Dengue: An emerging ocular problem.

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Abstract

Aim: Dengue is a multi-organ disease so ophthalmic examination for all patients will be included in management protocol.
Setting and design: This was a cross-sectional study, conducted at public hospital in Dhaka, Bangladesh from 1st August 2019 to 29 September 2019. (60 days) and total population was 4030.
Statistical analysis used: Though it was a cross-sectional study so frequency was shown in bar-chart and histogram and incidence were measured in percentage
Results: Among 4030 Dengue patient a total of 1457 patient was suffering from ocular problem and male, female ratio was 1.42:1. Consideration of age group 16-30 years was the most (47%) common. Among 4030 patients 1457 (36.15%) had ocular complaints, most of the patients were suffering from sub-conjunctival hemorrhage and it was 18.44% among the total dengue patient and 50.10% among the total ocular complications patients and retro-orbital pain (16.22% and 44.89%). The most devastating were endophthalmitis (0.07% and 0.21%) and panophthalmitis (0.10% and 0.27%).
Conclusion: Conclusion: There is a general proverb "Treat the man not the diseases," many systemic diseases has got ocular effect and now-a-days the uncommon disease is becoming common and epidemic due to climate change. Dengue is such a disease which involves ocular tissue from mild to severe form so knowledge of ocular involvement of Dengue is mandatory for an ophthalmologist.

Keywords: Dengue fever, Ocular complications, Retro-orbital pain, Retinal hemorrhage.

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Introduction

Among the ophthalmologist as well as the internist has shallow knowledge about ocular involvement of Dengue and text book has not written elaborately about it so our medical personnel have lack of knowledge about it. But last few years Dengue is increasing dramatically mainly 2019 Dengue has become epidemic in Bangladesh. And we the ophthalmologist is getting referred patient every day from different public hospital and also private clinic with some newer manifestation which we didn't come across previously.

The incidence of dengue has increased 30-fold over the past 50 years. Climate change is one of the important factors for current scenario [1]. At present, approximately 40% of the world's population is at risk for dengue [2]. Dengue is not an uncommon name to the mass population but at last century it was not known to educated people as well as preclinical medical student but last 20 years the scenario has changed. It increased dramatically within the last 20 years, becoming one of the worst mosquito-borne human pathogens. In addition to climate, there are many factors which are contributing spread of Dengue, among them growing incidence of developing urbanization, tourism, and trade [3]. But the lacking of infrastructure is a big concern [4]. According to the report of Global Climate Risk Index 2017 Bangladesh was judged to be the sixth hardest hit by climate calamities of 180 nations during the period 1996-2015. They also told, global mean temperature will rises 3.7°C above preindustrial levels by 2100 [5].

Dengue is transmitted by female Aedes mosquito, usually the *Aedes aegypti* mosquito though humans are not capable of transmitting the disease and are not contagious [6,7]. The global incidence of dengue has grown dramatically in recent decades. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas [8]. Dengue is widespread throughout the tropics, with local variations in risk influenced by rainfall, temperature and unplanned rapid urbanization [9].

Severe dengue was first recognized in the 1950's during dengue epidemics in the Philippines and Thailand. Today, severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children and adults in these regions.

In a current study globally by World Health Organization estimates that there are 390 million are infected per year [10]. This year that is 2019, Dengue is in alarming situation. According to Health Bulletin of CDC, DGHS, Bangladesh

Global and regional update of Dengue from 01 January 2019 is as follows:

Philippines: 130,463 cases, 561 deaths as of 13 July, 2019

Malaysia: 75,913 cases, 111 deaths as of 27 July, 2019

Vietnam: 115,186 cases, 12 deaths as of 21 July, 2019

Thailand: 44,671 cases, 62 deaths as of 16 July, 2019

Singapore: 8,020 cases as of 21 July, 2019

Sri Lanka: 234,078 cases, 47 deaths as of 05 August, 2019 [11,12].

Bangladesh has an estimated 163.05 million, population. The country has a population density of 1,115.62 people per square kilometer, (2,889.45/square mile), which ranks 10th in the world [13].

Bangladesh has a tropical monsoon climate characterised by heavy seasonal rainfall, high temperatures [14]. In the rainy season is particularly between July and September, is typically associated with cases of dengue fever [15]. Dengue is transmitted to humans through the bites of infected female mosquitoes, but humans are not capable of transmitting the disease and it is not a contagious so a dengue patient no need to quarantine. Sharing food, clothing, beds even sex is not restricted for him/her [16,17].

The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. The alternative name for dengue, "breakbone fever" the presence of **fever**, **rash**, and **headache** (the "dengue triad") is characteristic of dengue fever [18-20].

Manifestations of dengue in the eye, though rare in the past, are now more recently noted to be common in some outbreaks [20] and dengue is emerging day by day, and few patients come with ocular complain mainly retro orbital pain so it is now an issue for ophthalmologist. Ocular involvement of Dengue is still confusing but most common finding in anterior segment is sub-conjunctival hemorrhage [8] and posterior segment finding is retinal hemorrhage [21].

Subjects and Methods

It was a cross sectional study and study period conducted at a public hospital from 1st August 2019 to 30 September 2019, (60 days) and total population was 4030. Though Dengue is epidemic in this season, a special Dengue ward was open and most of the Dengue patient was admitted at that ward, in spite of that some patients were at the different ward in internal medicine.

Dengue viruses are comprised of four closely related serotypes: DEN-1, DEN-2, DEN-3, and DEN-4 [22,23]. Infection with one serotype does not provide protective immunity to the others [24]. The onset of dengue symptoms is marked by the presence of dengue non-structural protein 1 NS1 antigen in the patient's serum. Non-structural protein 1 (NS1) used to detect either primary or secondary infections in the earliest stages. IgM is positive approximately 5 days after infection in both primary and secondary infections, while IgG became positive about 2 to 4 weeks after onset of primary infection and almost immediately after onset of a secondary infection [25].

Our patient selection was based on serological test, that is if a patient was NS1 positive or IgM positive or both are positive we included him/her in our study because many patient admitted in hospital with fever out of fear of Dengue but after serological test it was not a dengue at all, so our inclusion criteria was based on serological test irrespective of gender, age etc. but only IgG positive does not indicate active infection and it means once she/he was infected with Dengue virus.

The global incidence of dengue has grown dramatically increases in recent decades. About half of the world's population is now at risk. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas [6].

Dengue is a mosquito-borne viral disease is transmitted by female mosquitoes mainly of the species *Aedes aegypti* [8] and it has different characteristic than other, it born in fresh, stagnant water. This mosquito also transmits Chikungunya, yellow fever and Zika infection [26].

Manifestations of dengue in the eye, was rare in the past, but now more recently noted to be common in some outbreaks [27,28].

All patients were examined with Snellen chart for visual acuity. Slit lamp biomicroscope for anterior segment and fundus was examined by direct ophthalmoscope after full dilatation with tropicamide and phenylephrine combination eye drop. In addition to that if there was any positive finding by direct ophthalmoscope indirect ophthalmoscopy, *Spectral-domain optical coherence tomography* (*SD-OCT*) was done.

Dengue can have various manifestations in the eye, and more recently a newer terminology of "dengue eye disease" has emerged [29,30]. Among the symptoms retro-orbital pain the most common symptom and sub-conjunctival haemorrhage is the most common sign of Dengue [31].

The retro-orbital pain subsides as the disease cure and sub-conjunctival hemorrhage is self-limiting. There are some other complications which are vision-threatening but we are lucky enough that they are not as frequent as other two are.

The above report was prepared by Health Emergency Operation Centre and Control Room of Director General of Health Services, Bangladesh (HEOCC, DGHS, B,D). It shows the year-wise affected Dengue patient in the country (but up to 2018 Dengue was confined in Dhaka city) from 2000 to 2018 and highest affected was at last year that is 2018 and total patient was 10148. But this year from January 1 to Sept 22 there are 69348 already affected with Dengue. October is yet to go and it will exceed 100,000 (Figures 1-3).

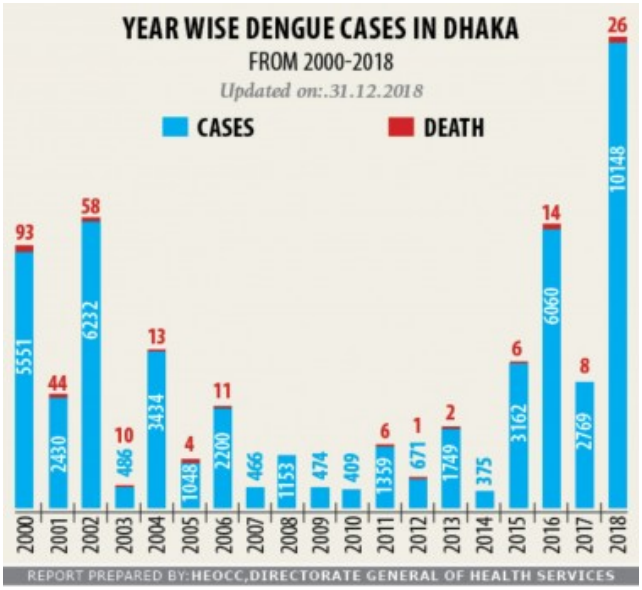

Figure 1. *Secondary data (source: DGHS. BD.*

Results

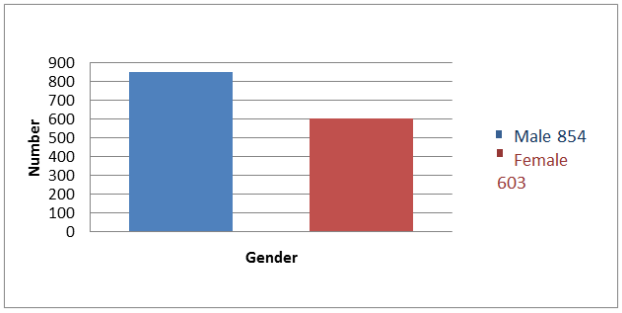

Figure 2. *Total number of male and female affected with ocular problem in Dengue.*

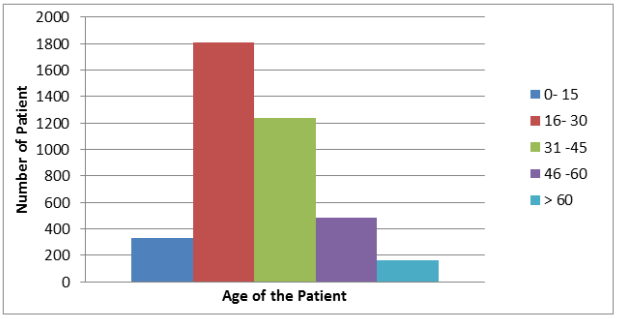

Figure 3. *The frequency distribution of age affected with Dengue fever.*

Discussion

A total of 1457 patient was diagnosed as Dengue fever among them 854 male (58.6%) and 603 female (41.4%) which is consistent with Ankera M, Arimab Y. in their study, country wise distribution of male is Lao People's Democratic Republic, 57.9%, Philippines, 57.2%, Singapore, 60.7%, Sri Lanka 61.8%, Cambodia 60.1% which is similar to our study [32].

Another study from Islam et al. [33] 60% was male and 40% female. Male are more prone to develop Dengue fever it may be their habit of dress (they wear lungi but no shirt) Dengue is transmitted by the bite of the Aedes mosquito that typically attacks during day time. Its favorite spots are below the elbow and below the knee [34]. The dress habit of male in this subcontinent is bare body of upper half and for the lower half they wear lungi [35]. (The lungi is a type of sarong originating from the Indian subcontinent and a traditional garment worn around the waist).

In our study mean age was 31.6 year but according to Medscape Ophthalmology in Asia Dengue is common in children than adult, but in America it is equally distributed among all age groups which contradict with our study, it is due to our study was based on a single hospital and it is a multidisciplinary hospital but children usually admitted in pediatric hospital [36]. But current epidemiological trends have shown a gradual shift in the burden of dengue from the paediatric to the adult population.

The incidence of dengue occurring in the elderly has been increasing consequently [37]. Our study is consistent with Sujatha et al. in their study mean age was 32 years (20–60 years) [38]. Our study also comparison with Yip et al. [21] the authors' search yielded 29 articles. A total of 686 patients with a mean age of 33.4 years (range 14-73 years). Proposed mechanisms of ocular involvement include direct viral infection as well as immunologic phenomena. Common manifestations include sub-conjunctival, vitreous, and retinal hemorrhages; anterior and posterior uveitis [39].

Table 1. *Ocular complications of Dengue fever (n=1457).*

Parameters	No. of Patients	% Among total patient (4030)	% Among ocular involvement patient (1457)
Retro-orbital pain	654	16.22%	44.89%
Sub-conjunctival Hemorrhage	743	18.44%	50.10%
Chemosis	282	6.10%	19.35%
Anterior uveitis	53	1.29%	3.57%
Keratitis	23	0.57%	1.58%
Poor vision	421	10.45%	-28.89%
Panophthalmitis	4	0.10%	-0.27%
Endophthalmitis	3	0.07%	-0.21%
Posterior segment findings			
Retinal hemorrhage	103	2.56%	7.07%
Vitreous hemorrhage	66	1.64%	4.53%
Macular edema	57	1.41%	3.91%
Neuroretinitis	4	0.10%	0.27%

In our study, from Table 1, among 4030 patients 1457 (36.12%) had ocular complaints, most of the patients were suffering from retro-orbital pain (654 patients were suffering from retro-orbital pain, it means 16.22% among the total patient and 44.89% out of 1457 patients) probably it was due to inflammation of sinus cavity and Sub-conjunctival hemorrhage (743 patients were suffering from sub-conjunctival hemorrhage, it means 18.44% among total 4030 patients and 50.10% out of 1457 patients) [40].

Among the total population 282 (6.10%) patients were suffering from conjunctival chemosis, which is similar with previous study of Dhar et al. [40] 2019 in their study it was 5.45% among the total patient. In our study we got 52 (1.29%) patients were suffering from anterior uveitis among the total 4030 patients, but previously it was not known to ophthalmologist and not a single case was reported before 1990 At present many studies show there is a positive correlation between Dengue and uveitis. Srinivasan R et al. from south India reported six uveitis cases in Dengue [41]. The cause of ocular complications from dengue fever is still not well understood. However, an immune-mediated cause has been suggested. "The release of cytokines with vasoactive and procoagulant properties in response to immunological activation might explain the occurrences of retinal vascular occlusion seen in patients with dengue infection," King, et al. noted [39] "In addition, these inflammatory mediators cause capillary leakage and breakdown of the blood aqueous barrier, resulting in anterior uveitis." In our study most of the patient with anterior uveitis was IgG positive so it means that the patient was previously exposed to Dengue virus of another serotype so current attack of uveitis was due to delayed hypersensitivity reaction. So, any patient came to us with uveitis we have to take the previous history of Dengue fever because during uveitis the patient may not have any dengue features.

The possible mechanism of corneal complication in our case is believed to be a result of complex immune-mediated process which might have caused autoantibody formation against corneal endothelial cells [42]. Among the total 4030 patient, 23 (0.57%) were involved with keratitis.

In our study, there were 4 (0.10%) cases of panophthalmitis and 3 (0.07%) cases of endophthalmitis, it means among the total Dengue patient 7 (0.17%) cases and panophthalmitis and endophthalmitis were noted. But there is no direct relationship between Dengue and panophthalmitis or endophthalmitis, it is may be due to platelet transfusion and there is series of case reports from Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India [43]. Platelet transfusion has got some adverse effect, according to Lancet Journal Mar 2017, shows that there were 13 adverse events in the platelet transfusion group and two in the control group [44]. There were 4 cases of neuroretinitis. There are some case series from Brazil, Nepal and India of neuroretinitis and Dengue [45,46].

Among the posterior segment findings retinal hemorrhage 103 (2.56%), Vitreous hemorrhage 66 (1.64%) and macular edema 57 (1.41%) which is not consistent with many other studies. And our study shows lower prevalence of posterior segment findings than other. In Singapore studies among 13 patients with ocular findings in Dengue fever shows macular oedema, blot hemorrhage, cotton wool spots, retinal vasculitis, exudative retinal detachment and anterior uveitis [20].

Another study from Dr. BR Ambedkar Medical College and Hospital, Bengaluru, Karnataka, India. A total of 120 patients were diagnosed with dengue fever and posterior segment findings were present in 16 patients (13.3%); of which, 14 (87.5%) had retinal hemorrhages [38].

Study from Bhubaneswar, Odisha, India, out of 110 hospitalised Dengue patients Ocular findings were present in 47 patients (42.72%) Posterior segments finding was present in 11 patients (10%), 7 patients (6.36%) had superficial retinal haemorrhage.

Their findings of posterior segment was higher with comparison to our study, it may be our data were collected by residents and trainee doctors and most of the patient was examined in their respective ward and due to scarcity of bed in ward many patients were in the floor and it is too tough to do ophthalmoscopy in this position. (This is the actual scenario of many public hospitals in Bangladesh, India, Nepal and Pakistan during an epidemic attack).

Conclusion

Ocular complications of Dengue was not known to an ophthalmologist in last century, but due to global changes Dengue became an epidemic problem from country to country and new ocular problem coming forward to an ophthalmologist which is unaware to him, so get update knowledge of ocular problem in Dengue needs more research.

Key message

Due to climate change, and change of technology, diseases pattern are changing dramatically and newer ocular problem coming into forward which is unaware to an ophthalmologist Dengue, Chikungunya, dry eye are examples, so ophthalmologist will be updated with knowledge of newer ocular problems.

Limitations of the Study

- It was a single centered public hospital based study. In Bangladesh usually lower income group people come to this hospital so our study doesn't reflect the whole community.
- Dengue is a newer disease in Bangladesh before 2000 our internist was not accustomed with the management of Dengue. In 2000 out of 5551 patient 93 was died (see above data HEOCC, DGHS, B,D) but the mortality rate is gradually decreasing due to expertise developed among the internist, also ocular involvement was unaware to the ophthalmologist still huge gap is there. In our study, we

didn't kept record of complete blood count (CBC) report but it is important to correlate platelet count and sub-conjunctival hemorrhage and retinal hemorrhage.

- Though it was a single center based hospital and children usually admitted to the specialized hospital so number of children did not reflect the age group
- The study was done by ophthalmologist and one junior internist but Dengue is a systemic disease so multidisciplinary (Internist, pathologist, hematologist) action have to include in the research group

Recommendation

- Multicenter study which will cover both public and private hospital in the country irrespective of district, because up to 2018 Dengue was confined in Dhaka only but this year 2019 most of the district affected by Dengue fever.
- It was a cross-sectional study, so single data was collected, but it needs follow-up so longitudinal study is the best option
- The research group will be consisted not only with ophthalmologist but internist, hematologist have to be include.

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