | CT brain and MRI brain: normal. | Topical prednisolone. | 1 week | VA 6/6 BE; AC deeper with loss of cells; choroidal effusions subsided. |
| Nainiwal et al., 2005 | Case report | 1/F | 2 days | Dengue fever | BOV BE; VA; RE PL LE 6/18. | Vitreous haemorrhage BE. | | | | |
| Chlebicki et al., 2005 | Case series | 4 M: 1 F | 625 days | Dengue fever | BOV (100%); VA reduced (100%); metamorphopsia (25%). | Blot haemorrhages within the vascular arcades BE (100%). | Standard supportive care (4 cases); platelet transfusion (2 cases). | | | |
| Mehta, 2005 | Case series | 5 M: F | 4:1 | Dengue fever | VA 6/6 (20%); rest had no VA performed. | SCH (60%); Roth spots (10%); intraretinal haemorrhage (60%); and yellow thickening in choroid and retina (40%). | Complete resolution within 2 days (3 cases); reduced VA and metamorphopsia after 2 months. | | | |
| Preechawat et al., 2005 | Case report | 1/M | 10 days | Dengue fever | BOV BE; VA OF BE. | Flame-shaped haemorrhage at fovea RE, mild bilateral optic disc hyperaemia. | FFA: no disc leakage. | IVMP followed by OPNL. | | VA: 6/6 BE; colour vision: normal. |
| Menia et al., 2019 | Case report | 43/ M | 5 days | Influenza Type A | BOV LE; VA 3/60 LE. | Yellowish-white, coin-shaped lesion at the foveas. | SD-OCT: hyperreflective lesion at foveas involving all retinal layers. | Oral corticosteroids. | 2 months | Lesion healed at 2 months. |

Table 1: Shows the published literature on post fever uveoretinal sequelae.

AC: anterior chamber; BCVA: best corrected visual acuity; BOV: blurring of vision; BE: both eyes; CMV: cytomegalovirus; CNP: capillary nonperfusion; CBC: complete blood count; CF: counting fingers; CWS: cotton-wool spots; DCP: deep capillary plexus; ESR: erythrocyte sedimentation rate; F: female; FAZ: foveal avascular zone; FFA: Fundus fluorescein angiography; HM: hand motion; HSV: herpes simplex virus; HIV: human immunodeficiency virus; H1N1: positive; HIV: negative; IVMP: intravenous methylprednisolone; NA: not available; NFL: nerve fibre layer; NSD: neurosensory detachment; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography; OPNL: outer plexiform and nuclear layer; PPRP: panretinal photocoagulation; pVEP: pattern visual evoked potential; PL: perception of light; RAPD: relative afferent pupillary defect; RE: right eye; RPE: retinal pigment epithelium; SD-OCT: spectral domain optical coherence tomography; SCH: subconjunctival haemorrhage; SCP: superficial capillary plexus; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum pyruvic acid transaminase; SLE: systemic lupus erythematosus; VDRL: venereal diseases research laboratory test; VA: visual acuity; VF: visual field; VZV: varicella zoster virus.
There may be presence of macular periphlebitis and occlusion. Common findings include disc leakage, arteriolar leakage, and macular oedema. Indocyanine green angiography may show presence of hypocyanescent spots suggestive of the involvement of choriocapillaris and the retinal pigment epithelium. 39-41

Chikungunya Virus

Chikungunya fever is a common arthropod-borne viral illness that commonly affects Asian countries and Pacific islands. Epidemics of chikungunya have recently been reported from several Asian countries, such as India. 2,42-44 Ophthalmic manifestations may be unilateral or bilateral. Retinitis presents between 2 and 4 weeks after febrile period of systemic disease. 33 Chikungunya retinitis can be differentiated from herpetic retinitis by less vitreous reaction and confluent posterior pole retinitis, whereas acute retinal necrosis is characterised by intense vitritis and peripheral multifocal or disseminated retinitis. 45,46 It can also simulate WNV retinitis, therefore, it is important to assess systemic symptoms to differentiate the aetiology of the manifestation. 47 All these patients have a good visual outcome with almost total recovery within 10–12 weeks. 9

It is presumed that an immune dysregulation, superantigen induction, hypersensitivity reaction, and molecular mimicry between stimulating virus-derived antigens and normal or altered host tissue proteins may be the cause of the optic nerve damage, while some hypothesise that ocular manifestations associated with chikungunya fever may be an immune-mediated process-like production of autoantibody rather than a direct viral infection. 4

The authors’ experience shows that anterior uveitis and retinitis are the most common ocular manifestations associated with chikungunya, with a typically benign clinical course. 14 However, long-term sequelae of the retinitis revealed thinning of the inner retinal layers.

Bilateral neuroretinitis associated with chikungunya infection has been reported. 15 Other viral infections caused by measles, influenza, Epstein–Barr, dengue, and Rift valley fever viruses can also present with neuroretinitis occurring subsequent to an acute viral systemic illness. Vishwanath et al. 1 showed that a patient who was positive for IgM chikungunya virus had bilateral anterior nongranulomatous uveitis and retinitis with optic nerve involvement in one eye showed a favourable response to oral steroids.

Zika Virus

Zika virus ocular manifestations are usually mild, such as nonpurulent conjunctivitis in adults, though it may be linked to uveitis, maculopathy, and hypertensive iridocyclitis later. 48 Miranda et al. 49 described ocular findings in three patients with microcephaly and a presumed Zika virus infection. All six eyes had pigmentary maculopathy ranging from mild to pronounced. Some showed well-delineated macular chorioretinal atrophy with a hyperpigmented ring, while others had vascular tortuosity and pronounced early termination of the retinal vasculature, washed-out peripheral retina with a hypoluculent spot, and scattered subtretinal haemorrhages external to the macula on photographic evaluation. One characteristic finding seen was peripheral pigmentary changes and clustered atrophic lesions resembling grouped congenital albinotic spots (polar bear tracks). 49

Some other studies have shown macular changes (thick pigment spots and/or chorioretinal atrophy) and optic nerve abnormalities (double ring hypoplasia, pallor, and/or increased cup-disc ratio). 50 Another case report described a patient with strongly positive value on a serum plaque reduction neutralisation technique with macular retinal pigment epithelium changes with a grey annulus around the fovea on posterior segment examination and disruption of outer retinal and retinal pigment epithelium integrity in the central macula evidenced on optical coherence tomography. 51

The first signs of congenital ocular involvement related to Zika virus were reported in January 2016 in three Brazilian children with microcephaly who were born to a mother who had been infected with the virus during pregnancy. 50,52,53 The presence of these complications was substantiated by Freitas et al. 54 who identified that among 29 newborns with microcephaly, 10 children had ocular abnormalities. The lesions consisted of zones of chorioretinal pigmentation or atrophy and bilateral in 70% of cases. Optic nerve changes described were hypoplasia, disc pallor, or large cups. 54 These abnormalities
were increasingly frequent with smaller cranial circumference and if the symptoms of Zika virus infection occurred during the first trimester of pregnancy.\textsuperscript{55} Also reported were atrophic and pigmented lesions resembling torpedo maculopathy, abnormal retinal vascular patterns, retinal haemorrhages, and lesions of the iris (coloboma) or lens (subluxation).\textsuperscript{54-56}

**Ebola Virus**

Shantha et al.\textsuperscript{57} have summarised a number of reports about the ophthalmic sequelae of Ebola virus disease in the recent and past outbreaks. The prevalence of uveitis has ranged from 18\% to 34\% of survivors; in their own series (from the recent outbreak in West Africa), more than one-third of those with uveitis were blind. In addition to cases of posterior uveitis, which can result in the retinal lesions described by Steptoe et al.,\textsuperscript{58,59} there were cases of isolated anterior uveitis and intermediate uveitis. Other ophthalmic conditions included optic neuropathy and other neuro-ophthalmic problems in some,\textsuperscript{60,61} while others progressed to phthisis.

As many as 20\% of convalescent patients, who may be asymptomatic for up to 2 months, develop hypertensive uveitis characterised by ocular pain, photophobia, hyperlacrimation, foreign body sensation, red eye, and progressive visual loss.\textsuperscript{62}

Ebola retinal lesions varied in size and shape, but distinctive linear borders with sharp angulations were characteristic. Multimodal imaging features varied according to severity and extent of retinal structures involved. Lesions appeared light grey on fundus photography and were predominantly nonpigmented.\textsuperscript{58}

**Influenza A (H1N1) Virus**

Studies show nonconfluent cotton wool spots in H1N1 representing milder versions of ischaemic retinopathy. Visual acuity normalised over several months in some, whereas patients with bilateral peripapillary cotton wool spots took over 3 weeks to resolve.\textsuperscript{63,64}

Ashfaq et al.\textsuperscript{65} reported a case series of acute macular neuroretinopathy associated with virologically confirmed acute influenza virus infection. Ocular symptoms range from pain, redness, and decreased visual acuity to uveal effusion syndrome and orbital inflammatory syndrome. Vision loss may also be caused by simultaneous retinal and lateral geniculate body infarction.\textsuperscript{66}

**West Nile Virus**

Posterior segment manifestation of WNV include chorioretinitis or only retinitis, anterior uveitis, retinal occlusive vasculitis in which arterial involvement is greater than venous involvement, optic neuritis, and congenital chorioretinal scarring optic neuropathies.\textsuperscript{67,68} The characteristic feature of WNV chorioretinitis is a curvilinear clustering of whitish-yellow chorioretinal scars with a ‘target-like’ appearance, following the course of the retinal nerve fibres.\textsuperscript{69} Sivakumar et al.\textsuperscript{3} reported a case series of WNV retinitis from South India which did not follow the classical pattern of WNV infection. Fundus examination revealed discrete, superficial, white retinitis; arteritis; phlebitis; and retinal haemorrhages with or without macular star. The fundus fluorescein angiography revealed areas of retinal inflammation with indistinct borders, vascular and optic disc leakage, vessel wall staining, or capillary nonperfusion.

**Coronavirus**

The most recent entrant to this list is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which was first detected in December 2019 in Wuhan, China.\textsuperscript{70} This outbreak was suspected when numerous unexplained pneumonia cases occurred. It has been established that infectious droplets and body fluids can easily contaminate the human conjunctival epithelium. Respiratory viruses are capable of inducing ocular complications in infected patients, which then leads to respiratory infection. SARS-CoV-2 coronavirus disease-2019 (COVID-19) is predominantly transmitted through direct or indirect contact with mucous membranes in the eyes, mouth, or nose. The fact that exposed mucous membranes and unprotected eyes increased the risk of COVID-19 transmission suggests that exposure of unprotected eyes to SARS-CoV-2 could cause acute respiratory infection. Posterior segment manifestations were recently reported by Marinho et al.\textsuperscript{71} They found hyper-reflective lesions at the level of ganglion cell and inner plexiform layers more prominently at the papillomacular bundle in both eyes and subtle cotton wool spots and microhaemorrhages along the retinal arcade.
BACTERIAL

Typhoid

In addition to causing enteric fever, septicaemia, gastroenteritis, and vasculitis, *Salmonella typhi* can affect the eye either by direct infection or rarely by immune-mediated mechanisms. Duke-Elder and Perkins\textsuperscript{72} reported typhoid-related uveal complications including iritis, retinal haemorrhage, choroiditis, endophthalmitis, panophthalmitis, vasculitis, and retinitis with macular neurosensory detachment post-typhoid fever.

*Salmonella* spp., including *enteritidis, typhimurium*, and *choleraesuis*, have been isolated from aqueous and vitreous samples in patients with endogenous endophthalmitis.\textsuperscript{73}

Other posterior segment manifestations reported are frosted branch angiitis; bilateral chorioretinitis with stellate maculopathy; vitritis; multifocal patches of retinitis; macular oedema; disc involvement in the form of hyperaemia, oedema or sphincter haemorrhages; and localised retinal vascular sheathing.\textsuperscript{74} Endogenous endophthalmitis is a rare complication of salmonella infections occurring in immunocompromised patients.\textsuperscript{75} Patients with bilateral confluent retinitis had significantly high Widal titres.\textsuperscript{76} Bilateral retinitis following typhoid fever was also reported.\textsuperscript{16,77} Multifocal choroiditis following simultaneous hepatitis A, typhoid fever, and yellow fever vaccination is an inflammatory disease characterised by multiple, small, yellow fundus lesions and vitreous inflammation which is because of the involvement of the eye which may be a result of direct invasion or immune-mediated phenomenon.\textsuperscript{75}

Rickettsioses

The spotted fever group includes Mediterranean spotted fever (MSF), Rocky Mountain spotted fever, and numerous other rickettsioses. MSF, also called ‘boutonneuse’ fever or tick-borne rickettsiosis, is caused by the organism *Rickettsia conorii* and is prevalent in Mediterranean countries and Central Asia, including India.\textsuperscript{78} Indian tick typhus and epidemic typhus could be the common subtypes seen in the South Indian population.\textsuperscript{7}

Ocular involvement includes anterior segment features such as conjunctivitis, keratitis, and anterior uveitis. Retinitis, retinal vascular involvement, and optic disc changes are the most common ocular findings presenting with white retinal lesions, typically adjacent to retinal vessels and associated mild or moderate vitreous inflammation in 30% of patients with acute MSF. The cotton wool spot-like retinal lesions could result from intraretinal multiplication of organisms or alternatively as a result of immune complex deposition along retinal vessels.\textsuperscript{78,79} Fluorescein angiography showed early hypofluorescence and late staining of large acute white retinal lesions and isofluorescence or moderate hypofluorescence of small active retinal lesions throughout the whole phase of dye transit. Optical coherence tomography shows serous retinal detachment and large foci of rickettsial retinitis which predominantly involves the inner retina.\textsuperscript{78,79}

Balasundaram et al.\textsuperscript{7} described a case series of patients with serologically proven Indian tick typhus (*R. conorii*) infection, in whom multifocal retinitis predominantly involved the posterior pole and macular involvement in the form of serous macular detachment or macular hard exudates. Doxycycline along with oral corticosteroids was effective in treating the condition. A case of bilateral *rickettsial* retinitis was reported which worsened on systemic steroids and responded dramatically to therapy with oral doxycycline and steroid taper.\textsuperscript{80} The authors’ experience with 19 eyes of 10 patients with retinitis on the posterior pole with a recent history of fever with or without skin rash and a positive Weil-Felix test suggested a presumed rickettsial aetiology.\textsuperscript{8}

PARASITE

Malaria

Malaria retinopathy is a condition which is a defining characteristic of cerebral malaria as a result of *Plasmodium falciparum* infection. This condition is usually bilateral and may be associated with papilloedema, patchy retinal whitening, focal changes in vessel colour, and white-centred haemorrhages.\textsuperscript{81}

However, there have been studies that showed patients who were positive for malaria parasite,
Table 2: Summary of post fever uveoretinal sequelae as reported in published medical literature.

| Symptoms                          | Signs                                           | OCT                                                                 | FFA                                                                 | Treatment                                     |
|-----------------------------------|-------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------|
| Dengue                            | Blurring of vision                              | Vitreous and retinal haemorrhages                                   | Three patterns of maculopathy: diffuse retinal thickening, CME, and  | Arteriolar leakage                           |
|                                   | Scotoma, Metamorphopsia Floaters*               | Posterior uveitis, Optic neuritis and maculopathy                   | foveitis*                                                          | Macular oedema                                |
|                                   |                                                  | Foveolitis, Macular oedema, RAPD, Vessel engorgement, Colour vision impairment, Loss of contrast sensitivity, Intraretinal cystoid spaces | Disc leakage, Chorioidal hyperfluoresence, Blocked fluorescence or capillary non-perfusion | Oral corticosteroids (1 mg/kg) Standard supportive care* |
|                                   |                                                  | Colour vision impairment, Loss of contrast sensitivity, Intraretinal cystoid spaces, Perifoveal telangiectasia, Intraretinal haemorrhages, Cotton wool spots, Microaneuromys, Retinitis, Chorioretinitis, Neuroretinitis, Roth spots, Pan retinal vasculitis, Exudative RD, Optic neuropathy | Foveolitis: area of thickening and high reflectivity at the subfoveal outer retina layer. There may be a tented elevation and separation of the highly reflective layer with accumulation of subretinal fluid. Serial OCT imaging demonstrate spontaneous rapid resolution of oedema |                                      |
|                                   |                                                  | Ocular neovascularisation, Panuveitis, Severe inflammation may result in exudative retinal detachment, Retinal vasculitis, Intermediate uveitis | Focal and multifocal patches of retinitis, Macular oedema, Severe detachment at the macula and localised involvement of the retinal vessel |                                      |
| Chikungunya                       | Decreased vision                                | Intraretinal haemorrhages, Chorioiditis, Retinitis, Optic neuritis, Neuroretinitis, and retinal neovascularisation, Panuveitis, Retinal oedema and opacification, Mild vitritis, Disc oedema, Severe inflammation may result in exudative retinal detachment, Retinal vasculitis, Intermediate uveitis | Early hyperfluorescence followed by late hyperfluorescence corresponding to area of retinitis | Systemic acyclovir and prednisolone (40 mg/day orally for 1 week) tapered over a period of 6 weeks |
|                                   | Central scotoma, Peripheral field defect, Colour vision defect |                                           |                                                                     | Topical 0.1% diclofenac sodium four times a day |
|                                   |                                                  |                                                                     |                                                                     |                                      |
| Zika                              | Decreased vision                                | Chorioretinal atrophy, Macular changes (thick pigment spots and/or chorioretinal atrophy with hyperpigmented ring), Optic nerve abnormalities (double ring hypoplasia, pallor, increased cup-disc ratio), Macular pigment mottling, Neuroretinal atrophy with macular involvement, Iris coloboma, Changes in retinal vasculature (congenital) | Nodular elevations in the outer retinal layers, Interruption of the outer retinal layers and an irregularity of the retinal pigment epithelial thickness | Hypofluorescent in the centre of the macula, Hyperfluorescent in the surrounding areas |
|                                   | Redness, Nonpurulent conjunctivitis*            |                                                                     |                                                                     |                                      |
| Ebola                             | Ocular pain, Photophobia, Hyperlacrimation, Foreign body sensation, Red eye, Progressive visual loss | Vitreous opacities, Vitritis, Multiple chorioretinal scars with hypopigmented halos, Small intraretinal haemorrhages, Posterior uveitis, Panuveitis | Multiple vertical discontinuities of the ellipsoid zone and interdigitation zone with overlying v-shaped increased reflectance of the ONL | Antiviral therapy with favipiravir, Periocular triamcinolone acetonide injection (40 mg/mL), Oral corticosteroids |

*References: 46-48, 52, 56, 58, 64, 78
### Table 2 continued.

|                   | Symptoms                                                                 | Signs                                                                 | OCT                                                   | FFA                                                                 | Treatment                                      |
|-------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------|
| **H1N1 (influenza A)** | Severe bilateral vision loss to the level of light perception within 24 hours of having fever and myalgias | Pain Redness66,89 Confluent ischaemic retinopathy                      | Inner retinal thickening and hyperreflectivity in both eyes; outer retinal layers were relatively spared82 | Arteriolar occlusions posteriorly with minimal late leakage and no retinal vascular abnormalities in the periphery69 | Oral corticosteroids56 |
|                   |                                                                          | Confluent and sharp-bordered ischemic retinal white patches59          |                                                       |                                                                      |                                                |
|                   |                                                                          | Dense anterior chamber inflammation                                     |                                                       |                                                                      |                                                |
|                   |                                                                          | Vitritis                                                                 |                                                       |                                                                      |                                                |
|                   |                                                                          | Peripheral retinal necrosis                                             |                                                       |                                                                      |                                                |
|                   |                                                                          | Choroiditis                                                              |                                                       |                                                                      |                                                |
|                   |                                                                          | Submacular haemorrhages                                                 |                                                       |                                                                      |                                                |
|                   |                                                                          | Macular oedema                                                          |                                                       |                                                                      |                                                |
|                   |                                                                          | Neuroretinitis                                                           |                                                       |                                                                      |                                                |
|                   |                                                                          | Vaso-occlusive retinal vasculitis80                                      |                                                       |                                                                      |                                                |
|                   |                                                                          | Frosted branch angiitis                                                 |                                                       |                                                                      |                                                |
|                   |                                                                          | Exudative retinal detachment86                                           |                                                       |                                                                      |                                                |
|                   |                                                                          | Optic neuritis65,68                                                     |                                                       |                                                                      |                                                |
| **West Nile fever** | Blurring of vision Visual field defects                                   | Active chorioretinal lesions appear as circular, deep, creamy lesions | Inner retinal oedema in active inflammation and retinal atrophy in the late stage67 | Active chorioretinal lesions: early hypofluorescence and late staining | Supportive care68,69 |
|                   |                                                                          | Inactive chorioretinal lesions appear partially atrophic and partially pigmented |                                                       |                                                                      |                                                |
|                   |                                                                          | Multifocal chorioretinitis69                                              |                                                       |                                                                      |                                                |
|                   |                                                                          | Dense anterior chamber inflammation                                      |                                                       |                                                                      |                                                |
|                   |                                                                          | Vitritis                                                                 |                                                       |                                                                      |                                                |
|                   |                                                                          | Peripheral retinal necrosis                                             |                                                       |                                                                      |                                                |
|                   |                                                                          | Choroiditis                                                              |                                                       |                                                                      |                                                |
|                   |                                                                          | Submacular haemorrhages                                                 |                                                       |                                                                      |                                                |
|                   |                                                                          | Macular oedema                                                          |                                                       |                                                                      |                                                |
|                   |                                                                          | Neuroretinitis                                                           |                                                       |                                                                      |                                                |
|                   |                                                                          | Vaso-occlusive retinal vasculitis80                                      |                                                       |                                                                      |                                                |
|                   |                                                                          | Frosted branch angiitis                                                 |                                                       |                                                                      |                                                |
|                   |                                                                          | Exudative retinal detachment86                                           |                                                       |                                                                      |                                                |
|                   |                                                                          | Optic neuritis65,68                                                     |                                                       |                                                                      |                                                |
|                   |                                                                          | Curvilinear clustering of whitish yellow chorioretinal scars with a ‘target-like’ appearance following the course of the retinal nerve fibres67-69 | | | |
| **Typhoid**       | Decreased vision                                                        | Disc pallor                                                             | Highly reflective and disorganised inner retina layer | Prednisolone (1 mg/kg body weight/day) Steroids tapered over 2 months with regular monitoring5 |                                                |
|                   | RAPD                                                                     | Vascultis                                                               | Serous retinal detachment                            |                                                                     |                                                |
|                   | Colour vision defect                                                    | Multiple whitish fluffy areas of deep retinitis54,76                     |                                                       |                                                                     |                                                |
|                   |                                                                          | Large neurosensory detachment in the macular area.                       |                                                       |                                                                     |                                                |
|                   |                                                                          | Cotton-wool spot                                                        |                                                       |                                                                     |                                                |
|                   |                                                                          | Retinal venous sheathing                                                |                                                       |                                                                     |                                                |
| **Rickettsiosis** | Diminished vision                                                        | Soft exudates                                                           | Vitreous cells                                        | Oral doxycycline                                                     |                                                |
|                   |                                                                          | Retinal haemorrhages78,82                                                | Neurosensory detachment                              | Oral prednisolone                                                    |                                                |
|                   |                                                                          | Retinal whitening                                                       |                                                       |                                                                     |                                               |

CME: cystoid macular oedema; ELM: external limiting membrane; FFA: fundus fluorescein angiography; OCT: optical coherence tomography; ONL: outer nuclear layer; OPL: outer plexiform layer; RAPD: relative afferent pupillary defect; RD: retinal detachment.
had a unilateral large retinitis patch with vascular sheathing, and relative afferent pupillary defect with no evidence of cerebral malaria.\textsuperscript{1} Table 2 summarizes the clinical features seen in PFURS.

**Management**

Treatment of arbovirus infection (dengue fever, chikungunya, Zika virus, WNV, and yellow fever) is essentially symptomatic because there are currently no effective antiviral treatments.\textsuperscript{9,14,15} In one case series, all patients with post fever retinitis were treated with oral prednisolone at 1 mg/kg body weight irrespective of aetiology, and the steroids were tapered based on clinical response over a period of 6 weeks; all patients had improvement in vision, despite the differences in aetiology.\textsuperscript{1,14} Oral doxycycline and/or acyclovir or valacyclovir can be started empirically while investigations are awaited.\textsuperscript{2} Other modalities of treatment are intravenous methylprednisolone, posterior sub-Tenon’s injection, intravitreal triamcinolone, intravitreal anti-VEGF injections (bevacizumab or ranibizumab).\textsuperscript{2}

However, a large number of patients have self-limiting disease and resolve spontaneously without any treatment. Some case reports and case series have documented successful conservative management, hence it is believed to be a self-limiting condition.\textsuperscript{1,32} Even though spontaneous recovery is possible in post febrile neuroretinitis, steroids help in hastening the resolution of retinitis and improving the vision, thus decreasing the time to recovery.\textsuperscript{76} Whereas, another report by the present authors mentioned successful treatment of macular oedema and retinitis without steroids.\textsuperscript{77}

**CONCLUSION**

Post fever retinitis of almost all aetiologies present with a similar morphological pattern because the condition manifests approximately 3 weeks after onset of fever and follows a preset natural course before resolution. These manifestations, which generally constitute inner retinitis at the posterior pole with or without optic nerve involvement, may be the result of a direct invasion by the pathogen or by indirect invasion mediated through immune-modulated mechanisms. It resolves in all cases without any relapses, but visual prognosis varies depending on macular ischaemic damage and optic nerve involvement. No specific treatment seems to be established based on the literature and patients may improve as a part of natural history of the disease process. However, some studies highlighted the need for a high index of suspicion by an ophthalmologist to diagnose this entity and for the early introduction of steroids for rapid improvement in symptoms and prevention of vision loss. Early referral to an ophthalmologist by the treating physician would result in a better functional outcome for the patients. This entity needs to be studied further to understand the detail of the natural history and histopathological and immunological aides. Further studies are needed to elucidate the mechanism of ophthalmic complications of viral, bacterial, and parasitic fevers.

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