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Prevalence of Ophthalmological Manifestations In Patients Hospitalized For Dengue Fever – A Three Year Prospective Study.

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Abstract:

The aim of this study was to record the various ophthalmological manifestations as well as their visual prognosis in 212 cases of dengue fever who were admitted to this centre over a 3 year period. Material and Methods: All patients who were admitted as serologically confirmed cases of dengue were subjected to a complete and detailed ophthalmologic examination, immaterial of the presence of any ocular complaints. Results: Out of the total of 212 patients admitted with dengue, ophthalmic manifestations were seen in 94 (44.34%) patients. The youngest patient was 3 years old and the oldest was 69 years, with the mean age being 27 years. A majority of the patients 52 (55.32 %) were males. 8 (8.51%) patients initially presented with ophthalmic manifestations as the first sign of dengue. Anterior segment findings were far more common, with subconjunctival haemorrhage seen in 38 (40.43%) patients, being the commonest ocular manifestation. Most of the patients showed a complete visual recovery within 3 months, however in 6 patients (6.38 %), 8 eyes, the vision recovered only partially with the final visual acuity being less than 6/12 even after 1 year of follow up. Conclusion: Ocular manifestations in dengue are relatively common. Sometimes they might be its only presenting sign. Hence it becomes imperative to be aware of these subtle signs and symptoms and always keep a dengue etiology in mind while dealing with such patients.

Keywords: Dengue ; Ophthalmological Manifestations; Visual Prognosis

Introduction:

Dengue fever, also known as break bone disease, is the commonest flavivirus infection in humans ^[1]. After malaria, it is the second most common mosquito-borne disease affecting human, and the most common mosquito-borne viral disease ^[2,3]. It has become one of the leading causes of morbidity and mortality

throughout the tropics and its virus is considered as the fastest re-emerging arbovirus today[4,5,6]. It's borne by four species of the female Aedes mosquitoes ie. Aedes aegypti, Aedes albopictus, Aedes polynesiensis and Aedes scutellaris, which act as vectors in the transmission of dengue infection. [4,6,7]. Out of these, A. Aegypti is the most important, being responsible for nearly two-thirds of the entire world's dengue [8]. Man and mosquitoes both act as reservoirs of dengue infection and the transmission cycle is "man-mosquitoman" [9] . This infection is endemic in over a 100 countries, majority of which are in the developing world. The world over, more than 2.5 billion people stay at risk, with over a 100 million individuals getting infected with dengue annually[4,10]. Many people infected with dengue virus are either asymptomatic or only have mild symptoms such as an uncomplicated fever. However there are around 500,000 cases annually that are serious enough to require hospitalization. It's also responsible for more than 15000 deaths annually with a case fatality rate of 0.2 to 5 %. [4,11] . The alarming fact being its growing incidence due to developing urbanization, tourism, and trade [4,12,13]. Southeast Asia, India, and the American tropics are the area's most affected. According to one particular multinational study, India bears the maximum burden of dengue infections, accounting for nearly a third of the total cases in the world [14]. In one of the recent outbreaks of dengue in India, during 2012, a total of 47,029 cases were reported [15] . There are four distinct but antigenically related serotypes of dengue arbovirus (DENV-1, 2, 3, 4) [5,15,16] . According to the World Health Organization, a person infected by dengue can develop symptoms ranging from high temperature, headache, myalgia, and arthralgia to the severe, potentially fatal, form known as dengue shock syndrome^[5,16]. Ocular findings in dengue fever were considered rare previously [12,17]. However now, a wide spectrum of ocular manifestations ranging from subconjunctival, vitreous, and retinal hemorrhages; anterior, intermediate and posterior uveitis; retinal vasculitis; exudative retinal detachment; optic neuritis; neuroretinitis, oculomotor and abducens nerve palsy, panophthalmitis, cotton wool spots, maculopathies such as foveolitis, hemorrhage, branch retinal vein occlusion and central retinal vein occlusion are now being reported^[2,4,12,18,19,20,21,22,23,24,25,26,27]. The mechanism being suggested implies both direct viral infection as well as immunologic phenomena [28]. This hospital being a tertiary level hospital caters to a large segment of population stretching over 3 states and has been receiving several cases of dengue over the last 3 years. Many of these patients had various ophthalmological complications associated with dengue. Most of these have been commonly mentioned in literature, while some others were quite rare. This study was carried out to determine the various ophthalmological manifestations of this infection as well as the visual recovery in these patients.

Materials and Methods:

A total of 212 dengue cases were managed at this centre over the past 3 years. The diagnosis of dengue fever was based on clinical features as well as laboratory investigations. Serological tests which were carried out in all cases were the hemagglutination inhibition test and immunoglobin G (IgG) or immunoglobin M (IgM) enzyme immunoassays to confirm the diagnosis^[4]. All patients were subjected to a detailed ophthalmological evaluation irrespective to whether they had any ocular signs or symptoms. This included a detailed history taking of any eye related complaints including blurring of vision, scotomata, metamorphopsia, and presence of floaters or ocular pain. A history of any pre-existing major systemic diseases like diabetes and hypertension as well as ocular diseases like refractive errors/ cataract / glaucoma too was taken .Subsequently all these patients underwent a comprehensive ophthalmological examination including best corrected visual acuity (BCVA) testing; Amsler grid testing; colour vision testing; slit lamp examination; and a dilated indirect ophthalmoscopy. Specialized investigations including fundus fluorescein angiography (FFA), optical coherence tomography (OCT), visual field testing and electrophysiology tests were however restricted to only those patients who had ocular complaints or were detected to have any abnormality during their initial ophthalmological examination. The visual acuity of all patients with visual complaints too was recorded at presentation as well as at the time of the final disposal. All of them claimed to be having no visual complaints prior to the onset of the dengue fever.

Results: A total of 212 patients of dengue were managed at this centre from July 2012 till June 2015, all of whom were subjected to a detailed ophthalmological examination.

Table 1: Month wise distribution of the reporting of dengue cases to our centre

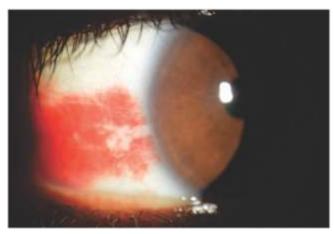
YEAR	2012							TOTAL					
MONTH	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	44
NUMBER							12	13	11	5			41
YEAR 2013													
MONTH	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	77
NUMBER		1	3	3	11	14	17	16	9	3			77
YEAR 2014													
MONTH	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	63
NUMBER			1	3	6	12	11	15	10	4	1		63
YEAR 2015													
MONTH	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	24
NUMBER			2	4	12	13			_	-			31

Ophthalmic manifestations were seen in 94 (44.34%) of these patients. 72 patients (76.60 %) had bilateral involvement, while the remaining 22 (23.40%) had only one of their eyes involved. The number of males affected was slightly more 52 (55.32 %), than the number of females who were 42 (44.68 %). The age group of the patients reflected mainly young individuals with the mean age being 27 years. However there was no significant difference between the number of males and females affected as far as the ages were considered [table 2].

Table 2: Age & Sex wise distribution of the patients with ophthalmological manifestations

S.No.	AGE GROUPS	MALES	FEMALES	TOTAL
1.	<1-10	2	-	2
2.	11-20	5	4	9
3.	21-30	20	14	34
4.	31-40	12	13	25
5.	41-50	7	6	13
6.	51-60	4	3	7
7.	61-70	2	1	3
8.	71-80	-	1	1
	Total	52	42	94

Ocular symptoms were present in most of these patients and included blurring of vision, which was the commonest complaint, present in 48 patients (51.06%). The other ocular symptoms included central scotomas, floaters, flashes, diplopia and ocular pain. The various signs noted were subconjunctival hemorrhage, [Figure1] the commonest, seen in 38 (40.43%) patients.

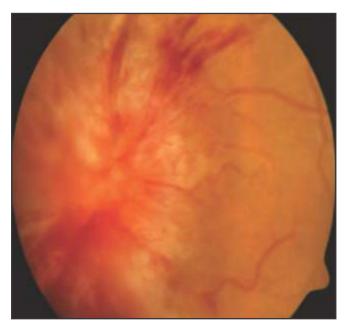


(Fig. 1 - subconjunctival hemorrhage)

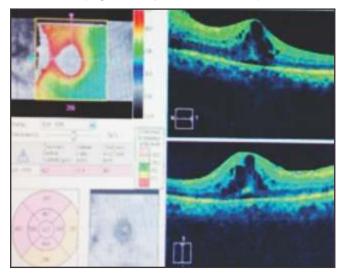
The other signs that were noted were uveitis, vitritis, retinal and macular hemorrhages, retinal vascular sheathing, maculopathy, retinochoroiditis, choroidal effusion, optic disc swelling, optic neuritis, neuroretinitis, and oculomotor and abducen nerve palsy [Table 3], [Figure 2a, 2b, 2c, 2d, 2e, 2f].

Table 3: Ocular signs and symptoms detected and their frequency

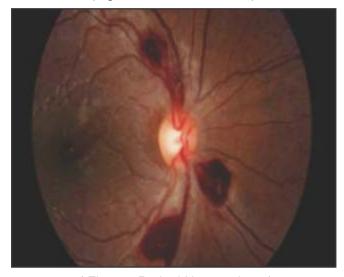
Sr. No.	Ophthalmic Symptoms	Frequency	Percentage
1.	Blurring of vision	48	51.06 %
2.	Scotomas	17	18.09 %
3.	Floaters	9	9.57%
4.	Ocular pain (Retrobulbar/Diffuse)	6	6.38%
5.	Diplopia	3	3.19%
6.	Flashes	3	3.19%
7.	Metamorphopsia	3	3.19%
8.	Micropsia	2	2.13%
9.	Defective colour vision	1	1.06%
	OPHTHALMIC SIGNS		
	Anterior Segment		
1.	Subconjunctival haemorrhage	38	40.43%
2.	Anterior uveitis	7	7.45%
3.	Intermediate uveitis	3	3.19%
4.	Acute angle closure	1	1.06%
	Posterior Segment		
1.	Retinal hemorrhages	24	25.53%
2.	Macular oedema	20	21.28%.
3.	Maculopathy	12	12.77%
4.	Choroidal effusion	4	4.26%
5.	Optic disc swelling	4	4.26%
6.	Vitritis	4	4.26%
7.	Vitreous haemorrhage	4	4.26%
8.	Posterior uveitis	2	2.13%
9.	Neuroretinitis	1	1.06%
10.	Optic neuritis	1	1.06%
11.	Retinochoroiditis	1	1.06%
12.	Abducens nerve palsy	1	1.06%



(Fig.2A - Optic disc oedema)



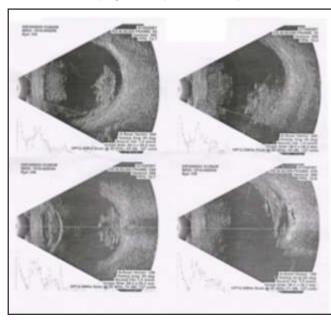
(Fig.2b - Macular oedema)



(Fig.2c - Retinal Haemorrhage)



(Fig.2d - Optic neuritis)



lateral rectus paralysis) (Fig.2e - Vitreous Haemorrhage)



(Fig.2f - Abducens nerve involvement, manifesting with

A history of fever was the most common presenting symptom; however 8 patients presented initially with an ophthalmological complaint eg. diminution of vision, subconjunctival hemorrhages, floaters or retrobulbar pain and were detected to have dengue subsequently on investigation [Table 4].

Table 4: Ophthalmological manifestations as the presenting feature in Dengue infection

Sr. No.	AGE GROUPS	MALES
1.	Blurring of vision	3
2.	Ocular pain	2
3.	Subconjunctival haemorrhage	2
4.	Floaters	1

There is no established treatment for the ocular manifestations of dengue fever^[4,12,19]. In addition most of these complications like subconjunctival hemorrhages, retinal and macular hemorrhages, and foveolitis, are known to resolve spontaneously with time as the patients recover from thrombocytopenia ^[29,30,31]. Hence the patients were mostly managed symptomatically and did not require any active intervention; however those requiring specific treatment like steroids and cycloplegics in cases with uveitis were actively treated for that particular complication. The vision of the patients with ocular involvement at presentation and their final visual status is given in [Table 5], which revealed that most showed a complete visual recovery.

Table 5 : Visual acuity at presentation and the final visual acuity on discharge in patients with complains of blurring of vision (N=78 EYES)

VISUAL ACUITY	AT PRESENT		ON DISCHARGE			
	Frequency	Percentage	Frequency	Percentage		
>6/12	15	19.23%	70	89.74%		
6/12 - 6/60	25	32.05%	4	5.13 %		
6/60 -3/60	23	29.49%	2	2.56%		
< 3/60	15	19.23%	2	2.56%		
No PL	-		-	-		
Total Eyes	78	100%	78	100%		

Discussion: Though man has been affected by dengue for centuries, however the first case of any ophthalmic manifestation in relation to dengue was reported of only in the late 1980s [19] . The exact pathogenesis of ocular complications in dengue fever is still not clear [12,16,24]. However, its clinical features as well as the further response of these complications points more towards an immunogenic aetiology rather than an infective one, involving both the viral as well as the host immune factors [28,32]. The ocular manifestations usually appear on the 7th day after the onset of the dengue fever i.e. during the convalescent phase of the disease and closely correlates with the nadir of thrombocytopenia further implicating a host immune response rather than a direct virus infection [10,30]. In our study too most of these complications were noticed at platelet counts of <50,000/mL. In addition to the above the serum complement C3 levels in patients with maculopathy are lower than those in patients without maculopathy [19] . Finally corticosteroids, local as well as systemic, have been effective in the management of dengue related maculopathies [2,4,20]. However we feel that still much more research is needed to adequately establish the pathogenesis of these ocular manifestations.

There have been some case reports reported over the past few years mentioning about these various ophthalmological complications of dengue [2,24,25,32]. However to the best of our knowledge there have been only two large scale studies wherein all patients of dengue were subjected to an ophthalmological examination i.e. even those patients who had no ophthalmological symptoms[19,29]. Among these too, one study was only restricted to the detection of only maculopathy [19] and did not take any other associated complications involving either the anterior or posterior segment into consideration. Whereas this study was a more complete endeavour wherein all the cases of dengue were comprehensively examined and the entire gamut of ophthalmological complications detected were documented in detail.

A large majority of our 212 dengue patients presented during the months of June / July and August of each year and the least number of cases were detected during the winter months i.e. Nov/Dec and Jan. Similar observation has been made in earlier studies from this country [1,6] as well as from nearby countries [25]. This correlates with the fact that the mosquito menace is the most during the period just following the rainy season in this part of the country and decreases with the onset of winters.

Ophthalmic manifestations were seen in 44.34% of our

patients. This incidence is similar to a large scale, similar study, conducted in Eastern India, wherein it was reported in 40.3% of the patients ^[29]. However it's much more than figures reported from a study at Singapore ^[30]. Most of our patients were young i.e. mean age of 27 yrs . Similar young profile of patients has been reported in earlier studies too ^[16,19,20,23,29,30]. Males were marginally more commonly involved, findings similar to other earlier studies ^[16,19,23,29,30].

The most common ocular manifestation seen in our study was subconjunctival hemorrhage, seen in 40.43% of patients. They were both, multiple, dot-like,

petechial type of haemorrhages as well as the diffuse type. This was comparable with the earlier studies, where it was seen in 37.3% - 60% of patients $^{[2,12,29]}$. The second most common ophthalmological sign was uveitis (anterior / intermediate and posterior) seen in 12 patients (12.77%). Similar incidence has been reported earlier too^[2]. However the presentation of dengue related uveitis was delayed, ie. seen nearly 3 -6 months after the infection. The most common posterior segment finding was retinal haemorrhage, seen in 24 (25.53%) patients. They were of both types i.e deep (dot and blot haemorrhage) or superficial (flameshaped haemorrhage). In many cases they were associated with vascular sheathing and vasculitis. Macular oedema too was seen in a significant number of patients 20 (21.28%). Similar high incidence of both these findings has been also mentioned earlier in literature 20,30. Other signs like optic neuritis, cranial nerve palsies and optic disc swellings too were detected in a few patients.

The most common presenting symptom was blurring of vision seen in 51.06 % patients. Similar finding i.e. 50-90% has been documented earlier in literature ^[2,4,20,30], Scotoma, 17(18.09 %), was the second most common presenting complaint. Similar high incidence of scotomas has been reported earlier too 2,20 and 30. The other symptoms like floaters, diplopia and ocular pain too were seen but in relatively fewer patients.

Most of these i.e. 76.60 % had bilateral involvement, while the remaining 22 (23.40%) had only one of their eyes involved. Earlier literature too reports a higher incidence of involvement of both eyes i.e. $73\%^{[4,19,2030]}$.

Dengue-related ocular pathologies are usually self-limiting and hence we too managed most of our patients conservatively [20,30]. However some patients who did not resolve spontaneously and those with specific complications like uveitis and optic neuritis required active intervention. As dengue-related ocular complications are considered to be immune-mediated,

immunosuppression with corticosteroids formed the backbone of the treatment. Depending upon the severity of the complication they were used in various forms ie. topical for anterior uveitis; oral steroids for posterior uveitis and pulse therapy of intravenous steroid followed by oral steroids in patients with optic neuropathy [2,20,30]. Most of our patients showed an excellent and complete visual recovery; however in six patients (eight eyes) the final visual acuity was < 6/12, in spite of all possible interventions.

Conclusion: Dengue fever is increasingly becoming a global problem. Due to the emergence of multiple dengue serotypes, the incidence of dengue fever is on the rise, especially in our part of the World. Ocular involvement is also now more commonly seen in association with dengue fever and therefore we should be prepared to face an increase in dengue related ophthalmic morbidity. Awareness of these ophthalmic complications among the treating physicians will help in timely referral of patients for appropriate ophthalmic management. Similarly Ophthalmologists too should be aware of the various ocular manifestations of dengue, as they can sometimes result in a permanent visual loss. Although there is no specific therapy, ophthalmic manifestations may be an indication for early and aggressive correction of thrombocytopenia. Hence an early diagnosis and referral for the necessary supportive therapy may reduce the mortality of this potentially fatal disease.

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