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## Major review

## Dengue eye disease

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## ABSTRACT

Dengue fever, a viral disease epidemic in some parts of the world, is of considerable international concern, with a growing incidence owing to developing urbanization, tourism, and trade. Ocular manifestations of dengue fever are uncommon, but of great significance. Proposed mechanisms include direct viral infection as well as immunologic phenomena. Common manifestations include subconjunctival, vitreous, and retinal hemorrhages; posterior uveitis; optic neuritis; and maculopathies such as foveolitis, hemorrhage, and edema. Main symptoms include blurring of vision, scotomata, metamorphopsia, and floaters. Diagnostic and monitoring investigations described included optical coherence tomography, fundus fluorescein and indocyanine green angiography, visual field analysis, and electrophysiologic tests. Management is based on clinical presentation and includes active surveillance as well as various anti-inflammatory and immunosuppressive therapies. There have been no prospective, randomized therapeutic trials, and it is unclear if the disease is self-limiting or if treatment is actually beneficial. Prognosis varies, ranging from full resolution to permanent vision loss despite intervention.

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## 1. Introduction

Dengue fever, a viral epidemic, imposes a large health care burden in endemic regions and is of increasing international concern as a result of growing urbanization, tourism, and trade. There are an estimated 50 million dengue infections and 500,000 dengue-related hospitalizations annually,<sup>18</sup> the majority from endemic regions such as the Americas,

Southeast Asia, and the Western Pacific.<sup>A</sup> There are an increasing number of case reports from outside endemic regions noting a history of travel to these areas.

Dengue viruses are flaviviridae of four serotypes (DEN-1, DEN-2, DEN-3, DEN-4) spread via mosquito vectors.<sup>20</sup> The predominant vectors are *Aedes aegypti* and *Aedes albopictus*.<sup>16,23</sup> Other species that have been implicated include *Aedes polynesiensis* and the *Aedes scutellaris* complex.<sup>35</sup>

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The clinical presentation of dengue fever ranges from a febrile illness to life-threatening dengue shock syndrome (DSS). Classically, the disease is characterized by symptoms that appear about 3–14 days after a bite from the vector. The main clinical features are an acute onset of high-grade fever ( $>40^{\circ}\text{C}$ ) lasting 2–7 days, accompanied by classical symptoms of headache, myalgia, arthralgia, body ache, skin erythema, and facial flushing. Nonspecific symptoms such as anorexia, nausea, and vomiting are also commonly present. Hemorrhagic manifestations such as petechiae and mucosal bleeding may also be observed.<sup>13</sup>

The pathogenesis of systemic dengue infection is currently believed to be multifactorial, complex, and as yet not fully understood, but factors that have been postulated in its pathogenesis include the humoral immune response, cell-mediated immune response, viral determinants, host genetic determinants, as well as other host determinants.<sup>53</sup>

## 2. Laboratory diagnosis of systemic illness

Based on guidelines published by the World Health Organization (WHO), polymerase chain reaction, virus isolation, or detection of viral antigens should be used before the fifth day of illness. After 5 days, dengue serologic tests such as IgM ELISA/rapid tests or IgG paired sera should be used because the viral load will have decreased.<sup>4</sup>

## 3. Classification of systemic illness

A new classification system adopted by WHO in 2009 categorizes dengue fever based on the severity of disease. Severe dengue fever is defined by at least one of the following: severe bleeding, severe organ impairment, or plasma leakage. Most of the literature available on the topic of dengue eye disease has used the 1997 dengue classification. This includes dengue fever and dengue hemorrhagic fever (DHF). DHF is defined by fever, hemorrhagic tendency, thrombocytopenia ( $\leq 100,000$  platelets/ $\text{mm}^3$ ), and evidence of plasma leakage. This is further sub-classified into four grades. Grades III and IV, where circulatory failure is present, are also known as DSS.<sup>35</sup>

## 4. Epidemiology of dengue-related eye disease

Traditionally, ocular pathology in dengue fever has been thought to be uncommon, although ocular involvement in dengue fever is increasingly recognized. Gupta et al reported that 137 out of a total of 1,719 patients (7.9%) with dengue infection seen at a tertiary hospital had ocular involvement.<sup>17</sup> The prevalence of ocular involvement in hospitalized patients with dengue infection in India was estimated to be between 16% and 40.3%.<sup>B,22</sup>

## 5. Risk factors

Age, sex, and ethnic group were not shown to be risk factors.<sup>45</sup> Chee et al reported the possibility of dengue maculopathy to

be serotype-specific. No maculopathy was reported during a DEN-2 epidemic, whereas there was a 10% incidence during a DEN-1 epidemic.<sup>7</sup> This has not been corroborated with other literature.

Significant predictors of ocular symptoms described include leukopenia and hypoalbuminemia. Seet et al postulated that these could predispose to opportunistic infection of the ocular tissues and increased vascular permeability, respectively.<sup>42</sup>

## 6. General symptomatology of dengue eye disease

Dengue eye disease can be either unilateral or bilateral. The time of onset of ocular symptoms ranged from 2 days to 5 months from the start of fever, but most ocular symptoms were noted to have occurred within 1 day of the nadir of thrombocytopenia ( $\sim 7$  days after the onset of fever).<sup>C,5</sup>

The main ocular complaints were eye strain (30%), retro-ocular pain (20%), blurring of vision (10%), diplopia (3%), foreign body sensation (3%), photopsia (2%), and floaters (1%).<sup>42</sup> Patients with established ocular pathology associated with dengue fever reported blurring of vision (60%), central scotomata (30%), floaters (6%), near-vision disturbances (6%), and metamorphopsia (4%). Bilateral involvement was observed in 30% of patients, and visual acuity ranged from 20/20 to counting fingers (CF), with a median of 20/40.<sup>50</sup>

## 7. Clinical features of dengue eye disease

Anterior segment abnormalities include subconjunctival hemorrhage, keratitis, corneal erosion, acute angle closure, anterior uveitis, and intermediate uveitis. Posterior segment pathology include retinal hemorrhages, posterior uveitis, foveolitis, maculopathy, retinal vascular occlusions, and serous retinal detachment. Neuro-ophthalmic disorders include optic neuritis, cranial nerve palsies, and neuromyelitis optica. Panophthalmitis, periorbital ecchymosis, and other hemorrhagic complications may also occur.

### 7.1. Subconjunctival hemorrhage

Subconjunctival hemorrhage is a common finding in dengue fever and may occur either unilaterally or bilaterally. The reported incidence ranged from 8–60%, independent of the platelet count.<sup>B,22</sup> Mehta et al reported 3 of 5 patients with DHF manifested subconjunctival hemorrhages during an intensive care unit stay.<sup>29</sup> In a prospective cohort study of 134 patients, an incidence of 37.3% was observed, of whom 90.7% had marked thrombocytopenia of  $<50,000/\mu\text{L}$ .<sup>22</sup> Another study of 50 patients with platelet counts of 13,000–40,000/ $\mu\text{L}$  had subconjunctival hemorrhages in 8%.<sup>B</sup>

### 7.2. Anterior uveitis

Iritis with dengue fever infection was first described in two cases in 1929.<sup>11,39</sup> Clinical diagnosis is based on the symptoms of eye pain, redness, and photophobia and signs of perilimbal

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