

Original Article

Dengue Fever seen through the Eyes : Ocular Manifestations of Patients with Dengue Fever with Thrombocytopenia

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Background & Objective : To study the ocular manifestations in Dengue fever patients with Thrombocytopenia.

Methods : The study was conducted over a period of two months at our Tertiary Care Centre. Hundred, serology confirmed cases of Dengue fever with Thrombocytopenia admitted in medicine department were included in the study. Complete Ophthalmic examination was done. Data were entered and analyzed in Statistical Package for the Social Science (SPSS) version 12 statistical software.

Results : Sample size was of 100 patients in our study. There were 62 males and 38 females. Maximum number of cases was found in age group 30-40 years. There were 54 urban and 46 rural patients. Twenty (20%) of our patients had ocular complaints. Anterior segment finding was seen in 15% of which Sub-conjunctival Hemorrhage (SCH) was commonest clinical presentation noted in 14 patients (14%). Posterior segment findings were present in 11 patients (11%). Retro-orbital pain was noted in seven patients (7%). Five had redness, eight had blurring of vision. Four patients (4%) had Superficial Retinal Hemorrhage (SRH), One patient (1%) had Vitreous Hemorrhage (VH), Two patients had Pre-retinal Haemorrhage (PRH)(2%), Two (2%) patient had hard exudates.

Interpretation & Conclusion : Ophthalmic manifestations are usually seen in patients who present with severe and moderate Thrombocytopenia. Despite good visual recovery and resolution of clinical signs in most patients, ophthalmologists and physicians should be cautious as isolated reports of cases of Dengue related ophthalmic complications with poor visual acuity refractory to treatment have been reported.

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Key words : Dengue, Ocular manifestations, Retinal Hemorrhage.

Dengue fever is a mosquito borne viral disease of tropical and subtropical area. It is clinically characterized by acute onset of biphasic, high-grade fever lasting for 3 days to 1 week associated with symptoms of malaise, fatigue, sore throat, rhinitis and cough, severe head ache, muscle ache, retro-orbital pain, joint pain, abdominal pain and rash. Dengue infection is usually a clinical diagnosis but can be confirmed with laboratory tests based on the time of presentation, virological method (RT-PCR) and serological method such as Enzyme-linked Immunosorbent Assay (ELISA) with the detection of Immunoglobulin M (IgM) or Immunoglobulin G (IgG)¹. Presentation of Dengue can be classified into nonspecific Febrile Illness, Classic Dengue, Dengue Hemorrhagic Fever, Dengue Hemorrhagic Fever with

Editor's Comment :

- The spectrum of ocular manifestations of Dengue fever with thrombocytopenia is wide and physicians should be aware of the vision threatening complications.

Dengue Shock Syndrome and other rare complications such as Encephalopathy and hepatitis. Both Dengue fever and Dengue hemorrhagic fever are known to be associated with a generalized bleeding tendency secondary to Thrombocytopenia. Ocular involvement has also been reported in various studies²⁻⁸. The precise pathophysiology of Dengue ophthalmic complications is not well understood; however, many studies have pointed towards the possibility of an immune-mediated process as a likely mechanism⁷⁻⁹. Since, we had an epidemic of Dengue in India that clinched our attention towards study on ocular manifestations of Dengue at our Centre. In this article, we aim to study the ocular manifestations in patients of Dengue fever with thrombocytopenia.

MATERIAL AND METHODS

A Prospective Observational study was conducted at a Tertiary Care Centre over a period of two months June-July, 2021. During this period there was an

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epidemic of Dengue. Hundred serological confirmed cases of Dengue fever with Thrombocytopenia were included in our study from Medicine Department, Dengue ward at our Tertiary Care Centre. Patients suffering from diabetes, hypertension, anaemia and other comorbid conditions were excluded from our study. A complete systematic evaluation was done including detailed clinical history systemic and ocular examination. Complete ocular examination like visual acuity, slit lamp examination, intra-ocular pressure by Goldman Applanation Tonometry and indirect Ophthalmoscopy were carried out. Detailed haematological evaluation with haemoglobin levels (Hb), Total Leukocyte Count (TLC), Platelet Count (PC), malarial antigen, slide test for malaria parasite, IgM antibodies and Widal test for typhoid was performed. All subjects were classified according to WHO guideline. Patients with Dengue fever with Thrombocytopenia were taken. Data were entered and analyzed in Statistical Package for the Social Science (SPSS) version 12 statistical software.

RESULTS

A total of 100 patients diagnosed as Dengue were enrolled in our study out of which 62 were males (62%) and 38 were females (38%). Mean age of presentation was 35 years (20-80years). Maximum number of cases was found in age group 30-40 years (Fig 1). Patient

mainly belonged to low socio-economic status with predominate labor and working class. There were 54 urban and 46 rural patients. Twenty (20%) of our patient had ocular complaints (Fig 2). Retro-orbital pain was noted in seven patients (7%). Five had redness and eight had blurring of vision. Ocular findings were present in 25 patients (25%) in which anterior segment was involved most-commonly (Table 1). Sub-conjunctival Haemorrhage (SCH)(Fig 3) was the most common ocular finding noted in fourteen patients (14%), peri-orbital oedema in one patient; Posterior segments finding was present in 11 patients (11%). Most common posterior segment finding was superficial retinal haemorrhage that was noted in four patients (4%), Pre-retinal haemorrhage and hard exudates were noted in two patients(2%) each respectively. Least common finding vitreous haemorrhage was noted in one patient (1%). The superficial haemorrhage were scattered in fundus and also found in Macula. Maculopathy was noted in two patients (2%). Association of Platelet Count with ocular finding was also seen. In our study thrombocytopenia was noted in all patients of whom 25 patients (25%) had ocular findings. 22 cases out of 25 patients we encountered in severe thrombocytopenia. Only 3 patients had moderate thrombocytopenia. We did not encounter single case

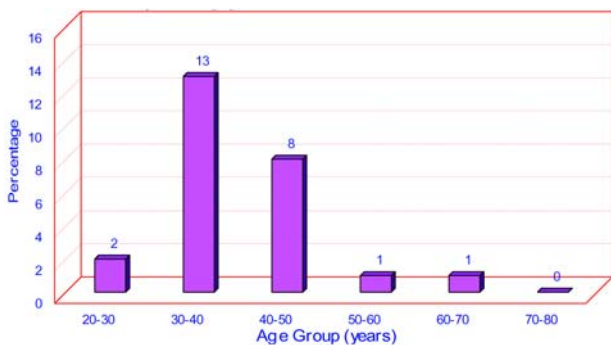


Fig 1 — Showing Age at Presentation

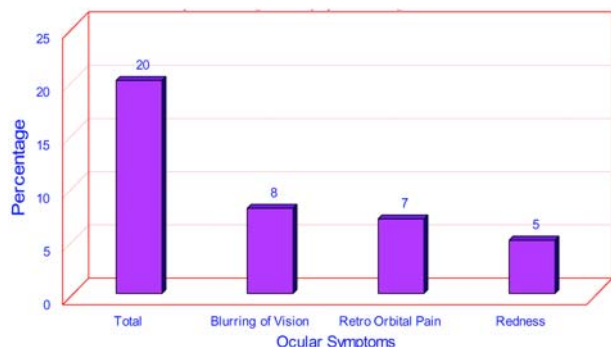


Fig 2 — Showing Ocular Symptoms in Dengue Cases

Ocular findings	No of cases of ocular findings	% out of total cases of Dengue fever
Anterior Segment Findings	15	15%
SCH	14	14%
Periorbital Oedema	1	1%
Posterior Segment Findings	11	11%
SRH	4	4%
Macular Oedema	2	2%
PRH	2	2%
Hard Exudate	2	2%
VH	1	1%



Fig 3 — Sub-conjunctival Hemorrhage

with mild form of Thrombocytopenia (Table 2). DHF is defined by WHO as DF associated with Thrombocytopenia ($<100 \times 10^9$ cells/L) and hemo-concentration (hematocrit $>20\%$ above baseline). Its most severe form, Dengue Shock Syndrome (DSS), is associated with hypotension, narrowing of pulse pressure (<20 mm Hg)¹. All patients of Dengue shock syndrome had ocular findings, 53.33% cases of dengue hemorrhagic fever and 18.07% cases of dengue fever had ocular manifestations (Table 3).

DISCUSSION

The incidence, clinical manifestation and geographical distribution of Dengue have increased due to increase in global temperature and population growth rate, unplanned urbanization, inefficient mosquito control, frequent air travel, and lack of health care facilities¹⁰⁻¹². Dengue affects human of all age group. In our study the mean age of presentation is 35 years (30-40 years) which is similar to other studies¹³ with a male preponderance¹⁴⁻¹⁵. Dengue has diverse of clinical manifestations starting from simple fever to severe encephalopathy. In our study all patient presented with fever (100%), followed by Myalgia (85%). Headache is one of common presentation found in 60% but retro-orbital pain which is a classical feature of Dengue was also seen in 7% of cases which is much less than other authors¹⁶⁻¹⁷ more than Kapoor, *et al*¹⁴. Most common complaint in our study was blurring of vision. All the patients, complaining of blurring vision had severe Thrombocytopenia. It was supported by similar studies in Singapore^{3,18,19}. In our study cause of blurring of vision was associated with posterior segment finding as discussed in later section. We reported SCH in 14 patients that constituted the most common anterior segment finding out of which five had diffuse SCH and rest had petechial haemorrhages. A study by Kapoor, *et al* accounted for the majority of cases of Dengue-related sub-conjunctival haemorrhage, in the 50 patients with sub-conjunctival haemorrhage, 42 (84%, n=50) patients had petechial haemorrhages present in the conjunctivae and eight (16%, n=50) patients had diffuse haemorrhages noted in one to four quadrants¹⁴. Another study in India reported sub-conjunctival haemorrhage as the only anterior segment finding in three out of five patients with dengue hemorrhagic fever²⁰. One other study reported sub-conjunctival haemorrhage present in 3 eyes of 50 patients (65 eyes) diagnosed with Dengue fever and had visual symptoms¹⁸. One patient had peri-orbital oedema pathogenesis of which is unknown and may be attributed to release of inflammatory mediators.

Laboratory parameter	With ocular Finding	Without ocular Finding
Platelets count (<150000 mm ³)	25	75
Mild (100000-150000)	0	25
Moderate (50000-100000)	3	37
Severe (<50000)	22	13

	DF	DHF	DSS
With ocular findings	15	8	2
Without ocular findings	68	7	0
Total case	83	15	2

Similarly one patient presented with periorbital lid oedema in a prospective observational based study conducted by Srikant, *et al* done in 2018. A case series by Gupta, *et al*²¹ reported dengue-related uveitis in six patients, with five isolated in the anterior chamber and only one with pan uveitis. Although Dengue related uveitis has been reported in few studies we did not encounter any such case in our study. In our study 11% cases have posterior segment finding which is almost similar to Kapoor, *et al*¹⁴. In our study most common posterior segment finding of superficial retinal haemorrhage in four patients. We reported maculopathy in two patients, hard exudate in two patients, pre-retinal haemorrhage in two patients. Least common finding vitreous haemorrhage was noted in one patient. All the posterior segment findings were noted in severe form of Thrombocytopenia. In our study 88% patients with ocular finding had severe Thrombocytopenia ie $<50,000$. This was consistent with Kapoor, *et al*. Of all laboratory parameters evaluated by them, marked thrombocytopenia (Platelet Count $<50,000/\mu\text{L}$) emerged to be significantly associated with ocular haemorrhage in their study too.

None of the patients in our study had retro-bulbar haemorrhage, optic neuritis and retinal vasculitis. The exact pathogenesis of these findings is not clearly defined in the literature. Multiple hypotheses have been suggested including low platelet counts pre-disposing to bleeding, and leakage due to increased permeability mediated by pro-inflammatory like IL-6 cytokines aided by coexistent inflammation as an immune-mediated hypothesis has also been suggested²¹⁻²². The usual timeline of eye involvement is seen in close association with the lowest platelet count values in both DF and DHF, a phenomenon observed by Chan, *et al*¹⁸. Auto-antibodies against endothelial cells and platelets as a result of increased interleukin (IL)-6 production or molecular mimicry against Dengue virus structural proteins have also been reported. However, raised

cytokine levels and auto-antibodies alone cannot explain the manifestations seen as this is also a feature in many infective diseases that do not result in increased vascular permeability. Infection of cells with Dengue virus has been postulated to cause a shift in balance of the cell-mediated immunity from Th1 and Th2 resulting in CD4/CD8 inversion and release pro-inflammatory mediators including IFN γ and Tumour Necrosis Factor (TNF- α) that can directly affect vascular endothelial cell apoptosis resulting in increased permeability²³⁻²⁴. Hence, probably the pathogenesis of these ocular manifestations is directly related to the immuno-pathogenesis of Dengue fever, which is a subject of ongoing research.

CONCLUSION

Multiple ocular complications are related to Dengue infection with most of them confined to the posterior pole of the fundus. The mechanism behind ocular involvement in Dengue is probably related to an immune-mediated process. DHF and DSS are mostly prone to develop ocular complications. These patients along with those having ocular complaints should have an early evaluation by ophthalmologist to prevent any vision compromising complications. Further studies are needed to evaluate the mechanism of ocular manifestations of Dengue.

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