

Editorial

Dengue-associated Eye Disease

Neethu Latif¹, Kowsigan Mageshan¹, Jyotirmay Biswas¹, Parthopratin Dutta Majumder¹
¹Department of Uvea, Sankara Nethralaya, Chennai, India

Introduction

Dengue fever remains the most common mosquito-borne viral disease in humans. The dengue virus belongs to the Flavivirus genus of the family Flaviviridae, and its members include the four antigenically related serotypes of dengue virus. It is transmitted to humans by the bite of an infected female *Aedes aegypti* mosquito. Recovery from infection with one serotype provides lifelong immunity against that serotype but confers only transient and partial immunity against subsequent infection by other serotypes. (Gubler 1998) Sequential infections with other serotypes may increase the risk of more serious systemic disease, such as dengue hemorrhagic fever or dengue shock syndrome, which are life-threatening. (Gubler 1998)(Gibbons and Vaughn 2002)

In recent years there has been a significant increase in literature on dengue-associated eye disease.(Chan et al. 2006)(Ng and Teoh 2015)(Su et al. 2007) A spectrum of clinical manifestations has been described in association with dengue fever and indicates several different pathophysiological mechanisms responsible for these clinical manifestations.(Su et al. 2007)(Bacsal et al. 2007)(Lim et al. 2004) In this review, we focus on growing literature on dengue-associated eye disease and aim to provide a comprehensive review as well as practical clues for how to recognize and treat some of these common ocular manifestations.

Epidemiology

World Health Organization (WHO) estimates approximately 3.6 billion people are at risk of dengue fever world-wide with an annual incidence ranging from 100 to 200 million cases.(Gubler 1998)(Gubler 2002)(Guzmán and Kourí 2002) Asia-pacific region remains one of the most highly affected zones by dengue. In fact, Dengue was first reported in some travelers travelling to South-East Asia.(Wilder-Smith and Gubler 2008) A major shift in the geographical range of the disease has been observed in Indian subcontinent also. Once considered primarily an urban disease, dengue has spread to rural areas and also to Himalayan countries such as Nepal, Bhutan etc.(Gupta et al. 2018a)(Gupta et al. 2018b) Several outbreaks have been reported in these region and prevalence of dengue in Nepal is considered much higher than it is estimated. (Gupta et al. 2018a)

A male predominance has been observed in various population-based studies on dengue including studies on ocular manifestations of dengue.(Kapoor et al. 2006) The young people in the age group of 25-30 years is reported to be involved with dengue associated

eye disease.(Su et al. 2007).(Kapoor et al. 2006) The mean duration between the onset of ocular symptom following dengue fever remains highly variable and usually ranges from 1 to 28 days.(Su et al. 2007).(Lim et al. 2004) Gupta and colleagues reported uveitis in six patients who presented 3 to 5 months after contracting dengue fever during the dengue epidemic without any other attributable cause for uveitis. (Gupta et al. 2009)

Clinical features

Patients can present with the complaints of eye strain or blurring of vision, ocular pain, flashes and floaters. A triad of symptoms - ocular flashes, blurring of vision and floaters was reported to be highly predictive of the development of retinal hemorrhages.(Seet et al. 2007) The most common anterior segment manifestation is subconjunctival hemorrhage. (Kapoor et al. 2006) Uveitis in dengue is usually rare but has been reported in in several case series. (Bacsal et al. 2007).(Lim et al. 2004).(Gupta et al. 2009) In a large case series of patients with ophthalmic involvement following acute dengue infection, anterior uveitis was noted in 17% patients, vitritis in 31% patients and both anterior uveitis and vitritis were observed in 11% of the patients. (Bacsal et al. 2007) Other less common anterior segment manifestation include supraciliary effusion resulting in shallow anterior chamber with acute angle closure glaucoma.(Pierre Filho et al. 2008).(Cruz-Villegas et al. 2003)

Maculopathy is considered to be the most common manifestation of dengue fever. Patients with maculopathy usually complaints of sudden drop in vision or blurred vision, scotoma and floaters.(Teoh et al. 2010) Maculopathy is thought to be serotype and geographic related.(Su et al. 2007).(Chee et al. 2009) The prevalence of dengue maculopathy among patients hospitalized for dengue fever

was reported to be 10% in a cross-sectional observation study.(Su et al. 2007) Dengue associated maculopathy remains largely an umbrella term for a vast spectrum of macular involvement (Figure 1) and includes flame and intraretinal hemorrhages (Figure 2), focal choroiditis (Figure 3)/chorioretinitis, macular edema and foveolitis.(Teoh et al. 2010) These findings were often reported to be associated with arteriolar sheathing, cotton wool spots, perifoveal telangiectasia and microaneurysm. Foveolitis is a term used to describe discrete, well-defined yellow-orange subretinal lesions with surrounding striae in the fovea. These lesions corresponded to disruption of the outer neurosensory retina and the inner segment/ outer segment junction. The incidence of foveolitis in patients with maculopathy ranged from 28 to 33.7%.(Bacsal et al. 2007) (Teoh et al. 2010)

Posterior uveitis following dengue fever has a varied spectrum of manifestations such as retinitis, choroiditis, retinochoroiditis and neuroretinitis.(Tabbara 2012).(Yadav et al. 2017) Retinal vasculitis, exudative retinal detachment though very rare, but have been described in patients of dengue.(Tabbara 2012) Optic nerve involvement in the form of optic disc swelling, hyperemia of the disc, and disc hemorrhages have been described. In a series by Teoh et al.(Teoh et al. 2010) disc swelling was observed in 3 % eyes with dengue-associated ocular involvement. Panophthalmitis has been reported in children and younger individuals suffering from dengue fever (Figure 4).(Saranappa S B and Sowbhagya 2012).(Ramananda et al. 2018).(Kamal et al. 2018) Though a role of immunologic and inflammatory response to the dengue virus infection has been implicated, panophthalmitis can be due to endogenous infection secondary to intravenous transfusion therapy.(Ramananda et al. 2018).(Kamal et al. 2018)

Table 1: Differential diagnosis of dengue associated eye disease

Differential diagnosis of dengue associated eye disease	
Malaria	Malarial retinopathy characterized by retinal whitening, capillary whitening, retinal hemorrhages, papilledema, cotton wool spot Relatively Uncommon: Uveitis Secondary glaucoma
Herpes virus infection	Follicular conjunctivitis, Necrotizing retinitis, Postherpetic neuralgia, Anterior uveitis, Secondary glaucoma, Postherpetic neuralgia (uncommon in patients below 50 years of age) Relatively Uncommon: Keratitis, Dacryoadentitis, Canaliculitis, Ophthalmoplegia, Scleritis , Optic neuritis
Chikungunya	Conjunctivitis, Keratitis, Anterior uveitis, Optic neuritis, Retinitis
Typhoid	Rare: Conjunctival petechiae or chemosis, Uveitis, Retinitis, Vitreous hemorrhage, Retinal hemorrhage

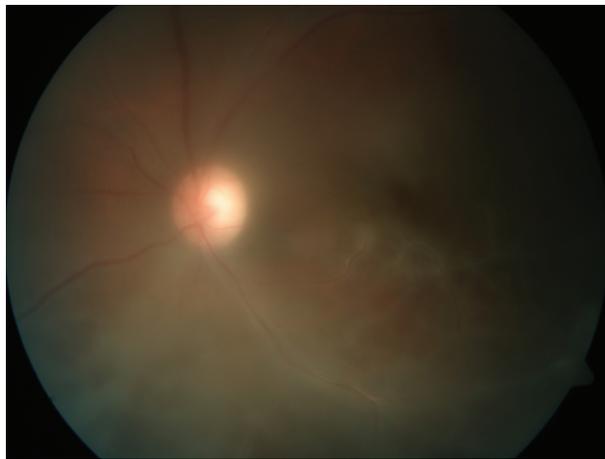


Figure 1: Fundus photograph showing vitritis with retinal vasculitis in a Dengue positive patient.

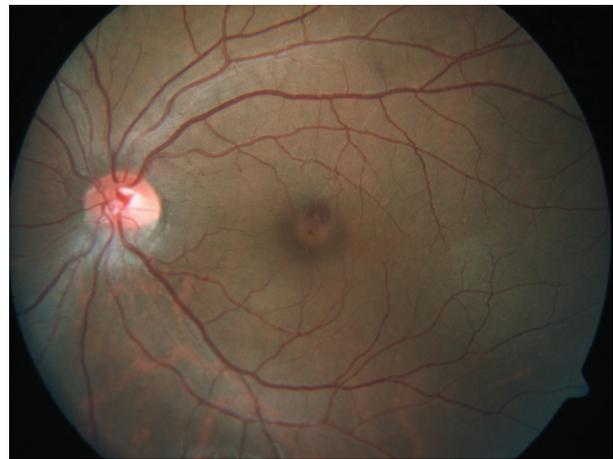


Figure 2: Fundus photograph showing macular hemorrhage with foveolitis following dengue fever.

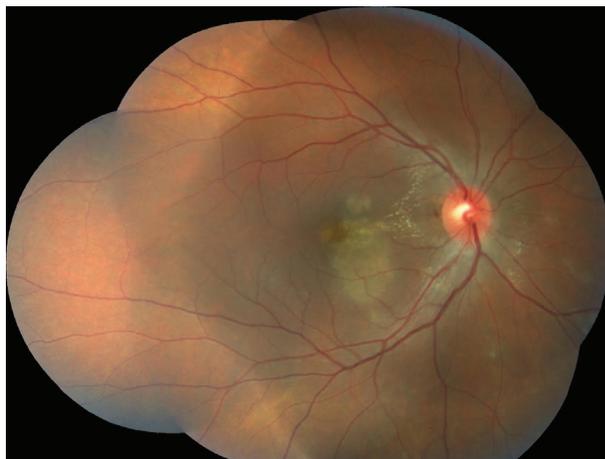


Figure 3: Fundus photograph showing choroidal involvement in a patient following dengue fever

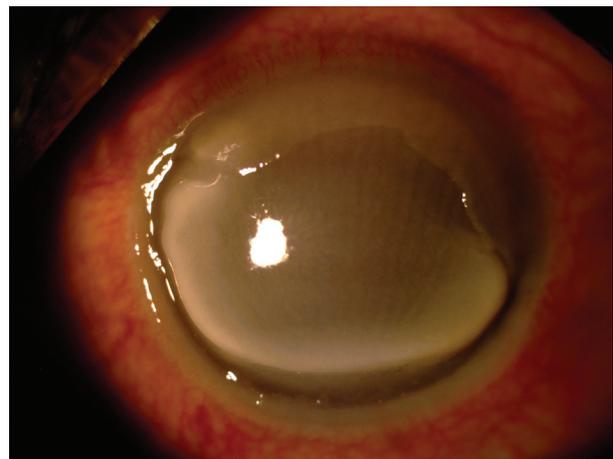


Figure 4: Slit-lamp photograph showing panophthalmitis in a patient who was infected with DEN1 serotype and had received platelet transfusions.

Differential diagnosis

Differential diagnosis of dengue associated eye disease includes ocular involvement following post-febrile illness. Various such entities have been summarized in Table 1.

Diagnosis

The role of laboratory confirmation of dengue infection in patients presenting with ocular involvement is limited and depends primarily on the time of presentation with ocular involvement. The choice of tests for dengue diagnosis depends on the timing and purpose. For the diagnosis of acute DENV infection, tests are based on DENV isolation, presence of dengue viral antigens, detection of viral nucleic acid in blood through techniques such as RT-PCR, IgM seroconversion, and/or a four-fold or greater rise in IgG antibody titre in paired blood samples collected at least 14 days apart. Dengue virus and antigen detection are the most accurate diagnostic tools during the first 5 days of illness, as IgG and IgM antibodies are not produced until 5–7 days after the onset of symptoms in primary infections. Dengue IgM antibodies are detectable five days after the onset of fever up to three months, while IgG appear on the tenth day after the onset of fever and can persist for several years and useful in detecting previous infection. During acute infection, the secondary immunological response is faster with a higher IgG production. Hence a higher prevalence of IgG is noted in febrile patients. The reverse transcriptase polymerase chain reaction has higher sensitivity during the febrile phase and gradually becomes negative as the fever settles down.(Barkham et al. 2006)(de Oliveira Poersch et al. 2005) Detection of dengue RNA using reverse transcription PCR amplification assay is no less complex or expensive, but it is faster.

Ancillary ophthalmic investigations in patients with dengue associated eye disease are

usually required mostly for better delineation of posterior segment pathology. The Amsler grid test is a simple test which can be used to document scotomas in patients with dengue-related maculopathy. Presence of a relative central scotoma was documented in 39% of the patients with dengue maculopathy using Amsler chart by Teoh et al. which corresponded well to the visual field by an automated Humphrey field analyzer.(Teoh et al. 2010)

Fundus fluorescein angiography (FFA) has aided in the diagnosis of retinal vascular involvement. In a study of 71 eyes of 41 patients with dengue-associated maculopathy, FFA demonstrated venular occlusion in 25% of eyes and vascular leakage was observed in 16% of eyes.(Bacsal et al. 2007) Literature on the use of indocyanine green angiography (ICG) is relatively sparse. Su et al. (Su et al. 2007) reported hypofluorescence on ICG, which corresponded to white or yellow dots in the macula. This finding was similar to the study by Bacsal et al. (Su et al. 2007) who noted that 50% of yellow subretinal dots in the macula corresponded to hypofluorescent spots on ICG.

Optical coherence tomography (OCT) is a simple, non-invasive tool which can be very helpful in evaluation of dengue associated maculopathy. OCT has been used in differentiating various types of macular involvement and correlating with visual acuity and prognosis.(Teoh et al. 2010) Using OCT, Teoh et al. (Teoh et al. 2010) has categorized dengue-associated maculopathy into three distinct patterns - diffuse retinal thickening, cystoid macular edema and cystic foveolitis. Their study showed that visual outcome in patients with dengue-associated maculopathy was independent of the extent of edema. The scotomata persisted longest in patients with foveolitis and shortest with those with diffuse retinal thickening despite clinical resolution of the disease.

Treatment

The dengue-associated ocular disease usually has a self-limiting course and the lesions resolve spontaneously without any treatment. However, option of treatment modality highly depends on the clinical presentation and initial visual acuity. Lesions which resolved over time includes conservative management was the treatment of choice in subconjunctival hemorrhages, retinal and macular hemorrhages, foveolitis, optic neuritis and posterior uveitis. One patient with foveolitis and superior temporal branch venular occlusion reported by Loh et al had spontaneous improvement in BCVA at the end of 3 weeks. Tabbara observed spontaneous resolution in 6–8 weeks in two patients with multifocal chorioretinitis. Reported cases of dengue associated panophthalmitis has been managed conservatively with intravenous fluid, antibiotics and platelet transfusion followed by evisceration of the eye. There are also reports of spontaneous improvement of visual acuity and clinical resolution of dengue-associated optic neuritis within 6 to 12 weeks. (Sanjay et al. 2008)

Corticosteroid were used in patients who were persistently symptomatic and had poor vision due to dengue-related ocular complications. Topical corticosteroid is prescribed in anterior uveitis. Good resolution of anterior uveitis without subsequent relapse on tapering steroids has been reported in the past. Bacsal et al used either periocular methylprednisolone or intravitreal triamcinolone in 12 patients with unilateral dengue maculopathy but no mention was made as to whether they recovered fully. Systemic corticosteroids have been used in patients with optic neuritis. Even though good resolution was obtained clinically, patients were left over with inferior scotoma, enlargement of blind spot and secondary optic atrophy. speedy recovery of vision along with resolution of clinical signs with no aggravation of systemic infection has been observed in patients with

extensive panretinal vasculitis and exudative retinal detachment.

Intravenous immunoglobulins are considered in cases poorly responding to systemic corticosteroids. Bacsal et al treated their patients with IVIG when there was no improvement noted after IV methylprednisolone. Chang et al started IVIG (0.4 g/kg/day for 3 days) after deterioration of vision when IV methylprednisolone was initiated and obtained a favourable outcome with IVIG.

Rare cases of dengue associated panophthalmitis has been reported in the past. All of these patients were treated with intravenous fluids and antibiotics followed by evisceration.

Conclusion

Dengue associated eye disease has a spectrum of ocular manifestations, ranging from non-specific symptoms to severe sight-threatening ocular involvement. Because of global expansion of dengue virus transmission and gradual increase in dengue outbreak in last few years, every ophthalmologist should be aware of various ocular manifestations of dengue associated eye disease.

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