

## **Review Article**

### **Dengue-related ocular pathology: A Review**

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#### **Abstract**

Dengue is the fastest resurging arthropod-borne viral infection. Over last few decades it has become an important public health problem with considerable increase in its geographical area of spread as well as number of cyclic epidemics. With increasing epidemicity of dengue virus, a surge has been seen in studies reporting dengue-related ocular pathology in the literature. These studies have reported a spectrum of ocular manifestations in dengue patients, ranging from non-specific symptoms to severe vision threatening complications. Considering the range of ocular involvement in dengue patients, we conducted an iterative search of the published literature through “Pubmed”, “Medline” and “Google Scholar” databases. Search terms “ocular manifestations”, “ocular complications”, “Dengue virus”, “dengue fever” and “dengue haemorrhagic fever” were used separately as well as in combinations. This review mainly describes the clinical picture, diagnosis and management of dengue-related ocular pathology in addition to brief discussion of epidemiology, clinical features, diagnosis and management of dengue itself.

**Keywords:** ocular manifestation; ocular complication; dengue virus; dengue fever; dengue haemorrhagic fever

#### **1. Introduction**

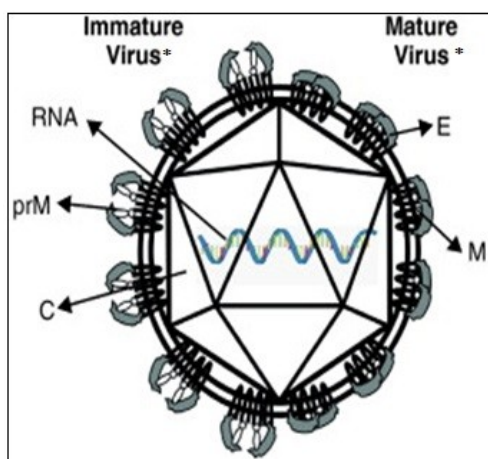
Ocular microbiology is an important part of ophthalmology. The role of all types of microorganism such as viruses, bacteria, fungi and parasites in ocular pathology is well known. These organisms can affect all the components of eye, directly or indirectly. In the recent years, emerging or re-emerging viral infections represent an important problem of public health. Ocular involvement in patients of these newly evolving or resurging viral diseases are being reported in several studies and case reports all over the world. Among these viral diseases, the frequency of ocular involvement in chikungunya, dengue, nephropathia epidemica (caused by Hantavirus), West Nile fever, and Rift Valley fever have been quite significant.<sup>1</sup>

Dengue virus is the fastest re-emerging arbovirus today. It has become a worldwide public health problem, especially affecting the South-East Asia.<sup>2</sup> A myriad of ocular manifestations, ranging from mild subconjunctival haemorrhage to vision threatening complications such as optic neuropathy and panophthalmitis, have been reported in literature.<sup>2-6</sup> Considering the range of ocular involvement in dengue patients, we conducted an iterative search of the published literature through “Pubmed”, “Medline” and “Google Scholar” databases. Search terms “ocular manifestations”, “ocular complications”, “Dengue virus”, “dengue fever” and “dengue haemorrhagic fever” were used separately as well as in combinations. This review mainly describes the clinical picture, diagnosis and management of dengue-related ocular pathology in addition to brief discussion of epidemiology, clinical features, diagnosis and management of dengue itself.

## 2. Epidemiology of Dengue

**2.1 Agent factor:** Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae*. It is a single-stranded positive-sense RNA virus, which is small (40-50 nm) and spherical with a lipid envelope [Figure 1]. There are four antigenically related, but, distinct, dengue virus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4), all of which can cause dengue.<sup>7</sup> All four serotypes are phylogenetically distinct, and often to the same degree as different species of flaviviruses.<sup>8</sup> Because of this dissimilarity between different serotypes, infection with one serotype provides lifelong immunity against that particular serotype, but no cross-protective immunity against others.<sup>9</sup> Double infection with more than one dengue serotype results in severe illness in the form of dengue hemorrhagic fever. The first infection probably sensitizes the patient, and the second infection causes an immunological catastrophe.<sup>10</sup>

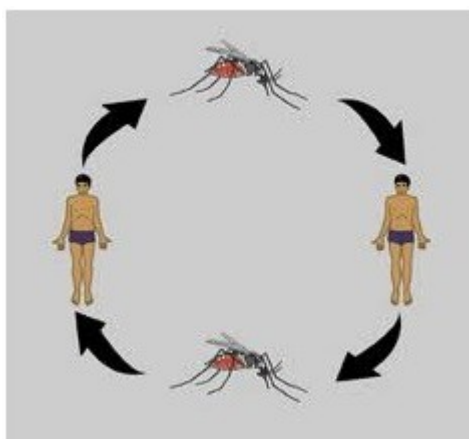
**Figure 1: Structure of Dengue virus**



\*Immature viruses become mature with conversion of prM gene into M gene coding for Membrane (M) protein.

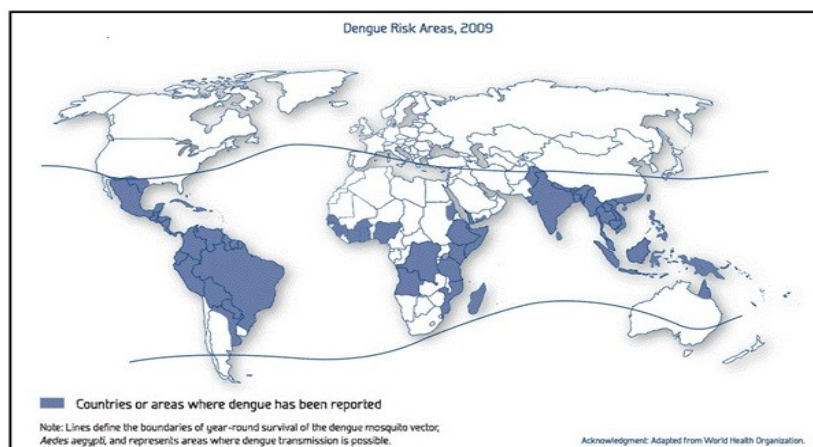
**2.2 Transmission:** Dengue is an arthropod borne viral infection and transmitted mainly by *Aedes aegypti* mosquito. *Aedes albopictus* and *Aedes polynesiensis* also play minor role in transmission of dengue virus. Both man and mosquitoes act as reservoir of dengue infection. The transmission cycle is “man-mosquito-man” [Figure 2].<sup>7,9</sup> The prevalence of *Aedes aegypti* and *Aedes albopictus* together in any particular area has been reported to be associated with outbreaks of dengue fever with shock.<sup>11</sup> The epidemics of dengue often start in rainy season when the breeding of the vector mosquitoes is generally abundant.<sup>9</sup> Temperature also plays an important role in the transmission of virus by mosquito as it has been reported that mosquitoes kept at 26°C fail to transmit DEN-2 virus.<sup>11</sup>

**Figure 2: Transmission cycle of Dengue virus**



**2.3 Public health problem:** Dengue is the fastest resurging arboviral infection of the tropical and subtropical regions. Over the past three decades, the geographic spread of both the mosquito vectors and the viruses has led to the global resurgence of the disease and dramatic increase in the number of cases [Figure 3].<sup>2,9</sup> During a pandemic of dengue, 1.2 million cases were reported from 56 countries in 1998.<sup>12</sup> It has become an endemic disease in most of the countries of South-East Asia region including India, Sri Lanka, Bangladesh, Indonesia, Thailand and Myanmar.<sup>9</sup> According to a WHO report, the maximum burden is borne by countries of the Asia-Pacific region. Among an estimated 2.5 billion population at risk globally, about 1.8 billion (more than 70%) reside in Asia Pacific countries.<sup>13</sup> According to a multinational study, the number of infections stood at 390 million a year and India had the highest burden, accounting for about a third of the world's cases.<sup>14</sup> In India the cyclical epidemics are becoming more frequent causing increasing number of hospitalization and death. The latest outbreak of dengue in India occurred in 2012 during which a total of 47,029 cases were reported.<sup>15</sup>

**Figure 3: World map showing geographical spread of Dengue virus**



### 3. Clinical features

Dengue virus infection in humans causes a spectrum of illness ranging from inapparent or mild febrile illness to severe and fatal haemorrhagic disease. The incubation period varies from 3 to 14 days.<sup>7</sup> Two most common presentations of dengue infection are dengue fever and dengue haemorrhagic fever.

**3.1 Dengue Fever:** Dengue fever (DF) is a self-limiting disease and represents majority of cases of dengue infection. All ages and both sexes are susceptible to dengue fever.<sup>9</sup> Classic dengue fever is characterized by sudden onset with chills and high fever, intense frontal headache, body aches, muscle and joint pains.<sup>7,9</sup> Retro-orbital pain develops within 24 hours of fever onset.<sup>9</sup> Other common symptoms include nausea, vomiting, anorexia, altered taste sensation, constipation, colicky pain, sore throat and cutaneous rashes.<sup>7,9</sup>

Fever lasts for 2 to 7 days and the temperature may rise to 102° to 105°F. Fever typically but not inevitably rebounds 12 to 24 hours later (biphasic curve).<sup>7,9</sup> A relative bradycardia, injected conjunctiva and lymphadenopathy is common.<sup>7</sup> The skin eruptions appear in 50-80% cases during remission or during second febrile phase. During the first half of febrile phase, rashes appear on face and neck in the form of diffuse flushing, mottling or fleeting pin-point eruptions lasting for 1-2 days. A second rash, maculopapular or scarlatiniform, may appear between days 2 and 6 of illness, which starts from chest and trunk and may spread to extremities and rarely to face. The second rash lasts for 2-3 days.<sup>7,9</sup>

Mild to severe haemorrhagic manifestations in dengue fever in patients are not uncommon and include skin haemorrhages like petechiae and purpura, gum bleeding, epistaxis and menorrhagia. Haematuria as well as jaundice is rare.<sup>7</sup>

**3.2 Dengue Haemorrhagic Fever:** Dengue haemorrhagic fever (DHF) is a syndrome that in its most severe form can threaten the patient's life. General features of this syndrome are similar to those of dengue fever. During the acute phase of illness, DHF is difficult to distinguish from dengue fever or other viral fever. Though DHF may affect adults, it is mainly a disease of the children below 15 years of age, with greater risk of developing haemorrhagic shock in infants below 1 year of

age.<sup>16</sup> The characteristic clinical features of DHF include high fever of sudden onset; haemorrhagic manifestations like petechiae, purpura, ecchymosis, epistaxis, gum bleeding, haematemesis and/or melaena; and hepatomegaly.<sup>9</sup> DHF is defined by WHO as a clinical syndrome characterized by these clinical features associated with thrombocytopenia (platelet count  $<100 \times 10^9$  cells/L) and haemoconcentration (hematocrit  $>20\%$  above baseline).<sup>17</sup>

Fever in DHF is typically acute in onset, high, continuous and lasts for 2 to 7 days.<sup>9</sup> The most common haemorrhagic manifestation observed is scattered petechiae, most often appearing on the extremities. Purpuric rash and large ecchymotic lesions may also develop. Most severely ill patients have gastro-intestinal haemorrhage, manifesting as haematemesis and/or melaena. Without early diagnosis and proper management, DHF patients develop shock due to excessive plasma leakage or less commonly due to blood loss.<sup>7</sup> This condition of DHF with shock is defined as Dengue Shock Syndrome (DSS). DSS, the most severe form of the disease, is associated with hypotension, narrowing of pulse pressure and circulatory failure in 30% of cases.<sup>17</sup> Hepatomegaly is a common but not constant finding in patients with DHF or DSS. Hepatomegaly varies from one epidemic to another, which indicates the differing role of virus strain/serotype in liver pathology.<sup>18</sup> Clinical severity of DHF is graded into four levels according to two pathophysiological hallmarks – shock and bleeding [Table 1].<sup>9</sup>

**Table 1: Grading of severity of DHF**

Grade I*	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Non-specific constitutional symptoms</li> <li>• Positive tourniquet test</li> </ul>
Grade II*	<ul style="list-style-type: none"> <li>• Grade I +</li> <li>• Spontaneous bleeding e.g. cutaneous, gastrointestinal</li> </ul>
Grade III	<ul style="list-style-type: none"> <li>• Circulatory shock</li> <li>• Rapid and weak pulse</li> <li>• Narrow pulse pressure (<math>\leq 20</math> mm Hg)</li> <li>• Hypotension</li> <li>• Cold clammy skin</li> </ul>
Grade IV	<ul style="list-style-type: none"> <li>• Profound shock with undetectable blood pressure</li> </ul>

\*The presence of thrombocytopenia with concurrent increased haematocrit value differentiates grade I and grade II DHF from DF and other diseases.

The mortality rate in untreated DHF/DSS can be as high as 10-15% if patients do not have emergency access to supportive treatment with intravenous fluids and platelet replacement.<sup>17</sup>

#### 4. Ocular manifestations of Dengue virus

Ocular involvement in dengue, though rare, is not uncommon. Various ocular pathologies, involving anterior as well as posterior segments, related to dengue have been reported in many studies including well conducted studies, case series and case reports. Dengue-related ocular complications have been widely studied in South-East Asian countries over last few years. Based on the review of these studies, ocular pathologies related to dengue virus have been described under following headings.

**4.1 Demographic features:** The prevalence of dengue-related ocular pathology ranges from 10% to 40%.<sup>3,19</sup> Ocular manifestations of dengue have been reported in patients of all age group, but younger adults, with mean age in early thirties, are more commonly affected.<sup>2-4,19</sup> Ocular complications has been reported in both sexes with no sex predilection,<sup>1,2</sup> while others have reported slight male predilection (M:F 3:2).<sup>3,4,19</sup> In majority of the patients ocular involvement is bilateral, but asymmetric.<sup>2,19,20</sup> Patients presenting with vision threatening complications report to the ophthalmologists usually one week after the onset of fever. This phase of dengue fever coincides with the nadir of thrombocytopenia – just before recovery of platelet count.<sup>2,4,21</sup> Most of the studies related to ophthalmic complications of dengue are from South-East Asian countries like Singapore, Thailand and Taiwan, and from India, with a surge in recent years correlating to the resurgence of dengue infection in this geographical part of the world.<sup>2-6,17,19-24</sup> Reporting of dengue-related ocular complications from other continents is relatively rare.<sup>25,26</sup>

**4.2 Symptoms:** Dengue patients may present with various symptoms including visual blurring, conjunctival redness, retro-orbital pain, scotoma and impairment of colour vision. The magnitude of these symptoms has been variable.

**Visual blurring** is the most common presenting ocular symptoms of the dengue patients varying from 50% to 90%.<sup>2,4,20,23,27</sup> Among patients of dengue-related maculopathy, higher frequency of visual blurring has been reported. In a study by Bascal *et al*, visual blurring was present in 87% of eyes (62 out of 71) with dengue-related maculopathy, while Chan *et al* reported visual blurring in 92.3% of patients (12 out of 13).<sup>2,20</sup> Patients of dengue-related maculopathy presents with impairment of central vision. The presenting best corrected visual acuity ranges from 6/6 to counting fingers.<sup>2,4,19,23</sup> Teoh *et al* compared level of visual blurring with three patterns of maculopathy based on Optical Coherence Tomography (OCT) and found that patient with macular oedema had poorer visual acuity and the level of visual loss and prognosis correlated with the amount of macular oedema.<sup>27</sup> However, in a study reported from India by Kapoor *et al*, ocular findings were present in 54% of dengue patients, but interestingly none of the patients presented with any visual complaints.<sup>3</sup> This unusual presentation may be explained by the fact that the fundus was affected in only 7.5% of eyes, and that too with sparing of macula in all eyes. This fact can further be explained by the study of Chee *et al*, in which it was found that the prevalence of dengue maculopathy and related findings differed during two epidemics caused by differing predominant virus serotypes.<sup>28</sup>

**Scotoma** is the second most common symptom reported by patients with dengue-related ocular pathology.<sup>2,4,20,21</sup> Its presence ranges from 30% as reported by Teoh *et al* to 92.3% as reported by Chan *et al*.<sup>2,4</sup> The areas of scotoma correspond to the area of oedema and haemorrhage in the macula.<sup>28</sup> However, scotoma is not present in all patients of dengue-related maculopathy as reported by Teoh *et al*.<sup>4</sup>

Other less commonly reported visual symptoms include metamorphopsia, floaters and impairment of colour vision. Metamorphopsia and micropsia were reported by patients having macular oedema and/or retinal haemorrhage.<sup>4,24,27,29</sup> Floaters were usually result of retinal haemorrhage.<sup>4,20,27,30,31</sup> Seet *et al* reported that the triad of ocular symptoms including floaters, eye flashes and blurring of vision is highly predictive for the development of retinal haemorrhages following dengue infection.<sup>31</sup> Impaired colour vision is very rarely reported symptom resulting from dengue-related optic neuropathy.<sup>5</sup>

Other than visual symptoms, ocular pain is a relatively common symptom. However, it is described by the patients of dengue fever even if there is no ocular involvement. Most of the patients describe it as retro-orbital or retro-bulbar pain. It usually develops within 24 hours of onset of fever.<sup>9,31</sup> Redness of eye is a very common finding in dengue patients due to conjunctival congestion or due to subconjunctival haemorrhage, but it is less commonly reported by patients as presenting complaint.<sup>4</sup>

### 4.3 Ocular signs and complications

**4.3.1 Anterior segment: Subconjunctival haemorrhage** is the manifestation of haemorrhagic nature of the disease, and is the most common anterior segment finding in dengue patients. However, its prevalence has varied significantly in different studies. In a study from eastern India in 2006, Kapoor *et al* reported subconjunctival haemorrhage as the commonest eye finding, seen in about 90% (50 out of 54) of eyes affected by dengue fever.<sup>3</sup> Among 50 eyes with subconjunctival haemorrhage, 84% eyes (n = 42) had characteristic petechial haemorrhage while rest eyes had diffuse haemorrhages. In another study from Singapore, subconjunctival haemorrhage was reported as uncommon ocular finding, seen in only 4.6% of eyes.<sup>4</sup>

**Uveitis** is the second most common, but relatively rare pathology involving the anterior segment of eye.<sup>2,23</sup> Teoh *et al* reported that anterior uveitis and intermediate uveitis were present in 7.7% and 12.3% of eyes with ocular involvement respectively.<sup>4</sup> In another study of 41 patients with dengue related ocular pathology, Bascal *et al* found prevalence of anterior, posterior and panuveitis as 17% (n = 12), 31% (n = 22) and 11% (n = 8) of eyes respectively.<sup>20</sup> In an Indian case series of six patients with uveitis following dengue fever, Gupta *et al* noticed anterior uveitis with no involvement of posterior segment in five patients, while one patient had severe vitritis.<sup>32</sup> Uveitis usually present as delayed complication with progressive decrease in vision and sometimes ocular redness due to ciliary congestion about 3-5 months after contracting dengue fever. Slit-lamp examination of these patients shows floating inflammatory cells in aqueous humour or in vitreous depending upon the location of uveitis.



Other rarely reported anterior segment signs include dengue-related shallowing of anterior chamber with normal intraocular pressure (IOP) following bilateral choroidal effusion, and shallow anterior chamber with raised IOP due to bilateral angle closure glaucoma in a patient with dengue fever.<sup>25,33</sup>

#### 4.3.2 Posterior segment

**4.3.2.1 Dengue-related Maculopathy:** The typical fundus picture with predominant macular involvement in dengue patient has been described as dengue-related maculopathy. Dengue-related maculopathy results from the involvement of retinal vessels and/or choroidal vessels with a predilection for macular area.<sup>1</sup> Studies have reported prevalence of maculopathy ranging from 7.5% to upto 80% among dengue patients.<sup>3,4</sup> This extreme range of maculopathy has been explained in the study of Chee *et al*, who concluded that the prevalence of maculopathy may differ during two epidemics caused by two different serotypes of dengue virus.<sup>28</sup> As described earlier, ocular symptoms range from mild blurring of vision to severe loss of vision, usually starting one week after onset of fever. Macular oedema and retinal haemorrhage are two most common fundus findings of dengue-related maculopathy, others being venular and arterial sheathing, yellow subretinal dots, round foveal swelling (foveolitis), disc hyperaemia and disc oedema.<sup>2-4,20-24</sup>

Macular oedema has been reported as the most common fundus finding in some studies. Teoh *et al* found macular oedema in 76.9% eyes (n = 50) out of 65 eyes with dengue-related ocular signs.<sup>4</sup> Similar frequency (10 patients out of 13) of macular oedema was reported by Chan *et al*.<sup>2</sup> Based on OCT features, Teoh *et al* described three patterns of dengue-related macular oedema namely diffuse oedema, cystic oedema and cystic foveolitis. They also concluded that the visual outcome was independent of the extent of oedema, but scotoma persisted longest in patients with foveolitis and shortest in those with diffuse macular thickening.<sup>28</sup>

Retinal haemorrhage in dengue related maculopathy may be deep or superficial intraretinal haemorrhage appearing as dot and blot haemorrhage, and flame-shaped haemorrhage respectively. It has been reported either as the most common or sometimes second most common fundus finding following macular oedema in patients with dengue maculopathy.<sup>2-4,20-24</sup> Teoh *et al* reported retinal haemorrhage in 69.2% eyes (45 out of 65 eyes), while it was present in 45% eyes (32 out of 71 eyes) as reported by Chan *et al*.<sup>2,4</sup> Retinal haemorrhage is usually associated with vascular sheathing and vasculitis.

Foveolitis is the term used for a distinct fundal finding of dengue maculopathy seen as yellow-orange lesion at fovea. This foveal lesion corresponds to a disruption of the outer neurosensory retina seen in OCT image. Dengue-related foveolitis term was first described by Loh *et al* in 10 eyes of 6 patients.<sup>34</sup> However, previously similar findings of yellow subretinal dots were reported by Su *et al* and Bascal *et al*.<sup>19,20</sup>

**4.3.2.2 Optic Neuropathy:** Optic neuropathy is relatively uncommon ocular complication in patients of dengue related ocular pathology. It commonly presents in the form of disc swelling, disc hyperaemia and disc haemorrhage.<sup>4,20</sup> Bascal *et al* noticed disc oedema in 11% eyes (n = 8) and disc hyperaemia in 14% eyes (n = 10).<sup>20</sup> Teoh *et al* reported disc swelling in only 3.1% eyes (n = 2) and optic neuritis in only one eye (1.5%).<sup>4</sup> In a case series of three patients of optic neuropathy associated with dengue fever, Sanjay *et al* reported the progression of the disease to optic atrophy with no light perception.<sup>5</sup>

**4.3.2.3 Other Posterior segment complications:** Panuveitis and posterior uveitis with vitritis are uncommon but not rare in dengue patients with posterior segment involvement.<sup>20,32</sup> Even a case of panophthalmitis with eventual loss of vision has been reported in a child with dengue fever.<sup>6</sup> Exudative retinal detachment is a rarely reported ocular complications due to vascular leakage from inflamed vessels.<sup>20,26,29</sup> Vitreous haemorrhage is another rarely reported complication in dengue patients.<sup>20,30</sup> Cases of retinal vascular occlusion resulting from occlusive vasculitis have also been reported in few studies.<sup>29,35</sup>

**4.4 Pathogenesis:** Haemorrhagic signs are manifestations of haemorrhagic nature of the disease and usually coincide with the nadir of thrombocytopenia. But, the pathophysiologic mechanism of dengue-related maculopathy is not clear. However, a number of factors suggest immune-mediated mechanism rather than direct viral involvement. The ocular symptoms usually appear with a delay of about one week after onset of dengue fever.<sup>2,4,21</sup> Dengue-related uveitis can present in otherwise normal patients at 3-5 months after contracting the infection.<sup>32</sup> The serum complement C<sub>3</sub> levels in patients with maculopathy have been found lower than those in patients without maculopathy.<sup>19</sup> In addition to these factors, use of

corticosteroids, local as well as systemic, has been reported for successful management of maculopathies.<sup>2,20,23</sup>

**4.5 Investigations for ocular complications:** OCT imaging and fundus angiography, fluorescein as well as Indocyanine green, are most valuable investigations to diagnose and evaluate the cases of dengue-related maculopathy. Other tests to evaluate scotoma and central visual defect are Amsler grid test and visual field perimetry.

OCT imaging of macula has been used to evaluate the retinal thickness and morphology. Teoh *et al* described three patterns of maculopathy based on OCT images of macula, while Loh *et al* described the term “foveolitis” for the lesions corresponding to an area of disruption of outer neurosensory retina seen on OCT.<sup>27,34</sup> OCT is also useful for assessing the severity and monitoring the progress of exudative retinal detachment in eyes with retinal vascular leakage.<sup>1</sup>

As maculopathy results from the involvement of the retinal and /or choroidal vessels, Fundus Fluorescein Angiography (FFA) and Indocyanine Green Angiography (ICG) provide important informations for evaluation of these conditions. The main FFA findings include blocked fluorescence, venular occlusion, venular leakage, arterial occlusion, arterial leakage, retinal pigment epithelial (RPE) window defect and capillary non-perfusion.<sup>20</sup> ICG is less commonly used for evaluation of maculopathy. However, ICG showed hypofluorescent spots during the mid to late phase, corresponding to yellow subretinal dots in 29% of cases as compared to only 15% of cases seen on FFA as early hyperfluorescent spots.<sup>20</sup>

## 5. Diagnosis<sup>7,9,36</sup>

A definitive diagnosis of dengue infection can be made only in the laboratory and depends on isolating the virus, detecting viral antigen or RNA in serum or tissues, or detecting specific antibodies in the patient’s serum.<sup>7</sup>

Among serological tests, IgM antibody capture- enzyme linked immunosorbent assay (MAC-ELISA) has become the most widely used serological test for dengue diagnosis in the past few years. MAC-ELISA works by capturing anti-dengue IgM antibody with high sensitivity and specificity. It is a simple, rapid test that can be performed with serum, blood on filter paper or saliva sample. Sample should ideally be collected on day 5 or later after onset of fever. Indirect IgG-ELISA is another serological test, which confirms recent infection if there is four fold or greater rise in IgG antibody between acute (day 5) and convalescent (after day 15) sera. Haemagglutination inhibition (HI), complement fixation (CF) and neutralisation test (NT) are other serological tests used for laboratory diagnosis of dengue.

Reverse transcriptase – polymerase chain reaction (RT-PCR) is a recently developed diagnostic modality for diagnosis of dengue infection. RT-PCR is based on detection of viral RNA and is a rapid, sensitive, simple and reproducible method. Detection of viral antigens like envelope/membrane (E/M) antigen and non-structural protein 1 (NS1) is also used for diagnosis. As all these tests are based on detection of viral elements, the sample collected during first five days after onset of fever can be used for early confirmation of the disease.

Virus isolation is the most specific test for virus identification, however, it is not routinely used for diagnostic purpose. The specimen should be collected before day 5 of fever onset i.e. during the period of viremia. The commonly used isolation system for dengue virus includes mosquito cell line C6/36 and AP61, mammalian cell line such as BHK21 and LLC-MK<sub>2</sub>, intrathoracic inoculation of adult mosquito and intracerebral inoculation of suckling baby mice. Virus isolation usually takes 1-2 weeks. Interpretation of dengue diagnostic tests has been summarised in Table 2.

**Table 2: Interpretation of dengue diagnostic tests**

Highly suggestive	Confirmed
One of the following: <ul style="list-style-type: none"> <li>• IgM antibody + in a single serum sample</li> <li>• IgG antibody + in a single serum sample with a HI titre of 1280 or greater</li> </ul>	One of the following: <ul style="list-style-type: none"> <li>• PCR +</li> <li>• Virus culture +</li> <li>• IgM antibody seroconversion in paired sera sample</li> <li>• IgG antibody seroconversion or four fold rise in IgG titre in paired sera sample</li> </ul>

In addition to microbiological tests used for confirmation of diagnosis, haematological tests are used to monitor the course of the disease and to adjust the volume replacement therapy. In dengue fever and DHF, thrombocytopenia is commonly seen and platelet count falls below 1lakh/ $\mu$ l. A rise in haematocrit value of 20% or more is suggestive of

hypovolemia resulting from increased vascular permeability and ongoing plasma leakage. In DHF, bleeding time (BT) and clotting time (CT) are also prolonged, with increase in prothrombin time and partial thromboplastin time.

## 6. Management

**6.1 Dengue fever, DHF and DSS:** The management of dengue fever is symptomatic and supportive. Bed rest, antipyretic and/or sponging are sufficient during acute febrile phase. Aspirin should be avoided in DHF endemic areas as it predisposes for haemorrhagic manifestations. Oral fluid and electrolyte therapy is recommended for patients with excessive sweating, vomiting and diarrhoea.<sup>9,11,37</sup>

The management of DHF during the febrile phase is similar to that of DF. However, parenteral fluid therapy is needed when haematocrit value starts to rise due to significant plasma loss. Hospitalization should be done in patients with any signs of bleeding and persistently high haematocrit. The crystalloid (five percent dextrose in lactated Ringer's solution) and colloidal (dextran 40 and plasma) are types of fluid used for volume replacement. The volume of fluid replacement should be titrated according to vital signs and should be kept to minimum, but sufficient to maintain effective circulation. DSS is a medical emergency that requires prompt and vigorous volume replacement therapy. Initially crystalloid fluid is used for rapid volume replacement, however, colloidal fluid is indicated in cases with massive leakage, and to whom a large volume of crystalloid fluid has been given. Blood transfusion is indicated in cases with profound or persistent shock despite declining haematocrit values after initial fluid replacement. Prophylactic platelet transfusions for severe thrombocytopenia in otherwise haemodynamically stable patients have not been shown to be effective and hence are not necessary.<sup>9,11,37</sup>

**6.2 Ocular complications:** Dengue-related ocular pathologies are usually self-limiting.<sup>1</sup> Clinical signs resolve spontaneously and rapidly within 3 days in majority of the patients as they recover from thrombocytopenia with conservative management.<sup>2,4,21</sup> However, for cases not resolving spontaneously a variety of treatment modalities have been tried in different studies. As immune-mediated pathogenesis has been suggested for dengue-related ocular complications, the mainstay of these treatment regimens was immunosuppression with corticosteroids. Corticosteroids have been administered through various routes like topical, periocular, oral and intravenous depending upon the location of ocular pathologies. No studies have reported adverse effect of steroids. Topical steroid drops have been used for early or delayed onset anterior uveitis, while periocular and oral steroids for posterior uveitis and panuveitis.<sup>2,4,20,32</sup> Use of oral and intravenous corticosteroids for severe retinal vasculitis and exudative retinal detachment has been reported successfully.<sup>2,4,20</sup> Patients with optic neuropathy should be treated with pulse therapy of intravenous steroid followed by oral steroid.<sup>4</sup> Prognosis for ocular complications of dengue is very good with or without treatment. However, patients may experience mild relative scotoma that may persists for months.<sup>2</sup>

**7. Concluding Remarks:** Dengue is an old disease and is endemic in tropical countries. However, over last few decades its area of geographical spread as well as number of cyclic epidemics have increased considerably. With resurgence in incidence of dengue cases, there is a sharp increase in reporting of dengue-related ocular complications in literature. This review concludes that dengue virus results in a spectrum of ocular manifestations, ranging from non-specific symptoms to severe vision threatening complications. The pathogenic mechanism of ocular involvement in dengue is not clear, but immune-mediated mechanism has been suggested based on various findings. Fortunately, prognosis is generally good as the disease is often self-limiting, resolving spontaneously even without treatment. Though rarely, sometimes the situation may get complicated and may end in permanent loss of vision. With increasing epidemicity and co-circulation of multiple dengue serotypes, an increase in the occurrence of DF and DHF, and hence, dengue-related ophthalmic morbidity can be expected. Therefore, a high level of awareness and attentiveness is required on the part of both physicians and ophthalmologists to provide timely and proper management for dengue-related ocular pathology.

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