

## OPHTHALMIC MANIFESTATIONS OF DENGUE FEVER

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### ABSTRACT

**Objective:** To describe the clinical spectrum of ophthalmic manifestations in patients presenting with dengue fever during the outbreak at Lahore in autumn of 2011.

**Study Design:** Prospective study.

**Place and Duration of Study:** Combined Military Hospital Lahore, from Sep 2011 to Dec 2011.

**Material and Methods:** This prospective study was conducted at CMH Lahore. At most 3005 clinical dengue cases were recruited for the study from 39930 cases that reported at OPD with suspected dengue fever. All these patients were screened for ophthalmic involvement. These patients were subjected to serological analysis for detecting dengue specific IgM antibodies (IgM enzyme-linked immunoassay) and blood test for thrombocytopenia after taking written informed consent. The patients with ophthalmic involvement were subjected to detailed history, ocular examination including anterior and dilated posterior segment examination. Ophthalmic manifestations in these patients were recorded and tabulated according to the frequency.

**Results:** The study showed that dengue fever could result in a variety of ocular complications. Majority of these complications were innocuous and self limiting. Most common is subconjunctival haemorrhage. Other includes retrobulbar haemorrhage, proptosis, increased IOP, vitreous haemorrhage, retinal haemorrhage and peri ocular ecchymosis. Vision threatening complications were seen in only 1% of cases.

**Conclusion:** Dengue fever can result in a range of ocular complications so ophthalmic examination should be performed in patients presenting with all forms of the disease. The most common is sub-conjunctival haemorrhage. The vision threatening complications among these occur with involvement of posterior segment including vitreous and retinal haemorrhages. This justifies detailed fund us examination of these patients with a dilated pupil.

**Keywords:** Dengue fever, Ocular manifestation, Sub-conjunctival haemorrhage, Thrombocytopenia, Retinal haemorrhage.

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## INTRODUCTION

Dengue fever is a painful, debilitating mosquito borne disease caused by any one of four closely related dengue viruses. It is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. Dengue fever is transmitted by the bite of an Aedes mosquito infected with a dengue virus. The

mosquito becomes infected when it bites a person with dengue virus in their blood. It can't be spread directly from one person to another person. According to worldwide statistics nearly 390 million dengue infections occur worldwide each year, out of which approximately 96 million result in illness. Most cases occur in tropical areas of the world, with the greatest risk occurring in The Indian subcontinent, Southeast Asia, Southern China, Taiwan, The Pacific Islands, The Caribbean (except Cuba and the Cayman Islands), Mexico, Africa, Central and South America (except Chile, Paraguay, and Argentina). In the subcontinent the infection is endemic borne by the Aedes mosquito<sup>1</sup>. The highest incidence of this disease occurs in

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Southeast Asia, India, and the American tropics<sup>2,3</sup>. Peak incidence of dengue fever in Pakistan is from Aug to Oct<sup>4</sup>. The death rate for untreated cases suffering from Dengue complications can be as high as 10-20% in places where emergency supportive treatment is not readily accessible<sup>5</sup>. Symptoms usually begin four to six days after infection and may last for up to 10 days. These include high fever, severe headache, pain behind the eyes, severe joint and muscle pain, fatigue, nausea, vomiting, skin rash (appears two to five days after the onset of fever) and mild bleeding (such a nose bleed, bleeding gums, or easy bruising). Sometimes, symptoms are mild and can be mistaken for those of the flu or another viral infection. Younger children and people who have never had the infection before tend to have milder cases than older children and adults. Complications that can occur in the course of disease include dengue hemorrhagic fever, characterized by high fever, damage to lymph and blood vessels, bleeding from the nose and gums, liver enlargement, and circulatory system failure. The symptoms may progress to massive bleeding, shock, and death. This is called dengue shock syndrome (DSS). Patients with compromised immune systems or having second or subsequent dengue infection are at greater risk for developing dengue hemorrhagic fever. The best way to prevent the disease is to prevent bites by infected mosquitoes, particularly if living in or traveling to a tropical area. This includes protecting oneself and making efforts to keep the mosquito population down. Preventive measures include avoiding heavily populated residential areas, if possible, Use mosquito repellents, even indoors, When outdoors, exposed skin area should be minimized by wearing long sleeved shirts and long pants tucked into socks, When indoors, use air conditioning if available, Window and door screens should be secured and sealed. Use of mosquito nets should be mandatory especially in endemic months. To reduce the mosquito population, their breeding areas should be removed from premises

including old tires, cans, or flower pots that collect rain.

## **PATIENTS AND METHODS**

A prospective observational case series study was conducted at CMH Lahore from Sep 2011 to Dec 2011. All most 3005 dengue cases confirmed by clinical signs, positive IgM dengue serology and thrombocytopenia were recruited for the study after taking written informed consent. Patients with history of bleeding disorders, diabetes, hypertension, anemia and taking anti coagulants were excluded from the study as all these can cause posterior segment involvement which mimic retinal signs of dengue fever. A detailed history, physical examination, laboratory results, visual complaints were recorded in these cases. Best corrected visual acuity was documented with snellen charts. Slit lamp anterior segment and dilated fundus examination was carried out in all patients. Cases with positive ophthalmic complications were followed up at four and eight weeks with examination including visual acuity, anterior segment slit lamp examination and examination of fundus under dilatation.

## **RESULTS**

The age of patients ranges between 9-72 years with mean age of 32 years. The gender distribution and unilateral or bilateral involvement is as shown in table-I & II. Thrombocytopenia was a common finding, occurring in 74% of cases. Ocular findings were present in 332 (11%) of cases. Snellen visual acuity varied from 20/25 to counting fingers only depending upon complication. A wide range of ocular complications were observed among dengue fever patients. The most common ocular finding was subconjunctival haemorrhage, occurring in about 284 (9.45%) patients. Other ophthalmic manifestations included retrobulbar haemorrhage, proptosis, increase IOP (Intraocular pressure), vitreous haemorrhage, retinal haemorrhage and periocular ecchymosis (table-III).

## DISCUSSION

Dengue fever is a global challenge and most important viral borne disease worldwide. In recent years, it has become a major international public health concern. Dengue is one of the most important emerging viral diseases affecting the humans, especially in Southeast Asian countries posing a public health problem<sup>10</sup>. It is a communicable disease transmitted by the bite of an Aedes mosquito infected with any one of the four dengue viruses (DEN-1, DEN-2, DEN-3, and DEN-4). Recovery from infection by one provides lifelong immunity against that particular serotype. Subsequent infections by other serotypes

blood pressure (hypotension). The dengue rash is characteristically bright red petechial lesions and usually appears on the lower limbs and the chest. The lymph nodes in the neck and groin are often swollen. In some patients, the skin involvement spreads to cover other areas of the body. Intestinal involvement may cause gastritis which manifests as abdominal pain, nausea, vomiting, or diarrhea. The classic dengue fever lasts about six to seven days, with a smaller peak of fever at the trailing end of the disease in a biphasic pattern). Clinically, the platelet count will be decreased till the patient's temperature remains high. A combination of sudden onset of high fever, severe headache which is primarily frontal,

**Table-I: Gender distribution.**

S No.	Gender	No of patients	%age of patients
1	Male	2344	78
2	Female	661	22

**Table-II: Unilateral/bilateral cases.**

S No.	Unilateral/bilateral cases	No of patients	%age of patients
1	Unilateral	153	46
2	Bilateral	179	54

**Table-III: Ophthalmic complications.**

S No.	Ophthalmic complications	No of patients	%age of patients
1	Sub conj haemorrhage	284	9.45
2	Proptosis	02	0.06
3	Increase IOP	04	0.13
4	Vitreous haemorrhage	10	0.33
5	Retinal haemorrhage	19	0.63
6	Retrobulbar haemorrhage	02	0.06
7	Peri ocular ecchymosis	11	0.36

increase the risk of developing severe dengue. The spectrum of disease presentation may range from mild febrile illness to a severe potentially life threatening hemorrhagic infection. Systemic dengue infection presents most commonly with dengue fever, a self limiting illness characterized by sudden onset of severe headache, chills, pain on ocular movements, and nagging low backache. Myalgias and arthralgias present as painful aching in the legs and joints and typically occur during the first hours of illness. This may be followed by a rise in body temperature, with relative low heart rate (bradycardia) and low

pain behind the eyes which worsens with movement of the eyes, dull body aches and severe joint pains, nausea or vomiting are the signs that clinically point towards a dengue infection. There is no specific treatment available and the mosquito control measures in most of the hyper endemic areas are inadequate<sup>15</sup>. Globally 2.5 billion people live in areas where dengue viruses can be transmitted<sup>16</sup>. The prevalence of ocular involvement in dengue fever may vary according to the subtype of the virus but it may be as high as 10% in patients suffering from dengue fever<sup>3,4</sup>. Both anterior segment and

posterior segment manifestations are seen in patients presenting with dengue fever. The main ocular findings include subconjunctival haemorrhages<sup>11-14</sup>, macular edema, scattered flame and blot shaped haemorrhages, retinal vasculitis and vitreous haemorrhage<sup>7,11,12,17</sup>. A majority of patients are reported to have residual visual impairment<sup>15,16,18</sup>. Less common features include exudative retinal detachment, chorioretinitis, optic neuropathy, cotton wool spots, and anterior uveitis<sup>9,19,20,21</sup>. The disease may involve both eyes with potential to make the patient irreversibly blind in both eyes by causing bilateral vitreous haemorrhage<sup>25</sup>, bilateral stellar neuroretinitis<sup>26</sup>, bilateral choroidal effusion<sup>27</sup> and even lead to bilateral acute angle closure glaucoma<sup>28</sup>, oculomotor paralysis<sup>29</sup> and optic neuropathy<sup>30</sup>. The "Seet Quek Lim triad" of flashes of light, floaters and blurring of vision<sup>31</sup> definitely warrants detailed ophthalmic examination because it can eventually lead to loss of vision, which might be irreversible. In addition to these, other rare ocular manifestations include an opsoclonus which may be secondary to an encephalopathy<sup>32,33</sup>. It is also imperative to note that in endemic areas, recurrence of infection may lead to recurrence of bilateral eye involvement<sup>34</sup> which might be due to different strain of Dengue virus. The pathogenesis of ocular complications of dengue fever is not well understood. The ocular features peak in acute dengue infection and correspond to the level of platelets and for this reason a common immunemediated pathogenesis has been postulated for the ocular manifestations<sup>36,38,39</sup>. Low complement C3 and C4 in dengue patients suggests an immunemediated mechanism<sup>39</sup>. The possibility of development of specific autoantibodies against various tissues of the eye has been suggested<sup>35,39</sup>. This includes the possibility of production of specific auto antibodies against retina, retinal pigment epithelium, and even choroid<sup>35,41,42</sup>. However, the precise mechanism responsible for the various ocular tissue alterations, leading to sensitization in dengue and there by, causing uveitis, is still unknown<sup>37</sup>. The release of cytokines with

vasoactive and procoagulant properties in response to immunological activation might be the causative pathology of retinal vascular occlusion seen in patients with dengue fever<sup>35</sup>. In addition, these inflammatory mediators can cause capillary leakage and breakdown of the blood aqueous barrier which results in anterior uveitis<sup>43</sup>. The spectrum of ophthalmologic manifestations would lead one to conclude that several pathophysiologic processes are involved. Thrombocytopenia in severe dengue may predispose to haemorrhage. The development of retinal haemorrhage implies local injury to retinal vessels, the cause of which remains unknown. On the other hand, increased vascular permeability in response to immunemediated cytokine release is known to occur in Dengue hemorrhagic fever<sup>22</sup>. Other postulates include viral mutations, viral virulence and host susceptibility. The commonest ocular symptom among these patients is blurring of vision followed by central scotoma. The areas of scotoma corresponds to the areas of edema and haemorrhage in the macula<sup>32</sup>. Retrobulbar or diffuse pain is also experienced by few patients. Less common symptoms are metamorphopsia, floaters and abnormal of colour vision. Ocular complications involving the anterior segment of the eye include subconjunctival haemorrhage and rarely anterior uveitis. One peculiar feature of uveitis in these patients is the absence of, or minimal ciliary congestion even in the presence of severe anterior segment inflammation. The keratic precipitates vary in size from fine to medium to large in size and are distributed through out the cornea in almost all the cases. Ocular complications involving the posterior segment of the eye include maculopathy. Dengue related maculopathy commonly presents with macular edema<sup>10,20,33</sup>. One series by Teoh *et al*<sup>36</sup> further categorized the type of macular edema based on their appearance on OCT. The three patterns of macular edema on OCT include type 1, which is diffuse edema, type 2, which is cystoid edema, and type 3, which is cystic foveolitis. Haemorrhages associated with dengue related maculopathy are mostly intraretinal and

can take the form of dot, blot, or flame shaped haemorrhages. Similar findings of intraretinal and flameshaped haemorrhages were also reported<sup>34</sup>. Macular haemorrhage<sup>6-11</sup> is the second commonest posterior segment sign of dengue fever. Dengue related foveolitis also occurs in few patients and is seen as yellow orange lesion at the fovea of patients with dengue maculopathy<sup>23</sup>, which corresponds to a disruption of the outer neurosensory retina in optical coherence tomography (OCT)<sup>34,35,11,12</sup>. Optic disc swelling, hyperemia, and disc haemorrhages are common presentations of dengue related optic neuropathy<sup>30</sup>. Other less common posterior segment sign is vitreous haemorrhage<sup>25</sup>. Ophthalmic investigations are performed mostly for posterior segment pathology. The Amsler grid test can detect scotomas in patients with dengue related maculopathy. Fundus fluorescein angiography (FFA) demonstrates mainly vascular occlusion or leakage, and aides in the diagnosis of vein occlusions<sup>11,31</sup> and vasculitis<sup>24,30,31</sup>. OCT and OCTA imaging of the macula evaluates retinal thickness and morphology<sup>24</sup>. Foveolitis is seen as an area of disruption to the outer retina of the fovea in OCT<sup>38</sup>. The most common ocular finding in our patients were sub conjunctival hemorrhages (9.45%) followed by retinal (0.63%) and vitreous haemorrhage (0.33%). Sub conjunctival haemorrhages were also commonest findings documented by Kapoor *et al*<sup>15</sup>. In our study the course of the ocular complications was generally self limiting. Anatomical and structural resolution usually starts within the first week in uncomplicated cases with good prognosis. Longer recovery period and residual visual impairment of varying degree in best corrected visual acuity is noted in severe cases. Further research work is important to assess the etiologies that are involved in ocular complications of dengue fever. In symptomatic cases with ocular involvement, steroids are the mainstay of treatment. Mostly the ocular symptoms and signs are self limiting and resolve with time. Steroids are administered topically for anterior segment involvement and systemically with posterior segment involvement. Topical

steroids are given to patients with dengue related uveitis<sup>20,30</sup>

## CONCLUSION

Ocular complications associated with dengue fever are rare but may result in permanent visual impairment. A heightened awareness of dengue related ophthalmic complications among clinicians involved in the care of patients with dengue would facilitate prompt referral for ophthalmologic assessment and management. Ocular abnormalities may be seen in patients with Dengue fever, therefore ophthalmic examination including fundoscopy should be performed in patients presenting with all forms of the disease. In cases suspected of Dengue related maculopathy, FFA and/or OCT should be done and appropriate therapy should be started to prevent visual loss.

## CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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