EVALUATION OF OCULAR MANIFESTATIONS AND ITS PREDICTORS IN DENGUE PATIENTS IN HOSPITAL SELAYANG

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotation and summaries which have been duly acknowledged.

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TABLE OF CONTENTS

ABSTRAK

Latar belakang:

Denggi adalah sejenis penyakit sebaran nyamuk yang paling menular di dunia yang menjadi punca beban kesihatan awam yang besar di Wilayah Pasifik Barat. Ia adalah punca kematian dan morbiditi utama di Malaysia. Malaysia adalah negara endemik untuk denggi, di mana terdapat kesemua serotaip virus denggi (DENV-1, DENV-2, DENV-3, DENV-4). Walau bagaimanapun, serotaip utama berubah dari tahun ke tahun dan juga di berbeza antara negeri-negeri di Malaysia.

Demam denggi mempunyai spektrum manifestasi klinikal yang sangat luas dengan tahap keterukan yang berbeza. Serotaip denggi yang berbeza mungkin punca kepelbagaian manifestasi tersebut. Sejak kebelakangan ini, terdapat peningkatan bilangan kes manifestasi mata dalam denggi, daripada penyakit yang ringan kepada keadaan yang mengancam penglihatan.

Objektif:

Objektif kajian ini adalah untuk menentukan kelaziman manifestasi ocular di kalangan pesakit denggi, untuk menentukan kaitan antara manifestasi mata dan serotaip virus denggi yang berbeza dan untuk mengenal pasti peramal manifestasi mata dalam denggi.

Kaedah kajian:

Ini adalah kajian rentas yang dijalankan di Hospital Selayang, Gombak, Malaysia. Seratus tiga puluh lapan pesakit yang di pastikan menghidap demam denggi telah

direkrut dari Januari 2017 hingga Januari 2018. Pemeriksaan mata yang lengkap untuk setiap pesakit termasuk penilaian ketebalan makula menggunakan mesin Heidelberg Spectral Domain Optical Coherence Tomography (OCT). Sampel darah dihantar untuk analisa dan identifikasi serotaip virus denggi. Kaedah *reverse transcription polymerase chain reaction* (RT-PCR digunakan untuk mengenal pasti serotaip denggi DENV-1, DENV-2, DENV-3 dan DENV-4. Hasil kajian dianalisa menggunakan Pakej Statistik untuk Sains Sosial (SPSS) yang membandingkan manifestasi mata di kalangan serotaip denggi yang berbeza.

Keputusan:

Manifestasi mata diperhatikan pada 18 (13%) pesakit dari kajian ini. Empat belas (10%) pesakit mengalami kemerahan mata. Pendarahan sub-konjunktiva adalah penemuan paling banyak ditemui melibatkan 14 pesakit di mana 9 (64%) pesakit telah dijangkiti oleh DENV-1($p=0.019$). Penemuan fundus pula terdapat pada hanya 3 pesakit termasuk 2 yang melibatkan makula. Seorang pesakit mengalami *anterior uveitis* dan ia ditemui berhubung kait jangkitan DENV-3 ($p= 0.014$). Umur, jantina, bangsa dan juga keputusan darah bukan merupakan peramal signifikan dalam ujian ini ($p>0.05$).

Kesimpulan:

Manifestasi mata adalah sangat lazim di kalangan pesakit denggi. Didapati bahawa manifestasi mata adalah berhubungkait dengan serotaip denggi yang tertentu. Tiada peramal signifikan untuk manifestasi mata denggi yang dikenal pasti dalam kajian ini. Kajian lanjut dan yang lebih meluas perlu dijalankan untuk menilai dengan lebih terperinci korelasi antara serotaip yang berbeza dengan manifestasi mata yang lain.

ABSTRACT

Background:

Dengue is the most rapidly spreading mosquito-borne disease in the world causing a substantial public health burden in the Western Pacific Region. It is a major cause of mortality and morbidity in Malaysia. Malaysia is hyperendemic for dengue, as evidenced by simultaneous presence of all four dengue serotypes (DENV-1, DENV-2, DENV-3, DENV-4). However, the predominant serotype differs from year to year and varies across the different states in Malaysia. Dengue fever has a wide spectrum of clinical manifestations with varying degrees of severity. Different dengue serotypes may contribute to the variability and severity of manifestations. Over the recent years, there has been increasing numbers of cases of ocular manifestations in dengue, from mild self-limiting presentation to sight threatening conditions.

Objectives:

The objectives of this study are to determine the prevalence of ocular manifestations in dengue patients, to determine the association between ocular manifestations and the different serotypes of dengue virus and to identify the predictors of ocular manifestations in dengue.

Methods:

This is a cross-sectional study conducted in Hospital Selayang, Gombak, Malaysia. One hundred and thirty eight patients diagnosed with dengue fever were recruited from January 2017 to January 2018. Complete ocular examination was done for each patient

including assessment of macula thickness using Heidelberg Spectral-Domain Optical Coherence Tomography (OCT). Serum blood sample is sent for full blood count and dengue serotype. Reverse transcription- polymerase chain reaction (RT-PCR) method was used to identify the dengue serotypes DENV-1, DENV-2, DENV-3 and DENV-4. Findings were analysed using Statistical Package for Social Sciences (SPSS) comparing ocular manifestations among the different dengue serotypes.

Results:

Ocular manifestations were present in 18 (13%) patients from the study. Fourteen (10%) patients had eye redness. Subconjunctival haemorrhage was the commonest eye findings seen in 14 patients in which 9 (64%) patients were infected by DENV-1 ($p=0.019$). Fundus findings were present in 3 patients including 2 maculopathy. One patient had anterior uveitis and is found to be associated with DENV-3 ($p= 0.014$)Age, gender, ethnicity and full blood count values including platelet level were found not to be significant predictors in this study ($p>0.05$).

Conclusion:

Ocular manifestations are prevalent amongst dengue patients. There is association between specific dengue serotype with ocular manifestations. There is no significant predictors of dengue ocular manifestation identified in this study. Further research and larger studies need to be conducted to evaluate correlation between the different serotypes with other types of ocular manifestation and its severity.

CHAPTER 1

INTRODUCTION

1.1 Epidemiology of dengue fever

Dengue fever is the most rapidly spreading vector borne disease in the world. World Health Organization (WHO) estimated 50 million dengue cases occur annually and approximately 2.5 billion people live in endemic countries.

This has turned this disease into a serious public health problem especially in tropical and subtropical countries (Teixeira et all, 2002). The dengue incidence in Malaysia from year 2000 to 2010 showed increasing trend, with percentage of dengue cases and dengue deaths increase by 14% and 8% per year respectively (Md. Shahin et al, 2013).

1.2 Dengue classification

The WHO 1997 dengue guideline classified dengue into dengue fever (DF), dengue haemorrhagic fever (DHF Grade 1 and 2) and dengue shock syndrome (DHF Grade 3 and 4). However, this classification is found to have many limitations. Alexander et al found that not all dengue shock cases fulfil the DHF criteria (Alexander et al, 2011). This result became the basis for the revision of the new WHO dengue guideline. The WHO 2009 guideline classified dengue according to severity; dengue without warning signs, dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets) and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure).

1.3 Dengue virus

The dengue virus (DENV) belongs to the family *Flaviviridae*, genus *Flavivirus* and is transmitted to humans by *Aedes aegypti* mosquitoes. It consists of four antigenically distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) and each serotype has several subtypes or genotypes (Shu et al, 2004; Martina et al, 2009). All four dengue serotypes are found in Malaysia but predominant serotype changes from year to year and varies across the different states in Malaysia (Mudin et al, 2015; Ng et al, 2015).

1.4 Dengue diagnostic tools

Previously, confirmatory laboratory tests used to diagnose acute DENV infection were one or a combination of the three basic laboratory diagnostic methods: DENV isolation, detection of viral nucleic acid amplification technology assay by reverse transcription polymerase chain reaction (RT-PCR), and serological demonstration of a four-fold or greater rise in antibodies (IgM and/or IgG) titre to DENV (De Paula et al, 2004; Chua et al, 2011). Recent scientific reports show that in acute DENV infection, the non-structural protein one (NS1) of the virus could be detected in infected patient's blood (Young et al, 2000). This finding led to the development of commercial dengue diagnostic test kits based on antigen-capture enzyme-linked immunosorbent assay (ELISA) for detection of circulating dengue NS1 antigen in acute dengue infection. Multiple studies found that NS1 ELISA test shows higher sensitivity for early dengue infection compared to other diagnostic methods such as virus isolation and RT-PCR (Kumarasamy et al, 2007; Hang et al, 2009; Osorio et al, 2010). Malaysian Ministry of Health (MOH) Clinical Practice Guideline (CPG) for management of dengue infection

in adults (3rd edition) recommends dengue rapid combo test or NSI antigen to be taken as soon as dengue is diagnosed. Dengue immunoglobulin M (IgM) is usually positive after day 5 to 7 of illness, thus a negative IgM before day 5 to 7 does not exclude dengue infection. Malaysian MOH CPG recommends repeating dengue IgM in recovery phase if initial dengue IgM is negative, and if repeat sample is still negative, dengue IgG should be done for diagnostic confirmation of secondary dengue infection. Reverse transcription- polymerase chain reaction (RT-PCR) method is used for dengue serotyping and identifying the different dengue serotypes (Johnson et al, 2005; Chien et al, 2006) . This test is only available in a few centres in Malaysia (e.g. Institute of Medical Research, National Public Health Laboratory, State Public Health Laboratories and University Malaya Medical Centre). In our study, the serum sample was sent to National Public Health Laboratory.

1.5 Dengue ocular manifestations

Ocular manifestations in dengue are relatively rare compared to other clinical manifestations. There is limited research in literature on the prevalence of ocular manifestations in dengue patients and none published on the prevalence in Malaysia (Lim et al, 2004; Kapoor et al, 2006; Chan et al, 2006). This limitation may be due to the variable severity of presentation in ocular manifestations whereby most cases are asymptomatic or self-limiting, and visual disturbance mostly presents in posterior segment involvement (e.g. dengue maculopathy, optic neuropathy) (Bacsal et al, 2007; Sanjay et al, 2008). The most common anterior segment manifestation is found to be subconjunctival haemorrhage (Kapoor et al, 2006). Several isolated case reports in Malaysia have been published over the recent years with maculopathy being more

commonly reported (Juanarita et al, 2012; Fhun et al, 2016; Boo et al, 2017, Chuah et al, 2017). Optical coherence tomography (OCT) is a reliable tool for diagnostic and prognostic purposes in dengue maculopathy (Teoh et al, 2010). Fundus fluorescein angiography (FFA) is useful for diagnosis of vein occlusion and vasculitis (Bacsal et al, 2007; Quek et al, 2009, Gupta et al, 2009). The outcome of ocular manifestations in dengue varies depending on its severity from self-limiting to permanent visual loss in severe cases.

1.6 Rationale of study

There is limited literature on association of serotype specific dengue virus infection with clinical manifestations and its severity. Halsey et al found that specific clinical manifestation are often represented by an individual DENV serotype. The study showed DENV-3 had a higher prevalence of musculoskeletal and gastrointestinal manifestations, while DENV-4 patients had a higher prevalence of respiratory and cutaneous manifestations (Halsey et al, 2012). In a study conducted by Yung et al, DENV-1 patients were found to have higher risk of developing DHF compared to patients with DENV-2 or DENV-3. DENV-1 cases were more likely to present with red eyes while DENV-2 cases were more likely to develop joint pain (Yung et al, 2015). DENV-2 was also associated with more severe infection (Vaughn et al, 2000; Balsameda et al, 2006). Based on these literatures, we think that there will be an association between ocular manifestations and dengue serotypes. However, to our knowledge, there is no study done to assess the association of ocular manifestations with dengue serotypes. Thus, our study aims to evaluate prevalence of ocular manifestations in dengue patients, to determine the

association between ocular manifestation and the different serotypes of DENV and to identify the predictors of ocular manifestations in dengue which may help in more specific and thorough screening of dengue ocular manifestations in the future.

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CHAPTER 2

OBJECTIVES OF THE STUDY

2.0 STUDY OBJECTIVES

2.1 General Objective

To evaluate ocular manifestations and its predictors in dengue patients.

2.2 Specific Objectives

2.2.1. To determine the prevalence of ocular manifestations in patients diagnosed with dengue fever.

2.2.2. To determine the association between ocular manifestations and the different serotypes of dengue virus.

2.2.3. To identify the predictors of ocular manifestations in dengue patients.

CHAPTER 3

MANUSCRIPT

3.1 Title page

EVALUATION OF OCULAR MANIFESTATION AND ITS PREDICTORS IN DENGUE PATIENTS IN HOSPITAL SELAYANG

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3.2 KEYWORDS

dengue fever; serology; serotypes; DENV; maculopathy; retinopathy; dengue ocular manifestation

3.3 ABSTRACT

Objectives:

The objectives of this study are to determine the prevalence of ocular manifestations in patients diagnosed with dengue fever, to determine the association between dengue ocular manifestations and the different serotypes of dengue fever and to identify predictors of ocular manifestations in dengue patients.

Methods:

A cross sectional study was conducted between January 2017 and January 2018 involving patients with confirmed dengue fever who were admitted to Hospital Selayang, Malaysia. Detailed information regarding clinical signs and symptoms was collected and complete ophthalmic examination was done. Evaluation of macular thickness was conducted using Heidelberg Spectral Domain Optical Coherence Tomography (OCT). Blood samples were collected and sent for full blood count and dengue virus serotyping. Statistical analysis was done using Statistical Package for the Social Science (SPSS Inc Version 24).

Results:

A total of 138 patients diagnosed with dengue fever were included into the study. The mean age was 32.8 years (SD 13.57) and 56.5% were females. The racial distribution was predominantly Malay (55.1%). Fourteen (10%) patients had eye redness but only 1 (0.7%) patient had associated blurring of vision. Ocular manifestations were present in 18 (13%) patients. Subconjunctival haemorrhage was the commonest eye findings seen in 14 (10.1%) patients in which 9 (64%) patients were infected by DENV-1 ($p= 0.019$). Fundus findings were present in 3 (2.1%) patients including 2 (1.4%) maculopathy. One (0.7%) patient had anterior uveitis and was infected by DENV-3 ($p= 0.014$). The clinical and laboratory predictors of ocular manifestation evaluated in this study were age, gender, ethnicity, and full blood count but none were found to be significant ($p > 0.05$).

Conclusion:

The prevalence of ocular manifestation in patients diagnosed with dengue fever was 13% in our study. There was significant association between DENV-1 infection with subconjunctival haemorrhage while infection with DENV-3 was found to be associated with anterior uveitis. There were no other significant demographic or laboratory predictors of dengue ocular manifestations found in our study.