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Full Length Article

Ophthalmic manifestations in seropositive dengue fever patients during epidemics caused by predominantly different dengue serotypes

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ABSTRACT

Purpose: Dengue fever (DF) epidemics in Singapore in 2005–2006 and 2007 were caused predominantly by dengue virus serotypes 1 (DENV-1) and 2 (DENV-2) respectively. We investigated the prevalence of ophthalmic manifestations during these consecutive epidemics.

Methods: Seropositive DF patients admitted to the hospital during two separate dengue epidemics were enrolled from June 2005 to December 2007. Demographic, ophthalmic, and laboratory data were collected. The primary outcome measures were differences in ophthalmic and laboratory features across the two epidemics. Factors associated with increased risk of developing various DF-related ophthalmic manifestations were the secondary outcome measures.

Results: Of the 115 patients enrolled, 109 (94.7%; 33 in 2005–2006 and 76 in 2007) completed the eye screening protocol. Majority of patients were Chinese (65, 59.6%) and males (81, 74.3%). The mean age was 40.8 years (range, 18–87). Colour vision impairment (12 vs 14 [36.4% vs 18.7%]; $P = 0.04$), cotton wool spots (10 vs 3 [30.3% vs 3.9%]; $P < 0.001$), bleeding diathesis (7 vs 3 [21.2% vs 3.9%]; $P = 0.004$) and abnormal liver function (mean alanine amino-transferase [150.2 U/L vs 68.28 U/L; $P = 0.001$], mean aspartate amino-transferase [196.86 U/L vs 99.53 U/L; $P = 0.002$], total protein [68.43 g/L vs 72.27 g/L; $P = 0.016$], serum albumin [36.86 g/L vs 40.5 g/L; $P = 0.001$]) were noted more often in DF epidemics predominantly caused by DENV-1 compared to DENV-2.

Conclusions: A higher prevalence of colour vision impairment, cotton wool spots, bleeding diathesis, and abnormal liver function was found in DF epidemics predominantly caused by DENV-1 compared to DENV-2.

1. Introduction

Dengue fever (DF) is an acute febrile illness caused by one of four serotypes of dengue virus which is usually transmitted through the bite of an infected female *Aedes aegypti* mosquito. DF is one of the most prominent resurgent tropical diseases and has an expanding geographical distribution of both the viruses and mosquito vectors.[1–3] DF is endemic in many countries around the world and DF epidemics are being reported more frequently and in an explosive manner worldwide.[2] Despite improvements in the diagnosis and management, as well as understanding of DF with the newer predictive mathematical models,[4–7] the number of dengue cases continues to rise. It is estimated that about 390 million dengue infections occur worldwide every year.[1] Asia-Pacific countries bear about three quarters of the global disease burden.[3] The dramatic increase in incidence and geographic distribution of DF over the past few decades is a grave public health threat globally and is thought to be related at least in part to global climate change.[1–3,8–10]

DF is endemic in Singapore because of the conducive environmental conditions required for virus transmission.[11] Singapore has seen major DF epidemics over the past two decades. Major epidemics occurred in 2005–2006 and in 2007.[12–14] The Dengue Serotype Surveillance Program initiated by the Environmental Health Institute, National

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Environmental Agency, Singapore, has been monitoring the spatial and temporal distribution of the four DF serotypes in Singapore since 2002.[12] Although all the four DF serotypes have been isolated during the epidemics, a predominant serotype is usually apparent in each epidemic. Based on laboratory surveillance data, DF epidemics in Singapore in 2005–2006 and 2007 were caused predominantly by dengue virus serotypes 1 (DENV-1) and 2 (DENV-2) respectively.[12–14]

The severity of clinical and epidemiologic characteristics of DF are known to vary depending on the circulating serotype. The impact of various dengue serotypes on systemic manifestations of DF have been well-studied,[15–17] but the effect on ocular manifestations of DF needs further elaboration. Although DF is associated with a wide spectrum of ocular findings,[9,10,18,19] differences in the relative prevalence of ophthalmic manifestations in infections with the various dengue serotypes is not well understood. We studied the prevalence of ocular manifestations in DF patients during epidemics caused predominantly by DENV-1 in 2005–2006 and DENV-2 in 2007 in Singapore.

2. Materials and methods

2.1. General information

All consecutive DF patients admitted to a multispecialty hospital in Singapore from June 2005 to December 2007 with clinical features consistent with DF and meeting the admission criteria of the Ministry of Health, Singapore were approached for enrolment in this prospective cross-sectional observational study. An informed consent was obtained from patients willing to undergo eye screening for ocular manifestations of DF. Medically unstable DF patients and those unwilling to undergo the eye screening were excluded. All the patients underwent ocular examination within seven days from the date of admission.

Patients who tested positive for the NS-1 antigen (Platelia™, BIO-RAD, France) were enrolled. They also underwent anti-dengue immunoglobulin M and G antibody testing. Primary infection was defined as an IgM-negative/IgG-negative or IgM-positive/IgG-negative within three days of symptom onset. Secondary infection was defined as an IgM-negative/IgG-positive or an IgM-positive/IgG-positive within three days of symptom onset.

2.2. Ophthalmic screening protocol

The ocular examination protocol included best-corrected visual acuity measurement, slit-lamp examination, intraocular pressure measurement, colour vision test (Ishihara pseudo-isochromatic plates, Kanehara Trading Company, Japan), Amsler chart test, visual field test using automated quantitative threshold perimetry (Humphrey® Field Analyzer, Carl Zeiss Meditech Inc., USA), colour fundus photography of the posterior pole (Visupac™ and FF 450^{plus}, Carl Zeiss Meditech Inc., USA) and macular optical coherence tomography (Stratus OCT™, Carl Zeiss Meditech Inc., USA). Patients unable to undergo retinal photography underwent clinical retinal examination with slit-lamp fundus biomicroscopy using a plus 78 dioptre lens (Volk™). Demographic data, date of onset of fever, date of onset of ocular symptoms, and details of the clinical, haematologic, and biochemical profiles were recorded. Data for the predominant serotype in the epidemics were obtained from the National Environmental Agency of Singapore.

2.3. Ethics approval and statistical analysis

This study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB). The study protocol adhered to the tenets of the Declaration of Helsinki. Statistical analysis of data was carried out at the 0.05 α-level using SPSS software ver. 17.0 (SPSS Inc., Chicago, IL, USA). Symptoms and signs were analysed as “present” or “absent”, and the percentages of positive answers were compared. To compare the clinical and laboratory features of DF patients across epidemics caused predominantly by DENV-1 and DENV-2, patients were divided the into two groups; Group I had patients enrolled during the 2005 and 2006 epidemics (predominantly caused by DENV-1) and Group II had patients enrolled during the 2007 epidemic (predominantly caused by DENV-2). Data were checked for outliers and errors. Univariate analyses were performed to identify statistically significant differences between the groups. Categorical variables such as gender, race, ocular symptoms, and signs were analysed using the chi-square test, and continuous variables such as various laboratory parameters were analysed using the two-tailed Student's t-test. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages. The Fisher's exact test and odds ratio calculation were also used for analysis.

3. Results

Out of 115 patients enrolled, 109 (94.7%) completed the eye screening protocol. The majority of patients were Chinese (65, 59.6%) with a male predominance (81, 74.3%). The mean age was 40.8 years (range, 18–87).

The majority (96, 88%) of the patients had their eyes screened within 10 days from the onset of fever. Of the 109 patients, 104 (95.4%) were diagnosed as DF and 5 (4.6%) as dengue haemorrhagic fever (DHF). Primary infection was present in 62 (56.8%) while 47 (43.2%) had secondary infection. A skin rash was noted in 43 (39.4%) patients and 11 (10%) patients presented with bleeding diatheses such as subconjunctival haemorrhage (3, 2.7%), bleeding gums (3, 2.7%), epistaxis (1, 0.9%), haemoptysis (1, 0.9%), menorrhagia (1, 0.9%), bleeding haemorrhoids (1, 0.9%), and a superficial hematoma (1, 0.9%).

3.1. Ocular symptoms and signs associated with dengue fever

The details of ocular symptoms and signs in symptomatic DF patients are listed in Table 1. Seven (6.4%) patients had ocular symptoms of which 4 (3.6%) had bilateral symptoms. The ocular symptoms were blurred vision (3, 2.7%), retro-orbital pain (2, 1.8%), impaired colour vision (1, 0.9%), and metamorphopsia (1, 0.9%). The mean duration of onset of the ocular symptoms from the onset of fever was 4.1 days (range, 0–7). Retro-orbital pain was reported on the day of onset of fever.

Overall, ocular signs were present in 52 (47.7%) patients (Table 2). The common ocular signs were yellowish white subretinal dots at the level of the retinal pigment epithelium in the macula (41, 37.6%), retinal haemorrhages (15, 13.7%), cotton wool spots (13, 11.9%), and subconjunctival haemorrhage (3, 2.7%). Mild colour vision impairment was noted in 26 (24.1%) patients while scattered non-specific visual field defects were present in 64 (60.4%) patients. However, there was no obvious clinical evidence of optic neuropathy in any of the patients.

Among the five patients with DHF, ocular abnormalities were present in 3 patients (60%) - cotton wool spots and retinal haemorrhages were noted in 2 patients (40%) while yellowish white subretinal dots were noted in the macula in 1 patient (20%). The majority of DHF patients had mild colour vision impairment (3, 60%) and non-specific visual field defects (4, 80%).

3.2. Laboratory investigations

The laboratory parameters are shown in Table 2. The mean platelet counts were lower than normal ($76.98 \pm 40.84 \times 10^9$/L) and the lowest recorded platelet count was $57.3 \pm 35.96 \times 10^9$/L. In the majority of patients with ocular symptoms (5, 71.4%), the nadir of the platelet counts correlated with the onset of ocular symptoms.

The liver enzymes were elevated suggesting abnormal liver function; mean alanine aminotransferase (ALT) was 92.69 ± 114.28 U/L and mean aspartate aminotransferase (AST) was 129.05 ± 144.77 U/L. The mean serum total protein, mean serum albumin, and the mean albumin globulin ratios were within the normal range.

Table 1
Characteristics of dengue fever patients with ocular symptoms.

S. no.	Age, sex, race	Year	Serology	Systemic features	Ocular symptoms (onset)[a]	Platelet count[b] (x 10^9/dL)	Ocular signs	CV[c]	VF[d]
1.	17, M[e], C[g]	2005	IgM + IgG -	Fever, rash, nausea, vomiting	Impaired CV OS[j] (7 days)	91	RH[m], CWS[n] OU	Abnormal	Paracentral defects OD[p]
2.	44, M, C	2006	IgM + IgG -	Fever, rash, epistaxis	Metamorphopsia OS (7 days)	67	SRD[o] OU RH, CWS OS	Normal	Nonspecific defects OU
3.	19, M, I[h]	2006	IgM + IgG +	Fever, rash bleeding gums, subcutaneous haemorrhage	Retroorbital pain OU[k] (1 day)	NA[l]	Nil	Normal	Nonspecific defects OU
4.	42, M, I	2007	IgM + IgG -	Fever, myalgia	Retroorbital pain OU (1 day)	NA	SRD OU RH OS	Normal	Paracentral defects OU
5.	36, M, Ma[i]	2007	IgM + IgG +	Fever, myalgia	Blur vision OU (6 days)	15	Nil	Normal	Normal
6.	52, M, I	2007	IgM + IgG -	Fever, myalgia	Blur vision OU (4 days)	18	SRD OU	Normal	Nonspecific defects OU
7.	46, F[f], C	2007	IgM + IgG +	Fever, vomiting	Blur vision OS (3 days)	33	SRD OS	Normal	Nonspecific defects OU

[a] Onset = Onset of ocular symptoms after fever in days. [b] Platelet count at onset of ocular symptoms. [c] CV = Colour vision. [d] VF = Visual fields. [e] M = Male. [f] F = Female. [g] C = Chinese. [h] I = Indian. [i] Ma = Malay. [j] OS = Left eye. [k] OU = Both eyes. [l] NA = Not available. [m] RH = Retinal haemorrhages. [n] CWS = Cotton wool spots. [o] SRD = Subretinal dots. [p] OD = Right eye.

3.3. Comparison of clinical and laboratory features between epidemics (Table 2)

Of the 109 patients enrolled in the study, 33 patients (30.2%) were enrolled during the 2005–2006 epidemics (Group I) while 76 patients (69.7%) were enrolled during the 2007 epidemic (Group II). Three patients (9.1%) in Group I had ocular symptoms while four patients (5.3%) in Group II had ocular symptoms. Colour vision impairment was reported more often in Group I compared to Group II (36.4% vs 18.7%; $P = 0.04$). Group I patients had a higher prevalence of cotton wool spots compared to Group II (30.3% vs 3.9%; $P < 0.001$). Bleeding diathesis were also more common in Group I compared to Group II (21.2% vs 3.9%; $P = 0.004$). All DHF patients belonged to Group I.

There were no significant differences in the mean platelet counts between the two groups. The liver enzymes were significantly higher in the Group I compared to Group II (mean ALT was 150.2 U/L vs 68.28 U/L, $P = 0.001$; mean AST was 196.86 U/L vs 99.53 U/L, $P= 0.002$). The total protein and the serum albumin were significantly lower in Group I compared to Group II (total protein was 68.43 g/L vs 72.27 g/L, $P = 0.016$; serum albumin was 36.86 g/L vs 40.5 g/L, $P = 0.001$).

3.4. Factors predicting risk of ocular involvement

We also evaluated factors which could be predictive of development of ocular manifestations in DF patients. Presence of ocular symptoms [odds ratio = 11.03 (2.18–55.9), $P = 0.001$] and lower mean platelet counts [odds ratio = 0.98 (0.96–1.0), $P = 0.02$] were significantly associated with an increased risk of retinal haemorrhages (Table 3). Presence of ocular symptoms [odds ratio = 6.90 (1.32–35.3), $P = 0.03$], colour vision impairment [odds ratio = 3.80 (1.1–13.0), $P = 0.03$], and visual field defects [odds ratio = 9.46 (1.1–75.8), $P = 0.006$] were significantly associated with presence of cotton wool spots (Table 4). A higher mean haemoglobin concentration [odds ratio = 1.27 (1.06–1.6), $P = 0.03$], a higher haematocrit [odds ratio = 1.11 (1.02–1.2), $P = 0.02$] and a higher red blood cell count [odds ratio = 2.17 (1.12–4.22), $P = 0.02$] were significantly associated with presence of yellowish white subretinal dots in the macula (Table 5).

4. Discussion

In a DF epidemic, the severity of clinical and epidemiologic characteristics of DF may vary depending on the predominant circulating serotype. While the effect of the predominant circulating serotype on systemic manifestations of DF is relatively well-known, more needs to be known about the prevalence of ophthalmic manifestations associated with different dengue serotypes.

The four dengue serotypes contribute to a wide spectrum of disease ranging from mild influenza-like illness to life-threatening haemorrhagic shock syndrome. Our study showed that the frequency of DF-related ocular manifestations varies between epidemics caused predominantly by different dengue serotypes; DENV-1 epidemics were more often associated with colour vision impairment, cotton wool spots, bleeding diathesis, and abnormal liver function compared to DENV-2 epidemics.

The dengue serotypes circulating in Singapore are DENV-1, DENV-2 and DENV-3, with sporadic reports of DENV-4.[17] DF epidemics are often associated with a resurgence of one of the four viral serotypes. Singapore has experienced major DF epidemics over the past two decades and each of these epidemics was associated with a predominant serotype. The majority of the serotyped cases in 2005 and 2006 were caused by DENV-1 (67.4% and 79% respectively) while majority of those in 2007 were caused by DENV-2 (78%).[12–14] The laboratory-confirmed DF cases reported in Singapore were 14,209 in 2005, 3,127 in 2006 and 8,826 in 2007.[12–14]

The DF patients admitted to our hospital during epidemics caused predominantly by DENV-1 and DENV-2 were comparable demographically. Males constituted a higher proportion of the DF cases compared to females during both epidemics similar to other studies.[17] Majority of the patients were Chinese reflecting the population distribution in Singapore which has an ethnic Chinese majority. There was no difference in the mean age between the two epidemics in our study unlike the higher incidence of DF reported with DENV-2 compared to DENV-1 among those aged >55 years in previous studies.[9,11,19]

Significant differences were noted in the frequency of certain ocular manifestations and laboratory parameters between the two groups in our study. A significantly higher proportion of colour vision impairment, cotton wool spots, bleeding diathesis, and liver dysfunction was noted in epidemics caused predominantly by DENV-1 compared to DENV-2. Although bleeding diathesis were more often reported with DENV-1, there was no significant difference in the mean platelet counts between the two groups. The transaminase levels (AST and ALT) were significantly higher while the total protein and the serum albumin were significantly lower in epidemics caused predominantly by DENV-1 compared to DENV-2.

Multiple factors such as age, viral load, type of infection (primary versus secondary) as well as the infecting serotype contribute to the severity of dengue infections.[17] Infection with different serotypes are associated with differences in clinical manifestations and severity of disease as seen with the extent of liver damage and the prevalence of

Table 2
Comparison of patient characteristics during epidemics caused by predominantly different dengue serotypes.

Category	2005–2006 Epidemics	SD	2007 Epidemic	SD	Total	SD	*P*- value
Predominant serotype	DEN-1[a]		DEN-2[a]				
Patients enrolled (n)	33		76		109		
Demographics							
Mean age (years)	39.8	17.1	40.2	15.6	40.1	16.0	0.92
Gender							
Male: Female	3.1:1		2.8:1		2.9:1		0.820
Race							
Chinese (%)	16 (48.5%)		49 (68.5%)		65 (59.6%)		0.118
Non-Chinese (%)	17 (51.5%)		27 (35.5%)		44 (40.4%)		
Clinical features							
Bleeding diathesis	7 (21.2%)	–	3 (3.9%)	–	10 (9.2%)		0.004
Ocular symptoms	3 (9.1%)	–	4 (5.3%)	–	7 (6.4%)		0.561
Colour vision impairment	12 (36.4%)	–	14 (18.7%)	–	26 (24.1%)		0.048
Visual field defects	19 (61.3%)	–	45 (60.0%)	–	64 (60.4%)		0.902
Ocular signs	17 (51.5%)	–	35 (46.1%)	–	52 (47.7%)		0.60
Subretinal dots	10 (30.3%)	–	31 (40.8%)	–	41 (37.6%)		0.299
Retinal haemorrhages	7 (21.2%)	–	8 (10.5%)	–	15 (13.8%)		0.137
Cotton wool spots	10 (30.3%)	–	3 (3.9%)	–	13 (11.9%)		<0.001
Investigations (normal range)							
Haemoglobin	14.66	2.2	14.66	1.9	14.68	1.98	0.995
Females (11.5–15.0 g/dL)							
Males (13.0–17.0 g/dL)							
Haematocrit (37.0–47.0%)	43.33	6.3	44.05	4.9	43.86	5.33	0.525
MCV[b] (80.0–96.0 fL)	87.11	8.25	86.49	6.64	86.68	7.10	0.675
MCH[c] (28.0 pg)	29.45	3.01	28.69	2.5	28.93	2.73	0.182
MCHC[d] (30–36 g/dL)	33.81	1.13	33.15	1.34	33.36	1.31	0.015
Total leucocyte count (4.00–11.00 × 10^9/L)	4.05	2.79	3.84	2.05	3.91	2.28	0. 667
Neutrophils (2.00–7.50%)	2.15	1.90	1.95	1.50	2.01	1.62	0.559
Lymphocytes (20–40%)	4.31	10.5	19.22	19.84	14.59	18.77	<0.001
Eosinophils (1–6%)	0.05	0.07	0.05	0.11	0.05	0.01	0.976
Basophils (0.0–1.0%)	0.06	0.07	0.09	0.11	0.08	0.01	0.129
RBC[e] (3.70–5.00 × 10^{12}/L)	5.05	0.88	5.10	0.55	5.08	0.67	0.571
Mean platelet count (130–400 × 10^9/L)	82.39	46.89	75.10	38.11	76.98	40.84	0.395
Mean lowest platelet count (x10^9/dL)	66.21	43.3	53.47	31.8	57.3	35.96	0.089
ALT[f] (10–36 U/L)	150.2	170.66	68.28	67.09	92.69	114.28	<0.001
AST[g](10–30 U/L)	196.86	197.79	99.53	104.4	129.05	144.77	<0.002
Total Protein (63–83 g/L)	68.43	6.65	72.27	7.34	71.40	7.32	0.016
Albumin (35–50 g/L)	36.86	4.47	40.5	4.70	39.46	4.90	<0.001
AGR[h]	1.20	0.23	1.30	0.23	1.28	0.25	0.072
Creatinine (60–130 mmol/L)	85.67	41.54	80.60	23.39	81.95	29.93	0.436
Urea (2.8–7.6 mmol/L)	4.20	3.04	4.33	2.47	4.30	2.63	0.823
Carbon Dioxide (23–29 mmol/L)	24.35	3.25	24.85	3.57	24.70	3.46	0.504
Prothrombin time (11.5–14 .0 s)	10.18	1.18	10.24	0.93	10.22	0.1	0,827
APTT[i] (23.4–36.6 s)	38.24	9.66	35.69	5.19	36.49	6.68	0.274
Chloride (96–108 mmol/L)	101.90	4.28	99.70	5.71	100.30	5.41	0.057
Sodium (135–145 mmol/L)	134.51	3.99	135.53	5.73	135.89	5.26	0.370
Potassium (3.5–5.1 mmol/L)	4.07	1.38	3.85	0.747	3.91	0.97	0.310

[a] DEN = Dengue virus serotype. [b] MCV = Mean corpuscular volume. [c] MCH = Mean corpuscular haemoglobin. [d] MCHC = Mean corpuscular haemoglobin concentration. [e] RBC = Red blood cell count. [f] ALT = Alanine aminotransferase. [g] AST = Aspartate aminotransferase. [h] AGR = Albumin globulin ratio. [i] APTT = Activated Partial Thromboplastin Time.

dengue maculopathy.[19] DENV-1 epidemics are more often associated with increased vascular permeability and plasma leakage while DENV-2 epidemics are associated with shock and internal haemorrhages.[16] We also found deranged liver function in a significantly higher proportion of patients in epidemics caused predominantly by DENV-1 compared to DENV-2 similar to the findings by Chee et al.[19] However, all of our DHF patients belonged to the epidemics caused predominantly by DENV-1. A Nicaraguan study of paediatric DF patients reported higher frequency of severe systemic manifestations requiring hospitalization for primary infections with DENV-1 compared to DENV-2.[16] Our study supports the finding that primary infections caused by DENV-1 are more severe compared to primary DENV-2 infections. In our study of hospitalized adult patients with DF, a slightly higher proportion of primary infections were noted with epidemics predominantly caused by DENV-1 (60.6%)

Table 3
Odds ratio for developing retinal haemorrhages.

Parameter	Total (n = 109)	Present (n = 15)	Absent (n = 94)	Odds ratio	*P*-value
Ocular symptoms	7 (6.4%)	4 (26.7%)	3 (3.2%)	11.03 (2.18–55.9)	0.001
Mean platelet count (x 10^9/dL)	76.98 (±40.84)	54.67 (±23.72)	80.92 (±41.96)	0.98 (0.96–1.0)	0.02

Table 4
Odds ratio for developing cotton wool spots.

Parameter	Total (n = 109)	Present (n = 13)	Absent (n = 96)	Odds ratio	*P*-value
Ocular symptoms	7 (6.4%)	3 (23.08%)	4 (4.17%)	6.90 (1.35–35.2)	0.03
Colour vision impairment	26 (24.1%)	6 (50%)	20 (20.83%)	3.80 (1.10–13.06)	0.03
Visual field defects	64 (60.4%)	12 (92.3%)	55 (55.91%)	9.46 (1.81–75.79)	0.006

Table 5
Odds ratio for developing yellowish white subretinal dots.

Parameter	Total (n = 109)	Present (n = 48)	Absent (n = 61)	Odds ratio	*P*-value
Haemoglobin (11.5–15.0 g/dL)	14.68 (±1.98)	15.19 (±1.44)	14.35 (±2.19)	1.27 (1.02–1.60)	0.03
Haematocrit (37.0–47.0%)	43.86 (±5.33)	45.40 (±3.9)	42.89 (±5.89)	1.11 (1.02–1.20)	0.02
RBC count (3.7–5.0 × 10^{12}/dL)	5.08 (±0.67)	5.28 (±0.57)	4.97 (±0.70)	2.17 (1.12–4.22)	0.02

compared to DENV-2 (55.2%) although this difference was not statistically significant. As the majority of patients in both groups had primary infections, this could possibly explain the more severe manifestations seen in group I compared to group II.

Infection with one of the four serotypes of the dengue virus provides life-long immunity against that serotype, but confers only transient protection against subsequent infection by other serotypes. In general, secondary infections are more severe compared to primary infections which is possibly related to sequence of infecting virus serotypes, particular virus strains, and the interval between first and second infection.[16] DENV-2 is more often associated with secondary infections as compared with other serotypes.[20,21] Secondary DENV-2 infections have more severe disease compared to secondary DENV-1 and DENV-3.[16] In contrast, primary DENV-1 cases are more overt whereas primary DENV-2 and DENV-3 cases are usually silent infections.[22] Our study did not find any significant difference in ocular manifestations between primary and secondary DF infections similar to a previous study from Fiji.[23]

Ocular symptoms associated with DF range from retrobulbar pain, loss of vision, impaired colour vision and scotomas.[9,10,24–26] The majority of our patients were asymptomatic. DF patients with ocular manifestations are often asymptomatic unless they have severe ocular findings such as significant maculopathy, optic neuritis, or vitreous haemorrhage.[9,10,24–38] The majority of symptomatic patients in our study complained of blurred vision while retro-orbital pain and metamorphopsia were infrequent symptoms. A small proportion of our study patients had ocular symptoms (6.7%) and there was no significant difference in frequency of ocular symptoms between epidemics caused predominantly by DENV-1 compared to DENV-2. A study from Puerto Rico also showed no significant difference in systemic symptom frequency for infections due to different DF serotypes in virologically proven cases.[15] Ocular symptoms were noted in both groups in our study unlike the lack of ocular symptoms reported with epidemics caused predominantly by DENV-2 in another study.[19]

The mean duration of onset of ocular symptoms from the onset of fever in our study was 4.1 days (range, 0–7). Other studies have reported a slightly longer mean duration of onset of ocular symptoms (6.25–7.26 days).[9,18,32,34,37] In our study, two patients presented with retro-orbital pain, which has been reported to occur in as many as 4.5–63% of DF patients.[10,15,35] As retro-orbital pain usually appears on the day of onset of fever, this could explain the shorter duration of onset of ocular symptoms noted in our study. It is interesting to note that most of the previous studies reporting ophthalmic manifestations have not included retro-orbital pain as an ocular symptom.[9,18,32,36] When we excluded the patients with retro-orbital pain in our study, the mean duration of onset of ocular symptoms increased to 5.4 days. Flashes and floaters may predict the development of dengue-related retinal haemorrhages.[35] But none of our patients complained of photopsia or floaters despite presence of retinal haemorrhages in 13.7% patients. In our study, the onset of ocular symptoms correlated with the nadir of thrombocytopenia as reported in literature.[18]

A wide variety of ocular signs such as subconjunctival haemorrhage, anterior uveitis, vitreous haemorrhage, dengue maculopathy, macular edema, foveolitis, retinal vasculitis, retinal arterial and venous occlusions, exudative retinal detachment, choroidal effusion, choroiditis, panuveitis, neuroretinitis, panophthalmitis, and optic neuritis have been reported with DF.[9,10,18,19,24–41] Almost half of our DF patients had ocular signs (51.5% in group I and 46.1% in group II). This is much higher than the reported prevalence of dengue maculopathy (10%) among seropositive DF patients in a previous study.[9] The referral pattern to a particular hospital may have an impact on the prevalence and severity of ocular complications reported. Tertiary hospitals receiving DF patients with more severe disease are likely to report more severe forms of ocular involvement. Our study shows that DF-associated subtle ophthalmic signs may be present in absence of any ocular symptoms. The most common retinal finding in our study were focal subretinal yellowish white dots at the level of the retinal pigment epithelium followed by retinal haemorrhages and cotton wool spots. Focal yellowish white dot like retinal lesions and areas of retinal pigment epithelial thickening are known to occur in the macula DF patients. We believe that these yellowish white subretinal lesions represent areas of focal retinal pigment epithelial thickening associated with inflammatory cellular infiltration in the choroid. These lesions may represent a spectrum of findings associated with dengue maculopathy ranging from innocuous asymptomatic retinal lesions to overtly symptomatic foveolitis.[27,28] The relatively high incidence of mild colour vision impairment and non-specific scattered visual field defects noted in our study could correlate with retinal lesions as there were no other obvious signs of optic neuropathy in any of the patients.

Spontaneous haemorrhages are known to occur with DF and these have been associated with significant thrombocytopenia.[6,29] Subconjunctival haemorrhages were the most common eye findings (37.3%) in a previous study.[10] However, only three patients (2.7%) in our cohort presented with subconjunctival haemorrhages. The higher incidence of bleeding diathesis in the earlier study is likely to be related to lower mean platelet counts (91% patients with ocular haemorrhage had platelet count $<50 \times 10^9$/dL)[10], compared to our study (mean platelet count = 76.98×10^9/dL). Overall, one-tenth (10%) of our DF patients presented with a bleeding diathesis such as subconjunctival haemorrhage, bleeding gums, epistaxis, haemoptysis, bleeding haemorrhoids, and a superficial hematoma.

The risk factors for ocular involvement associated with DF are not well understood. We believe that the differences in ophthalmic manifestations of DF in various epidemics could result from differences in the virulence of the predominant dengue virus serotypes, severity of disease, and genetic makeup of the population. Physicians should be aware of a higher frequency of ocular involvement and deranged liver function in epidemics caused predominantly by DENV-1 compared to DENV-2. Symptomatic DF patients with ocular symptoms should promptly be referred to an ophthalmologist for evaluation.

Our study has some limitations. This is a hospital-based screening study and may not reflect the actual prevalence of DF-related ocular manifestations in the wider population as only the more severe cases of the disease are admitted to a hospital. We enrolled fewer patients in 2005–2006 compared to 2007. It is possible that a larger proportion of mildly symptomatic patients got admitted to hospitals in 2007 due to the increased awareness of the disease. We are unable to elaborate on fundus lesions in the retinal periphery as the retinal photographs did not document the peripheral fundus. Peripheral retinal lesions, however, are also less likely to be visually significant. We did not enrol medically unstable patients as they would not have been able to undergo the eye screening protocol effectively. We enrolled serologically positive DF cases and did not individually serotype our DF patients hence we are unable to confirm whether majority of the patients were infected with the predominant serotype.

5. Conclusions

Ophthalmic manifestations are seen in about half of hospitalized DF

patients in epidemics caused predominantly by DENV-1 and DENV-2, although most patients are asymptomatic. A higher prevalence of colour vision impairment, cotton wool spots, bleeding diathesis, and abnormal liver function occurs in DF epidemics caused predominantly by DENV-1 compared to DENV-2. Studies comparing DF-related ocular manifestations in epidemics caused by other serotypes in different population groups are welcomed to further elucidate possible factors contributing to the observed differences.

Study Approval

This study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) in Singapore. The study protocol adhered to the tenets of the Declaration of Helsinki.

Author Contributions

The authors confirm contribution to the paper as follows: Conception and design of study: AMW, AEKG; Data collection: AMW, SRH; Analysis and interpretation of results: AMW, SRH; Drafting and editing the manuscript: AMW, SS, AEKG; All authors reviewed the results and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

DF	Dengue fever
DHF	Dengue haemorrhagic fever
DENV-1	Dengue virus serotypes 1
DENV-2	Dengue virus serotypes 1
DEN	Dengue virus serotype
MCV	Mean corpuscular volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
RBC	Red blood cell count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AGR	Albumin globulin ratio
APTT	Activated Partial Thromboplastin Time

References

1. World Health Organisation. Dengue and severe dengue: fact sheet. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue/. Accessed October 14, 2021.
2. Guo C, Zhou Z, Wen Z, Liu Y, et al. Global epidemiology of dengue outbreaks in 1990-2015: a systematic review and meta-analysis. *Front Cell Infect Microbiol*. 2017; 317, 10.3389/fcimb.2017.00317.
3. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. *Nature*. 2013;496:504–507. https://doi:10.1038/nature12060.
4. Srivastava HM, Jan R, Jan A, et al. Fractional-calculus analysis of the transmission dynamics of the dengue infection. *Chaos*. 2021;31, 053130. https://doi:10.1063/5.0050452.
5. Fatmawati R Jan, Khan MA, et al. A new model of dengue fever in terms of fractional derivative. *Math Biosci Eng*. 2020;17:5267–5288. https://doi:10.3934/mbe.2020285.
6. Asamoah JKK, Yankson E, Okyere E, et al. Optimal control and cost-effectiveness analysis for dengue fever model with asymptomatic and partial immune individuals. *Results Phys*. 2021;31, 104919. https://doi:10.1016/j.rinp.2021.104919.
7. Boulaaras S, Jan R, Khan A, et al. Dynamical analysis of the transmission of dengue fever via Caputo-Fabrizio fractional derivative. *Chaos, Solit. Fractals*. 2022;8, 100072. https://doi:10.1016/j.csfx.2022.100072.
8. Lee KS, Lai YL, Lo S, et al. Dengue virus surveillance for early warning, Singapore. *Emerg Infect Dis*. 2010;16:847–849. https://doi:10.3201/eid1605.091006.
9. Su DH, Bacsal K, Chee SP, et al. Prevalence of dengue maculopathy in patients hospitalized for dengue fever. *Ophthalmology*. 2007;114:1743–1747. https://doi:10.1016/j.ophtha.2007.03.054.
10. Kapoor HK, Bhai S, John M, et al. Ocular manifestations of dengue fever in an East Indian epidemic. *Can J Ophthalmol*. 2006;41:741–746. https://doi:10.3129/i06-069.
11. Rajarethinam J, Ang LW, Ong J, et al. Dengue in Singapore from 2004 to 2016: cyclical epidemic patterns dominated by Serotypes 1 and 2. *Am J Trop Med Hyg*. 2018;99:204–210. https://doi:10.4269/ajtmh.17-0819.
12. Ministry of Health. *Singapore, Communicable diseases surveillance in Singapore*; 2005: 3–15. Available from: https://www.moh.gov.sg/resources-statistics/reports/communicable-diseases-surveillance-in-singapore-2005. Accessed October 14, 2021.
13. Ministry of Health. *Singapore, Communicable diseases surveillance in Singapore*; 2006: 1–13. https://www.moh.gov.sg/resources-statistics/reports/communicable-diseases-surveillance-in-singapore-2006. Accessed October 14, 2021.
14. Ministry of Health. *Singapore, Communicable diseases surveillance in Singapore*; 2007: 4–15. https://www.moh.gov.sg/resources-statistics/reports/communicable-diseases-surveillance-in-singapore-2007. Accessed October 14, 2021.
15. Cobra C, Rigau-Perez JG, Kuno G, et al. Symptoms of dengue fever in relation to host immunologic response and virus serotype, Puerto Rico, 1990-1991. *Am J Epidemiol*. 1995;142:1204–1211. https://doi.org/10.1093/oxfordjournals.aje.a117579.
16. Balmaseda A, Hammond SN, Perez L, et al. Serotype specific differences in clinical manifestations of dengue. *Am J Trop Med Hyg*. 2006;74:449–456. PMID: 16525106.
17. Yung CF, Lee KS, Thein TL, et al. Dengue serotype-specific differences in clinical manifestation, laboratory parameters and risk of severe disease in adults, Singapore. *Am J Trop Med Hyg*. 2015;92:999–1005. https://doi:10.4269/ajtmh.14-0628.
18. Chan DP, Teoh SC, Tan CS, et al. Ophthalmic complications of dengue. *Emerg Infect Dis*. 2006;12:285–289. https://doi:10.3201/eid1202.050274.
19. Chee E, Sims JL, Jap A, et al. Comparison of prevalence of dengue maculopathy during two epidemics with differing predominant serotypes. *Am J Ophthalmol*. 2009; 148:910–913. https://doi:10.1016/j.ajo.2009.06.030.
20. Fried JR, Gibbons RV, Kalayanarooj S, et al. Serotype-specific differences in the risk of dengue haemorrhagic fever: an analysis of data collected in Bangkok, Thailand from 1994 to 2006. *PLoS Neglected Trop Dis*. 2010;4:e617. https://doi: 10.1371/journal.pntd.0000617.
21. Clapham H, Cummings DA, Nisalak A, et al. Epidemiology of infant dengue cases illuminates serotype-specificity in the interaction between immunity and disease, and changes in transmission dynamics. *PLoS Neglected Trop Dis*. 2015;9, e0004262. https://doi: 10.1371/journal.pntd.0004262.
22. Guzzman MG, Alvarez A, Vazquez S, et al. Epidemiological studies on dengue virus type 3 in Playa municipality, Havana, Cuba, 2001-2002. *Int J Infect Dis*. 2012;16: e198–203. https://doi: 10.1016/j.ijid.2011.09.026.
23. Kuberski T, Rosen L, Reed D, et al. Clinical and laboratory observations on patients with primary and secondary dengue type 1 infections with haemorrhagic manifestations in Fiji. *Am J Trop Med Hyg*. 1977;26:775–783. https://doi: 10.4269/ajtmh.1977.26.775.
24. Koh YT, Sanjay S. Characteristics and ophthalmic manifestations of the classic dengue fever epidemic in Singapore (2005-2006), Asia. *Pac. J. Ophthalmol. (Phila)*. 2013;2:99–103. https://doi: 10.1097/APO.0b013e31828a1917.
25. Somkijrungroj T, Kongwattananon W. Ocular manifestations of dengue. *Curr Opin Ophthalmol*. 2019;30:500–505. https://doi: 10.1097/ICU.0000000000000613.
26. Yip VC, Sanjay S, Koh YT. Ophthalmic complications of dengue fever: a systematic review. *Ophthalmol. Ther*. 2012;1:2. https://doi: 10.1007/s40123-012-0002-z.
27. Loh BK, Bacsal K, Chee SP, et al. Foveolitis associated with dengue fever: a case series. *Ophthalmologica*. 2008;222:317–320. https://doi:10.1159/000144074.
28. Agarwal A, Aggarwal K, Dogra M, et al. Dengue-induced inflammatory, ischemic foveolitis and outer maculopathy: a swept-source imaging evaluation. *Ophthalmol. Retina*. 2019;3:170–177. https://doi: 10.1016/j.oret.2018.09.008.
29. Li M, Zhang X, Ji Y, et al. Acute macular neuroretinopathy in dengue fever: short-term prospectively followed up case series. *JAMA. Ophthalmol.* 2015;133:1329–1333. https://doi: 10.1001/jamaophthalmol.2015.2687.
30. Yadav HM, Majumder PD, Biswas J. Dengue associated choroiditis: a rare entity. *J. Ophthalmic. Inflamm. Infect.* 2017;7:14. https://doi.org/10.1186/s12348-017-0132-5.
31. Kanungo S, Shukla D, Kim R. Branch retinal artery occlusion secondary to dengue fever. *Indian J Ophthalmol*. 2008;56:73–74. https://doi:10.4103/0301-4738.37606.
32. Bacsal KE, Chee SP, Cheng CL, et al. Dengue-associated maculopathy. *Arch Ophthalmol*. 2007;125:501–510. https://doi:10.1001/archopht.125.4.501.
33. Venkatramani J, Lim WK. Bilateral vitreous haemorrhage associated with dengue fever. *Eye*. 2006;20:1405–1406. https://doi:10.1038/sj.eye.6702259.
34. Sanjay S, Wagle AM, Au Eong KG. Optic neuropathy associated with dengue fever. *Eye*. 2009;22:722–724. https://doi:10.1016/j.ophtha.2008.08.015.
35. Seet RC, Quek AM, Lim EC. Symptoms and risk factors of ocular complications following dengue infection. *J Clin Virol*. 2007;38:101–105. https://doi:10.1016/j.jcv.2006.11.002.
36. Lim WK, Mathur R, Koh A, et al. Ocular manifestations of dengue fever. *Ophthalmology*. 2004;111:2057–2064. https://doi:10.1016/j.ophtha.2004.03.038.

37. Cruz-Villegas V, Berrocal AM, Davis JL. Bilateral choroidal effusions associated with dengue fever. *Retina*. 2003;23:576–578. https://doi:10.1097/00006982-200308000-00031.
38. Somkijrungroj T, Kongwattananon W. Ocular manifestations of dengue. *Curr Opin Ophthalmol*. 2019;30:500–505. https://doi:10/1097/ICU.0000000000000613.
39. Sanjay S, Agrawal S, Jain P, et al. Permanent visual impairment in dengue fever following platelet transfusion: a series of 5 cases. *Ann Acad Med Singapore*. 2021;50:588–592. https://doi:10.47102/annals-acadmedsg.202154.
40. Sanjay S, Anilkumar A, Mahendradas P, et al. Inflammatory branch retinal artery and vein occlusion with panuveitis secondary to dengue fever. *Indian J Ophthalmol*. 2020;68:1958–1960. https://doi:10.4103/ijo.IJO_1368_20.
41. Mahendradas P, Sanjay S, Kawali A, et al. Commentary: evidence of dengue virus in eviscerated specimens of panophthalmitis secondary to dengue fever: a possible cause-effect phenomenon. *Indian J Ophthalmol*. 2022;70:970. https://doi:10.4103/ijo.IJO_2604_21.