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Ocular manifestations of dengue fever in University Malaya Medical Centre

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Abstract. This time-framed study describes the spectrum of ocular manifestations in patients with dengue fever and the association between maculopathy with the stages of dengue fever. This cross sectional prospective study involved 145 dengue inpatients recruited from University Malaya Medical Centre. Observed parameters were stages of dengue infection, abnormal fundus and types of maculopathy. Retinal abnormalities involved the peripheral region in 3 patients (1.03%) and the macula in 13 patients (4.48%). The types of maculopathy encountered were macular oedema 7 (53.8%), cystic appearance 4 (30.8%), macular haemorrhage 1 (7.7%) and yellow spots 1(7.7%). Reduced distance VA, visual scotoma and metamorphopsia and abnormal Amsler grid test correlated with maculopathy, $p< 0.05$. Maculopathy correlated well with dengue with severe leakage ($p= 0.025$). Our study found the prevalence of maculopathy in dengue infection to be 4.48% in UMMC. The significant predictors of maculopathy were dengue with severe leakage, visual scotoma, metamorphopsia, distance VA impairment and abnormal Amsler grid test. This study was funded by a University Malaya Grant - URMG no: RP006D-13HTM.

INTRODUCTION

Over the past five decades, there has been an alarming 30-fold increase in the incidence of dengue worldwide. In 2012, dengue ranked as the most important mosquito borne viral disease in the world (WHO, 2012). Caused by 4 serotypes of dengue virus from the family Flaviviridae and genus Flavi virus, dengue is transmitted by mosquitoes of the genus *Aedes* (Gubler, 1998).

A dengue viral infection may induce auto-antibodies against endothelial cells, platelets, and coagulatory molecules which lead to their abnormal activation or dysfunction (Dewi *et al.*, 2004) (Steinberg *et al.*, 2012) (Chuang *et al.*, 2013). Aberrant activation of T cells and overproduction of soluble factors cause an increase in vascular permeability. We infer that similar autoantibodies may be the cause of fundus abnormalities.

Previously, ocular findings in dengue fever were considered rare (Gowen *et al.*, 2010). Published ocular findings include macula and retinal haemorrhages, Roth's spots, exudative maculopathy and choroidal effusion (Cruz-Villegas *et al.*, 2003). Su *et al.* (2007) found the prevalence of dengue maculopathy among patients hospitalized for dengue fever is 10% in Singapore. Another study by Kapoor *et al.* (2006) found subconjunctival haemorrhage in approximately one third of patients with dengue hemorrhagic fever. Optic neuropathy has also been reported in dengue fever and occasionally results in permanent and significant visual impairment (Sanjay *et al.*, 2009).

This study provides a baseline database of findings for dengue infection associated ocular problems in University Malaya Medical Centre, Malaysia.

MATERIAL AND METHODS

Research design
This is a cross sectional prospective study.

Research setting: study period, place and population
This study was conducted in the eye clinic of UMMC from 1st December 2012 to 31st May 2013. Patients who met the inclusion criteria and agreed to participate in this study were recruited.

Selection of patient

Inclusion criteria
Patients aged 12 years and above, regardless of gender, and able to provide informed consent were selected. These patients were admitted to UMMC and diagnosed with dengue fever according to WHO criteria.

Exclusion criteria
Clinically unstable patients and patients with systemic illness and potentially similar ocular findings in dengue such as Diabetes Mellitus, hypertension, leukaemia, anaemia and pre-existing thrombocytopaenia were excluded from the study. Past ocular injury causing abnormal ocular morphology or presence of media opacities that would impact fundus visualization were also excluded. To avoid the possible confusion with post-operative macular oedema, patients who had undergone surgery to the eye within 3 months prior to admission were also excluded.

Research Methodology
All patients admitted to UMMC who were diagnosed to have dengue fever according to WHO guidelines (WHO, 1997) were recruited. Brief history on the nature of the fever, date of onset and ocular symptoms were taken. Patients were classified according to severity (dengue with no warning sign, dengue with warning sign and severe dengue with plasma leakage) based on WHO criteria (WHO, 2009).

Examination of distance visual acuity (VA) using LogMAR VA chart at 3 meter and near VA using Printer's types of N series chart was done. Relative afferent pupillary defect (RAPD) was tested and Amsler grid test was performed to detect any metamorphopsia. Dilated fundus examination was carried out with portable binocular indirect ophthalmoscopy.

Further examinations include macula OCT scans performed on a spectral domain system Cirrus high definition optical coherence tomography (HD-OCT) and fundus photos. Subjects with fundus/ macula abnormality underwent FFA and ICG.

Patients with positive fundus findings were followed up until the lesion resolved. The interval between ocular examination and regression of fundus lesion were documented.

Data collection
All data collected were stored in Statistical Package for Social Sciences (version 16, SPSS Inc., Chicago, IL).

Statistical analysis
The data was analyzed using T-test, Chi-square, analysis of variance (ANOVA) and logistic regression to describe the spectrum of ocular fundus findings in dengue patients. The presence of any ocular changes correlated with patient's severity of dengue fever and laboratory parameters.

RESULTS

The total number of adult patients admitted to UMMC for dengue fever from 1st December 2012 to 31st May 2013 was 235. During this study period, 145 patients fulfilled the inclusion criteria and agreed to participate in this study.

The mean interval between the onset of the fever and admission to the ward was 5.01 days and the mean interval between the onset of the fever and ocular examination was 6.37 days.

The age of the patients ranged from 12 to 68 years old, with the mean age of 30.38 (±12.29) (Figure 1). 82% of these patients were below 40 years of age.

A quarter of the patients were found to be foreigners. There were 108 (74.5%) Malaysians and 37(25.5%) foreigners. All 145 patients lived in urban areas (100%).

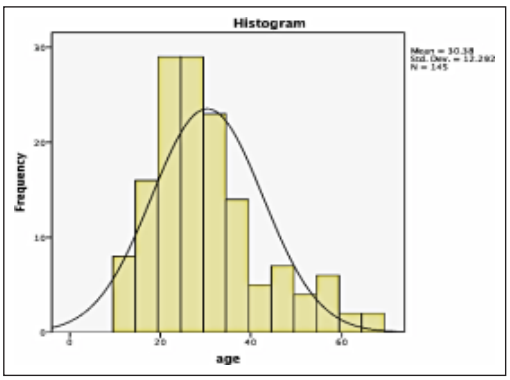

Figure 1. Distribution of dengue patients according to age.

114 patients had dengue with warning signs (78.6%), while there were only 25 (17.2%) without warning signs. 6 (4.1%) presented with severe leakage. 17.2% of the patients had bleeding tendencies.

The spectrum of retinal abnormalities involved both the peripheral fundus 3 (1.03%) and macula area 13 (4.48%). Peripheral retinal changes seen in patients with dengue infection include retinal exudate in one eye and vessel tortuosity in 2 eyes of another patient.

Sociodemographic characteristic of patients with dengue maculopathy

In term of nationality, most patients with maculopathy were Malaysian 5 (62.5%) and only 3 (37.5%) were foreigners. Among the foreigners, 2 were Bangladeshi and 1 was Sri Lankan.

Patterns of dengue maculopathy

There were 13 eyes (4.48%) from 8 patients who had maculopathy. Among the changes seen in macula due to dengue infection

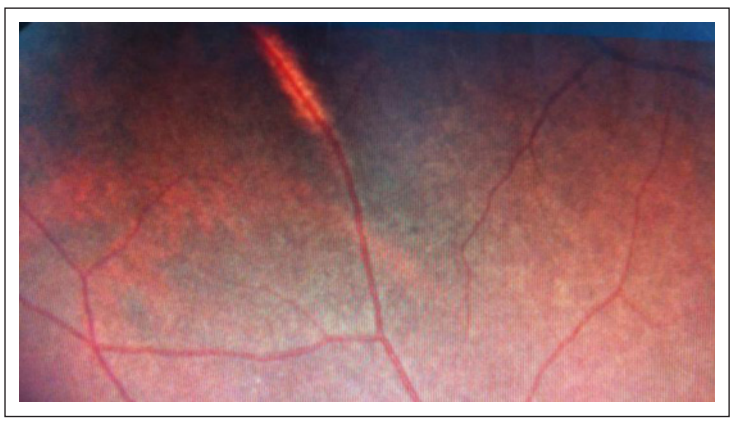

Figure 2. Fundus photo showing retinal exudate along the superotemporal vessel of the right eye.

Figure 3. Vascular tortuosity in dengue patient.

was: macula oedema 7 (53.8%), macula haemorrhage 1 (7.7%), cystic appearance 4 (30.8%) and yellow spot 1 (7.7%).

These macula lesions resolved within 3 weeks to 2 months of clinical presentation.

Out of 145 patients, 65 (44.7%) of them experienced visual symptoms such as central scotoma 1(0.7%), diffuse scotoma 7(4.8%), metamorphopsia 7(4.8%), retrobulbar pain 44(30.3%) and eye redness 6(4.1%). Among the patients with maculopathy, 5(62.5%) patients experienced visual scotoma and metamorphopsia. Symptoms of visual scotoma and metamorphopsia correlated well with maculopathy **(p< 0.01).**

The worst distance visual acuity was LogMAR 0.40 and this was contributed mainly by early cataract; in which retinal view was still not obscured. Otherwise, most of the patients; 260 eyes (89.65%) had visual acuity better than LogMAR 0.15 even with maculopathy. Among maculopathy patients, 4 (30.8%) eyes had visual acuity worse than LogMAR 0.15. There was a significant association between reduced distance vision and maculopathy, **p= 0.024.**

There were only 2 patients had near visual acuity N6 or worse in maculopathy group. There was no significant association between reduced near vision and maculopathy, p= 0.092.

We found that patients with maculopathy had some defects in Amsler grid test. This resulted in changes in 7 eyes (53.8%) with **p< 0.01.**

Association between maculopathy and stages of dengue fever

Table 1 shows the association of maculopathy and dengue stages. There was a significant association between dengue stages and maculopathy, p=0.037.

Figure 4. Fundus photo of macula haemorrhage secondary to dengue.

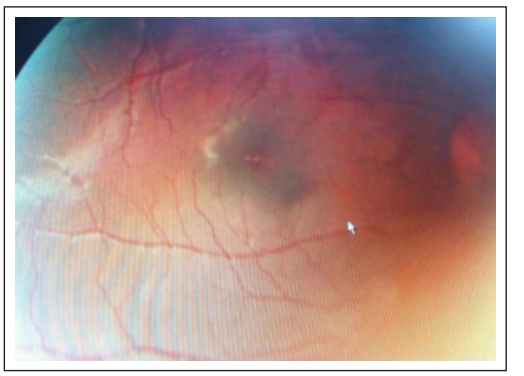

Figure 5. Fundus photo of yellow spot at the parafoveal region due to dengue.

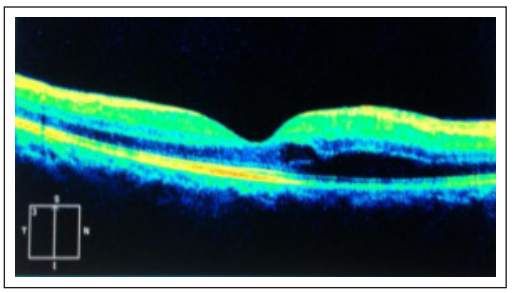

Figure 6. OCT shows macula oedema in a dengue patient.

Table 1: Summary of association between dengue stages and maculopathy

		Maculopathy			
		positive	negative	χ^2	P
Classification	No warning sign	0(0%)	50 (17.2%)		
	Warning sign	11 (3.8%)	217(74.8%)		
	Severe dengue with plasma leakage	2 (0.7%)	10 (3.4%)	6.569	0.037

Logistic regression test showed that in patients with severe dengue, there was a 4 folds increment (p= 0.025) in tendency to develop maculopathy.

Anterior segment ocular presentations of dengue infection include subconjunctival haemorrhage 15 (5.17%), conjunctival hyperaemia 6 (2.06%), lid oedema 1 (0.34%) and jaundice 1 (0.34%) due to liver failure.

Only 3 out of 11 patients consented for FFA, and none of the patients agreed for ICG. Among those patients, none of them showed any significant vascular leakage.

DISCUSSION

Dengue fever is caused by the dengue virus (DENV) from the family Flaviviridae and comprises of 4 serotypes (DENV1, DENV2, DENV3, DENV4). It is transmitted by the female *Aedes aegypti* and is usually endemic in urban and semi-urban populations (Gubler DJ, 1998) (Hassan M. Khormi, 2011).

The incidence of dengue is growing dramatically around the world. It is estimated that 40% of the world's population, close to 2.5 billion people, are at risk from dengue. WHO currently estimates there may be 50–100 million dengue infections annually worldwide (WHO, 2014).

In Malaysia, an average of 5000 dengue cases were reported annually in the early 1990s (MOH, 2004). The incidence shows an upward trend from 44.3 cases/100,000 population in 1999 to 181 cases/100,000 population in 2007 (MOH, 2012). In 2013, there was almost a two-fold increase of reported cases relative to 2012 (WPROWHO, 2014).

Rapidly developing areas with high population density have higher numbers of dengue cases. This includes areas around University Malaya Medical Centre such as Kuala Lumpur and Selangor. The reported dengue cases in Selangor increased dramatically by 42.0% from 1056 cases with 6 deaths in 2009, to 1501 cases with 7 deaths in 2010 (MOH, 2012).

The manifestations of dengue infections vary from asymptomatic to undifferentiated dengue fever (DF) and severe dengue infections causing dengue haemorrhagic fever (DHF) (Smith AW *et al.*, 2004). The clinical features of classical dengue fever include fever, headache, retro-orbital pain, myalgias and arthralgias, nausea, vomiting and often a rash. Dengue haemorrhagic fever patients develop thrombocytopenia and haemoconcentration. Some patients may develop hemorrhagic manifestations, such as hematuria, gum bleeding, epistaxis, haematemesis, melaena, and ecchymosis. Dengue itself is rarely fatal, but dengue haemorrhagic fever (DHF) can be complicated with dengue shock syndrome (DSS) which can lead to death if not properly treated (Khan MI *et al.*, 2013) (Rajapakse S, 2011).

There are several factors associated with the occurrence of dengue infection in the community: socio-demographic factors such as age, gender and ethnicity, climate variability, (Bangs MJ *et al.*, 2006) (Guha-Sapir D, Schimmer B, 2005) (Hii YL *et al.*, 2012) (Koh BKW *et al.*, 2008) dengue vector ecology, community participation and population distribution (Gubler, DJ, 1998). Risk factors for a more severe dengue infections included past dengue infection, high viral load and increase viral virulence, host genetic background, T-cell activation and auto-antibodies (Khan MI *et al.*, 2013) (Zompi S *et al.*, 2012).

We observed one quarter (25.5%) of our patients were foreigners. The presence of foreign workers in Malaysia have led to social and economic implications in local communities (Abdul Rahman H *et al.*, 2012). This is further accentuated by overcrowding and poor sanitation, leading to an increase in breeding sites for *Aedes* mosquitoes, especially in construction sites where many foreigners work in Malaysia.

Retinal examination in patients with dengue infection could be valuable in the assessment of dengue. The small caliber retinal vessels can be examined easily to predict severity in dengue infections.

In our study, the prevalence of maculopathy was 13(4.48%) eyes out of 8 patients during the epidemic of dengue infection. The most common visual complaint

was metamorphopsia and visual scotoma, which was either diffuse or central, and this showed significant association with maculopathy ($p<0.01$). Presence of maculopathy also correlated well with abnormal Amsler grid test ($p<0.01$). Therefore, metamorphopsia and an abnormal Amsler grid test are good predictors of maculopathy in dengue infection.

We found that the spectrum of maculopathy included macula oedema, cystic changes, macula haemorrhage and yellow spots. This was similar to the findings in the other studies (Kapoor HK *et al.*, 2006) (Su DH *et al.*, 2007). However, the cause of macula abnormalities has yet to be determined. There is no exact explanation for the pathophysiology of the disease process in the eye. We postulate that the pathophysiology could be similar to the immune related inflammatory reaction in the eyes, which lead to increased vascular permeability causing exudation of the plasma contents into the intraretinal spaces.

In our observation, dengue maculopathy resolved spontaneously within 2 months from the onset of the fever. However, despite its resolution and normal near and distance VA, one patient still continued to experience metamorphopsia after 2 months. We are unsure whether this was due to a relatively severe oedematous retina or due to retinal pigment epithelium (RPE) disorder. Further evaluation on RPE function in dengue maculopathy patients should be done to understand this phenomenon. We suggest for all dengue patients to be given an Amsler grid chart for monitoring at home, as presence of metamorphopsia may indicate that they are having plasma leakage and may require ward admission.

Of the patients with maculopathy, 5(62.5%) were Malaysians and 3(37.5%) were foreigners. This was not significant in predicting maculopathy ($p=0.391$). We observed that 82% of the affected patients were below 40 years of age (range from 12–33). As this age group represented the productive age group of our community, dengue outbreaks can lead to a significant socioeconomic burden in our country.

Clinical evidence of severe plasma leakage was also a determining factor of maculopathy ($p= 0.025$). Literature reviews suggest that the release of cytokines from the dengue virus can disrupt the tight junction of the vessels (Rathakrishnan A *et al.*, 2012), causing plasma leakage. This occurs during the defervescence period (Hassan M Khormi, 2011), which usually occurs on day 6 to 8 from the onset of fever. Therefore, adequate patient education regarding the warning signs of dengue and extra precautions during the period of defervescence is beneficial for early stabilization and prevention of complications.

Limitations of the study

The small sample size is not a true representation of our country's population. Patients aged less than 12 years old, unstable and non-hospitalized patients were not included. Thus, this might be the cause of low prevalence of maculopathy in our study.

There were limited numbers of angiographic assessment as most patients declined the examination. Furthermore, the patients required bed rest and strict observation in their ward, thus, they could not spend long periods in the ophthalmology clinic.

We recommend a larger sample size, with fundus fluorescent angiography and indocyanine green examination for more accurate findings.

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